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ASCP 2020 Annual Meeting ORAL ABSTRACTS



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Friday, May 29, 2020

COVID-19 TALK

8:30 a.m. – 9:30 a.m.

COVID-19 TALK

ABSTRACT NOT INCLUDED

TELEPSYCHIATRY IN THE AGE OF COVID

Jay Shore, University of Colorado Anschutz Medical Campus

Individual Abstract: The COVID crisis is an unprecedented public health emergency that is having far ranging impacts to society and the practice of psychiatry. Technologies have been widely and rapidly deployed in response to COVID with psychiatric organizations and individual practitioners having to rapidly virtualize their practices and operations. Telepsychiatry, in the form of videoconferencing and other technologies has been a critical component of this response. This talk will address 1) The history and development of the field of telepsychiatry leading up to the COVID era; 2) The use and deployment of telepsychiatry in response to COVID including national policy changes and individual provider and patient response; 3) Guidance on how individual psychiatric providers and organizations can continue to integrate technology into their COVID response and 4) preparation for organizational and individual provider transition to a post COVID environment.

Learning Objective:

1. Audience members will become familiar with the use and deployment of telepsychiatry during the COVID crisis including administrative, clinical and technical implications.

Literature Reference:

1. Shore JH, Schneck CD, Mishkind MC. Telepsychiatry and the Coronavirus Disease 2019 Pandemic—Current and Future Outcomes of the Rapid Virtualization of Psychiatric Care. *JAMA psychiatry*. 2020 May 11.

FEDERAL AGENCY UPDATES PLENARY

9:45 a.m. – 12:15 p.m.

FEDERAL AGENCY UPDATES PLENARY

ABSTRACT NOT INCLUDED

AN UPDATE ON DRUG DEVELOPMENT EFFORTS AT NIMH

ABSTRACT NOT INCLUDED

EVIDENCE-BASED SCIENCE UPDATE ON THE PREVENTION, DIAGNOSIS AND TREATMENT OF ALCOHOL USE DISORDER FROM NIAAA

George Koob, National Institute of Health - NIAAA

Individual Abstract: Alcohol use disorder (AUD) causes an enormous amount of human suffering, loss of productivity and cost to our medical care system and the nation's economy. AUD is estimated to cost U.S. society 249 billion dollars each year with 14.5 million individuals in the U. S. suffering from AUD and 50% of liver disease caused by AUD. Deaths due to AUD have increased steadily since 1999 and AUD contributes significantly to the deaths of despair in U. S. society. Advances in the science of alcohol use disorders can lead the way to better diagnosis, treatment and prevention of this significant public health problem. Conceptualizing alcohol use disorder from a heuristic framework a binge/intoxication stage, a withdrawal/negative affect stage, and a pre-occupation/anticipation (craving) stage representing the domains of incentive salience/ pathological habits, negative emotional states and executive function has allowed identification of key neurocircuits that underlie addiction to alcohol. Understanding developmental trajectories provides fundamental knowledge of vulnerability to alcohol pathology across the lifespan. Using these heuristic frameworks, current challenges include medications development, women and alcohol, older adults and alcohol, pain and alcohol, sleep and alcohol, and closing the treatment gap. Addressing such challenges will facilitate the implementation evidence-based treatment for AUD in primary care, mental health, and other health care settings.

Learning Objective:

1. To understand the cost of AUD in the U.S. and the challenges for treatment.

Literature Reference:

1. U.S. Department of Health and Human Services (HHS), Office of the Surgeon General, Facing Addiction in America: The Surgeon General's Report on Alcohol, Drugs, and Health. Washington, DC: HHS, November 2016.

SAMHSA UPDATES: NSDUH DATA, ENDING THE HIV EPIDEMIC EFFORTS

Neeraj Gandotra, SAMHSA

Individual Abstract: This presentation will provide an update on the Substance Abuse and Mental Health Services Administration (SAMHSA)'s portfolio. Specifically, it will present data from SAMHSA's National Study on Drug Use and Health (NSDUH) to highlight recent trends in substance abuse and mental health disorders in the United States. Additionally, an overview of SAMHSA's efforts in Ending the HIV Epidemic will be provided.

Learning Objectives:

1. To understand recent data and trends on mental illnesses from SAMHSA's National Survey on Drug Use and Health data source.
2. To understand SAMHSA efforts toward Ending the HIV Epidemic.

Literature Reference:

1. Substance Abuse and Mental Health Services Administration. (2020). Key substance use and mental health indicators in the United States: Results from the 2018 National Survey on Drug Use and Health Rockville, MD: Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration.

PCORI: IMPROVING OUTCOMES IMPORTANT TO PATIENTS

Elisabeth Houtsmuller, PCORI

Individual Abstract: The Patient Centered Outcomes Research Institute (PCORI), authorized in 2010 and reauthorized in 2020, funds stakeholder-informed, patient-centered Comparative Effectiveness Research (CER). This presentation will include a review of PCORI's role as a funding organization and its approach to stakeholder engagement in patient-centered CER, its funding priorities, and its portfolio in the areas of opioids and of mental health. PCORI's opioids portfolio spans the continuum of the opioid crisis, including studies on alternatives to opioids for pain management, approaches to changing prescription patterns for opioids, and the treatment of Opioid Use Disorder. PCORI's Mental Health portfolio includes studies on a wide range of conditions and populations, including studies comparing treatments for Treatment-Resistant Depression, improving physical healthcare for patients with Serious Mental Illness, and improving access to mental healthcare for rural populations, among others. The presentation will focus on highlights of these portfolios, as well as the more recent funding announcements related to COVID 19.

Learning Objective:

1. Understand which research the Patient Centered Outcomes Research Institute (PCORI) funds.

Literature Reference:

1. Selby JV, Forsythe L; Sox HC. Stakeholder-Driven Comparative Effectiveness Research An Update From PCORI. JAMA. 2015;314(21):2235-2236.

DRUG ABUSE AND ADDICTION IN AMERICA: CHALLENGES AND OPPORTUNITIES

Kurt Rasmussen, NIDA/NIH

Individual Abstract: Recent data from the annual Monitoring the Future Study, funded by the National Institute on Drug Abuse (NIDA), indicates that vaping of nicotine and/or marijuana is on the rise among young people. And despite new evidence of its potentially harmful effects on the user's brain and body, marijuana use is being recorded at historic highs among college-age adults. This country's opioid epidemic remains at alarming levels and the use of stimulant drugs like methamphetamine is showing a resurgence. This presentation will highlight current

trends in the use of drugs of abuse, provide an update on the opioid epidemic, and describe relevant policy and research initiatives currently being supported by NIDA and the National Institutes of Health (NIH) to help address some of the most pressing challenges currently confronting the drug use and addiction field.

Learning Objectives:

At the conclusion of this lecture, participants will be able to describe:

1. Increasing trends in vaping of nicotine and/or marijuana among 8th, 10th and 12th graders.
2. Recent increases in marijuana use and its effects on the brain and body.
3. State of the opioid crisis and scientific solutions being employed by NIDA and the NIH to curtail it.

Literature Reference:

1. Volkow ND: Personalizing the Treatment of Substance Use Disorders. *Am J Psych* 2020 177:113-116.

Panel I

2:15 p.m. - 3:45 p.m.

***DIFFICULT TO TREAT DEPRESSION: WHAT ARE THE IMPLICATIONS FOR RESEARCH AND PRACTICE?**

A. John Rush, National University of Singapore

Overall Abstract: Presently, sustained symptom remission is the treatment goal for mood-disordered patients. But- in actual practice- achieving this ideal becomes ever more elusive especially in the context of ever-increasing numbers of failed treatment trials as suggested in STAR-D and other studies (Rush et al 2006). Further, there is no evidence-based guidance about which bio-medical, neuropsychological, or psychosocial evaluations are to be recommended to help identify treatable causes of treatment failures patients with difficult-to-treat depressions. The practice of excluding complex, chronic, or comorbidly-ill depressed patients with failed prior trials in Phase 3 registration studies, the rare funding of truly definitive Phase 4 trials, and the often narrow foci of clinical research priorities in PCORI and NIH unfortunately contribute to the dearth of evidence as to what clinicians should do to better evaluate and care for persons with difficult-to-treat depressions (DTDs).

Recent focus on DTD (Rush, Aaronson, Demyttenaere, 2018) and a subsequent consensus conference on the definition of DTD (McAllister-Williams et al, under review) and its clinical and research implications, forms the bases for this interactive workshop.

Hamish McAllister-Williams will present the results of this recent consensus conference-which examined whether DTD might be a preferred clinical heuristic to "treatment-resistant depression" (TRD), given the clinical features/presentation and its action-plan implications. His presentation will promote discussion on the clinical practice implications of DTD and its impact on identifying deficiencies in our current clinical practice guidelines.

A. John Rush will highlight and discuss the challenges that arise in considering the design and conduct of patient-centered clinical investigations that aim to evaluate essential steps in identifying treatable causes of DTD or evaluating treatments for DTD. This presentation will

promote discussion on how to select participants with DTD, define “adequate” prior trials, select outcomes that go beyond single- occasion, symptom-focused outcomes, and consider the issue of “sufficient trial duration”.

Larry Alphas will consider the DTD heuristic from the perspective of trial design for regulatory (Phase 1-4) purposes. His presentation will promote discussion on possible innovations aimed at evaluating external validity, given the heterogeneous nature of the depressive and even bipolar syndromes. Should for example, extended patent life be considered when new treatment studies are conducted in DTD patients who were excluded from the initial Phase 3 trials in the pursuit of internal validity?

Madhukar Trivedi will discuss the implications of the DTD for the development of biomarkers to guide treatment selection or to measure the biology of the underlying disease process. What bio- measurements can help identify these persons earlier rather than later? Can biomarkers help unpack the heterogeneity entailed in DTD?

Each presenter will be limited to 15 minutes which leaves 5-7 minutes for discussion after each presentation.

Learning Objectives:

1. Participants will be able to specify 3 strengths and 3 weaknesses in the heuristic of treatment-resistant depression (TRD) and in the heuristic of difficult to treat depression (DTD).
2. Participants will be able to identify 3 clinical research and clinical care system management challenges posed by the heuristic of DTD and specify some potential solutions.

THE IDENTIFICATION, ASSESSMENT AND MANAGEMENT OF DIFFICULT-TO-TREAT DEPRESSION: AN INTERNATIONAL CONSENSUS MODEL

R. Hamish McAllister-Williams, Newcastle University

Individual Abstract: While antidepressants are undoubtedly effective both acutely and in relapse prevention, many patients fail to respond adequately with either non-response or continuing sub-threshold symptoms. Such patients may be described as having ‘treatment resistant depression’ or perhaps more appropriately as ‘difficult to treat depression’ (DTD). Further, the STAR*D trial provides evidence of lower remission and higher relapse rates with each successive treatment trial. Such bleak findings can fuel the sense of hopelessness inherent in the management of DTD.

This presentation will present an international consensus model, drawn from the management of difficult to treat physical illness, as to how one might optimally manage patients with DTD. A major element of the model is an appropriate use of both conventional and less conventional treatments. Various treatment options will be reviewed. The presentation will discuss when it might be appropriate to move towards the use of less conventional treatments that might be beyond those recommended in standard guidelines.

Learning Objectives:

1. Awareness of the elements of a comprehensive assessment of a patient with difficult to treat depression.
2. Awareness of a model for the chronic disease management of patients with difficult to treat depression, utilizing a broad range of therapeutic options.

Literature References:

1. Rush, A.J., Aaronson, S.T., Demyttenaere, K., 2019. Difficult-to-treat depression: A clinical and research roadmap for when remission is elusive. *Aust. N. Z. J. Psychiatry* 53, 109–118.
2. McAllister-Williams, R.H., Arango, C., Blier, P., Demyttenaere, K., Falkai, P., Gorwood, P., Hopwood, M., Javed, A., Kasper, S., Malhi, G.S., Soares, J.C., Vieta, E., Young, A.H., Papadopoulos, A., Rush, A.J., 2020. The identification, assessment and management of difficult-to-treat depression: An international consensus statement. *J. Affect. Disord.* under review.

WHAT ARE THE IMPLICATIONS FOR DTD FOR CLINICALLY-ORIENTED RESEARCH?

A. John Rush, National University of Singapore

Individual Abstract: While DTD can identify a large proportion of depressed patients for whom care is challenging, what challenges does this heuristic itself pose for developing high impact clinical research evidence by which to better identify early, differentially diagnose, select and implement treatments for and optimally manage these patients?

This presentation will pose several questions to promote discussion around these issues. (1) Can we identify DTD patients early in the course of care- whether the difficulties are due to patient behaviors that interfere with care delivery (e.g. uninformed beliefs about medication or depression) or an underlying biology or physiology of their depression for which we lack interventions. (2) In large care systems, can we identify the top 10 medical causes of DTD thereby informing us as to which test to do when in which patients thereby avoiding a shot gun approach to expensive testing in too many patients with too little pay off? (3) Over what period of time, with what frequency of measurement and what measurement tools should one assess the therapeutic outcomes of persons with DTD, assuming treatable causes have been eliminated? (4) Can psychosocial management programs that address environmental challenges, patient attitudes, beliefs, and negative cognitions, that aim at symptom control and functional enhancement be developed and tested for DTD patients? (5) Since many DTD patients have caregivers, can we more affectively engage them to assist in the management of the DTD patient or the acquisition of important outcome measures? (6) Can educational, group-based or individual interventions be developed for DTD patients to enhance day to day function or interpersonal relations? (7) Can a more systematic approach be developed to identify and ultimately address the most common perpetuating factors that contribute to ongoing DTD? (8) Overall does the DTD heuristic advance the clinical relevance of clinical research for depression or does it muddy the waters?

Learning Objectives:

1. As a result of attending this lecture, participants will be able to identify four critical baseline clinical features that would likely affect outcome in persons with DTD.
2. As a result of attending this lecture, participants will be able to identify two additional key outcomes beyond symptom control in persons with DTD.

Literature References:

1. Rush AJ, Aaronson ST, Demyttenaere K: Difficult-to-treat depression: A clinical and research roadmap for when remission is elusive. *Aust N Z J Psychiatry* 2019;53:109–118.

2. Rush AJ, Thase ME: Improving depression outcome by patient-centered medical management. *Am J Psychiatry* 2018;175:1187-1198.

WHAT ARE THE IMPLICATIONS OF DTD FOR OBTAINING REGULATORY APPROVAL FOR NEW MOOD DISORDER TREATMENTS?

Larry Alphs, Janssen Scientific Affairs, LLC

Individual Abstract: Regulatory-focused trials for pharmacological treatments of depression typically exclude persons with difficult to treat depression (DTD). In fact, three of four depressed outpatients enrolled in the STAR-D trial would likely not have been eligible for trials design for regulatory approval because of a high risk of suicidality, concurrent psychiatric or general medical comorbidities, or a chronic course of illness (Wisniewski et al, *Am J Psychiatry*. 2009;166(5):599-607).

This presentation will promote discussion about the potential implications of using a DTD heuristic for regulatory approval through phase 3 and phase 4 stages of drug development. Decisions around patient inclusion in such trials necessarily involve competing tensions among needs for scientific clarity, establishing safety, internal validity and external generalizability. Heterogeneity of treatment response in persons with depressive disorder is increasingly recognized. Many (25-50%) patients with general medical conditions also qualify for a diagnosis of a major depressive episode. Yet, currently available antidepressant drugs are not always safe or effective for these individuals. Further, strong, placebo-controlled, blinded evidence for efficacy is limited. Phase 4 studies are often not definitive as they are usually underpowered without placebo- or alternative treatment controls.

One reason for the failure to address the safety and efficacy of chemical entities in special populations is the cost of completing such trials is not fiscally prudent. Such trials require extensive human and financial resources and are extremely risky. Yet the need for deeper understanding of treatment response in these DTD patients is high. What are the challenges that must be addressed to find more effective treatments for DTD and what incentives might be developed to promote solutions to this public health need?

- Public health need is an increasingly important driver for conducting clinical trials. What would we need to know about the degree of improvement in function or quality of life that is clinically meaningful search the trials in these patients could be done systematically across sites and countries?
- Social support can be a major factor in outcome in persons with depression. Yet the type and degree of support is highly variable and culturally dependent. How can this ancillary support be best characterized and controlled for in clinical trials?
- Could large healthcare systems be engaged in supporting conduct of these clinical trials?
- How might artificial intelligence and machine learning be used to identify (which kinds of patients have a good or poor response? Which groups should conduct such trials? How should they be regulated? How can regulations around the world be better harmonized?
- Could patent life of a drug be extended analogous to extending patent life for evidence and children and adolescents or conceivably for those over 75 years of age?

Learning Objectives:

1. Increase awareness of challenges to conducting regulatory-grade high science clinical trials to establish safety and efficacy of pharmacologic treatments for difficult to treat depression.
2. Provide novel models for conducting clinical trials in patients with difficult to treat depression.

Literature References:

1. Wisniewski SR, Rush AJ, Nierenberg AA, Gaynes BN, Warden D, Luther JF, McGrath PJ, Lavori PW, Thase ME, Fava M, Trivedi MH: Can phase III trial results of antidepressant medications be generalized to clinical practice? A STAR*D report. *Am J Psychiatry* 2009;166(5):599-607.
2. Pigott HE, Leventhal AM, Alter GS, Boren JJ: Efficacy and effectiveness of antidepressants: current status of research. *Psychother Psychosom* 2010;79:267–279.

THE ROLE OF BIOMARKERS IN DIFFICULT TO TREAT DEPRESSION

ABSTRACT NOT INCLUDED

Panel II

4:00 p.m. - 5:30 p.m.

***PUBLIC-PRIVATE PARTNERSHIPS: PATHWAYS TO SCHIZOPHRENIA DRUG DEVELOPMENT**

Linda Brady, DNBBS/NIMH/NIH

Overall Abstract:

The need for novel pharmacotherapeutics for individuals with schizophrenia and other psychotic disorders has never been greater. New targets and compounds are necessary if we are to address the needs of those with treatment-resistant psychotic symptoms. Full recovery also demands better treatments for cognitive and negative symptoms. Encouraging continued progress in the psychopharmacology of psychotic disorders will require the full cooperation of public research enterprises, such as the U.S. National Institute of Mental Health (NIMH), and private organizations, including pharmaceutical companies and non-profit research and advocacy organizations. This panel will discuss efforts in drug development for schizophrenia and other psychotic disorders from both the public and private perspective, with a lens focused on examples of and opportunities for synergistic cooperation. Dr. Linda Brady (NIMH) will introduce the issue and discuss tools and resources for drug development supported by the NIMH as well as provide specific examples of how such tools can enable early phase drug development by private partners. Drs. Kenneth Koblán (Sunovion) and Michael Sand (Boehringer-Ingelheim) will detail the pathways that led to the novel compounds each company is currently testing, and how these pathways leveraged platforms and discoveries built with the help of public support. Finally, Ken Duckworth (National Alliance on Mental Illness) will discuss the role of advocacy organizations in fostering public-private partnerships.

Learning Objectives:

1. Participants will understand the unmet needs in schizophrenia drug development.
2. Participants will learn of the role of public-private partnerships in schizophrenia drug development.

INITIATIVES TO ENABLE EARLY INTERVENTION IN SCHIZOPHRENIA

Linda Brady, DNBBS/NIMH/NIH

Individual Abstract: Schizophrenia is one of the top 15 leading causes of disability worldwide. One promising approach for intervention in schizophrenia is early identification and treatment in the at-risk population. NIMH and international organizations have invested in deep phenotyping of subjects at clinical high risk (CHR) for psychosis to identify biomarkers that can help predict conversion to psychosis, as well as other outcomes including persistent cognitive and functional impairments. Efforts to date have focused on approaches that include clinical, cognitive, imaging (structural and functional), genetic, electrophysiological, and emerging technologies such as speech samples for natural language processing. The identification and validation of biomarkers and functional outcome measures to identify and stratify help-seeking CHR subjects would provide much needed tools to enable the testing of new, targeted pharmacological interventions that address mechanistic hypotheses regarding the progression of the disease. Such treatments could preempt or delay the onset of schizophrenia. New NIMH and public-private initiatives that target the validation of tools to enable early intervention approaches for individuals at CHR for psychosis will be discussed.

Learning Objectives:

1. Participants will learn about ongoing efforts to validate biomarkers and functional outcome measures that define the trajectory of illness in individuals at clinical high risk for psychosis.
2. Participants will learn about public-private consortia efforts to enable early intervention in schizophrenia.

Literature References:

1. Lam, M, Lee, J., Rapisarda, A, et al: Longitudinal cognitive changes in young individuals at ultrahigh risk for psychosis. *JAMA Psychiatry* 2018; 75: 929-934.
2. Allswede DM, Addington J, Bearden CE, et al: Characterizing covariant trajectories of individuals at clinical high risk for psychosis across symptomatic and functional domains. *Am J Psychiatry* 2019; doi: 10.1176/appi.ajp.2019.18111290. [Epub ahead of print].

LEVERAGING PUBLIC-PRIVATE PARTNERSHIPS: DEVELOPMENT OF SEP-363856, A NOVEL NON-DOPAMINE D2 RECEPTOR BLOCKADE TREATMENT FOR SCHIZOPHRENIA

Kenneth Koblan, Sunovion Pharmaceuticals, Inc.

Individual Abstract: In the 65 years since chlorpromazine was introduced for the treatment of schizophrenia, antipsychotic drugs have produced clinical benefit via direct blockade of dopamine D2 or the combination of D2/5-HT2A receptors. Novel programs (non-D2/5-HT2A) for the treatment of schizophrenia have stalled with clinical-stage failures targeting key features of the illness, such as negative symptoms (e.g., blunted affect, anhedonia) and cognitive

impairment. As a result, schizophrenia treatments continue to target D2 and 5-HT2A, with an efficacy and safety profile characteristic of the entire class of antipsychotics. Stemming from the pharmacological blockade of D2 receptors, all current antipsychotics have a benefit-risk marred by substantial and adverse effects of movement, metabolic, and neuroendocrine disorders, and a profile of efficacy limited to effects on reducing hostility and positive symptoms.

Drug-discovery efforts with novel targets have relied on animal models sensitive to D2-based pharmacological mechanisms. However, this approach alone has not translated into clinical efficacy and might not be suitable for the development novel treatments. Recently a paradigm shift has occurred with the introduction of drug discovery methods employing in vivo screening of behavioral phenotypes. This represents a novel approach to develop compounds that are phenotypically similar to a specific drug but act through novel mechanisms. SEP-363856 was discovered in a medicinal chemistry effort utilizing a high throughput, mouse-behavior phenotyping platform (SmartCube®), in combination with in vitro screening, aimed at developing non-D2 (anti-target) compounds that could nevertheless retain efficacy in putative rodent models of schizophrenia.

Key advances in understanding SEP-363856's mechanism of action have been achieved by leveraging platforms and discoveries made possible through collaborations spanning government institutions (NIDA, FDA), biotechnology companies (PsychoGenics, SRI, invicro, Certarra, ChemPartner, Porsolt, InterVivo, Neurosolutions, Biotrial), public and private universities (Manchester University, Oxford University, King's College London, Emory, MIT, UCSD, Northeastern, Mount Sinai, Northwestern) and clinical-stage Contract Research Organizations (P1Vital, IQVia).

In the first randomized, double-blind, placebo-controlled trial, SEP-363856 demonstrated significant efficacy in the treatment of schizophrenia in patients with an acute exacerbation. Overall, the tolerability of SEP-363856 was similar to placebo, and its safety profile was consistent with a non-D2 mechanism of action, with an absence of effects on movement disorder measures, an absence of prolactin effects, and minimal effects on weight and metabolic parameters. SEP-363856 has been granted FDA Breakthrough Therapy Designation in the treatment of schizophrenia and is currently undergoing Phase III testing.

Learning Objectives:

1. Novel approaches to drug discovery.
2. Hypothesis testing in clinical development.

Literature References:

1. Dedic N, Jones PG, Hopkins SC, Lew R, Shao L, Campbell JE, Spear KL, Large TH, Campbell UC, Hanania T, Leahy E, Koblan KS. SEP-363856, a Novel Psychotropic Agent with a Unique, Non-D2 Receptor Mechanism of Action. *J Pharmacol Exp Ther*. 2019 Oct;371(1):1-14.

THE IMPORTANCE OF EXTERNAL COLLABORATION IN DEVELOPING DRUGS FOR SERIOUS MENTAL ILLNESS

ABSTRACT NOT INCLUDED

ADVOCACY ORGANIZATIONS: CATALYSTS IN FOSTERING PUBLIC-PRIVATE PARTNERSHIPS (PART OF THE PANEL ON PUBLIC-PRIVATE PARTNERSHIPS: PATHWAYS TO SCHIZOPHRENIA DRUG DEVELOPMENT)

Ken Duckworth, National Alliance on Mental Illness

Individual Abstract: This panel will discuss drug development efforts for schizophrenia and other psychotic disorders from both the public and private perspective, with a lens focused on examples of and opportunities for cooperation through public-private partnerships. Ken Duckworth, NAMI, will discuss the role of advocacy organizations in fostering partnerships for schizophrenia diagnostic tools and drug development.

NAMI is the largest grassroots mental health organization dedicated to building better lives for the millions of Americans affected by mental illness. We are highly motivated to find better diagnostic tools and increase treatment options that will improve the lives of individuals with serious mental illness. We see the major benefit of public-private partnerships to incite innovation through mutually beneficial cooperation to create medical advancements which otherwise would not be possible. People living with mental illness need better care and the demand for mental health care is increasing throughout all corners of society.

NAMI sees the pathway to success based on collaboration between academic institutions, government agencies, pharmaceutical companies and advocacy organizations. There is a need to create better diagnostic tools to not only get people help early but to also identify people in high-risk categories in order to intervene before they endure a mental health crisis. We need to find new and innovative ways for people living with serious mental illness to have access to better treatment options including medications with less adverse side effects. People with mental illness on average are dying 10 years earlier due to a variety of factors and through creative medical advancements we can change the status quo.

Diagnostic tools and effective medication that lessens symptoms and improve quality of life should be a reality for the 47.6 million people in the U.S. with a mental health condition. We think public-private partnerships are a way to realize that goal effectively because this can't be accomplished by any one group on their own. We need to work collectively, in an aligned manner to make real progress in this complicated and often underfunded area of medical discovery. For example, we are seeing impressive strides being made in the area of identifying biomarkers for mental illness which in time could make it possible to diagnose people early and created targeted treatment options.

NAMI has developed strong and lasting relationships with research institutions, pharmaceutical companies and NIMH. We have worked to leverage those relationships to bring everyone to the table and create partnerships that spur discovery and find solutions through ground-breaking private-public partnership such as AMP-Schizophrenia. NAMI's goal in this process is to make sure the patient and caregiver voice is taken into consideration throughout the process and that innovations more closely support the daily needs of people living with mental illness.

Learning Objectives:

1. Understand and appreciate the role advocacy organizations can play in promoting public-private partnerships for drug development.
2. Identify opportunities for collaboration at the national level with patient advocacy and other nonprofit organizations.

Saturday, May 30, 2020

Panel III

8:00 a.m. - 9:30 a.m.

***CLINICAL UTILITY OF TARGETING ANGER AND IRRITABILITY TO GUIDE NOVEL THERAPEUTICS FOR PATIENTS WITH DEPRESSION**

ABSTRACT NOT INCLUDED

ASSOCIATION BETWEEN IRRITABILITY AND SUICIDALITY: FINDINGS FROM FOUR CLINICAL TRIALS OF ADULTS WITH MAJOR DEPRESSIVE DISORDER OR STIMULANT USE DISORDER

Manish Jha, Icahn School of Medicine at Mount Sinai

Individual Abstract: *Background:* Irritability is an important yet understudied symptom domain in adults. Recent reports suggest that irritability in children and adolescents is associated with suicidality in children and adolescents. However, the association between irritability and suicidality in adults remain poorly understood.

Methods: Adults with major depressive disorder (MDD) [Combining Medications to Enhance Depression Outcomes (CO-MED, n=665), Establishing Moderators and Biosignatures of Antidepressant Response in Clinical Care (EMBARC, n=296), and Suicide Assessment Methodology Study (SAMS, n=266)] or stimulant use disorder [STimulant Reduction Intervention Using Dosed Exercise (STRIDE), n=302] were included. Repeated-measures mixed model analyses estimated concurrent associations between irritability (5-item irritability domain of Concise Associated Symptom Tracking scale) and suicidality (3-item suicidal thoughts factor of Concise Health Risk Tracking scale) and compared it with overall depression (excluding suicidality-related item). Linear regression analyses predicted suicidality at week-8 using baseline and baseline-to-week-4 changes in irritability and overall depression. Longer-term outcomes were evaluated in CO-MED, EMBARC, and STRIDE.

Results: Irritability and suicidality were positively correlated ($r=0.27-0.73$) across visits and their concurrent association was 2-11 times stronger than overall depression. Higher baseline irritability predicted higher levels of suicidality at week-8 in CO-MED ($\beta=0.15$, $p=0.011$), EMBARC ($\beta=0.62$, $p<0.0001$), and STRIDE ($\beta=0.32$, $p=0.007$) but not in SAMS ($\beta=0.12$, $p=0.21$). Further, greater baseline-to-week-4 reduction in irritability predicted lower levels of suicidality at week-8 in CO-MED ($\beta=-0.21$, $p=0.007$), EMBARC ($\beta=-0.61$, $p<0.0001$) and STRIDE ($\beta=-0.39$, $p<0.0001$) but not in SAMS ($\beta=-0.17$, $p=0.065$). Similarly, lower baseline and greater reductions in irritability were both associated with lower levels of suicidality at week-28 of CO-MED, week-16 of EMBARC, and week-36 of STRIDE.

Discussion: Across multiple clinical trials and psychiatric illnesses, the association of irritability with suicidality was stronger than that of depression severity and suicidality. These findings support careful assessment of irritability in suicide prevention.

Learning Objectives:

1. Identify the association between irritability and suicidality.
2. Recognize clinical utility of assessing and treating irritability in patients with psychiatric illnesses.

Literature References:

1. Jha MK, Minhajuddin A, South C, Rush AJ, Trivedi MH. Irritability and Its Clinical Utility in Major Depressive Disorder: Prediction of Individual-Level Acute-Phase Outcomes Using Early Changes in Irritability and Depression Severity. *The American journal of psychiatry*. 2019;176:358-366.
2. Berk L, Hallam KT, Venugopal K, Lewis AJ, Austin DW, Kulkarni J, Dodd S, de Castella A, Fitzgerald PB, Berk M. Impact of irritability: a 2-year observational study of outpatients with bipolar I or schizoaffective disorder. *Bipolar disorders*. 2017;19:184-197.

NOVEL THERAPEUTICS FOR IRRITABILITY IN PATIENTS WITH MOOD DISORDER

James Murrough, Icahn School of Medicine at Mount Sinai

Individual Abstract: *Background:* Irritability is one of the diagnostic criterion symptoms of major depressive disorder (MDD) in youths (age <18) and of mania/hypomania for bipolar disorder. Yet, to date, there is no treatment that specifically targets irritability. In fact, medications such as antidepressants that are commonly used to treat irritability are associated with marked worsening of irritability in a sizeable proportion of patients with MDD. Recently, irritability has been linked with suicidality. This report seeks to evaluate the effect of ketamine on reduction in irritability and how it relates to changes in suicidality.

Methods: Data for this secondary analysis were obtained from a double-blind randomized controlled trial of ketamine versus midazolam that recruited 24 patients hospitalized for suicidality. Of these, 13 had primary diagnosis of MDD while 7 had bipolar disorder, 3 had post-traumatic stress disorder, and 1 had borderline personality disorder as their primary diagnosis. Overall depression severity was measured with the 16-item Quick Inventory of Depressive Symptomatology Self-Report (QIDS-SR) and the 10-item clinician-rated Montgomery Asberg Depression Rating Scale (MADRS). Irritability was measured with the 5-item irritability domain of Concise Associated Symptom Tracking scale (CAST-IRR) while suicidality was measured with the 3-item suicidality factor of Concise Health Risk Tracking Scale (CHRT Suicidal Thoughts). Assessments were conducted at baseline, 24 hours, 48 hours, 72 hours and 7 days. Repeated measures analyses of variance evaluated changes in these symptoms over time. Correlations analyses were used to evaluate if changes in irritability were associated with changes in suicidal ideations.

Results: There was a statistically significant difference in changes in irritability with ketamine versus midazolam ($F=5.8$, $df=1,21$, $p=0.025$). Participants randomized to ketamine experienced greater reduction in irritability as compared to those randomized to midazolam within 24 hours of infusion and this difference persisted until 7 days. Notably, there was no significant difference in changes in QIDS-SR ($F=1.16$, $df=1,20$, $p=0.30$) and MADRS ($F=2.0$, $df=1,21$, $p=0.17$) scores between ketamine and midazolam suggesting the effect of ketamine on irritability was not completely accounted for by changes in overall depression severity. Furthermore, there was a strong correlation between baseline-to-7-day changes in both irritability and suicidal ideation (Pearson's correlation coefficient $r=0.66$, $p<0.001$).

Conclusion: A single-dose intravenous infusion of ketamine is associated with marked reduction in irritability in patients with mood disorders. This reduction in irritability, in turn, is associated with marked reduction in suicidal ideation.

Learning Objectives:

1. Identify the effect of ketamine on reduction in irritability among patients with mood disorders.
2. Recognize the association between changes in irritability and suicidality.

Literature References:

1. Murrough JW, Soleimani L, DeWilde KE, Collins KA, Lapidus KA, Iacoviello BM, Lener M, Kautz M, Kim J, Stern JB, Price RB, Perez AM, Brallier JW, Rodriguez GJ, Goodman WK, Iosifescu DV, Charney DS. Ketamine for rapid reduction of suicidal ideation: a randomized controlled trial. *Psychol Med.* 2015 Dec;45(16):3571-80.
2. Jha MK, Minhajuddin A, South C, Rush AJ, Trivedi MH. Irritability and Its Clinical Utility in Major Depressive Disorder: Prediction of Individual-Level Acute-Phase Outcomes Using Early Changes in Irritability and Depression Severity. *Am J Psychiatry.* 2019;176:358-366.

ELUCIDATING NEURAL CORRELATES OF IRRITABILITY IN ADULTS WITH MAJOR DEPRESSIVE DISORDER: FINDINGS FROM THE EMBARC STUDY

Cherise Chin Fatt, University of Texas Southwestern Medical Center

Individual Abstract: *Background:* Irritability is an important yet understudied symptom domain in patients with major depressive disorder (MDD). We recently showed that improvement in irritability with antidepressant treatment is independent of changes in depressive symptom severity. Further, early changes in irritability can be used to prognosticate longer-term clinical outcomes. This report aims to elucidate the neural circuit underlying irritability in order to identify the treatment targets to identify and validate novel mechanistically guided treatments.

Methods: Participants of Establishing Moderators and Biosignatures of Antidepressant Response for Clinical Care for Depression (EMBARC) study, randomized to sertraline or placebo, were included (n=296). Irritability was assessed with 5-item irritability domain of Concise Associated Symptom Tracking scale (CAST-IRR). Functional magnetic resonance imaging was used to compute resting state functional connectivity (FC) after parcellating cortical and subcortical regions in 121 parcels, and an elastic net approach was used to identify FC pairs associated with irritability.

Results: Sertraline was more effective than placebo in reducing irritability (effect size = 0.40). Using an elastic net approach, we found that 76 FC pairs (out of 7260) were associated with irritability in the EMBARC study. Over half (43/76) of these FC pairs included either striatum or amygdala. We found that lower connectivity of limbic network (LN) with executive control network, dorsal attention network, and visual network were associated with higher severity of irritability. Stronger connectivity of default mode network (DMN) with LN was associated with higher irritability, while stronger connectivity of DMN with salience network was associated with lower severity of irritability.

Conclusion: irritability is associated with widespread changes in brain circuits. These include aberrant functional connectivity of amygdala and striatum with brain regions in default mode, executive control, and dorsal attention networks.

Learning Objectives:

1. Understand the biological mechanisms underpinning anger and irritability.
2. Recognize the role of amygdala and striatum as key hubs in neural circuits associated with irritability.

Literature References:

1. Chin Fatt CR, Jha MK, Cooper CM, Fonzo G, South C, Grannemann B, Carmody T, Greer TL, Kurian B, Fava M, McGrath PJ, Adams P, McInnis M, Parsey RV, Weissman M, Phillips ML, Etkin A, Trivedi MH. Effect of Intrinsic Patterns of Functional Brain Connectivity in Moderating Antidepressant Treatment Response in Major Depression. *The American journal of psychiatry*. 2019;appiajp201918070870.
2. Jha MK, Minhajuddin A, South C, Rush AJ, Trivedi MH. Irritability and Its Clinical Utility in Major Depressive Disorder: Prediction of Individual-Level Acute-Phase Outcomes Using Early Changes in Irritability and Depression Severity. *The American journal of psychiatry*. 2019;176:358-366.

IRRITABILITY AND ANGER ATTACKS IN MAJOR DEPRESSIVE DISORDER

Maurizio Fava, Massachusetts General Hospital

Individual Abstract: Irritability is frequently reported by patients suffering from major depressive disorder. After excluding bipolar spectrum disorders, irritability during depressive episodes was reported by roughly half of respondents with lifetime DSM-IV MDD in the National Comorbidity Survey Replication. Irritability in the absence of either sad mood or loss of interest, in comparison, was found to be rare in the same study. Irritability in MDD was associated with early age of onset, lifetime persistence, comorbidity with anxiety and impulse-control disorders, fatigue and self-reproach during episodes, and disability. In some MDD patients, irritability is associated with anger attacks. Anger attacks are sudden intense spells of anger that resemble panic attacks but lack the predominant affects of fear and anxiety associated with panic attacks. They typically occur in situations in which an individual feels emotionally trapped and experiences outbursts of anger that are later described by the patient as being uncharacteristic and inappropriate to the situation at hand. Anger attacks consist of both behavioral and autonomic features, and various criteria and an Anger Attacks Questionnaire have been designed to identify the presence of these attacks. The prevalence of anger attacks in depressed patients is approximately 30% to 40%, and the attacks stop in 53% to 71% of depressed patients treated with serotonergic antidepressants. A fenfluramine challenge study has shown a significantly greater serotonergic dysregulation in MDD with anger attacks compared to MDD without anger attacks. This presentation discusses the development of the concept of anger attacks in MDD, its biological correlates and its treatment approaches.

Learning Objectives:

1. Learn about the clinical characteristics of anger attacks in depression.
2. To become familiar with the treatment approaches to irritability and anger attacks in depression.

Literature References:

1. Fava M, Rosenbaum JF. Anger attacks in patients with depression. *J Clin Psychiatry*. 1999;60 Suppl 15:21-4.
2. Fava M, Hwang I, Rush AJ, Sampson N, Walters EE, Kessler RC. The importance of irritability as a symptom of major depressive disorder: results from the National Comorbidity Survey Replication. *Mol Psychiatry*. 2010 Aug;15(8):856-67.

ASCP/AFSP

9:45 A.M. – 10:45 a.m.

ASCP/AFSP

Madhukar Trivedi, UT Southwestern Medical Center

CLINICAL TRIALS FOR SUICIDE PREVENTION: IMPORTANCE AND CONSIDERATIONS

Jill Harkavy-Friedman, American Foundation for Suicide Prevention

Individual Abstract: Over one-third of individuals with most mental health conditions engage in suicidal ideation or behavior and 90% of those who die by suicide have a diagnosable and potentially treatable mental health condition. Only about one-third of people who die by suicide are in treatment at the time of their death. By excluding suicidal individuals from clinical trials research much is lost, especially for use of treatments in the broader population. In addition to discussing the importance of including individuals in clinical trials, considerations for facilitating their safe inclusion will be discussed. If suicidal individuals must be excluded from a clinical trial, Project STARR 911, provides guidance on best practice in this situation and will be described. The American Foundation for Suicide Prevention funds research grants and requires the inclusion of individuals with suicidal ideation or behavior in the studies they fund. The impact of this research in terms informing clinical trials will be discussed.

Learning Objectives:

1. Describe the value of including suicidal people in clinical trials.
2. List three considerations for including suicidal individuals in clinical trials.

Literature References:

1. The National Institute of Mental Health: <https://www.nimh.nih.gov/funding/clinical-research/conducting-research-with-participants-atelevatedrisk-for-suicide-considerations-for-researchers.shtml>
2. Law MK, Furr RM, Arnold EM, Mneimne M, Jaquett C, Fleeson W. Does assessing suicidality frequently and repeatedly cause harm? A randomized control study. *Psychol Assess.* 2015;27(4):1171-1181. doi:10.1037/pas0000118

LESSONS LEARNED FROM A SMALL PILOT RANDOMIZED CONTROLLED TRIAL OF PRAZOSIN IN PTSD NIGHTMARE SUFFERERS WITH SUICIDALITY

William McCall, Medical College of Georgia; Augusta University

Individual Abstract: Suicidal ideation, suicidal behavior, and suicide death are linked with sleep complaints, and nightmares has been consistently shown to be the sleep disorder with the highest associated risk for suicide. Nightmares are a common feature of posttraumatic stress disorder (PTSD), and suicide is similarly at increased risk in PTSD as compared to the general population. There are no FDA-approved treatments for nightmares, but the α -1 adrenergic receptor blocker prazosin has been suggested as a treatment for symptoms of hypervigilance in PTSD, including PTSD nightmares. We conducted a small randomized controlled trial (RCT) of bedtime-only doses of prazosin versus placebo as an add-on treatment in suicidal PTSD patients with nightmares, with the intent of showing that a prazosin-induced reduction in nightmares would lead to a corresponding reduction in suicidality. Twenty suicidal adult PTSD patients, all with concurrent mood disorders and nightmares were randomized 1:1 to prazosin vs placebo at bedtime, in an escalating dosing schedule, over 8 weekly visits. Participants completed a mean of 5 visits, and reached a mean prazosin dose of 5.5 mg for prazosin and 7.6 mg for placebo. Remarkably, the prazosin group experienced less improvement ($p < 0.05$) than the placebo group for nightmares, insomnia, and depression scores. One patient in each group required emergency psychiatric hospitalization. This pilot study: (1) provides no reason to further pursue bedtime-only doses of prazosin in suicidal PTSD patients, but leaves open the possibility that twice daily dosing deserves future study, (2) emphasizes the value of studying interventions specifically in suicidal persons, and not assuming that their response will follow the typical pattern seen in non-suicidal persons, and (3) illustrates the feasibility of including suicidal persons in RCTs.

Learning Objectives:

1. The learner will understand the link between nightmares and suicide.
2. The learner will be able to describe the merits, or lack of merit, of prazosin in the treatment of suicidal PTSD patients.

Literature References:

1. McCall WV, Pillai A, Case D, McCloud L, Nolla T, Branch F, Youssef NA, 1 2020 ASCP Annual Meeting Moraczewski J, Tauhidul L, Pandya CD, Rosenquist PB. A pilot, randomized clinical trial of bedtime doses of prazosin versus placebo in suicidal posttraumatic stress disorder patients with nightmares. *Journal of Clinical Psychopharmacology* 2018;38:618-621
2. McCall WV, Benca RM, Rosenquist PB, Youssef NA, McCloud L, Newman JC, Case D, Rumble ME, Szabo ST, Phillips M, Krystal AD. Reducing suicidal ideation through insomnia treatment (REST-IT): a randomized clinical trial. *American J Psychiatry* 2019; 176: 957-965

CLINICAL UPDATES IN PSYCHOPHARMACOLOGY SESSION

11:00 a.m. – 12:30 p.m.

***CLINICAL UPDATES IN PSYCHOPHARMACOLOGY SESSION**

Erika Saunders, Penn State College of Medicine, Penn State Health

Overall Abstract: Frances Levin will provide an update on comorbid ADHD and Substance Use Disorder. Joseph Goldberg will provide an update on recent pharmacotherapy advances in bipolar disorder. Boadie Dunlop will provide an overview of pharmacogenomic testing for major depressive disorder.

COMORBID ADHD AND SUD

Frances Levin, New York State Psychiatric Institute and Columbia University

Individual Abstract: Attention deficit/hyperactivity disorder (ADHD) is the most common psychiatric disorder in children and adolescents. Adults with ADHD are at increased risk for co-occurring substance use disorders (SUDs). Adults with substance use disorders and co-occurring ADHD, as well as other psychiatric disorders, are overrepresented in clinical populations, and are typically among the most challenging patients to treat. The most commonly used medication treatments for ADHD are psychostimulants, and the use of these medications in patients with substance use disorders is complex. Common diagnostic and clinical management issues in treating adults with co-occurring ADHD and SUDs will be discussed, with special attention focused on the complicated issues that arise when prescribing controlled substance (stimulants) to adults with SUDs.

Learning Objective:

1. To become knowledgeable of the complex issues of treating individuals with ADHD and SUDs.

Literature Reference:

1. Levin FR, Mariani JJ, Specker S, Mooney M, Mahony A, Brooks DJ, Babb D, Bai Y, Eberly LE, Nunes EV, Grabowski J: Extended-Release Mixed Amphetamine Salts vs Placebo for Comorbid Adult Attention-Deficit/Hyperactivity Disorder and Cocaine Use Disorder. *JAMA Psychiatry* 2015; 72:593.

RECENT PHARMACOTHERAPY ADVANCES IN BIPOLAR DISORDER

Joseph Goldberg, Icahn School of Medicine at Mount Sinai

Individual Abstract: Recent pharmacotherapy trials for bipolar disorder have continued to focus heavily on the role of newer second-generation antipsychotics (SGAs) for acute episodes but with varying results within-class. Notably, cariprazine has demonstrated robust efficacy in both acute mania and depression, with secondary analyses showing efficacy for anxiety. A Phase II forerunner study predating the pivotal bipolar I depression trials failed to separate from placebo, a finding attributed to underdosing and heterogeneity from including bipolar II subjects that possibly inflated placebo responsiveness (Yatham et al., 2020).

Brexpiprazole failed to separate from placebo in two as-yet unpublished Phase III trials in acute mania. Lumateperone demonstrated efficacy for bipolar depression in one 6-week Phase II trial (effect size=0.56) but failed to differ from placebo in a second study. With respect to maintenance pharmacotherapy, a 28-week randomized trial of lurasidone versus placebo added to lithium or divalproex failed to reach its primary endpoint for relapse prevention – although post hoc analyses suggested that efficacy may be moderate by presence of an index depressed phase of illness among non-rapid cyclers (Calabrese et al., 2017).

Apart from trials involving SGAs, innovative studies have examined putative anti-inflammatory and neuroprotective compounds. Notable examples include infliximab, which failed to separate from placebo for acute bipolar depression, but a secondary analysis found that a history of childhood maltreatment favorably moderated drug responsiveness (McIntyre et al., 2019). A small (n=37) randomized trial of pioglitazone for bipolar depression just missed statistical significance as compared to placebo (p=0.056), attributed to underpowering (Aftab et al., 2019), while a recent trial of N-acetylcysteine in bipolar depression also failed to differ from placebo with a strikingly high placebo response rate (55.6%) (Elegaard et al., 2019).

Collectively, recent trials point to notable efficacy for some but not all SGAs across phases of bipolar disorder, alongside the need for adequate statistical powering and recognition of possible moderators of treatment outcome in emerging studies using novel agents.

Learning Objectives:

1. To understand the clinical significance of recent clinical pharmacotherapy trial findings using newer second-generation antipsychotics across phases of bipolar disorder.
2. To differentiate failed from negative randomized trials and issues of statistical underpowering in recent trials of innovative compounds for bipolar depression.

Literature References:

1. Aftab A, Kemp DE, Ganocy SJ, et al. Double-blind, placebo-controlled trial of pioglitazone for bipolar depression. *J Affect Disord* 2019 Feb 15;245:957-964.
2. Calabrese JR, Pikalov A, Streicher C, et al. Lurasidone in combination with lithium or valproate for the maintenance treatment of bipolar I disorder. *Eur Neuropsychopharmacol* 2017; 27: 865-878.
3. Elegaard PK, Licht RW, Nielsen RE, et al. The efficacy of adjunctive N-acetylcysteine in acute bipolar depression: A randomized placebo-controlled study. *J Affect Disord* 2019 Feb 15;245:1043-1051.
4. McIntyre RS, Subramaniapillai M, Lee Y, et al. Efficacy of adjunctive infliximab vs placebo in the treatment of adults with bipolar I/II depression: a randomized clinical trial. *JAMA Psychiatry* 2019; 2019 May 8. doi: 10.1001/jamapsychiatry.2019.0779. [Epub ahead of print].
5. Yatham LN, Vieta E, Earley WR. Evaluation of cariprazine in the treatment of bipolar I and II depression: a randomized, double-blind, placebo-controlled, phase 2 trial. *Int Clin Psychopharmacol* 2020 May;35(3):147-156.

OVERVIEW OF PHARMACOGENOMIC TESTING FOR MAJOR DEPRESSIVE DISORDER

Individual Abstract: This presentation provides an overview of the evidence base supporting the use of pharmacogenetic testing for helping prescribers select medications for patients with major depressive disorder. Results from five published randomized controlled trials utilizing four different pharmacogenetic tests are reviewed. The presentation concludes with a summary of the strengths and limitations of the randomized trials and their implications for clinical applications of pharmacogenetic testing.

Learning Objective:

1. Identify the strengths and limitations of the evidence for using pharmacogenetic testing in the management of major depressive disorder.

Literature Reference:

1. Bousman CA, Arandjelovic, K, Serafino G, Mancuso SG, Eyre HA, Dunlop BW. Pharmacogenetic decision support tools and symptom remission: A meta-analysis of prospective randomized controlled trials in major depressive disorder. *Pharmacogenomics*, 2019; 20(1):37-47.

Panel IV

2:15 p.m. - 3:45 p.m.

***ASSESSING THE IMPACT OF STIMULANTS ON FUNCTIONAL OUTCOMES IN ADHD**

Joseph Biederman, Massachusetts General Hospital

Overall Abstract: ADHD is a prevalent and morbid neurobiological disorder estimated to afflict at least 10% of children and 5% of adults. It is associated with a wide range of morbid and costly functional outcomes including educational and occupational under attainment, mood and anxiety disorders, addictions, and accidents and injuries. Despite strong clinical trial data documenting that stimulants are safe and highly effective in the treatment of ADHD and could help mitigate many of its adverse complications, non-adherence to stimulant treatment in ADHD is amongst the highest in medicine, with some studies estimating it to be as high as 87%. Our first speaker, Dr. Ronna Fried, will present our qualitative review (N=40) and meta-analysis (N=24) of present literature examining the effect of pharmacological treatments for ADHD on various functional outcomes. Our qualitative review demonstrated a robust protective effect of ADHD medication treatment on mood disorders, suicidality, criminality, accidents and injuries, traumatic brain injuries, motor vehicle crashes, and educational outcomes. Our meta-analysis also demonstrated a protective effect of such medications on accidents and injuries in those with ADHD. These findings support the literature that demonstrates adherence to ADHD medication treatment can reduce risk of the development and occurrence of certain functional outcomes. Our second speaker, Maura DiSalvo, will discuss our analysis to help quantify the protective effects of stimulant treatment on functional

outcomes in ADHD using the number needed to treat (NNT) statistic and examine whether these effects are moderated by sex. Our results revealed low NNTs, ranging from 3 to 10, indicating that stimulants have strong protective effects on important functional outcomes in youth with ADHD that are not moderated by sex. These results strongly support the critical importance of early identification and treatment of children with ADHD of both sexes. Our third speaker, Joseph Biederman MD, will present a study that evaluated rates and correlates of patient engagement to stimulant treatment in an adult sample using data derived from electronic medical records (EMR) from a large healthcare organization. The analysis utilized a novel definition of patient engagement operationalized as a timely renewal of an index prescription using the electronically recorded issuance of a stimulant prescription in the EMR. Findings provide compelling new evidence of poor rates of patient engagement in stimulant treatment for ADHD calling for active efforts aimed at improving this state of affair. Our fourth speaker, Amos Adler, will present the results of our novel disease management text messaging intervention aimed at improving adherence to stimulant medications in children with ADHD. The intervention was piloted in children treated at a large healthcare facility and comparators were matched from the EMR of the same facility. Results showed a significantly greater percent of the SMS intervention group refilled their prescriptions in a timely manner compared to patients receiving treatment as usual. Our findings showed that a novel ADHD-centric digital health intervention using SMS significantly improved the poor rate of adherence to stimulant treatment in children. Our discussant is Maurizio Fava, M.D., Psychiatrist-in-Chief, Director, Division of Clinical Research / MGH Research Institute, Executive Director, Clinical Trials Network & Institute (CTNI) Massachusetts General Hospital, Associate Dean for Clinical & Translational Research, and Slater Family Professor of Psychiatry Harvard Medical School who will integrate these four talks into a relevant and current conceptual framework.

Learning Objectives:

1. Participants will learn how untreated ADHD can affect functional outcomes.
2. Participants will have more knowledge about how a technology intervention can help patients diagnosed with ADHD can be more adherent.

A SYSTEMATIC LITERATURE REVIEW AND META-ANALYSIS EXAMINING THE EFFECTS OF MEDICATIONS FOR ADHD ON FUNCTIONAL OUTCOMES USING DATA FROM REGISTRY AND LARGE DATASETS BASED STUDIES

Ronna Fried, MGH/Harvard Medical School

Individual Abstract: Attention-deficit/hyperactivity disorder (ADHD) is a prevalent and morbid neurobiological disorder estimated to affect up to 11% of children and 5% of adults. It is associated with high rates of many adverse functional outcomes including comorbid psychiatric disorders, academic impairments, accidents and injuries, car accidents, among many others. While treatment with ADHD medication, particularly stimulants, has been shown to improve the core symptoms of ADHD, less information is available on their effects on ADHD-associated functional impairments. As such, we conducted a qualitative review (N=40) and meta-analysis (N=24) of present literature to examine the effect of pharmacological treatments for attention-deficit/hyperactivity disorder (ADHD) on various functional outcomes. Our qualitative review demonstrated a robust protective effect of ADHD medication treatment on these functional outcomes, including mood disorders, suicidality, criminality, accidents and injuries, traumatic brain injuries, motor vehicle crashes, and educational outcomes. Our meta-analysis also demonstrated a protective effect of such medications on accidents and injuries in individuals with ADHD. These findings are supportive of the literature

that demonstrates adherence to ADHD medication treatment can reduce risk of the development and occurrence of certain functional outcomes.

Learning Objectives:

1. Participants will become familiar with the extent of the literature pertaining to functional outcomes in ADHD in relation to stimulant medication.
2. Participants will have more knowledge about specific functional outcomes and the degree to which stimulant medication may or may not have a protective effect.

Literature References:

1. Chang Z, Quinn PD, Hur K, et al. Association Between Medication Use for Attention-Deficit/Hyperactivity Disorder and Risk of Motor Vehicle Crashes. *JAMA Psychiatry* 2017;74(6):597-603.
2. Dalsgaard S, Nielsen HS, Simonsen M. Consequences of ADHD medication use for children's outcomes. *J Health Econ* 2014;37:137-151.

QUANTIFYING THE PROTECTIVE EFFECTS OF STIMULANTS ON FUNCTIONAL OUTCOMES IN ADHD: A FOCUS ON NUMBER NEEDED TO TREAT (NNT) STATISTIC AND SEX EFFECTS

Maura Disalvo, Massachusetts General Hospital

Individual Abstract: *Purpose:* To help quantify the protective effects of stimulant treatment on important functional outcomes in ADHD using the number needed to treat (NNT) statistic and examine whether these effects are moderated by sex.

Methods: Subjects were derived from three independent samples, two similarly designed case-control, ten-year prospective follow-up studies of boys and girls with and without ADHD grown up, and a cross-sectional randomized clinical trial of lisdexamfetamine on driving performance and behavior. For all studies, subjects were evaluated with structured diagnostic interviews. To measure psychopharmacological treatment in the follow-up studies, we collected information about each subject's stimulant medication use, age at onset and age at termination of treatment. Subjects in the driving study underwent two driving simulation assessments (pre-medication and after six weeks of treatment on lisdexamfetamine or placebo). For each outcome, we ran a logistic regression model that included an interaction between sex and treatment status. Lifetime rates were used to calculate the NNT statistic. We also calculated adjusted NNT statistics that accounted for sex, age, socioeconomic status, and family intactness.

Results: The NNTs were very low, ranging from 3 to 10. No interaction effects with sex were detected (all $p > 0.05$). The adjusted NNTs mostly remained the same with the exception of any substance use disorder which increased after controlling for age.

Conclusions: Stimulants have strong protective effects on functional outcomes in youth with ADHD that are not moderated by sex. These results support the critical importance of early identification and treatment of children with ADHD of both sexes.

Learning Objectives:

1. Understand the protective effects that stimulant treatment in childhood has against the development of numerous adverse functional outcomes in ADHD.
2. Learn that the beneficial effects of stimulant treatment on important functional outcomes in ADHD are similar in males and females.

Literature References:

1. Biederman J, Monuteaux MC, Spencer T, et al: Do stimulants protect against psychiatric disorders in youth with ADHD? A 10-year follow-up study. *Pediatrics* 2009;124:71-78.
2. Chang Z, D'Onofrio BM, Quinn PD, et al: Medication for attention-deficit/hyperactivity disorder and risk for depression: A nationwide longitudinal cohort study. *Biol Psychiatry* 2016; 80(12):916-922.

FURTHER EVIDENCE OF LOW ADHERENCE TO STIMULANT TREATMENT IN ADULT ADHD: AN ELECTRONIC MEDICAL RECORDS STUDY

Joseph Biederman, Massachusetts General Hospital

Individual Abstract: *Background:* ADHD is a prevalent and morbid neurobiological disorder affecting up to 5% of adults. While stimulants have been documented to be safe and effective in adults with ADHD, uncertainties remain about adherence to these treatments.

Objectives: The main aim of this article is to evaluate contemporaneous rates and correlates of adherence to stimulants in adults with ADHD using data from electronic medical records from a large healthcare organization.

Methods: Subjects were patients 18 to 44 years of age who had been prescribed a stimulant between January 1, 2015 and December 31, 2016. Prescription and sociodemographic data were extracted from the Partners HealthCare Research Patient Data Registry (RPDR) to calculate adherence to stimulant medication. We defined a patient as being adherent in treatment if they refilled their Index stimulant prescription defined as the first prescription recorded in the electronic record for the period under investigation.

Results: We identified 2,689 patients with an index prescription for a stimulant medication. Results showed that only 42% of patients refilled their prescriptions in a timely enough fashion to be considered consistently medicated.

Conclusions: Results indicate that patient adherence to stimulant treatment for adults with ADHD is poor.

Learning Objectives:

1. The audience will learn about poor rate of adherence to stimulant medication in ADHD.
2. The audience will learn about potential correlates of poor adherence to stimulants in ADHD.

Literature References

1. Perwien A, Hall J, Swensen A, et al: Stimulant treatment patterns and compliance in children and adults with newly treated attention-deficit/hyperactivity disorder. *J Manag Care Pharm* 2004; 10(2):122-129.
2. Faraone SV, Asherson P, Banaschewski T, et al: Attention-deficit/hyperactivity disorder. *Nat Rev Dis Primers*. 2015 Aug 6;1:15020.

AN INNOVATIVE SMS INTERVENTION TO IMPROVE ADHERENCE TO STIMULANTS IN CHILDREN WITH ADHD: PRELIMINARY FINDINGS

Amos Adler, MEMOTEXT Corporation

Individual Abstract: Although large datasets document that stimulants decrease the risk for many adverse ADHD-associated outcomes, compliance with stimulants remains poor. This study examined the effectiveness of a novel ADHD-centric text messaging-based intervention aimed to improve adherence to stimulant medications in children with ADHD. Subjects were 87 children ages 6-12, who were prescribed a stimulant medication for ADHD treatment. Prescribers gave permission to contact patients for participation in the study. Subjects were primarily from the primary care setting, but we also included a subsample of psychiatrically referred subjects for comparison purposes. For comparators, we identified at a 3-to-1 ratio (age- and sex-matched) pediatric patients from the same pool of prescriber-approved subjects that did not participate. Timely prescription refills (within 37 days) were determined based on the prescription date. 85% of the SMS intervention group refilled their prescriptions in a timely manner compared to only 62% of patients receiving treatment as usual (OR=3.46, 95% CI: 1.82, 6.58; p<0.001). The number needed to treat (NNT) statistic was computed as five, meaning for every five patients who receive the text messaging intervention, we can keep one adherent with their stimulant treatment. Findings provide strong support for the utility of this readily accessible technology to improve the poor rate of adherence to stimulant treatment in children with ADHD. To the best of our knowledge, this study is the first digital health intervention aimed at improving adherence to stimulant medication for children with ADHD.

Learning Objectives:

1. Participants will understand the extent of low rates of adherence to stimulant medication for treatment of ADHD across all demographic areas.
2. Participants will see how the use of an SMS intervention sent to adults can improve adherence to medication for children consistent with the improvement seen in adults with ADHD using a similar intervention.

Literature References:

1. Biederman J, Fried R, DiSalvo M, et al: A Novel Text Message Intervention to Improve Adherence to Stimulants in Adults With Attention Deficit/Hyperactivity Disorder. *J Clin Psychopharmacol* 2019b;39: 351-356.
2. Gajria K, Lu M, Sikirica V, et al: Adherence, persistence, and medication discontinuation in patients with attention-deficit/hyperactivity disorder - a systematic literature review. *Neuropsychiatr Dis Treat* 2014; 10: 1543-1569.

Pharmaceutical Pipelines

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

EFFICACY AND SAFETY OF AXS-05, AN ORAL NMDA RECEPTOR ANTAGONIST WITH MULTIMODAL ACTIVITY, IN MAJOR DEPRESSIVE DISORDER: RESULTS FROM THE GEMINI PHASE 3, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL

Cedric O'Gorman^{*1}, *Amanda Jones*¹, *Dan Iosifescu*², *Herriot Tabuteau*¹

¹*Axsome Therapeutics Inc.*, ²*Nathan S Kline Institute/New York University School of Medicine*

Abstract: *Background:* Major depressive disorder (MDD) is a debilitating and prevalent condition with over 17 million U.S. adults experiencing at least one major depressive episode in a given year. Nearly two-thirds of treated patients with MDD do not experience an adequate response to first-line therapy, and most of these inadequate responders also fail second-line treatment. Time to clinically meaningful response with currently available antidepressants (up to 6-8 weeks) is also suboptimal. There is an urgent need for new, more effective, mechanistically novel, and faster-acting MDD treatments.

AXS-05 (dextromethorphan/bupropion modulated delivery tablet) is a novel, oral, investigational NMDA receptor antagonist with multimodal activity, including sigma-1 receptor agonism. AXS-05 is being developed for the treatment of MDD.

Objective: To evaluate the efficacy and safety of AXS-05 versus placebo in MDD.

Methods: The GEMINI study was a Phase 3, randomized, double-blind, placebo-controlled, multi-center, U.S. trial, in which 327 adult subjects with a diagnosis of moderate to severe MDD were randomized to treatment with either with AXS-05 (45 mg DM/105 mg bupropion) (n=163), or placebo (n=164), twice daily for 6 weeks.

Results: On the primary endpoint, AXS-05 demonstrated a statistically significant mean reduction from baseline in the MADRS total score of 16.6 points versus 11.9 for placebo (p=0.002) after 6 weeks of treatment. AXS-05 rapidly, robustly and durably reduced depressive symptoms, demonstrating a statistically significant improvement compared to placebo on the key secondary endpoint of change from baseline in the MADRS total score at Week 1, the earliest time point measured (p=0.007), and at all timepoints thereafter. Rates of response (\geq 50% MADRS improvement) were statistically significantly greater for AXS-05 compared to placebo at Week 1 (p=0.035) and at every time point thereafter, being achieved by 54% of AXS-05 patients versus 34% of placebo patients at Week 6 (p<0.001). Rates of remission (MADRS \leq 10) were statistically significantly greater for AXS-05 compared to placebo at Week 2 (p=0.013) and at every time point thereafter, being achieved by 40% of AXS-05 patients versus 17% of placebo patients at Week 6 (p<0.001).

The observed rapid and durable antidepressant effects translated into early and statistically significant improvements in daily functioning as measured by the Sheehan Disability Scale, and in quality of life as measured by the Quality of Life Enjoyment and Satisfaction Questionnaire.

AXS-05 was safe and well tolerated with the most commonly reported adverse events being dizziness, nausea, headache, diarrhea, somnolence and dry mouth. Treatment with AXS-05 was not associated with psychotomimetic effects. Rates of discontinuation due to adverse events in the trial were low (6.2% for AXS-05 and 0.6% for placebo).

Conclusion: Treatment with AXS-05 resulted in rapid, substantial, durable and statistically significant improvements in depressive symptomatology across multiple efficacy endpoints as compared to placebo in patients with MDD. Symptomatic benefits translated into statistically significant improvements on validated measures of daily functioning and quality of life. AXS-05 was safe and well tolerated in this trial and was not associated with psychotomimetic effects.

EFFECT OF THE NMDAR ANTAGONIST LANICEMINE (BHV-5500) ON STARTLE REACTIVITY, GAMMA OSCILLATORY RESPONSE, AND HYPERAROUSAL IN PTSD

ABSTRACT NOT INCLUDED

PSILOCYBIN THERAPY FOR TREATMENT-RESISTANT DEPRESSION: RESULTS FROM A PHASE I, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL WITH EXPLORATORY EFFICACY MEASURES

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Abstract: *Background:* Before psilocybin (the active ingredient in so-called ‘magic mushrooms’) was classified as a Schedule I substance in the US in 1970, there were published reports of its use in clinical research and alongside psychodynamic oriented psychotherapy. However, there was a lack of controlled research done at this time. Research into psilocybin therapy has of late re-emerged and due to promising evidence of efficacy in depressive states from recent small studies, COMPASS Pathways have begun the clinical development of psilocybin therapy for treatment-resistant depression (for which they gained FDA Breakthrough Therapy designation in 2018). Depression is a prevalent, costly and disabling illness, with many patients not responding to existing treatments signaling the importance for development of novel treatments for resistant patients.

Objective: Here we present safety results from the first trial in this clinical pipeline – a phase I trial in healthy participants. An international phase IIb, double-blind, dose ranging trial in patients with treatment-resistant depression is currently ongoing.

Methods: This was a phase I, placebo-controlled, double-blind trial to evaluate the effects of two doses of psilocybin. Healthy volunteers were randomised 1:1:1 to placebo, 10mg, or 25mg of COMP360 (psilocybin). Prior to dosing, participants took part in a preparatory group session. The drug was administered orally and with one-to-one psychological support to up to six participants simultaneously. Participants were followed up for 12 weeks post-dosing and completed safety assessments and a range of validated measures of cognitive function and emotional processing.

Results: 89 participants were randomised to placebo (n=29), 10mg (n=30), or 25mg (n=30) psilocybin (average age 36.1±9.1 years, 41 females). A total of 511 adverse events (AEs) were reported throughout the 12-week study: 217 in the 25mg psilocybin arm; 203 in the 10mg psilocybin arm; and 91 in the placebo arm. There were no serious adverse events and no AEs led to study withdrawal. Psilocybin induced expected transient psychedelic experiences with 67% of all AEs reported both starting and resolving on the day of dosing which included 62 reports of hallucination, 47 reports of illusion, 18 reports of somatic hallucination, 10 reports of euphoric mood, and 10 reports of time perception being altered. Extensive assessments of cognitive and emotional functions showed no negative impact of psilocybin.

Conclusion: The present phase I trial, the largest randomised controlled trial of psilocybin to date, provides evidence for the safety and feasibility of psilocybin administration with 1:1 psychological support and simultaneous dosing. This may provide an effective and efficient

model in clinical populations. This study and the ongoing phase IIb trial in treatment-resistant depression will help inform phase III trial design in this development programme.

THE PHARMACOKINETIC AND SAFETY PROFILE OF CTP-692 (DEUTERATED D-SERINE) IN HEALTHY VOLUNTEERS: PHASE 1 PROGRAM RESULTS

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Abstract: Schizophrenia is associated with low levels of D-serine, the most important synaptic co-agonist of the N-methyl-D-aspartate (NMDA) type glutamate receptor in the brain. Genetic and neurobiological findings have linked NMDA receptor hypofunction to the etiology of schizophrenia. CTP-692 is a deuterated analog of D-serine with demonstrated advantages in safety and pharmacokinetics (PK) in nonclinical studies. Antipsychotic drugs that act by blocking D2 receptors or both the D2 and 5-HT_{2a} receptors have been the mainstay of treatment for schizophrenia for many years. However, a substantial proportion of patients remain symptomatic due to lack of efficacy or poor tolerability. While treatment of patients with schizophrenia with D-serine has been reported to result in improvement of positive and negative symptoms and cognitive function, its development has been limited due to potential renal safety concerns. The *in vitro* binding and functional activity of CTP-692 are nearly identical to those of D-serine at the NMDA receptor. In rats, administration of high doses of CTP-692 did not cause increased serum creatinine and blood urea nitrogen levels, indicative of renal toxicity, as is observed with non-deuterated D-serine. The CTP-692 early clinical development program characterized the single- and multiple-dose plasma PK and safety profile to guide dose selection in subsequent efficacy studies in patients with schizophrenia. In the single ascending dose (SAD) study, healthy subjects were administered 0.5, 1, 2, 3, or 4 g of CTP-692 or placebo, once-daily, in a double-blind design. Following the completion of the SAD study, the multiple-ascending dose (MAD) study was conducted in which healthy subjects were administered 1, 2, or 4 g of CTP-692 or placebo, once-daily, in a double-blind design for 7 consecutive days. Blood samples for PK analysis were obtained at several time points after dose administration. Safety assessments in the SAD and MAD studies included monitoring of adverse events, ECGs, and clinical laboratory testing including monitoring of kidney function. CTP-692 was well-tolerated in both the studies. The most common treatment-emergent adverse event was headache, with no dose-related trends. All adverse events were mild to moderate in severity and recovered/resolved by the end of each study. Serum and urine kidney function parameters remained within the normal range in both studies and there were no clinically significant CTP-692-related effects on other clinical laboratory parameters. CTP-692 had a well-defined PK profile with low inter-individual variability. The CTP-692 dose-exposure relationship was linear following single and multiple doses (at Day 7). The terminal half-life of CTP-692 was approximately 19 hours which enables once-daily dose administration. Accumulation of CTP-692 was minimal to modest following 7 consecutive days of administration. Based on the results of the Phase 1 studies, once-daily CTP-692 doses of 1, 2, and 4 g are being evaluated in an ongoing double-blind, placebo-controlled Phase 2 study to evaluate the safety and efficacy of CTP-692 as an adjunctive treatment in adult patients with schizophrenia with a novel mechanism of action.

A COMBINATION DRUG CANDIDATE FOR TREATMENT OF SUBSTANCE USE DISORDERS

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Abstract: [MPh-IR + Ond-PR2], comprising an immediate-release (IR) formulation of methylphenidate (MPh) and a delayed pulsatile-release (PR) formulation of ondansetron (Ond) is a first-in-kind, clinical-stage drug candidate being developed for the treatment of substance use disorders and trauma and stressor-related disorders (DSM-5). The impetus for the development of this combination drug candidate derives from the concept of “pharmacologically-mediated reactivation and reconsolidation blockade” of “dysfunctional neural circuits” that underlie the targeted neuropsychiatric disorders (see Lee et al. *Drug Alcohol Depend.* 124: 11-18).

In a proof-of-concept single-site, randomized, double-blind, placebo-controlled clinical trial (ClinicalTrials.gov identifier: NCT01290276), we determined the efficacy of [MPh-IR + Ond-PR2] in reducing craving and cue-reactivity in abstinent psychostimulant (cocaine and/or methamphetamine) use disorder (PUD) patients, using standard behavioral rating scales and cue-reactivity and resting-state neuroimaging paradigms. The neuroimaging procedures were performed 1-7 days before and 2-7 days after the 2-week treatment to ensure a complete washout of [MPh-IR + Ond-PR2]. In addition, a short version of the Shiffman-Jarvik Withdrawal Scale (SJWS) was administered to assess the efficacy of [MPh-IR + Ond-PR2] in reducing nicotine withdrawal symptoms, as the majority of PUD patients also use tobacco products regardless whether they are secondarily diagnosed with tobacco use disorder (TUD). Subjects were treated with either [MPh-IR + Ond-PR2] (containing equivalents of 20 mg methylphenidate hydrochloride and 8 mg ondansetron hydrochloride) or identical-appearing placebo (qd x 2 weeks) under a protocol approved by the Duke University Health System Institutional Review Board.

A total of 30 qualifying subjects were randomized into either [MPh-IR + Ond-PR2] or placebo treatment group. Twenty-eight subjects completed the 2-week drug treatment and pre- and post-treatment behavioral rating and fMRI assessments. Compared to placebo, [MPh-IR + Ond-PR2] induced significant changes in the psychostimulant cue-induced activation in selected prefrontal, parietal and anterior cingulate cortical areas. Furthermore, “seed-to-voxel” analyses showed reduced resting-state connectivity between selected cortical and striatal/cerebellar areas following [MPh-IR + Ond-PR2] treatment. The combination treatment also significantly reduced scores on SJWS craving and negative affect subscales.

There are currently no drugs approved by the FDA for PUD treatment. Follow-up clinical trials are planned to confirm the preliminary results that [MPh-IR + Ond-PR2] may provide for an effective option for the treatment of PUD and/or TUD.

SEP-363856: A COMPOUND WITH A NON-D2 RECEPTOR MECHANISM OF ACTION FOR THE TREATMENT OF SCHIZOPHRENIA: UPDATE

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Abstract: Background: Antipsychotic drugs have produced clinical benefit via antagonist or partial agonist effects at post-synaptic dopamine D2 receptors. We undertook a medicinal chemistry effort aimed at identifying non-D2 binding compounds that retained antipsychotic-like efficacy across multiple animal models. This resulted in the identification of SEP-363856, which has no clinically relevant D2/5-HT2A binding.

Methods: We will summarize the medicinal chemistry effort utilizing in vitro anti-target (non-D2) screening and a high throughput mouse-behavior phenotyping platform (SmartCube®) that resulted in the identification of SEP-363856. We will also summarize results of preclinical models of psychosis utilizing SEP-363856. We will then summarize the results of the first randomized trial of SEP-363856 (50 or 75 mg/day; n=120) versus placebo (n=125) for adults with acute schizophrenia. The primary endpoint was week 4 change in the Positive and Negative Symptom Scale total score (PANSS); secondary efficacy endpoints included the Brief Negative Symptom Scale (BNSS). Patients who completed the acute study were given the option to enroll in an extension study in which they were treated, open-label, with flexible doses of SEP-363856 (25/50/75 mg/day) for 26-weeks.

Results: SEP-363856 has demonstrated efficacy in rodent models of psychosis, including phencyclidine (PCP)-induced hyperactivity and deficits in social interaction, and prepulse inhibition of the acoustic startle response. While the mechanism of action of SEP-363856 has not been fully elucidated, preclinical data suggest that agonism at trace amine-associated receptors (TAAR)1 and 5-HT1A receptors make important contributions to its efficacy. In the short-term trial, patients with an acute exacerbation of schizophrenia demonstrated statistically significant improvement in PANSS total score at Week 4 vs. placebo (-17.2 vs. -9.7; p=0.001; effect size, 0.45). SEP-363856 exhibited broad-spectrum activity across a range of positive, negative, depressive, and general psychopathology symptoms. Improvement in negative symptoms was notable, with an effect size of 0.48 on the Brief Negative Symptom Scale. The tolerability and safety profile of SEP-363856 was similar to placebo. Consistent with preclinical findings indicating an absence of clinically-relevant D2 receptor binding, patients treated with SEP-363856 did not exhibit akathisia or extrapyramidal symptoms. SEP-363856 had no effect on prolactin levels; and there were minimal effects on weight and metabolic parameters. Progressively greater improvement in psychotic symptoms was noted during the 26-week open-label extension study, with additional mean reduction in PANSS total score from open-label baseline to endpoint of -22.6. Finally, we will summarize results of neuroimaging studies profiling the effects of SEP-363856 across cognitive and connectivity biomarkers relevant to the antipsychotic/antidepressant profiles detected during preclinical development.

Results: The results of preclinical studies and randomized clinical trials suggest that SEP-363856 (which has been granted breakthrough therapy designation by the FDA) may have significant efficacy in the treatment of schizophrenia, without the side-effects associated with D2blockade observed with currently available treatments. SEP-363856 is currently being evaluated as a treatment for Parkinson's Disease Psychosis in a randomized, double-blind, placebo-controlled proof-of-concept trial.

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ADVANCE: PHASE 2, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF ADJUNCTIVE PIMAVANSERIN IN PATIENTS WITH NEGATIVE SYMPTOMS OF SCHIZOPHRENIA

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Abstract: *Background:* Approximately 50% of schizophrenia patients experience negative symptoms, which can lead to reduced quality of life, poor social functioning, and long-term disability. Negative symptom treatment remains a huge unmet need. Pimavanserin is a selective, 5-hydroxytryptamine (5-HT)_{2A} inverse agonist/antagonist with lower activity at 5-HT_{2C} receptors, and no affinity for adrenergic, dopaminergic, histaminergic, and muscarinic receptors. Previous studies have shown beneficial effects of pimavanserin as adjunctive therapy in patients with schizophrenia including significant improvement of negative symptoms. ADVANCE was a Phase 2 study to evaluate the effects of adjunctive pimavanserin on negative symptoms of schizophrenia.

Methods: This was a 26-week, randomized, double-blind, placebo-controlled study conducted in stable outpatients with predominant negative symptoms from Europe and North America. Eligible schizophrenia patients had a score of ≥ 20 on the sum of the 7 PANSS Marder negative factor items at screening and baseline and a score of ≥ 4 on at least 3, or ≥ 5 on at least ≥ 2 , of these negative symptom items. A sum of the 8 PANSS Marder positive factor items ≤ 22 , no score ≥ 5 , and a score of 4 on no more than two of P1, P3 or P6 items also was required. Patients were randomized to pimavanserin or placebo added to main antipsychotic (AP) therapy. The initial dose was 20 mg once daily, with dose adjustments allowed to 34 mg or 10 mg until Week 8. The primary endpoint was change from baseline to Week 26 on the Negative Symptom Assessment-16 (NSA-16) total score. The key secondary endpoint was change from baseline to Week 26 on the Personal and Social Performance (PSP) scale. Safety and tolerability also were assessed. The change from baseline in NSA-16 total score was analyzed using mixed model repeated measures (MMRM), and treatment difference (LS mean) at Week 26 was tested at an alpha level of 0.05 (2-sided).

Results: 403 patients were randomized, and 400 (201 placebo, 199 pimavanserin) patients were included in the efficacy analysis. Mean age was 37.2 years; 87.8% of patients were from European sites. The final dose of pimavanserin was 34 mg in 53.8%, 20 mg in 44.7%, and 10 mg in 1.5%. Significant improvement was observed for the NSA-16 total score at 26 weeks with pimavanserin vs. placebo (LS mean: -10.4 vs. -8.5, $p=0.043$, effect size: 0.21). Improvement was greater over placebo in patients ($n=107$) whose last dose level of pimavanserin was 34 mg (LS mean: -11.6 vs. -8.5; unadjusted $p=0.0065$, effect size: 0.34). No significant difference was observed for the key secondary endpoint. The incidence of any adverse event (AE) was 35.1% with placebo and 39.8% with pimavanserin. The most common AEs were headache (5.0% and 6.5%) and somnolence (5.0% and 5.5%) with placebo and pimavanserin, respectively. Serious AEs occurred in 0.5% and 2.0% of patients with placebo and pimavanserin, respectively, and AEs leading to discontinuation occurred in 3.0% with placebo and 5.0% with pimavanserin, respectively. No clinically relevant effects were observed with pimavanserin for vital signs, weight, metabolic syndrome, or extrapyramidal symptoms.

Discussion: A significant improvement in negative symptoms was observed with pimavanserin vs. placebo in stable patients with predominant negative symptoms of schizophrenia. Greater improvement was observed at a 34 mg dose. The tolerability profile of pimavanserin was comparable to placebo with similar incidence rates of any adverse events.

KARXT (A COMBINATION OF THE CHOLINERGIC AGONIST XANOMELINE WITH TROSPIUM TO ENHANCE TOLERABILITY), IS SUPERIOR TO PLACEBO IN PATIENTS WITH SCHIZOPHRENIA: PHASE 2 CLINICAL TRIAL RESULTS

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Abstract: *Background:* Several lines of investigation have implicated muscarinic receptors in the pathophysiology of schizophrenia. Xanomeline is a muscarinic agonist that preferentially activates M1 and M4 receptors. This agent demonstrated antipsychotic efficacy in previous Alzheimer's disease and schizophrenia clinical trials. However, xanomeline was associated with classical peripheral muscarinic adverse events (AEs) which precluded further development. Trospium is a peripherally restricted muscarinic antagonist that does not appreciably cross the blood brain barrier. KarXT is a novel co-formulation of xanomeline and trospium, where trospium is designed to prevent activation of peripheral muscarinic receptors in order to improve tolerability, while maintaining xanomeline's beneficial effects in the CNS. We showed in recent phase 1 healthy volunteer studies that the combination of xanomeline plus trospium substantially reduced the pro-muscarinic AEs associated with xanomeline. Here we present the results of the efficacy and safety of KarXT in a phase 2 study of acute psychosis in patients with schizophrenia.

Methods: This was a double-blind, placebo-controlled, monotherapy (non-adjunctive), 5-week inpatient trial conducted at 12 US sites using a flexible dose design. After two days of dose titration, xanomeline/trospium was administered 100mg/20mg BID with an optional increase to 125mg/30 mg BID after day 7 based on tolerability as determined by the site physician. Subjects had the option to stay on 100/20 if there were tolerability issues, but the intent was to achieve a dose of 125/30. One down titration back to the dose of 100/20 was allowed if needed for tolerability. The primary endpoint was change in PANSS total score from baseline versus placebo at week 5.

Results: 182 patients with schizophrenia were randomized (KarXT N=90; placebo N=92). The study met the primary endpoint with the PANSS total score showing a 11.6 point improvement compared to placebo at $p < 0.0001$ (-17.4 KarXT vs. -5.9 placebo) at week 5. Statistical improvement ($P < 0.0001$) on the total PANSS was achieved at every assessment time point (weeks 2, 4, and 5). 91% of patients escalated to the high dose of KarXT. These efficacy results were confirmed in a completers analysis and with data from remote raters blind to site, visit and drug assignment. Negative symptoms also showed a 2.3 point separation from placebo ($p < 0.001$) at week 5. KarXT was well tolerated and the number of discontinuations due to treatment emergent AEs was low and equal in the KarXT and placebo groups (N=2 per group). Muscarinic agonist AEs were substantially lower than in previous xanomeline trials. Somnolence, weight gain, and extrapyramidal symptoms/akathisia were similar to placebo and there was no syncope or mean changes in blood pressure.

Conclusions: KarXT demonstrated robust, consistent antipsychotic efficacy in patients with Schizophrenia compared to placebo across a number of outcome measures and a favorable side effect profile. Results of additional safety information will be presented.

HARNESSING THE GUT-BRAIN AXIS TO DEVELOP NOVEL CENTRAL NERVOUS SYSTEM (CNS) THERAPEUTICS TO IMPROVE THE QUALITY OF LIFE FOR PEOPLE WITH CNS DISEASES AND DISORDERS

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Abstract: Axial Biotherapeutics is a clinical stage biopharmaceutical company building a unique class of gut-targeted, small molecules for treating CNS diseases and disorders as well as oncology. There is growing consensus that the gut-brain axis is implicated in the etiology of many CNS diseases, which is a departure from the belief that all neurological disorders originate exclusively in the brain. There have been numerous publications supporting a gut-brain connection for diseases, including Parkinson's Disease (PD), Autism Spectrum Disorder (ASD) as well as multiple sclerosis and Alzheimer's. Through metagenomic and metabolomic analysis and Axial's proprietary platform, we have elucidated mechanisms by which the gut microbiome may impact diseases in defined subsets of CNS patients. We initiated studies in both our Autism (ASD) and Parkinson's programs (PD) and expanded our pipeline beyond CNS into Oncology. The ASD study is expected to deliver top-line data later this year with a full data read-out in Q1 2020. The PD study is expected to deliver top-line data read-out in Q3 2020. The talk will highlight our preclinical and top-line clinical results.