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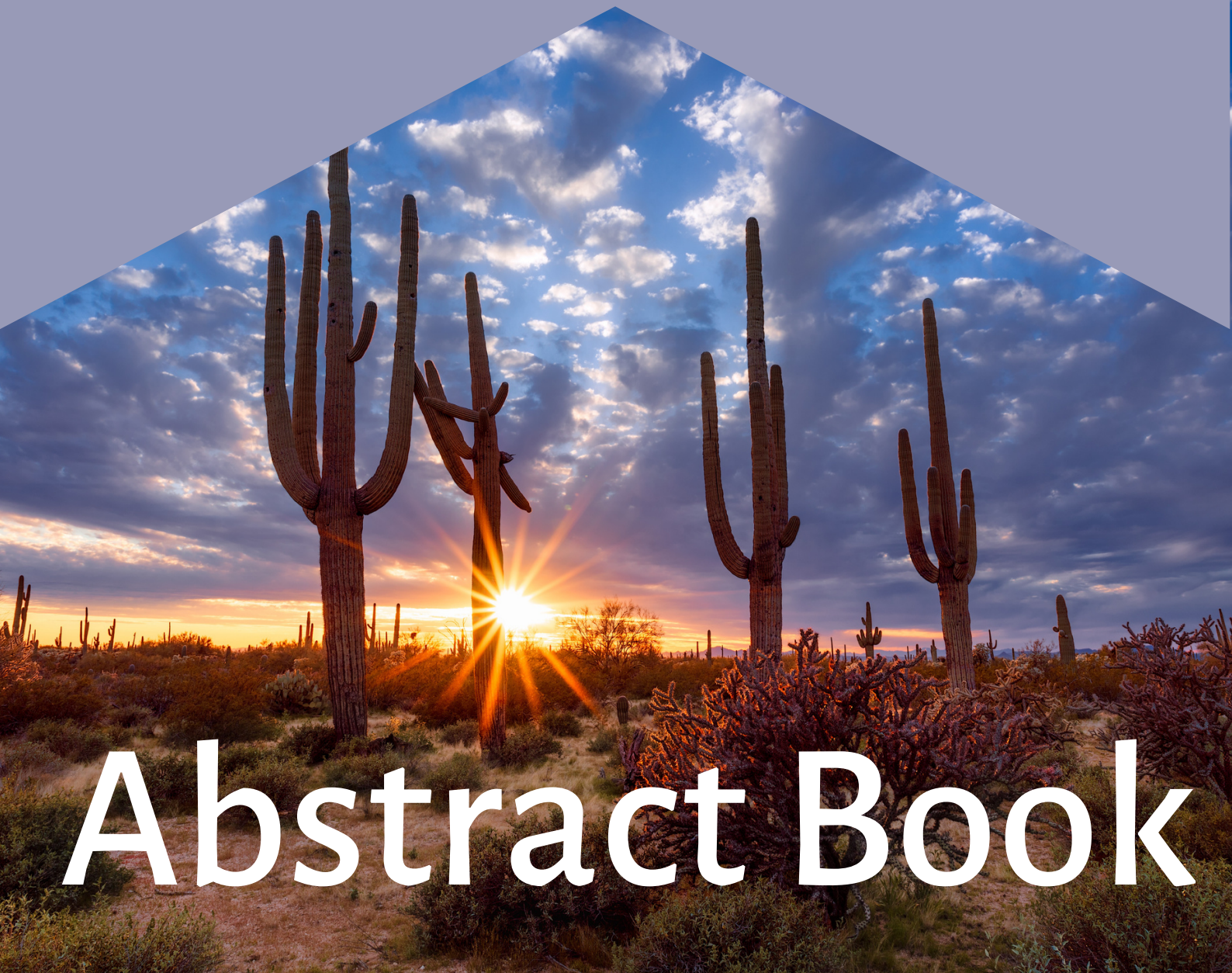
2022 ANNUAL MEETING

Reassessing Research and Clinical Practice in the Peri-pandemic Era

Fairmont Scottsdale Princess
Scottsdale, AZ



Abstract Book

Tuesday, May 31, 2022

Panel Sessions

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

BIOMARKERS IN CLINICAL STUDIES: IS THE JUICE WORTH THE SQUEEZE?

William Potter, Foundation of the National Institutes of Health

Overall Abstract: For almost 50 years biomarkers have been explored in the hope of demonstrating utility in CNS drug development. This panel will address whether the last several years of technological/methodological/clinical trial advances overcome the past limits of biomarker deployment, i.e., the inclusion of EEG/ERP, imaging, behavioral, and/or CSF modalities in evaluating drug effects. We believe that to determine/interpret complex biomarker data and seek for convergent findings, goes beyond the expertise of any individual, academic department, or company. But is the field sufficiently mature to justify increased education and training of scientists, establishment of consortia, and foster multidisciplinary collaborations to support the utilization of biomarker data? Do results of biomarker studies (frequently translational models), support expansion and confidence in "go, no-go" decisions? Should CNS therapies proceed to large scale clinical trials in the absence of a biomarker effect? Should biomarker evaluation strategies be scalable to support later phase drug development or are the demands required for implementation too great to limit their practical use?

The panel addresses (across a range of settings) the promise/challenges/barriers of biomarker informed clinical studies. Dr. Meg Grabb shares the NIH experience to address funding, training, investigator "buy in", and collaborative efforts (across departments/institutions/pharma) as well as examples of the yields from various programs that have been put in place. Dr. Raquel Gur describes the motivation to create teams in academia and beyond, supporting multimodal biomarker studies across various patient populations including pediatrics. She will also address the pros and cons of selecting biomarkers that are more readily accepted by investigators and participants vs those, such as CSF studies, which are perceived to be less palatable. Third, Dr. Scott Hobson describes an industry CNS drug development strategy where biomarker informed decisions might incorporate use of patient populations and preliminary behavioral biomarker readouts. The utility and rationale for adoption of these strategy (ies) will be shared. Fourth, Dr Brett English (ApexSci) will serve as a discussant from the perspective of how the demands generated by CNS biomarker studies relates to challenges in the evolution of clinical sites to support the depth and breadth of biomarker studies, including realistic expectations from early phase data. The goal is to highlight gaps between the biomarker information one like to get and what is questioned by some as either that important or feasible.

The co-chairs, Drs Larry Ereshefsky and Bill Potter will take turns leading a discussion with the audience. Duration of talks will be controlled to allow for a lively discussion including whether NIH and industry are perceived as having gone too far in expecting biomarker incorporation either prior to or as part of efficacy studies of compounds.

Learning Objectives:

1. Extend the understanding of why both NIH and industry believe that biomarker technologies are sufficiently mature to be expected as either preceding or being a part of clinical efficacy studies of drugs.

2. Be cognizant of the current state of the most reliable biomarkers of brain state and function relevant to drug development and how these might be assessed in both academic and for profit service sectors.

HOW BIOMARKERS CAN INFORM TRIAL DESIGN OR TRIAL OUTCOMES: A PROGRAM OFFICER'S PERSPECTIVE ON PORTFOLIO NEED

Margaret Grabb, National Institute of Mental Health

Individual Abstract: With the large failure rates of late-stage drug trials in psychiatry, many of the pharma/biotech companies have redesigned early-stage clinical trials to be mechanistically focused, using clinical pharmacologic -based approaches. In parallel to this effort, since 2014 the National Institute of Mental Health (NIMH) has supported early-stage pharmacologic trials that incorporate biomarker measures, including pharmacodynamic (PD) measures, into the designs. The rationale for this approach is to objectively determine whether the drug candidate can affect CNS function in a dose dependent manner, before pursuing efficacy trials, in an effort to build more confidence of central drug action in humans. While this goal remains a priority to NIMH, the numbers of academic pharmacologic-based studies testing novel targets submitted to NIMH have been lower than hoped for, compared to the number of brain stimulation or cognitive behavioral therapy studies that have been submitted using similar staged designs. Meanwhile, CNS imaging methods have continued to evolve over the last few years. Thus, NIMH is actually investing significantly in developing various biomarkers to be used in clinical trials through efforts such as the Autism Biomarkers Consortium for Clinical Trials (ABC-CT) and the Accelerating Medicines Partnership® Program - Schizophrenia (AMP® SCZ) – large scale collaborative programs with industry, regulatory, foundations, NIH and academic partners, designed to establish data collection training and standards across sites, with central data processing and analysis. These programs will determine biomarker/biosignature utility and limits for future trial designs. All methods and data are made available for other researchers.

In this session, Dr. Grabb will present examples of biomarker development supported by NIMH (including EEG, eye tracking and fMRI), through a mechanistic trial and through these large scale biomarker development efforts. The goal is to describe how they can be incorporated into trials and to highlight why it's vital to understand the limits of the biomarker's behavior when designing mechanistic trials. Finally, she will present various NIMH funding opportunities to support this research, and training opportunities for the next generation of trialists.

Learning Objectives:

1. Understanding the need for subject level biomarker data to inform clinical trial design.
2. Understanding the types of funding opportunity announcements available for researchers to support early stage pharmacologic designs.

Literature References:

1. Javitt D.C. et. al. Utility of Imaging-Based Biomarkers for Glutamate-Targeted Drug Development in Psychotic Disorders: A Randomized Clinical Trial. JAMA Psychiatry 2018; 75(1): 11-19.
2. McPartland et. al. The Autism Biomarkers Consortium for Clinical Trials (ABC-CT): Scientific Context, Study Design, and Progress Toward Biomarker Qualification. Front. Integr. Neurosci. 2020: 14:1-7.

THE POTENTIAL OF NEUROGENETIC DISORDERS WITH NEUROPSYCHIATRIC PRESENTATION TO IMPROVE THE JUICE CONCENTRATION FOR THE BIOMARKER SQUEEZE

Raquel Gur, University of Pennsylvania

Individual Abstract: A challenge facing discovery and validation of biomarkers for psychiatric disorders is the underlying polygenicity and phenotypic heterogeneity. Elucidation of specific mechanistic pathways is further is further hampered by difficulties in obtaining phenotypic data with sufficient granularity to chart the links from biomarkers to outcome. Furthermore, effect sizes for polygenic risk scores are relatively small. Rare CNVs, by contrast, allow better genomic characterization and some confer large effect sizes for association with neurodevelopmental psychiatric disorders. Here the challenge is to obtain sufficiently large sample to power biomarker discovery and this challenge is beginning to be addressed by the G2MH Network supported by NIMH. The presentation will highlight the goals and approach of the Network and illustrate progress in 22q11.2 Deletion Syndrome (22q11DS). Notably, this syndrome is associated with ~25- fold increase in incidence of schizophrenia with onset in late adolescence and early adulthood. 22q11DS provides a translational window to advance underlying biology and therapeutics. The results provide early support for a potential mechanistic pathway into psychosis where deleted genes reduce biogenesis and lack of compensatory mitochondrial function eventuates in SCZ. The importance of social cognition in the pathway to SCZ is supported by fMRI and neurobehavioral findings in humans that show deficits related to symptoms and functioning. Extending the paradigm to other CNVs will allow elucidation of other pathways underlying neuropsychiatric disorders and the harmonized deep phenotyping across projects will allow unprecedented progress on the road toward novel therapeutics. Thus, while rare CNVs are, as defined, rare, the Network effort can address this obstacle and provide unique data on large samples of intensively studied youths with longitudinal data and highly enriched for neurodevelopmental disorders. Another important advantage of this population is that it represents individuals from around the globe with diverse environments allowing investigation of G X E interactions. Importantly, there is evidence that common variants add to the rare variant in predicting psychosis. In conclusion, this hard to squeeze rare CNV fruit may yet yield highly informative torrent of actionable biomarkers.

Learning Objectives:

1. Understand the neuropsychiatric manifestations of rare CNVs.
2. Appreciate the rationale for studying individuals with rare CNVs to improve biomarker yield.

Literature References:

1. Jacquemont S, Huguet G, Klein M, Chawner SJRA, Donald KA, van den Bree MBM, Sebat J, Ledbetter DH, Constantino JN, Earl RK, McDonald-McGinn DM, van Amelsvoort T, Swillen A, O'Donnell-Luria AH, Glahn DC, Almasy L, Scherer S, Robinson E, Bassett AS, Martin CL, Finucane B, Vorstman JAS, Bearden CE, Gur RE, and the Genes to Mental Health Network. Genes To Mental Health (G2MH): A framework to map the combined effects of rare and common variants on dimensions of cognition and psychopathology. Am J Psychiatry 2021; 00:1–15; doi: 10.1176/appi.ajp.2021.21040432.

2. Fiksinski AF, Bearden CE, Bassett AS, et al. A normative chart for cognitive development in a genetically selected population. Neuropsychopharmacology, 2021 Mar 29 Online ahead of print.

ENABLING PRECISION PSYCHIATRY: WHY SHOULD BIOMARKERS BE INCORPORATED INTO CNS DRUG DISCOVERY FROM PRE-CLINICAL RESEARCH TO CLINICAL APPLICATION AND WHAT DO THEY DELIVER?

Scott Hobson, Boehringer Ingelheim Pharma GmbH and Co KG

Individual Abstract: Progress in the discovery and development of new therapeutics for neuropsychiatric indications has been hampered by the high failure rates in clinical studies, leading to few novel treatment options over the last few decades. One of the primary reasons for these high failure rates is the lack of efficacy in the designated patient population in clinical trials. This raises the question of what can be done to improve/optimize a) selection of targets to treat clinical symptoms, b) patient population selection, c) proper selection of doses to be tested in clinical settings and d) readouts that provide indication of efficacy.

Over the course of many years of research, a wide array of biomarkers have been developed to provide potential solutions to all of the above mentioned issues. These range from biomarkers that can be used to demonstrate specific target and/or brain circuit engagement, to differentiate patients with the same diagnosis according to DSM5 criteria, and to obtain readouts correlated with various symptom domains which can detect clinical efficacy. In short, these biomarkers promise to enable a more precise means to clinically address psychiatric indications. However, to what extent are these biomarkers delivering on their promise?

The CNS Therapeutic Area Function at Boehringer Ingelheim is actively engaged in addressing this question by exploring various types of biomarkers to better design, as well as interpret the results from, clinical studies. This entails the entire drug discovery process ranging from explorative studies of potential biomarkers during early pre-clinical research stages to challenge studies in healthy individuals as well as to imaging and electrophysiological assessments of patient populations. Examples of CNS biomarkers will be highlighted including the specific connection of biomarkers to the target pharmacology as well as the benefits provided both in dose selection and detection of clinical efficacy.

Learning Objectives:

1. The potential that different biomarkers provide in the drug discovery process.
2. Examples of how biomarkers are being implemented in and benefit clinical assessment.

Literature References:

1. Rodrigues-Amorim D, Rivera-Baltanas T, Lopez M, et al: Schizophrenia: A review of potential biomarkers. J Psychiatr Res 2017; 93: 37-49
2. Garcia-Gutierrez MS, Navarrete F, Sala F, et al: Biomarkers in Psychiatry: Cencept, Definition, Types and Relevance to the Clinical Reality. Front Psychiatry 2020; 15:11:432. doi: 10.3389

*IMPROVING SCHIZOPHRENIA TREATMENT OUTCOME: NEW DATA AND NEW STRATEGIES

Ira Glick, Stanford University School of Medicine

Overall Abstract: The past decade has seen a major increase of early-onset and long-term studies of treatment of schizophrenia aimed at improving outcome, including quality of life. This session will summarize these advances.
John Davis, MD and Stefan Leucht, MD will summarize outcome studies of medication including meta-analyses of relative effectiveness and side effects of antipsychotics.

Donald Goff, MD will present pharmacological strategies for treatment of early onset schizophrenia.

JP Lindenmayer, MD will focus on recognition and treatment of refractory schizophrenia including earlier use of long-acting injectables (LAIs)

Ira Glick, MD, Danielle Kamis, MD, and Nina Cerfolio, MD will present first, a series of studies from different clinical settings focusing on 20-40 year long-term outcome.

John Lauriello, MD – Discussant

Learning Objectives:
At the conclusion of this session focusing on schizophrenia treatment, participants will be aware of, and be able to integrate into their practice:

1. New strategies for integrating multi-modal treatment including medication, psychosocial and digital technology interventions.
2. Be aware of the relative efficacy of all antipsychotics (new and old) including Long-Acting Injectables (LAIs) and for how long to continue antipsychotic treatment.
3. Be aware of augmentation strategies to improve treatment response.

INTERPRETING META-ANALYSIS OF ANTIPSYCHOTICS

John Davis, University of Illinois at Chicago

Individual Abstract: We will present our interpretation of the general principal of interpretation of Meta-Analysis of psychotropic medication focusing on antipsychotic drugs. We will focus on how to place pivotal studies of a new drugs in the context of Meta-Analysis of previous drugs. Meta-Analysis summarizes the effect size of outcome, such as efficacy and several side effects from studies selected by systematic search of the literature for studies meeting certain standard of quality, and quantitatively summarizes the results. This can reduce random error within studies. However, studies are deliberate done, and are not randomly done. While Meta-Analysis can statistically estimate to what degree they seem to differ from what variability might be expected by statistical variability. We will discuss how bias of one or more studies influences meta- analysis results. Bias in a few studies are reflected in the Meta-Analysis, not cancel out. We will explain Network Meta-Analysis estimates the effect sizes of outcomes from studies without the necessity of a common comparator but is bases on strong statistical assumptions. The placebo response to antipsychotics has increased over the years. The dose response cure is generally a sigmoid curve with a log-linear portion but after the log-linear part the increment in response with increase in dose decreases substantially and disappears. The initial registrational studies may not necessarily be dosed correctly, consequently the clinical need to attentive to dose response differences. . We will discuss dose response curves of maintenance antipsychotics and examine whether a long dose can be used for maintenance. We will discuss the time course of acute studies and contrast that with the time course of maintenance studies. Some antipsychotic efficacy is apparent with the first dose but with the ½ to full efficacy being several weeks. The time for patients' relapse of very

graduate if switched to placebo. We will discuss whether the dose for maintenance studies is the same as that of acute studies. Studies done before antipsychotics were discover, find that some individuals have a psychotic episode but never relapse, but maintenance studies of patients who have had several relapses indicate that virtually all patients' relapses. We will discuss low long to treat first episode patients. Meta-Analysis can quantify outcome but cannot balance qualitative differences. We will compare the efficacy outcome of drugs used in psychiatry with commonly used drugs in general medicine.

Learning Objectives:

1. To appreciate the underlying assumptions of Meta -analysis.
2. To understand the dose response curve.

Literature References:

1. Leucht S, Bauer S, Siafis S, Hamza T, Wu H, Schneider-Thoma J, Salanti G, Davis JM. Examination of Dosing of Antipsychotic Drugs for Relapse Prevention in Patients With Stable Schizophrenia: A Meta-analysis. JAMA Psychiatry. 2021 Nov 1;78(11):1238-1248. doi: 10.1001/jamapsychiatry.2021.2130. PMID: 34406325; PMCID: PMC8374744.
2. Leucht S, Crippa A, Siafis S, Patel MX, Orsini N, Davis JM. Dose-Response Meta-Analysis of Antipsychotic Drugs for Acute Schizophrenia. Am J Psychiatry. 2020 Apr 1;177(4):342-353. doi: 10.1176/appi.ajp.2019.19010034. Epub 2019 Dec 16. Erratum in: Am J Psychiatry. 2020 Mar 1;177(3):272. PMID: 31838873.

AN UPDATE ON THE PHARMACOLOGIC TREATMENT OF EARLY PSYCHOSIS

Donald Goff, NYU Langone Medical Center

Individual Abstract: While coordinated specialty care has improved outcome in first episode psychosis, several issues remain unresolved. These issues include challenges with retention of patients and adherence, a lack of effective interventions for negative symptoms and cognition, and evidence for a decline in functioning over the longer-term. The question of whether antipsychotic medication is neuroprotective or potentially neurotoxic also remains unresolved. Results of the NYU/Shanghai Mental Health Center Early Psychosis Project will be reviewed in relation to these issues. This project included a comprehensive study of 75 medication-free patients and matched healthy controls followed during the first 8 weeks of treatment and a 12 month placebo-controlled add-on trial of citalopram maintenance treatment following initial stabilization of 100 first episode schizophrenia patients. Results of clinical ratings, imaging, and molecular biomarkers from the two studies will be presented.

Learning Objectives:

1. Become familiar with associations between hippocampal volume loss, duration of untreated psychosis and biomarkers for inflammation and oxidative stress during the first 8 weeks of antipsychotic treatment.
2. Become familiar with evidence for efficacy of citalopram for negative symptoms during maintenance treatment of first episode schizophrenia patients.

Literature References:

1. Goff DC, Zeng B, Ardekani BA, Diminich ED, Tang Y, Fan X, Galtzer-Levy I, Li C, Troxel AB, Wang J. Association of hippocampal atrophy with duration of untreated psychosis and molecular biomarkers during initial antipsychotic treatment of first episode psychosis. JAMA Psychiatry 2018; 75:370-378. PMID 29466532

2. Goff DC, Freudenreich O, Cather C, Holt D, Bello I, Diminich E, Tang Y, Ardekani BA, Worthington M, Zeng B, Wu R, Fan X, Li C, Troxel A, Wang J, Zhao J. Citalopram in first episode schizophrenia: The DECIFER trial. Schiz Res 2019. 208:331-337. PMID: 30709746

UPDATE ON STRATEGIES FOR TREATMENT RESISTANT PSYCHOSIS

Jean-Pierre Lindenmayer, New York University Grossman School of Medicine

Individual Abstract: Approximately 20–33% of people with schizophrenia have treatment-resistant schizophrenia (TRS) (Agid et al., 2011) with significant ongoing symptoms and functional impairment despite adequate antipsychotic and adherent trials. TRS is a significant psychological burden for both patients and caregivers. This presentation will review the definition of TRS based on the consensus TRIPP guidelines (Howes et al., 2017) and discuss the underlying pathogenetic mechanisms, based on recent PET data and dysfunctions in the glutamatergic systems. The different pathways to TRS will be discussed. More recent data on clozapine's indications and efficacy will be reviewed together with barriers on its use and recommendations for improving its early and more effective use. The New REMS requirements will be discussed and experiences with the new system will be presented. There will be a systematic analysis of the evidence for treatments when clozapine is not fully effective, covering dopaminergic, gaba-ergic, glutaminergic and electro-convulsive enhancements of treatment resistant positive, negative and cognitive symptoms.

Learning Objectives:

1. Develop a better understanding of the relative efficacy of clozapine in treatment resistant schizophrenia.
2. Develop a better understanding of the underlying etiologies of treatment resistant schizophrenia.

Literature References:

1. Howes OD, McCutcheon R, Agid O, et al. Treatment-Resistant Schizophrenia: Treatment Response and Resistance in Psychosis (TRRIP) Working Group Consensus Guidelines . Am J Psychiatry . 2017;174(3):216 216-229.
2. Howes OD, Kapur S: A neurobiological hypothesis for the classification of schizophrenia: type A (hyperdopaminergic) and type B (normodopaminergic). Br J Psychiatry 2014; 205:1–3.

SHOULD ANTIPSYCHOTIC MEDICATIONS FOR SCHIZOPHRENIA BE GIVEN FOR A LIFETIME? SUMMARY OF FOUR NATURALISTIC, 6-53 YEAR LONG-TERM, FOLLOW-UP STUDIES OF ANTIPSYCHOTIC TREATMENT FOR SCHIZOPHRENIA

Ira Glick, Stanford University School of Medicine

Individual Abstract: Background: Because ethically and practically a randomized controlled trial of lifetime antipsychotics maintenance will never be done, we recently conducted four long-term, naturalistic follow-up studies in four different clinical settings of patients with chronic schizophrenia on antipsychotic medication. We initially found that better medication adherence was a statistically significant predictor of better long-term global outcome and life satisfaction. For the first time, we here present findings from a 4th site, and combine all of the

data. The aim is to translate research into clinical practice to change the paradigm, that is suggesting efficacious lifetime treatments for schizophrenia.

Method: These were retrospective, naturalistic, longitudinal (6-53 years) studies of antipsychotic treatment (mean average, 20) follow-ups of a consecutive series of patients from an academic setting, a V-A, a clinical research organization, and a community clinic. Lifetime data were collected on (1) their medication adherence, (2) long-term global outcome, and (3) life satisfaction. Outcomes were rated by 2 different clinicians, 1 with information on medication adherence (nonblind rater) and 1 without (blind 21 rater). We used linear regression models adjusted for age, family support, substance use disorder, race, marital status, and number of years in treatment to estimate the association between adherence and each outcome.

Results: A total of 109 patients (mean age, 45 y; mean years of possible medication since onset of treatment, 21 y) were assessed. Medication adherence was a statistically significant predictor of better long-term global outcomes and life satisfaction, both in Spearman rank order correlations and in covariate-adjusted linear regressions (all P values <0.01). Poor medication adherence was associated with poor outcomes, often disastrous, with low life satisfaction. For example, the rank order correlation was .50, p=.002 for an academic clinic of patients rating and the correlation of the blind clinicians rating was .83, p<.000 for the VA clinic) Other variables such as presence of substance use disorders or family support did not explain the difference between those who adhered and those who did not. Study limitations include that this is an observational study, where those with the best prognosis are more likely to adhere to medical treated, and the potential for residual confounding.

Conclusions: In this report, patients who adhered to antipsychotic medication had clinically much improved long-term global outcomes than those who had lesser, especially, poor adherence. This sample provides data consistent with the recommendation for most patients for continuous, long-term treatment for chronic schizophrenia.

Unique Data: No one has ever done continuation studies for so many years with the detail of outcome data that we have produced.

Learning Objectives:

At the conclusion of this presentation, participants will be aware of:

1. Most efficacious psychopharmacologic and psychotherapeutic treatment.
2. How long to continue treatment.

Literature References:

1. Glick I D, Zamora D, Davis J et al: Are Patients with Schizophrenia Better Off with Lifetime Antipsychotic Medication: Replication of a Naturalistic Long-term Follow-up Study of Antipsychotic Treatment, J Clinical Psychopharmacology, 2020, 40:145-148.
2. Glick ID, Cerfolio NE, Kamis D, Laurence M: Domestic terrorist mass shooters: Prevalence of untreated psychiatric illness. J Clin Psychopharmacology. 2021; 41:366-369, DOI: 10.1097/JCP.0000000000001417

*KETAMINE/ESKETAMINE IN PSYCHIATRIC DISORDERS ACROSS THE LIFESPAN: THERAPEUTIC POTENTIAL AND THE UNDERLYING BIOLOGICAL MECHANISMS

Madhukar Trivedi, UT Southwestern Medical Center

Overall Abstract: Ketamine has been studied as novel treatment for a range of psychiatric disorders including major depressive disorder (MDD), post-traumatic stress disorder, bipolar depression, and substance use disorders. Intranasal esketamine, the s-enantiomer of ketamine, in conjunction with an oral antidepressant is approved by the Food and Drug Administration (FDA) for treatment-resistant depression (TRD) in adults and for the treatment of depressive symptoms in adults with MDD with acute suicidal ideation or behavior. While the FDA-approval of intranasal esketamine marked the availability of first non-monoaminergic antidepressant, evidence for its efficacy across the lifespan remains limited. The phase 3 study of intranasal esketamine in elderly patients with MDD did not meet its primary end-point and the study in adolescents is still ongoing (NCT03185819). Furthermore, studies of esketamine have not evaluated the role of irritability, which is a common yet often ignored feature of depression that is associated with persistently elevated suicidal ideation and lower likelihood of acute-phase remission or meaningful benefit.
The first presentation of the proposed panel will evaluate the impact of baseline irritability on treatment outcomes with intranasal esketamine in a secondary analysis of pooled data from two phase 3 studies of adults with TRD. Additional results on changes in irritability with esketamine versus placebo will also be presented. The second presentation will focus on the evidence for the use of ketamine in adolescent depression and suicidality, with an emphasis on secondary analyses from a pediatric randomized controlled trial. Key remaining research questions will be identified, and the unique developmental considerations and scientific challenges that apply to this work will be discussed. The third presentation will evaluate the clinical and biological effects of intravenous ketamine for late-life treatment-resistant depression (LL-TRD) by assessing changes in depressive symptom severity and in gamma power (EEG measure). The fourth and final presentation will include new data characterizing the relationship between immune system and neural circuits, especially as it relates to stress response. This presentation will also include novel findings of how changes in immune response may underlie the therapeutic effects of ketamine. Finally, the discussant who is a leader in clinical psychopharmacology research will summarize the presented findings and will lead an engaged conversation between the panel and audience.

Learning Objectives:

1. Understand the therapeutic potential of ketamine and its s-enantiomer (esketamine) in treatment of psychiatric disorder.
2. List the biological mechanisms that may underlie the therapeutic effects of ketamine.

IRRITABILITY IN ADULTS WITH TREATMENT-RESISTANT DEPRESSION (TRD) AND TREATMENT OUTCOMES WITH INTRANASAL ESKETAMINE

Ibrahim Turkoz, Janssen R and D, LLC

Individual Abstract: Background: Irritability is an important, yet often under-recognized symptom in adults with major depressive disorder (MDD), and its association with clinical features in adults with treatment-resistant depression (TRD) remains poorly understood. Furthermore, the impact of irritability on treatment outcomes with esketamine nasal spray (ESK) in adults with TRD has not been evaluated.
Methods: A post hoc analysis of pooled data from two similarly designed phase 3, double-blind, 4-week studies (TRANSFORM-1 [NCT02417064] and TRANSFORM-2

[NCT02418585]) was conducted. Adult participants (N=560) with TRD were randomized to a newly initiated oral antidepressant (AD) plus ESK (fixed or flexible dose; ESK+AD) or an oral AD plus placebo (PBO) (AD+PBO). Irritability was assessed with Item 6 of the Generalized Anxiety Disorder 7-item scale (GAD-7). Baseline irritability was characterized as high, varying, or low based on consistency of GAD-7 Item 6 response being above or below the cutoff score (≥2) at both screening and baseline. In addition to assessing baseline characteristics across irritability groups, the extent to which baseline irritability and treatment impacted changes in mean depression severity (Montgomery Asberg Depression Rating Scale [MADRS] total score) was evaluated using repeated measures mixed model analyses. Rates of treatment response (≥50% decrease from baseline in MADRS total score) and remission (MADRS total score ≤12) over the course of the 4-week study were examined using multiple logistic regression models. Changes in the irritability item of GAD-7 from baseline to day 28 and incidence of adverse events were also assessed.

Results: Of the 560 participants with TRD, 296 (60.5%) had high irritability at screening and baseline, 130 (23.9%) had low irritability at both visits, and 134 (23.2%) had varying levels of irritability. Compared with the low irritability group, the high irritability group was younger at diagnosis of MDD ($p < 0.001$) with more frequent lifetime suicidal behavior as quantified by the Columbia-Suicide Severity Rating Scale ($p < 0.05$), and had longer duration of current episode ($p < 0.05$), more previously prescribed antidepressants ($p < 0.05$), more anxiety based on the Anxiety factor of the Inventory of Depressive Symptomatology – Clinician Version ($p < 0.05$), more comorbid anxiety disorders at screening ($p < 0.001$), and higher body mass index (BMI; $p < 0.001$).

Depressive symptoms improved more in patients in the ESK+AD group than in patients in the PBO+AD group over the course of the 28-day trial. This pattern of results was consistent across the three irritability groups. Greater improvement was observed in the ESK+AD group at day 28 regardless of baseline irritability level (change in MADRS score from baseline to day 28: $p < 0.001$, treatment response: $p < 0.05$, remission: $p < 0.05$). Both treatment groups reported less irritability at day 28, but the extent of change in irritability did not differ significantly between treatment groups. Percentages of patients reporting adverse events were generally consistent across irritability groups.

Conclusion: Irritability is common in adults with TRD and is associated with younger age at MDD diagnosis, more lifetime suicidal behavior, higher levels of anxiety, and higher BMI. Post hoc results support efficacy of esketamine nasal spray plus an oral antidepressant in patients with TRD, regardless of baseline irritability.

Learning Objectives:

1. List the ways that high levels of irritability may be associated with baseline characteristics of patients presenting with treatment-resistant depression (TRD).
2. Explain the impact that irritability may have on treatment outcomes with esketamine nasal spray + a newly-initiated oral antidepressant vs. a placebo nasal spray + a newly-initiated oral antidepressant in patients with TRD.

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. Am J Psychiatry 2019;176(5):358-366. (In eng). DOI: 10.1176/appi.ajp.2018.18030355.

2. Popova V, Daly EJ, Trivedi M, et al. Efficacy and safety of flexibly dosed esketamine nasal spray combined with a newly initiated oral antidepressant in treatment-resistant depression: a randomized double-blind active-controlled study. Am J Psychiatry 2019;176(6):428-438. (In eng). DOI: 10.1176/appi.ajp.2019.19020172.

A BAYESIAN ADAPTIVE RANDOMIZATION TRIAL TO OPTIMIZE INTRAVENOUS KETAMINE DOSING FOR LATE-LIFE TREATMENT-RESISTANT DEPRESSION

Sanjay J. Mathew, Baylor College of Medicine and Michael E. DeBakey VA Medical Center

Individual Abstract: BACKGROUND: Evidence of the rapid antidepressant efficacy of the NMDA receptor antagonist ketamine (and its S-enantiomer) has grown. The biological mechanisms of response durability are attributed to sustained patterns of increased excitation/inhibition (E/I) balance which outlast the short elimination half-life of ketamine. However, the clinical and biological effects of IV ketamine for late-life treatment-resistant depression (LL-TRD) have not been extensively investigated to date. We examined the sustained clinical and neurophysiological effects of several doses of IV ketamine (KET) relative to midazolam (MID) in patients with LL-TRD.

METHODS: Thirty-three veteran patients (55-72 years, mean age: 62.9 ± 5.86, 30.3% female), were enrolled in a randomized, double-blind, placebo-controlled design, and randomized to either a single 40 min infusion of IV ketamine (0.1, 0.25, or 0.5 mg/kg) or midazolam (0.03 mg/kg). Randomization was achieved using Bayesian adaptive randomization (BAR) with an initial allocation ratio of 1:1:1:1. The allocation ratio was updated as patients completed the study to prioritize the comparison of the most clinically effective conditions. Patients completed evaluations on six visits to assess clinical efficacy and durability (baseline and 1, 2, 3, 7, and 28 days post infusion).

Our primary endpoint was change in MADRS score between baseline and 7 d post-infusion. Durability was evaluated by estimating the probability of a clinical response to a single infusion at the 28 day visit for patients who demonstrated response to infusion at day 7. Gamma power was evaluated at 3 different time scales (-1 to +4 hr relative to infusion; 24 hr post-infusion; 24 hr to 7 d post-infusion). All analyses controlled for data values at the baseline time point. Kendall's tau correlations were performed to draw inferences on the relationship between gamma power and change in MADRS.

RESULTS: Infusions in all conditions were safe and well tolerated. The BAR stopping rules terminated randomization to 0.1 and 0.25 mg/kg ketamine conditions at N=4 and N=5, respectively, due to inferior clinical performance. Sixteen patients (48.5%) achieved a clinical response at 7 d (KET 0.5 = 8, KET 0.25 = 2, MID = 6). Ketamine 0.5 mg/kg demonstrated a strong absolute probability (ap) of achieving a response at 7 d (ap = 0.7, 95% credible interval (95%-CrI) = 0.43 – 0.90), and was consistent with a higher response at 7 d than MID (Posterior Probability (pp) [KET 0.5 > MID] = 0.89). Probability of a clinical response was lower for ketamine 0.25 (ap = 0.42, 95%-CrI = 0.11 – 0.78) and 0.1 mg/kg (ap = 0.13, 95%-CrI = 0.01 – 0.53). Response durability at 28 d among responders at 7 d was greatest for KET 0.5 (N = 7, ap = 0.82, 95%-CrI = 0.52 – 0.97), and reduced proportionally with lower doses; KET 0.25 (N = 1, ap = 0.5, 95%-CrI = 0.09 – 0.90), MID (N = 2, ap = 0.37, 95%-CrI = 0.10 – 0.71).

There was a significant time*condition interaction amounting to divergent effects of drug on gamma power (pp [KET 0.5 > MID] = 0.92). Gamma power rapidly increased during the

infusion period for KET 0.5 and then gradually returned to baseline levels approximately 4 hr post-infusion (pp = 0.92), while MID was associated with a continuous upwards trend in gamma power (pp = 0.91). At 24 hr, there was low evidence of differences in gamma power between the conditions (pp [KET 0.5 > MID] = 0.37). Peak gamma power during infusion was associated with greater change in MADRS score at 7 d for KET 0.5 (τ = -0.5, p = .08), but not for MID (τ = 0.05, p = 0.84).

CONCLUSIONS: Our results suggest that IV ketamine at 0.5 mg/kg is clinically effective and tolerable in LL-TRD. Our EEG findings provide preliminary evidence that the reactivity of gamma power might reflect susceptibility to enhanced clinical effects.

Learning Objectives:

1. To understand the Bayesian Adaptive Randomization approach to early stage clinical trials to detect optimal dose-response.
2. To study the role of EEG in understanding psychopathology associated with imbalances in excitatory: inhibitory neurotransmission.

Literature References:

1. Fava M, Freeman MP, Flynn M, Judge H, Hoeppner BB, Cusin C, Ionescu DF, Mathew SJ, Chang LC, Iosifescu DV, Murrough J, Debatista C, Schatzberg AF, Trivedi MH, Jha M, Sanacora G, Wilkinson ST, Papakostas G: Double-blind, placebo-controlled, dose-ranging trial of intravenous ketamine as adjunctive therapy in treatment-resistant depression (TRD). Molecular Psychiatry 2018; PMID:30283029.
2. O'Brien B, Green CE, Al Jurdi RK, Chang LC, Lijffijt M, Iqbal S, Iqbal T, Swann AC, Mathew SJ. Bayesian adaptive randomization trial of intravenous ketamine for veterans with late-life treatment resistant depression. Contemporary Clinical Trials Communications 2019; 16: 100432.

ROLE OF STRESS AND INFLAMMATION IN THE MECHANISMS OF DEPRESSION AND THERAPEUTIC EFFECTS OF KETAMINE

James Murrough, Icahn School of Medicine at Mount Sinai

Individual Abstract: Stress exposure is a key risk factors for the development of major depressive disorder (MDD) and emerging data suggest that stress-sensitive pathways that regulate immune function in the body may drive specific aspects of depressive pathophysiology and may represent novel target for treatment development. We have recently completed a series of studies that provide novel evidence for exaggerated immune cell reactivity in the periphery in patients with MDD, consistent with emerging work conducted in rodent stress models. The current talk will present new data characterizing the relationship between peripheral immune pathways and neural circuits controlling specific phenotypic aspects of depression. Using functional MRI (fMRI) and an incentive flanker task to probe neural responses to reward anticipation (MDD, n=30; HC, n=21), we found that higher peripheral immune score is associated with reduced neural responses to reward anticipation within the ventral striatum (VS) (r=-0.39, p=0.01), and with reduced self-reported anticipation of pleasure as measured (r=-0.318, p=0.023). Using fMRI with the emotional face matching task in an overlapping cohort (MDD, n=20; HC, n=17), we also show that higher peripheral immune score is associated with increased amygdala activation during perception of threat (r=0.331, p=0.045) and higher amygdala activation is associated with greater anxious arousal (r=0.390, p=0.017).

In our study higher self-reported perceived stress was positively associated with both inflammatory response (r=0.367, p=0.026) and amygdala response to threat (r=0.325, p=0.050), although neither inflammation nor amygdala activation fully accounted for the effect of perceived stress on anxious arousal. To examine in more detail the molecular mechanisms related to depression and response to ketamine we recently investigated whole blood transcriptional profiles related to treatment-resistant depression (TRD) and gene expression changes associated with treatment response to ketamine. Whole blood was collected at baseline (TRD, n=26; HC, n=21) and then again in patients with TRD 24 hours following a single intravenous infusion of ketamine (0.5 mg/kg). We performed RNA-sequencing and analyzed a) baseline transcriptional profiles between patients with TRD and HC, b) responders vs. non-responders before ketamine treatment, and c) gene expression signatures associated with clinical improvement. At baseline, patients with TRD compared to HC showed a gene expression signature indicative of interferon signaling pathway activation. Prior to ketamine administration, the metabotropic glutamate receptor gene GRM2 and the ionotropic glutamate receptor gene GRIN2D were upregulated in responders compared to non-responders. Response to ketamine was associated with a distinct transcriptional signature, however, we did not observe gene expression changes indicative of an anti-inflammatory effect. Altogether, the current will present new data which adds to a growing understanding of the role of stress and inflammatory pathways in depression and in the therapeutic action of ketamine.

Learning Objectives:

1. Identify the relationship between peripheral immune pathways and neural circuits controlling specific phenotypic aspects of depression.
2. Understand changes in gene expression profiles that may be relevant to the antidepressant effect of ketamine.

Literature References:

1. Costi S, Morris LS, Collins A, Fernandez NF, Patel M, Xie H, Kim-Schulze S, Stern ER, Collins KA, Cathomas F, Parides MK, Whitton AE, Pizzagalli DA, Russo SJ, Murrough JW. Peripheral immune cell reactivity and neural response to reward in patients with depression and anhedonia. Transl Psychiatry. 2021 Nov 5;11(1):565.
2. McIntyre RS, Rosenblat JD, Nemeroff CB, Sanacora G, Murrough JW, Berk M, Brietzke E, Dodd S, Gorwood P, Ho R, Iosifescu DV, Lopez Jaramillo C, Kasper S, Kratiuk K, Lee JG, Lee Y, Lui LMW, Mansur RB, Papakostas GI, Subramaniapillai M, Thase M, Vieta E, Young AH, Zarate CA Jr, Stahl S. Synthesizing the Evidence for Ketamine and Esketamine in Treatment-Resistant Depression: An International Expert Opinion on the Available Evidence and Implementation. Am J Psychiatry. 2021 May 1;178(5):383-399.

KETAMINE FOR PEDIATRIC TREATMENT RESISTANT DEPRESSION AND SUICIDALITY: ADVANCES AND CHALLENGES

Jennifer Dwyer, Boehringer Ingelheim

Individual Abstract: Nearly one in five adolescents will experience major depressive disorder (MDD), and suicide is the 2nd leading cause of death in this age group. 40% of adolescents with MDD fail to respond to initial treatment with selective serotonin reuptake inhibitors, and of those, nearly half remain depressed despite switching medications and adding psychotherapy. Better treatments for adolescent treatment resistant depression (TRD) and suicidality are urgently needed. Intravenous ketamine has efficacy in adult TRD, but there is little rigorous evidence in pediatric populations. The adolescent brain is a unique

neuropharmacologic substrate and novel interventions must be specifically tested in pediatric patients, with careful attention to neurodevelopmental context. Our objectives are to critically evaluate what is known regarding ketamine's efficacy and safety in this developing population, describe the unique developmental considerations and scientific challenges that apply to this work, and identify key remaining research questions.

Here we will review the available studies of ketamine in youth with treatment refractory mood disorders. Adding to the current literature of case reports and open label investigations, we will emphasize secondary analyses from a recent randomized, midazolam-controlled single dose crossover clinical trial. In this trial, adolescents with TRD (ages 13-17, failed at least one prior antidepressant trial prior to enrollment) were randomized to receive ketamine (0.5mg/kg infused over 40 minutes) or midazolam (0.045mg/kg infused over 40 minutes), separated by two weeks (n=17). We have previously reported the primary outcome, Montgomery-Asberg Depression Rating Scale (MADRS) score at 1 day, with a significant reduction in depressive symptoms following ketamine infusion relative to midazolam. Ketamine was associated with transient, self-limited dissociative symptoms, and there were no serious adverse events. Secondary outcomes include measures of implicit associations with depression, suicide, anxiety, and self-harm, and explicit measures of anxiety.

We will also discuss ongoing efforts to study repeat dosing paradigms, highlighting specific areas where additional care is warranted in pediatric trial designs. Ketamine and esketamine have an increasingly robust evidence base for adult TRD, and a much smaller, but growing, evidence base in pediatric refractory mood disorders. While promising, there are unique developmental issues that require careful consideration, particularly regarding repeat dosing and the potential for enhanced vulnerability to neurotoxicity in adolescents. Important avenues for future study include identifying optimal dosing paradigms, adjunctive treatments to extend efficacy (e.g. cognitive behavioral therapy), and biomarkers that predict treatment response.

Learning Objectives:

1. To describe the state of the pediatric evidence base for ketamine as a rapid-acting treatment for depression and suicidality, and to compare it with the adult evidence base.
2. To appreciate the unique developmental considerations that apply to testing and implementing novel therapeutics in the pediatric population.

Literature References:

1. Dwyer JB, Landeros-Weisenberger A, Johnson JA, Londono Tobon A, Flores JM, Nasir M, Couloures K, Sanacora G, Bloch MH. Efficacy of Intravenous Ketamine in Adolescent Treatment-Resistant Depression: A Randomized Midazolam-Controlled Trial. Am J Psychiatry. 2021 Apr 1;178(4):352-362. PMID: 33653121.
2. Dwyer JB, Stringaris A, Brent DA, Bloch MH. Annual Research Review: Defining and treating pediatric treatment-resistant depression. J Child Psychol Psychiatry. 2020 Mar;61(3):312-332. PMID: 32020643.

Panel Sessions

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

***TOPICS IN REPRODUCTIVE PSYCHIATRY**

Jennifer Payne, University of Virginia

Overall Abstract: Reproductive psychiatry focuses on psychiatric disorders associated with hormonal changes in women. This panel will highlight novel therapeutics being used to treat psychiatric disorders in women including postpartum depression, perimenopausal depression, and hypoactive sexual desire that are believed to be triggered by hormonal changes associated with various reproductive stages. The first talk will describe the unified theory behind the use of neuroactive steroids to treat not only "reproductive depression" associated with times of hormonal change such as postpartum and perimenopausal depression but also depressive episodes not associated with times of hormonal change. The second talk will highlight data supporting the use of synthetic allopregnanolone preparations to treat postpartum depression and perimenopausal depression including clinical trial data, animal data and neuroactive steroid levels during and after pregnancy that are associated with peripartum depression. The third talk will discuss neuroendoctine factors that mediate sexual dysfunction and depression in women, focusing on the mechanism of action of neuropeptide melanocortin agonists. All speakers will accentuate the mechanisms of action of these novel therapeutics, how they are thought to work in "reproductive" depression and sexual dysfunction in women, and how these therapeutics may work in nonreproductive depressive disorders. The discussion that follows will highlight two ideas: 1) Focusing on understanding the pathophysiology of "reproductive" depression, the onset of which can be predicted due to timing of reproductive events, may ultimately shed light on the pathophysiology of non-reproductive depressive disorders. 2) The development of novel therapeutics that target systems that were previously unidentified as being involved in psychiatric disorders leads not only to improved treatments but to an increased understanding of the biological underpinnings of psychiatric illness in general. The need for further research and directions of future research will also be discussed in detail.

Learning Objectives:

1. Identify the mechanism of action of novel pharmacological agents for the treatment of postpartum depression and major depression.
2. Name a new pharmacological agent for the treatment of hypoactive sexual desire disorder in women.

NEUROACTIVE STEROIDS: MECHANISM OF ACTION AND INVESTIGATIONAL TREATMENT FOR DEPRESSIVE DISORDERS

Mercedes Szpunar, Massachusetts General Hospital, Center for Women's Mental Health

Individual Abstract: Neurosteroids are produced in the brain from cholesterol, and they can generate excitability or anxiolytic effects depending on brain region and specific neurosteroid. When produced in peripheral endocrine organs, they have been termed neuroactive steroids (NAS). Due to their lipophilic nature, NAS must be produced de novo and cannot be stored. The NAS allopregnanolone (ALLO) is a derivative of the hormone progesterone, and ALLO levels in the brain and plasma change in parallel with progesterone. ALLO is a positive allosteric modulator (PAM) of gamma-aminobutyric acid-A (GABA-A) receptors, inducing more potent effects than benzodiazepines in vitro. ALLO levels increase after an acute stressor. Chronic stress and hypothalamic-pituitary-adrenal axis dysregulation have been implicated in the pathogenesis of major depressive disorder (MDD), and it is plausible that altered GABA-A neurotransmission - specifically via changes in ALLO production or signaling - may play a role in this pathophysiology. Several investigations have determined reduced ALLO levels in individuals with MDD compared with healthy controls, but after successful treatment with SSRIs, ALLO resumed comparatively normal levels. Two oral medications that act as PAM of GABA-A receptors have been investigated as treatment for MDD and postmenopausal

depression: ganaxolone and zuranolone. Rapid and robust antidepressant effects of these oral therapies have been detected, but sedation has been observed as an adverse effect. Studies are ongoing to determine optimal dose, frequency, and duration of treatment. Thus, PAM of GABA-A receptors may have therapeutic implications for multiple depressive disorders, but further investigation is required to optimize therapeutic outcomes.

Learning Objectives:

1. Describe the mechanism of action of the neurosteroid allopregnanolone, a positive allosteric modulator of gamma-aminobutyric acid-A (GABA-A) receptors, and its theorized role in depressive disorders.
2. Summarize interventional studies utilizing synthetic oral GABA-A receptor positive allosteric modulators for the treatment of depression.

Literature References:

1. Rubinow DR, Schmidt PJ: Is there a role for reproductive steroids in the etiology and treatment of affective disorders? Dialogues Clin Neurosci 2018;20:187-96.
2. Schweizer-Schubert S, Gordon JL, Eisenlohr-Moul TA, et al: Steroid hormone sensitivity in reproductive mood disorders: On the role of the GABA-A receptor complex and stress during hormonal transitions. Front Med 2021;7:47969646.

NEUROACTIVE STEROIDS IN "REPRODUCTIVE DEPRESSION"

Jennifer Payne, University of Virginia

Individual Abstract: Reproductive Psychiatry focuses on treatment of psychiatric disorders in women during the reproductive years, particularly during times of hormonal change. These include the premenstrual and perimenopausal time-periods, pregnancy and postpartum and depressive episodes that occur during these time-periods have been termed "reproductive depression." Neuroactive steroids are endogenous or exogenous steroids that rapidly alter neuronal excitability through interaction with ligand-gated ion channels and other cell surface receptors. Over the past several years there has been a growth of synthetic neuroactive steroids that are being investigated for the management of psychiatric disorders that have been triggered by hormonal change in women. This presentation will discuss the background research, including animal studies and clinical trial data that led to this trend as well as the data that support the use of neuroactive steroids in women with reproductive depression. Data demonstrating alterations in endogenous neuroactive steroids, including allopregnanolone, pregnanolone, pregnenolone and others in peripartum depression will be presented. The presentation will synthesize the current theory on why neuroactive steroids may work to treat reproductive depression and what this implies regarding the underlying biology of reproductive depressive episodes and in turn what it may imply in terms of the underlying biology of major depression in general. Future research directions will be emphasized.

Learning Objectives:

1. Define "reproductive depression."
2. Identify the mechanisms by which newly developed synthetic neuroactive steroids are thought to treat reproductive depression.

Literature References:

1) Payne JL, Teitelbaum-Palmer J, Joffe H. A reproductive subtype of depression: conceptualizing models and moving towards etiology. Harvard Review of Psychiatry 2009; 17(2): 72-86.

2) Schweizer-Schubert S, Gordon JL, Eisenlohr-Moul TA, Meltzer-Brody S, et al. Steroid hormone sensitivity in reproductive mood disorders: on the role of the GABA-A receptor complex and stress during hormonal transitions. Frontiers in Medicine 2021; 7;479646.

NEUROENDOCRINE FACTORS MEDIATE SEXUAL DYSFUNCTION AND DEPRESSION

Anita H. Clayton, University of Virginia

Individual Abstract: Under a unified theory of depression, genetic and epigenetic susceptibility plus environmental triggers lead to synaptic mechanism dysfunction with pathophysiology in inflammatory mechanisms, HPA-Axis hyperactivity, neurotransmitters (serotonin, norepinephrine, dopamine, GABA and glutamate), and endogenous neuroactive steroids, resulting in reduced neuroplasticity and neural network dysfunction manifested as symptoms of major depressive disorder (MDD). Some women may be particularly sensitive to normal fluctuations in hormones across the lifespan, increasing the risk of MDD. Particularly important are exogenous hormones like hormonal contraceptives, perimenpausal/menopausal status as indicated by FSH/LH, prolactin and thyroid function. Similar mechanisms are associated with sexual dysfunction (SD), particularly in women. This overlap may explain the significant comorbidity of MDD and SD. The bio-psycho-social model is useful in identifying factors contributing to depression and sexual dysfunction including medical and psychiatric illnesses, substances, psychological factors/trauma, etc. whereas attention to excitation vs. inhibition enhances understanding of neuroendocrine processes and the mechanism of action (MOA) of various agents. The neuropeptide melanocortin agonists (e.g. bremelanotide for hypoactive sexual desire disorder) that act at transmembrane G-protein coupled receptors impact immunomodulatory effects not unlike the effects of neuroactive steroid GABA-A receptor agonists positive allosteric modulators (e.g. brexanolone for postpartum depression) that 1) allosterically enhance the channel current (synaptic and extrasynaptic receptor sites) and 2) bind to metobotropic G-protein coupled membrane progesterone receptors. Further discussion of the overlap in pathology and MOA of various treatment modalities in MDD and sexual dysfunction will be important in our understanding and treatment of patients with these conditions.

Learning Objectives:

At the conclusion of the presentation, the participation will be able to:

1. Articulate the overlap in etiology and pathophysiology for major depressive disorder and sexual dysfunctions.
2. Describe the mechanism of action of available treatments for MDD and sexual dysfunctions that impact neuroendocrine function.

Literature References:

1. Dean J, Keshavan M. The neurobiology of depression: An integrated view. Asian J Psych 2017;27:101-111
2. Johannes CB et al. Distressing sexual problems in United States women revisited: Prevalence after accounting for depression. J Clin Psychiatry 2009;70(12):1698-1706

NOVEL PHARMACOTHERAPIES FOR POST-TRAUMATIC STRESS DISORDER

George Papakostas, Massachusetts General Hospital

Overall Abstract: Post-traumatic stress disorder (PTSD) can affect approximately one out of three individuals exposed to a traumatic experience, and has been associated with significant occupational and social impairment, increased risk of suicide, as well as higher medical and psychiatric co-morbidity. In addition, the prevalence of PTSD has been estimated between 5 and 10%, rendering it as one of the most common Psychiatric conditions. Although trauma-focused therapy is most often recommended as first-line treatment, very few pharmacotherapies have been developed for PTSD. Specifically, of a number of antidepressants and non-antidepressant medications tested in randomized, double-blind, placebo-controlled trials only paroxetine and sertraline have received approval by the U.S. Food and Drug Administration for the treatment of PTSD. Clearly, expanding the treatment armamentarium for clinicians and patients alike is a major priority for the field. Recently, a number of non-monoaminergic neurotransmitter systems have received attention as possible targets to develop novel pharmacotherapies for PTSD. In the present panel, we will review these leads.

Learning Objectives:

1. At the end of this panel, attendees will be able to discuss the role of Glutamate and GABA in developing novel treatments for PTSD.
2. At the end of this panel, attendees will be able to discuss the role of Neuropeptide Y, Cannabinoids and other brain circuitry in developing novel treatments for PTSD.

ROLE OF GABAERGIC AND RELATED NMDA RECEPTOR-ACTIVE NEUROSTEROIDS IN NOVEL TREATMENT DEVELOPMENT FOR POSTTRAUMATIC STRESS DISORDER (PTSD)

Ann Rasmusson, Boston University School of Medicine

Individual Abstract: PTSD affects 8.3% of the U.S. population (11.0% of women, 5.4% of men, and higher percentages of those exposed to particularly high-risk trauma, such as combat, sexual assault, and compound community trauma). Trauma-focused psychotherapies, such as Cognitive Processing Therapy and Prolonged Exposure, show general but highly variable efficacy, and many clients do not achieve clinically meaningful improvement. The SSRIs, sertraline and paroxetine, which remain the only FDA-approved medications for PTSD, also show highly variable inter-individual efficacy and have modest overall effect sizes. Both treatment modalities show generally poor efficacy in U.S. active-duty military personnel and veterans. Therefore, based on growing insight into the multiple, interactive, individually variable neurophysiological systems dysregulated in PTSD, precision medicine principles have been embraced in new PTSD treatment development efforts. These efforts involve characterization of individually variable biomarkers to define pre- or early-treatment endophenotypes that predict symptom change while discriminating between clinical responses to active vs. control or placebo treatments. Active and placebo treatment responses in PTSD, however, can be magnified when the 'threat' of trial novelty wears off or if trial participants adventitiously engage in neural processes that promote recovery (e.g., extinction, extinction retention, and cognitive reprocessing). These phenomena may confound drug treatment trials in PTSD generally but pose a particular challenge to development of promising new

GABAergic neurosteroid therapeutics because endogenous GABAergic neurosteroids participate in these phenomena. Such development efforts may be de-risked, however, by considering: 1) Use of mass spectrometry to measure allopregnanolone (Allo) and pregnanolone (PA), as well as their neuroactive beta-isomers and sulfated metabolites (that antagonize NMDA receptors) as supported by pre-clinical and clinical studies showing: a) subpopulation variability in the synthesis of these neurosteroids, and b) a role for all in predicting PTSD treatment response. 2) Sex-specific enzyme deficiencies limit GABAergic neurosteroid synthesis in PTSD. Sex- and reproductive state-specific indices of synthesis deficiency thus may help identify individuals more likely to respond to GABAergic neurosteroid therapeutics. 3) Due to predictable dynamics between central and peripheral GABAergic neurosteroid production, the utility of neurosteroid measurements is increased by controlling for current stress and other activators of de novo neurosteroid synthesis. 4) Individual differences in synthesis of antagonistic 3beta-isomers of Allo and PA shape PTSD symptom profiles and may affect the efficacy of GABAergic neurosteroid-based treatments or change dosing requirements. 5) Timing of GABAergic neurosteroid-based drug dosing may be critical. Raising GABAergic neurosteroid levels may acutely reduce PTSD symptoms but interfere with trauma memory circuit activation, which is critical to PTSD recovery. Well-timed dosing may enhance extinction learning and retention or therapeutically block trauma memory reconsolidation. 6) Efficacy of upstream activators or potentiators of GABAergic neurosteroid synthesis (e.g., monoaminergic and NMDA receptor-active drugs or endocannabinoids) may rely on adequate downstream GABAergic neurosteroid synthetic enzyme function. Measuring GABAergic neurosteroid responses to these agents may help explicate treatment resistance and improve drug targeting.

Learning Objectives:

1. To understand sex differences in enzymatic deficiencies that limit synthesis of GABAergic neurosteroids in PTSD and relevance to the assessment of such deficiencies and the targeting of therapeutics.
2. To understand the potential influence of drug dose and dose-timing on therapeutic effects of neurosteroids used in the treatment of PTSD.

Literature References:

1. Rasmusson, A. M., King, M. W., Valovski, I., Gregor, K., Scioli-Salter, E., Pineles, S. L., ... and Pinna, G. (2019). Relationships between cerebrospinal fluid GABAergic neurosteroid levels and symptom severity in men with PTSD. Psychoneuroendocrinology, 102, 95-1042.

2. Rasmusson, A. M., and Pineles, S. L. (2018).
3. Neurotransmitter, peptide, and steroid hormone abnormalities in PTSD: biological endophenotypes relevant to treatment. Current psychiatry reports, 20(7), 1-20.

CBD IN THE TREATMENT OF POSTTRAUMATIC STRESS DISORDER

Michael Telch, The University of Texas at Austin

Individual Abstract: Approximately 70% of individuals world-wide will experience a trauma during their lifetime and of those approximately 11% will go on to develop a threshold diagnosis of posttraumatic stress disorder. The burden of illness for PTSD is staggering and confers significant interference in work, social functioning, as well as increased risk for other physical and mental health problems. Although trauma-focused psychotherapies for PTSD have been shown to outperform more traditional supportive psychotherapy or

pharmacotherapy, they are associated with high rates of treatment refusal and treatment drop-outs, and highlight the need to develop PTSD treatments that are both effective and more palatable to patients.

Recently, there's been considerable attention paid to the potential therapeutic use of cannabidiol (CBD) products in the treatment of a variety of physical and mental health problems. The endocannabinoid system (ECS) is a logical therapeutic target for combating PTSD and other fear-based disorders given that cannabinoid receptors and other molecular mediators crucial for ECS signaling are richly expressed in a variety of brain regions that govern the regulation of learned fear and defensive behavior.

Mounting evidence from studies primarily with rodents suggests that CBD may confer significant promising health-related benefits including anti-inflammatory, pain-relieving, anti-cancer, and memory enhancement.

Unlike existing pharmacological treatments for PTSD, CBD is unique in that it may have the capacity to attenuate PTSD symptoms through multiple therapeutic pathways including: (1) Stress/anxiety attenuation]; (2) Enhancement of fear extinction learning; 3. Reconsolidation disruption of aversive memories ; and (4) Sleep enhancement.

Several published retrospective case studies have provided some support for the potential therapeutic effects of CBD in the treatment of PTSD and trauma-related disturbance. In a recent prospective randomized open label study with trauma-exposed health care professionals caring for COVID-19 patients, 300 mg of CBD added to standard care led to greater reductions in job burn-out and exhaustion relative to standard care without CBD.

Despite these promising findings, the evidence supporting the efficacy of daily CBD for PTSD is quite weak based on the lack of placebo-controlled RCTs.

This presentation will provide an overview of the scientific evidence supporting the (a) safety, (b) clinical efficacy, and (c) putative therapeutic pathways for the use of CBD in the treatment of posttraumatic stress disorder.

In addition, the talk will briefly review an ongoing 8-week single-site Phase II randomized double-blind placebo-controlled fixed dose clinical trial aimed at (a) comparing the efficacy of an 8-week daily regimen of two distinct CBD oil formulations relative to placebo oil in reducing clinician and patient-rated PTSD symptoms at post treatment and one month follow-up; and (2) assessing whether a broad spectrum formulation of CBD that includes 300 mg of CBD along with other cannabinoids and terpenes confers superior clinical efficacy relative to 300 mg of pure CBD isolate.

Participants recruited throughout the United States (N=150) meeting DSM-5 criteria for posttraumatic stress disorder are randomly assigned to one of three treatment arms: (a) 300 mg. CBD Isolate; (b) 300 mg. CBD Broad Spectrum; and (c) Placebo oil. The primary outcome is the PCL-5 assessed at baseline, posttreatment (Week 9), and follow-up (Week 13). Secondary outcomes including patient-rated PTSD symptoms, depression, sleep disturbance, and Quality of life are assessed weekly throughout the trial. Safety and CBD adherence are assessed daily throughout the trial.

Learning Objectives:

1. Provide an overview of the current evidence supporting the efficacy of CBD in the treatment of PTSD.
2. Provide an overview of the putative therapeutic pathways through which CBD may attenuate PTSD symptoms.

Literature References:

1. Steardo L Jr, Carbone EA, Menculini G, et al.: Endocannabinoid System as Therapeutic Target of PTSD: A Systematic Review [Internet]. Life 2021; 11:214Available from: http://dx.doi.org/10.3390/life11030214
2. Crippa JAS, Zuardi AW, Guimarães FS, et al.: Efficacy and Safety of Cannabidiol Plus Standard Care vs Standard Care Alone for the Treatment of Emotional Exhaustion and Burnout Among Frontline Health Care Workers During the COVID-19 Pandemic: A Randomized Clinical Trial [Internet]. JAMA Netw Open 2021; 4:e2120603Available from: http://dx.doi.org/10.1001/jamanetworkopen.2021.20603

POTENTIAL OF INTRANASAL NEUROPEPTIDE Y FOR PREVENTION AND TREATMENT OF PTSD AND ASSOCIATED NEUROPSYCHIATRIC DISORDERS

Esther Sabban, New York Medical College

Individual Abstract: Neuropeptide Y (NPY) is an endogenous 36 amino acid amidated neuropeptide which is abundantly expressed in the brain and in the periphery. Compelling evidence in animals and humans with a variety of approaches demonstrate that NPY in the brain can provide resilience to development of many stress -elicited symptoms. NPY is emerging as one of the most important regulators mediating resilience to harmful effects of stress. Although NPY has great potential to provide resilience or resistance to harmful effects of stress on the brain, translational studies have been hampered because of its effects in the periphery where NPY is co-released with norepinephrine during sympathetic excitation and enhances the vasoconstrictor effect of norepinephrine as well as that of angiotensin II.

We have carried out preclinical studies to examine if intranasal delivery to the brain can provide non-invasive therapeutics. We have shown that intranasal administration can deliver it to a variety of brain regions involved in mediating the responses to stress. Intranasal NPY was administered shortly before (prophylaxis), immediately after (early intervention) or after several weeks when the symptoms associated with PTSD were already manifested (reversal of symptoms). We found that intranasal NPY delivery to the brain had beneficial effects in reducing or preventing behavioral and molecular changes associated with PTSD. Intranasal administration of NPY prevented the development of many PTSD associated neuroendocrine changes and behaviors, such as hyperarousal, depressive/despair behavior, anxiety, impaired social interaction, extinction of fear memory, etc. This was even more pronounced using a selective NPY receptor subtype 1 (Y1R), but not subtype 2 (Y2R) agonist1d by exposure to the Single Prolonged Stress (SPS) one of the best rodent models of human PTSD.

In addition to preventing development of many of the traumatic stress triggered impairments, by early intervention shortly before or after SPS, we found that intranasal administration of NPY to rats was able to reverse SPS triggered symptoms of anxiety, depressive-like behavior, and hyperarousal when measured as long as one or two weeks after SPS. The reversal of hyperarousal lasted for at least one week after administration of intranasal NPY.

We used radiotelemetry and echocardiography to determine effects of intranasal NPY on cardiovascular functions in absence and presence of stress in SPS model of PTSD. Overall, the results demonstrate no major cardiovascular effects of intranasal NPY and

indicate possible benefit from transient amelioration of HR response in line with its translational potential in combat PTSD and for comorbid impairments.

Interestingly a much higher dose of NPY was required to be effective in females, compared to male, rats and was enhanced by pretreatment with omaragliptin, an inhibitor of DPP4, which would result in reduced degradation of NPY from a pan-NPY receptor agonists, to one does not activate the Y1R, which requires an intact N-terminus.

Two small human clinical trials were performed with intranasal administration of NPY to reverse symptoms of PTSD and depression (Sayed etal, 2018, Mathe et al., 2020). In both NPY was well tolerated. Sayed et al16 performed a dose escalation study with intranasal administration of NPY dissolved in saline to individuals with PTSD. While some encouraging results on anxiety and depression were obtained at the highest dose, they did not reach the maximal tolerated dose.

Further studies are needed to translate the preclinical findings to benefit people exposed to traumatic stress.

Learning Objectives:

1. Advantages of intranasal delivery to the brain.
2. Therapeutic potential of neuropeptide Y for stress-triggered neuropsychiatric disorders.

Literature References:

1. Sabban EL, Alaluf LG, Serova LI. Potential of neuropeptide Y for preventing or treating post-traumatic stress disorder. Neuropeptides. 2016; 56:19-24.
2. Kautz M, Charney DS, Murrough JW. Neuropeptide Y, resilience, and PTSD therapeutics. Neurosci Lett. 2017; 649:164-169.

REVIEW OF THE CURRENT PTSD PIPELINE

George Papakostas, Massachusetts General Hospital

Individual Abstract: Post-traumatic stress disorder (PTSD) can affect approximately one out of three individuals exposed to a traumatic experience and has been associated with significant occupational and social impairment, increased risk of suicide, as well as higher medical and psychiatric co-morbidity. In addition, the prevalence of PTSD has been estimated between 5 and 10%, rendering it as one of the most common Psychiatric conditions. Although trauma-focused therapy is most often recommended as first-line treatment, very few pharmacotherapies have been developed for PTSD. Specifically, of a number of antidepressants and non-antidepressant medications tested in randomized, double-blind, placebo-controlled trials only paroxetine and sertraline have received approval by the U.S. Food and Drug Administration for the treatment of PTSD. Clearly, expanding the treatment armamentarium for clinicians and patients alike is a major priority for the field. Recently, a number of non-monoaminergic neurotransmitter systems have received attention as possible targets to develop novel pharmacotherapies for PTSD. In the present talk, I will review such pertinent leads not discussed by the first three speakers.

Learning Objectives:

1. By the end of this talk, attendees will be able to discuss the potential efficacy of potential leads as novel therapies in posttraumatic stress disorder.
2. By the end of this time, attendees will be able to discuss the relative safety and tolerability of potential leads as novel treatments for posttraumatic stress disorder.

Literature References:

1. Murrough JW, Yaqubi S, Sayed S, Charney DS. Emerging drugs for the treatment of anxiety. Expert Opin Emerg Drugs. 2015 Sep;20(3):393-406. doi: 10.1517/14728214.2015.1049996. Epub 2015 Jun 1. PMID: 26012843; PMCID: PMC4869976.
2. Lago TR, Brownstein MJ, Page E, Beydler E, Manbeck A, Beale A, Roberts C, Balderston N, Damiano E, Pineles SL, Simon N, Ernst M, Grillon C. The novel vasopressin receptor (V1aR) antagonist SRX246 reduces anxiety in an experimental model in humans: a randomized proof-of-concept study. Psychopharmacology (Berl). 2021 Sep;238(9):2393-2403. doi: 10.1007/s00213-021-05861-4. Epub 2021 May 10. PMID: 33970290; PMCID: PMC8376758.

MAJOR DEPRESSIVE DISORDER WITH INSOMNIA SYMPTOMS: CHARACTERIZING CLINICAL BURDEN AND ELUCIDATING BIOLOGICAL MECHANISMS TO DRIVE NOVEL TREATMENT DEVELOPMENT

Manish Jha, University of Texas Southwestern Medical Center

Overall Abstract: Major Depressive Disorder (MDD) is a widely prevalent and chronically disabling illness that affects one in five adults in the United States during their lifetime. Burden of MDD is compounded by the limited efficacy of currently available antidepressants. The landmark Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study showed that only one in three adults with MDD attain remission with the initial antidepressant treatment. Furthermore, STAR*D found that symptoms of insomnia were common in adults with MDD even after symptomatic remission and were associated with higher likelihood of relapse. The proposed panel of diverse presenters from various backgrounds (academia, industry and NIH) will cover a broad range of topics about insomnia/sleep disturbances in MDD.

The first presentation will focus on the burden of moderate or severe insomnia using data from the 2019 United State (US) National Health and Wellness Survey (NHWS). This cross-sectional survey included 75,000+ respondents who were representative of the US population. The study found that individuals with MDD and moderate/severe insomnia (MDDIS) had significantly greater impairments in work productivity and non-work-related daily activities, poorer quality of life and higher levels of depressive and anxiety symptoms. Furthermore, in individuals with MDD, higher levels of insomnia were associated with higher levels of anxiety, depression, daytime sleepiness, absenteeism, presenteeism, and overall work productivity impairments. The second presentation will focus on data from an NIMH-funded study of sertraline versus placebo and characterized individuals as those without any insomnia, those with mild insomnia, and those with MDDIS. The study found that difference in remission rates with sertraline vs. placebo was markedly higher in the MDDIS group as compared to no insomnia or mild insomnia groups. Furthermore, presence of MDDIS was associated with distinct abnormalities in reward processing in hippocampal region. The third and final presentation will characterize the links between sleep disturbances and suicidal ideation in adults with MDD. Specifically, the role of sleep-related hyperarousal process in increasing suicide risk will be discussed along with potential of targeting these processes for development of novel treatments. The discussant will engage the panelists and audience in a conversation

around the presented findings and how currently available treatments as well as those in development may mitigate the burden associated with MDDIS.

Learning Objectives:

1. Identify the presence of moderate/severe insomnia symptoms in patients with major depressive disorder.
2. Understand the burden associated with MDDIS and biological mechanisms that can serve as targets for development of novel treatments.

SUICIDE IDEATION, NOCTURNAL WAKEFULNESS AND KETAMINE

Elizabeth Ballard, National Institute of Mental Health

Individual Abstract: While there is a robust research literature linking MDD to insomnia, a growing research literature has suggested that sleep difficulties also represent a critical risk factor for suicidal thoughts, attempts and deaths. This presentation will focus on the neurobiological link between sleep difficulties, characterized by nocturnal wakefulness and hyperarousal, and suicide risk. Previous work by our group has demonstrated that polysomnography (PSG)-determined nocturnal wakefulness is associated with next-day suicidal thoughts and this relationship is normalized by ketamine administration; such that suicide ideation (SI) responders to ketamine demonstrate decreased nocturnal wakefulness the night after ketamine administration. More recently, our group has established that oscillations in overnight beta power, as evaluated using a functional data analytic approach, are associated with next-day SI, suggestive of a sleep-related hyperarousal process associated with suicide risk. Furthermore, in placebo-controlled trials of patients with treatment-resistant depression, ketamine administration is associated with changes in beta oscillations, highlighting the potential role of ketamine in reducing sleep-related hyperarousal. Further discussion of the role of sleep in the antidepressant and antisuicidal response to ketamine will be presented.

Learning Objectives:

1. By the end of this presentation, audience members will be able to describe the research connecting sleep research to suicide risk.
2. By the end of this presentation, audience members will be able to explain the effects of ketamine on sleep-related processes.

Literature References:

1. Vande Voort JL, Ballard ED, Luckenbaugh DA, et al. Antisuicidal Response Following Ketamine Infusion Is Associated With Decreased Nighttime Wakefulness in Major Depressive Disorder and Bipolar Disorder. J Clin Psychiatry. 2017;78(8):1068-1074.
2. Ballard ED, Greenstein D, Duncan WD, Hejazi N, Gerner J, Zarate CA JR. The Dynamic Relationship Between Alpha and Beta Power and Next-Day Suicidal Ideation in Individuals with Treatment-Resistant Depression. Biological Psychiatry: GOS, In Press.

THE IMPACT OF INSOMNIA SYMPTOMS ON CLINICAL AND PATIENT-CENTRIC OUTCOMES IN MAJOR DEPRESSIVE DISORDER: FINDINGS FROM THE NATIONAL HEALTH AND WELLNESS SURVEY

Kruti Joshi, Janssen Scientific Affairs, LLC

Individual Abstract: Background and Objective: Insomnia is one of the criterion symptoms of major depressive disorder (MDD). The landmark Sequenced Alternatives to Relive Depression (STAR*D) found that 85% of treatment seeking outpatients with MDD have significant insomnia symptoms, and the presence of insomnia symptoms was associated with more severe depressive symptoms. Given that MDD is often undiagnosed and untreated in the United States (US), there is an urgent need to characterize the burden of insomnia among patients with MDD at the population level. Furthermore, data on the impact of insomnia symptoms on patient-centric outcomes such as work- and non-work-related productivity and health-related quality of life (HRQoL) in patients with MDD is limited. Therefore, we used data from the 2019 US National Health and Wellness Survey to assess the impact of insomnia symptoms on clinical and patient-centric outcomes.

Methods: Two complementary approaches were used on the retrospective data from the 2019 National Health and Wellness Survey. The first approach categorized respondents of NHWS as follows: 1) respondents with MDD and moderate or severe insomnia symptoms (MDDIS; Insomnia Severity Index [ISI] score ≥15); 2) adults with MDD and no or mild insomnia symptoms (other-MDD; either insomnia not experienced in past 12 months or ISI score <15); and 3) adults in the general US population without MDD (non-MDD). Matched bivariate and multivariable analyses assessed each clinical and patient-centric outcome as a function of depression and insomnia status. The second approach was limited to respondents with MDD and assessed the relationship between severity of insomnia symptoms (ISI score) as a continuous measure and health outcomes. Multivariable analyses assessed the association of ISI score with clinical and patient-centric outcomes, while controlling for depression severity and other covariates.

Results: Findings from the first (categorical) approach: Of 74,994 respondents, 2,045 (2.7%) were identified with MDDIS. After adjustments for matching criteria, MDDIS respondents reported greater depression severity (measured by 9-item Patient Health Questionnaire) than other-MDD (n=4,090) and non-MDD (n=4,090) respondents ($p<0.001$). After adjustment for covariates, including depression severity, respondents with MDDIS reported significantly more absenteeism, presenteeism, work impairment, and activity impairment than other-MDD and non-MDD respondents (all $p<0.05$). Compared to non-MDD respondents, MDDIS respondents reported lower mental and physical health functioning, and poorer health-related quality of life (HRQoL) (all $p<0.05$).

Findings from the second (continuous) approach: The mean ISI score was 15.8 (range 0-28) (n=3,278); higher ISI was associated with greater depression severity ($r=0.49$, $p<0.001$). After adjustments, higher ISI scores were significantly associated with higher levels of anxiety and daytime sleepiness, greater absenteeism, greater presenteeism, greater overall work productivity impairment, and greater non-work-related activity impairment, as well as poorer mental and physical functioning, and poorer health-related quality of life (all $p<0.01$).

Conclusions: This study highlights the burden of MDDIS, with greater work and activity impairment observed than with other-MDD, and lower HRQoL and greater work and activity impairment and healthcare resource use than observed with non-MDD. Additionally, it identified that the higher levels of insomnia symptoms are associated with worse health-related outcomes.

Learning Objectives:

1. Identify insomnia as a key feature of illness in patients with MDD.

2. Understand burden of insomnia symptoms on clinical and patient-centered outcomes.

Literature References:

1. Sunderajan P, Gaynes BN, Wisniewski SR, Miyahara S, Fava M, Akingbala F, DeVeaugh-Geiss J, Rush AJ, Trivedi MH. Insomnia in patients with depression: a STAR*D report. CNS Spectr. 2010;15:394-404.
2. Zhdanava M, Pilon D, Ghelerter I, Chow W, Joshi K, Lefebvre P, Sheehan JJ. The Prevalence and National Burden of Treatment-Resistant Depression and Major Depressive Disorder in the United States. The Journal of clinical psychiatry. 2021;82.

ABERRANT REWARD FUNCTION IN ADULTS WITH MAJOR DEPRESSIVE DISORDER AND MODERATE/SEVERE INSOMNIA AND ASSOCIATION WITH ACUTE-PHASE TREATMENT OUTCOMES

Manish Jha, University of Texas Southwestern Medical Center

Individual Abstract: Objective: Insomnia is a common feature of major depressive disorder (MDD) and persistence of insomnia after initial treatment response is linked to poor antidepressant outcomes. In this report, we evaluated whether presence of moderate/severe insomnia is associated with aberrant reward neurocircuitry and predicts differential outcomes to antidepressant versus placebo.

Methods: Participants of the Establishing Moderators and Biosignatures of Antidepressant Response in Clinical Care (EMBARC) study with reward task-based functional magnetic resonance imaging (fMRI) data available were included (n=296). Insomnia was assessed with the first three items of the Quick Inventory of Depressive Symptomatology Self-Report (QIDS-SR) scale. Participants were categorized as follows: no insomnia (scores ≤1 on all three insomnia items of QIDS-SR), mild insomnia (score of ≤5 on the sum of three QIDS-SR insomnia items), and moderate/severe insomnia (score ≥6 on the sum of three QIDS-SR insomnia items). Reward circuit functioning was assessed with a validated reward task where participants completed 24 trials of a game of chance. In 12 trials, money was lost for a wrong guess but not gained for a correct guess. In the other 12 trials, money was gained for a correct guess but not lost for a wrong guess. This allows measurement of a participant's differential brain activation to punishing vs. rewarding trials (reward expectancy, RE). RE contrasts were obtained for 121 regions of interest based on functional parcellation of the 7 major cortical networks [default mode (DMN), dorsal attention (DAN), executive control (ECN), limbic (LN), somatomotor (SMN), salience (SN), and visual (VN)], the striatum, amygdala, thalamus, and hippocampus. Remission, defined as 17-item Hamilton Depression Rating Scale (HAMD-17), was the primary outcome measure.

Results: Of the 296 participants with MDD in EMBARC study, 47 (15.9%), 145 (49.0%), and 104 (35.1%) has no, mild, and moderate/severe insomnia, respectively. Those with MDDIS were older in age [mean (SD) = 39.6 (14.0) years] as compared to those with mild [mean (SD) = 36.9 (13.3) years] or no [mean (SD) = 32.0 (10.1) years] insomnia. Activation in bilateral hippocampal regions during reward expectancy (differential brain activation to punishing vs. rewarding trials) were significantly lower in those with moderate/severe insomnia as compared to those with mild or no insomnia. Remission rates overall were markedly lower in those with moderate/severe insomnia (29.6%) as compared to those with mild (34.1%) or no (50%) insomnia. However, difference in remission rates with sertraline vs. placebo were higher in

those with moderate/severe insomnia (37.8% vs. 22.6%) as compared to those with mild (32.8% vs. 35.3%) or no (46.2% vs. 55.0%).

Conclusion: Presence of moderate/severe insomnia in adults with MDD is associated with reduced hippocampal activation during monetary reward anticipation and is associated with poorer acute-phase treatment outcomes.

Learning Objectives:

1. Identify the aberrant neurocircuitry that is associated with moderate/severe insomnia symptoms in adults with major depressive disorder.
2. Understand the impact of pre-treatment insomnia on acute-phase treatment outcomes.

Literature References:

1. Trivedi MH, McGrath PJ, Fava M, Parsey RV, Kurian BT, Phillips ML, Oquendo MA, Bruder G, Pizzagalli D, Toups M, Cooper C, Adams P, Weyandt S, Morris DW, Grannemann BD, Ogden RT, Buckner R, McInnis M, Kraemer HC, Petkova E, Carmody TJ, Weissman MM. Establishing moderators and biosignatures of antidepressant response in clinical care (EMBARC): Rationale and design. Journal of psychiatric research. 2016;78:11-23.
2. Mason BL, Davidov A, Minhajuddin A, Trivedi MH. Focusing on insomnia symptoms to better understand depression: A STAR*D report. Journal of affective disorders. 2020;260:183-186.

*DIFFERENTIAL DIAGNOSIS OF BIPOLAR II DISORDER: WHAT DO WE KNOW AND WHAT DOES IT MEAN FOR AN EXPERT BY EXPERIENCE

Trisha Suppes, Stanford University

Overall Abstract: This symposium focuses on the differential diagnosis of bipolar II disorder (BD II). While this may seem an old topic, there continues to be difficulty and controversy around diagnosis of this bipolar phenotype, plaguing clinicians, and researchers alike. Potential confounds include bipolar spectrum disorders, including the DSM-5 diagnosis of major depression disorder (MDD) with mixed features and borderline personality disorder (BPD). The first talk will include an overview of BD II and strategies for distinguishing BD II from MDD with mixed features; the speaker will highlight pertinent changes noted in the recently released DSM-5-TR (expected release, May 2022; speaker: H.Swartz). The second talk will focus on distinguishing BD II from BPD, with a review of data supporting both misdiagnosis and overdiagnosis of both conditions (speaker: M. Zimmerman). Both speakers will discuss implications for treatment, expected course of illness, and entry into clinical trials. The third talk will be given by someone who has personally experienced several key issues relevant to the differential diagnosis of BD II. The perspective of an individual who has lived experience with BD II gives this topic added urgency and provides voice for those for whom research, treatment, diagnoses, and regulations are developed (speaker: S. Schley). The discussant for this symposium will be Dr. Trisha Suppes who has written and studied extensively on these topics.

Learning Objectives:

1. Understand the differential diagnosis of bipolar II and major depression disorder.
2. Be able to discuss how borderline personality disorder differs from bipolar II disorder.

BIPOLAR II DISORDER AND MAJOR DEPRESSIVE DISORDER WITH MIXED FEATURES: THE SAME OR DIFFERENT?

Holly Swartz, University of Pittsburgh School of Medicine

Individual Abstract: This presentation will focus on an overview of the nosology of bipolar II disorder and major depressive episodes with mixed features. It will explore areas of overlap, differences, and implications for treatment.

Bipolar disorder is a cyclical illness characterized by alternating episodes of mania or hypomania with depression, which are expressed as changes in energy levels and behavior. Patients are classified as having bipolar I disorder if they experience at least one manic episode in their lifetime. Bipolar II disorder (BD II) is diagnosed in patients who have at least one major depressive episode and one hypomanic episode. Although mania and hypomania are the main features used to diagnose bipolar disorder, depressive episodes are more prevalent. On average, patients with BD II spend between 32% and 50% of their time depressed, as compared with only 1-9% of the time in hypomanic episodes. As a result, diagnostic confusion often ensues when patients present in the context of a major depressive episode (MDE), a problem made worse when the episode is characterized by the presence of co-occurring mixed features—i.e., symptoms of opposite polarity to depression.

Although debate continues on how best to characterize MDE with mixed features, DSM 5 defines this state as meeting full syndromal criteria for MDE plus three additional non-overlapping (i.e., non-overlapping among hypomania, mania, and depression) symptoms. Traditionally, mixed states have been associated with greater illness complexity and worse treatment outcomes. Although some have argued that that having as few as one symptom of opposite polarity in the context of MDE merits the mixed designation, DSM-5 and now DSM-5-TR take the conservative position that the presence of 3 non-overlapping symptoms limits case-definition and decreases risk of non-specificity. Detractors argue that this definition may be too stringent and, when diagnosed in the context of a major depressive disorder (MDD), is more likely to identify those who eventually progress to a diagnosis of bipolar disorder. There is also a broader debate about the specificity of MDD with mixed features specifier, its relationship to BD II (or the bipolar spectrum), and whether medications for MDD without mixed features should be different than for MDD with mixed features. To date, there is a paucity of trials to inform clinical decision making in this population. There are two randomized controlled trials of pharmacotherapy in patients will well-defined MDE with mixed features, both comparing second generation antipsychotics (ziprasidone and lurasidone) to placebo. Both trials were positive, suggesting promise for this approach, although notably the ziprasidone sample included individuals with both MDD and BD II. By contrast, there are no randomized controlled trials of antidepressant monotherapy for MDE with mixed features.

Should we consider MDD with mixed features a stop along an inevitable developmental trajectory towards bipolar disorder or a diagnostic entity distinct from it? Much uncertainty persists around these conceptual frameworks, despite a pressing clinical need for clarification. Much more information is needed about treatment options. Further, individuals who initially present with MDE with mixed features would like to know whether they are at increased risk for progressing to a bipolar disorder. This discussion will highlight what is known and not know about these important clinical issues.

Learning Objectives:
Upon completion of this activity, participants will be able to:

1. Distinguish between major depressive disorder with mixed features and bipolar II disorder.
2. Discuss risk profiles of using antidepressant and antipsychotic medications to treat major depressive episodes with mixed features.

Literature References:

1. McIntyre RS, Soczynska JK, Cha DS, Woldeyohannes HO, Dale RS, Alsuwaidan MT, Gallagher LA, Mansur RB, Muzina DJ, Carvalho A, Kennedy SH. The prevalence and illness characteristics of DSM-5-defined "mixed feature specifier" in adults with major depressive disorder and bipolar disorder: Results from the International Mood Disorders Collaborative Project; Journal of Affective Disorders 2015; 172:259-264
2. McElroy SL, Guerdjikova AI, and Romo-Nava F (2021). Diagnosing and treating major depressive episodes that lie along the mood disorders spectrum: focus on depression with mixed features. CNS Spectrums 26(2), 133–139.

DIAGNOSING BIPOLAR DISORDER AND BORDERLINE PERSONALITY DISORDER

Mark Zimmerman, Brown University

Individual Abstract: Both bipolar disorder and borderline personality disorder (BPD) are significant public health problems. Both disorders are associated with impaired functioning, increased use of health care services, increased rates of anxiety and substance use disorders, and suicidality. Patients with bipolar disorder or BPD most commonly present for the treatment of depression, therefore, it is not surprising that both disorders are frequently underdiagnosed. Calls for improved recognition have been voiced for both disorders.

For years there has been controversy as to how to conceptualize the relationship between bipolar disorder and BPD. Some authors suggested that BPD is part of the bipolar spectrum. Several review articles summarized the evidence in support of and opposition to the hypothesis that BPD belongs to the bipolar spectrum, with most of the recent reviews having concluded that BPD and bipolar disorder are valid and distinct diagnostic entities. A growing body of research that directly compares patients with BPD and bipolar disorder has demonstrated that patients with the 2 disorders differ in clinical characteristics, frequency of suicide attempts, neurobiological substrates, neuropsychological profiles, maladaptive self-schemas, temperament, and history of childhood abuse and neglect. In this presentation I will review clinical features that can be used to help distinguish patients with bipolar disorder and BPD and will discuss how screening for these disorders might or might assist with differential diagnosis.

Learning Objectives:

1. Improve diagnostic accuracy of bipolar disorder and borderline personality disorder.
2. Understand the advantages and limitations of screening for bipolar disorder and borderline personality disorder.

Literature References:

1. Zimmerman M, Balling C, Dalrymple K and Chelminski I (2019). Screening for borderline personality disorder in psychiatric outpatients with major depressive disorder and bipolar disorder. Journal of Clinical Psychiatry 80, e1-e6.
2. Zimmerman M and Morgan TA (2013). The relationship between borderline personality disorder and bipolar disorder. Dialogues in Clinical Neuroscience 15, 79-93.

***INSIGHTS FROM AN "EXPERT BY EXPERIENCE" WHO HAS LIVED WITH BIPOLAR II FOR FOUR DECADES**

Sara Schley, B Corp

Individual Abstract: Bipolar II disorder and related bipolar spectrum illnesses are easily misdiagnosed and misunderstood. The average time for diagnosis is 11 years. In the interim people suffer with a brutal disease that wreaks havoc on all aspects of their lives. Yet, with a proper diagnosis and rigorous attention to brain health, it is possible to live fully and with vitality with this disease.

This presentation will provide a first person narrative from someone who has lived with bipolar II disorder for four decades and is (at least) a 3rd generation survivor. It will discuss years of misdiagnosis, perils of antidepressant monotherapy, and the lack of understanding about bipolar spectrum disorders in the psychiatric community. It will also offer a comprehensive account of "practices for a healthy brain," disciplines that have been helpful on a personal journey toward wellness and that anyone can implement to live a full and vital life.

Learning Objectives:

At the end of this presentation, participants will:

1. Recognize the toll that misdiagnosis and mistreatment of bipolar II disorder takes on someone who has lived experience with the illness.
2. Develop familiarity with self-help practices for wellness that have been useful for one individual with bipolar II disorder.

Literature References:

1. Swartz HA, Suppes T., eds. Bipolar II Disorder: Recognition, Understanding and Treatment. Washington, D.C.: American Psychiatric Association Publishing, 2019.
2. Schley, Sara, BrainStorm: From Broken to Blessed on the Bipolar Spectrum. Wendell, MA, Bear Mountain Press, 2021

Pharmaceutical Pipelines

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

BRAINSONIX TECHNOLOGY OF LOW INTENSITY FOCUSED ULTRASOUND PULSE (LIFUP) FOR TARGETED TRANSCRANIAL NEUROMODULATION AND DELIVERY OF BIOLOGICAL SUBSTANCES IN THE BRAIN

Alexander Bystritsky*[1], *Sheldon Jordan*[2]

[1]UCLA Semel Institute for Neuroscience and Human Behavior, [2]University of California, Synaptec Network, Inc., Neurological Associates - The Interventional Group

Abstract: Brainsonix Technology of Low Intensity Focused Ultrasound Pulse (LIFUP) for targeted transcranial neuromodulation and delivery of biological substances in the brain.
Transcranial Focused Ultrasound (tFUS) is one of the rapidly developing areas in brain research and clinical sciences. High Intensity Focused Ultrasound is used as a surgical intervention by heating precise areas of the brain within the skull. Approximately 20 years ago, the founder of Brainsonix and UCLA professor Alexander Bystritsky filed the first patent proposing that Low Intensity (tFUS or LIFUP) administered as a train of impulses could alter neuronal conductivity and firing of neurons. After a series of animal research at UCLA and Brigham and Women's Hospital demonstrating that ultrasonic pulses can activate and inhibit the neurons, several other patents were filed. These patents were the grounds on which Brainsonix and the experimental device were created.

The Brainsonix Corp. device Bx Pulsar1002 is fully MRI compatible and was used in several IDE-driven human clinical trials. The investigational device has been used for brain mapping and altering pain threshold in volunteers and in several experimental clinical trials in humans including epilepsy, coma, anxiety, OCD, and Alzheimer's Disease. The main targets of the stimulation were the amygdala, temporal lobe, thalamus, ventral capsule of the ventral striatum (VCVS), and hippocampus. No significant side effects were found in any of the trials, and preliminary results have been particularly promising for the reduction of anxiety and obsessive-compulsive (OCD) symptoms. For example, in the treatment-resistant generalized anxiety disorder (GAD) open-label trial the sonication of the right amygdala was performed and caused a significant reduction (35% or more) of anxiety symptoms measured by the Beck Anxiety Inventory in 11 out of 14 patients. The preliminary trial of stimulation in VCVS in the treatment-resistant OCD, which is the usual site for deep brain stimulation, demonstrated significant improvement of OCD symptoms as measured by Yale-Brown OCD Scale (YBOCS). In this small open-label clinical trial 4 patients out of 6 demonstrated significant improvement in YBOCS scores and in 3 of them the reduction of the symptoms exceeded 35% from the baseline. The company is about to start a pivotal trial for the treatment of coma under the FDA Break-Through, Fast Track program. Also, using grants from Tiny Blue Dot Foundation and the Breakthrough Award from International Obsessive-Compulsive Disorders Foundation (IOCDF), investigators in Harvard, Baylor, and the Medical University of Southern Carolina are starting sham-controlled pilot trials in treatment-resistant OCD and GAD. Synaptec Research, Inc. holds patents on using low-intensity tFUS for biologicals and drug deliveries in specific areas of the brain across the blood-brain barrier. Brainsonix Corp. in collaboration with Synaptec Research Inc. started a series of animal experiments demonstrating the feasibility of delivering exosomes to the brain. In a collaboration with the City of Hope, Brainsonix, and Synaptic Research, the Bx Pulsar 1002 device was used to demonstrate selectively increased concentration of an I.V. infused radiotracer within a rat brain target (sized on the order of millimeters). The clinical applications are endless for a technology that can non-invasively neuromodulate deep areas of the brain and deliver small molecules to precise brain targets.

AURICULAR TRANSCUTANEOUS HI-FREQUENCY E-MMUNOTHERAPY SEQUENCES (ATHENS) FOR MAJOR DEPRESSIVE DISORDER (MDD) WITH PERIPARTUM ONSET WITH AND WITHOUT CONCOMITANT ANTIDEPRESSANT USE: A MULTICENTER, OPEN-LABEL PILOT STUDY

Kristina Deligiannidis*[1], *Thalia Robakis[2], Sarah Homitsky[3], Erona Ibroci[2], Bridget King[2], Sunu Jacob[4], Diana Coppola[1], Shane Raines[4], Konstantinos Alataris[5]*

[1]Zucker Hillside Hospital, [2]Icahn School of Medicine at Mount Sinai, [3]Women's Behavioral Health at Allegheny Health Network, [4]2b Analytics, [5]Nesos Corp.

Abstract: Background: Peripartum depression (PPD) has a high prevalence in the U.S. (~13%) and often goes untreated/undertreated. Invasive vagus nerve stimulation is FDA-approved for treatment-resistant depression but carries the risks of surgery and stimulation of the vagus nerve efferent fibers (1, 2). We conducted a multicenter, open-label, proof-of-concept trial to assess safety and preliminary efficacy of ATHENS, a non-invasive high frequency auricular vagus nerve therapy, for treatment of adult females with PPD.

Methods: Women (n=25), ages 18–45, within 9 months postpartum, diagnosed with PPD were enrolled at 3 sites. The study included 6 weeks of open-label therapy (15 minutes/day) and 2 weeks of observation (no treatment; Weeks 7 and 8). Safety and tolerability were assessed by adverse event (AE) reports. Efficacy outcomes included change from baseline (CFB) in Hamilton Rating Scale for Depression (HAM-D17) total scores, HAM-D17 response and remission, Hamilton Anxiety Rating Scale (HAM-A), Edinburgh Postnatal Depression Scale (EPDS), Generalized Anxiety Disorder Scale (GAD-7) total scores and patient and clinician global impression of change (PGIC, CGIC) scores. Baseline characteristics are reported as mean with standard deviation (SD). Efficacy outcomes were analyzed using mixed-effects models for repeated measures with CFB reported as least squares (LS) mean with standard error (SE).

Results: Of the 25 women who met eligibility criteria and were enrolled into the 6-week treatment phase, 24 completed the 8-week study and 1 discontinued due to noncompliance with the therapy. At baseline, mean (SD) age was 33.7 (3.9) years, mean (SD) HAM-D17 total score was 18.4 (5.3), and 10 (40%) were on a stable dose of antidepressant medication. Baseline HAM-D17 total score was similar for those on (17.8) vs off (18.9) antidepressants. For the 23 participants with data available at Week 6, LS mean (SE) CFB in HAM-D17 total score was 9.7 (0.87) overall, -8.7 (1.24) for those on antidepressants (n=8), and -10.3 (1.14) for those off antidepressants (n=15); response and remission were achieved by 74% and 61% of women overall respectively, 75% and 75% of women on antidepressants, and 73% and 53% of women off antidepressants. LS mean (SE) CFB in the overall population at Week 6 for the secondary outcome measures were 7.6 (0.88) for HAM-A, 6.6 (0.48) for GAD-7, and 7.9 (0.75) for EPDS. Of participants with PGIC/CGIC/satisfaction data available at Week 6, at least some improvement in condition was reported by 21/22 (95%) clinicians on CGIC and 22/23 (96%) participants on PGIC; 20/23 (87%) participants reported device satisfaction. A total of 21 AEs occurred in 13/25 (52%) participants, with 12 deemed treatment-related. None led to discontinuation, and all resolved without intervention. The most common AEs (≥5%) were discomfort (n=5), headache (n=3), and dizziness (n=2). No serious AEs or deaths occurred.

Conclusion: While further evaluation in larger sham-controlled studies is needed, results from this open-label proof-of-concept study suggest that the Nēsos ATHENS based therapy is well

tolerated in postpartum women, with or without concomitant antidepressant use, and may be an effective non-invasive, nonpharmacological treatment option for MDD with peripartum onset.

EMERGING PROFILE OF TAAR1 AGONIST ULOTARONT: PRECLINICAL AND CLINICAL EVIDENCE FOR AN EMERGING PHARMACOLOGICAL CLASS

Seth C. Hopkins*[1]

[1]*Sunovion Pharmaceuticals, Inc.*

Abstract: Background: Ulotaront is a TAAR1 agonist with serotonin 5-HT1A agonist activity, distinguished from current antipsychotics by lack of D2 and 5-HT2A receptor blockade. Results of Phase 2 trials in schizophrenia support the efficacy and safety of ulotaront, which has received FDA Breakthrough Therapy designation in the treatment of schizophrenia. The WHO has assigned ulotaront the INN naming convention specifying the "-taront" stem common to the pharmacological class of TAAR1 agonists. Here we update ongoing research characterizing ulotaront as a member of the new pharmacological class of TAAR1 agonists.
Methods: Several preclinical studies were conducted to investigate the effect of ulotaront in rodent models of schizophrenia, weight gain and hyperglycemia. Also presented are new human studies, including clinical pharmacology results, analyses of negative symptom change in subjects enriched for having the Marder PANSS negative symptom (MPNS) construct, and new analyses of the safety of ulotaront relative to the adverse events expected for the dopamine D2-class effects in spontaneous reports in FAERS (FDA Adverse Event Reporting System).

Results: In a translational, PET-based mouse model of presynaptic dopamine dysfunction, treatment with ulotaront significantly reduced ketamine-induced elevation of striatal dopamine synthesis capacity. In a series of metabolic studies, ulotaront treatment in rats on high fat diet resulted in a dose-dependent reduction in body weight, food intake and liver triglycerides. Ulotaront also reversed olanzapine- and corticosterone-induced weight gain in rats and mice, respectively. In addition, acute ulotaront treatment dose-dependently reduced plasma glucose excursion in naive and diabetic mice during an oral glucose tolerance test, likely driven by TAAR1-mediated inhibition of gastric emptying. The beneficial metabolic effects may reflect peripheral TAAR1 activation and/or direct modulation of homeostatic and hedonic neurocircuits regulating energy balance. In clinical pharmacology studies ulotaront was well-absorbed with a median time to peak concentration of 2.8 hours. Ulotaront was eliminated primarily via hepatic clearance with an effective half-life of 7 hours. In vitro studies indicated ulotaront was a substrate of CYP2D6 hepatic enzyme. A clinical DDI study with co-administration of paroxetine as a CYP2D6 inhibitor increased ulotaront Cmax and AUC0-inf by approximately 30% and 70%, respectively. In clinical trials of acute schizophrenia, subjects enriched for the maximum amount of variance explained on the Marder PANSS negative symptom (MPNS) construct prior to randomization went on to achieve an endpoint MPNS factor score effect size of approximately 0.8. In clinical studies, ulotaront demonstrated markedly lower cumulative risk for the FAERS-defined dopamine D2 class-related adverse events (AEs) compared with atypical antipsychotics.

Discussion: The implications of the preclinical and clinical findings of the TAAR1 agonist ulotaront will be discussed, most notably the targeted attenuation of elevated striatal dopamine

synthesis capacity characteristic of schizophrenia, the enhanced effect in treating negative symptoms in schizophrenia, the clinical pharmacology, and the unique AE profile that differs markedly from the class-specific AE profile for atypical antipsychotics.

A PHASE 1/2 TRIAL OF GH001, A VAPORIZED 5-METHOXY-N,N-DIMETHYLTRYPTAMINE FORMULATION, IN PATIENTS WITH TREATMENT-RESISTANT DEPRESSION

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Abstract: Introduction: 5-Methoxy-N,N-dimethyltryptamine (5-MeO-DMT) is a potent, fast-acting, naturally-occurring psychoactive tryptamine, acting at both the 5-HT1A and the 5-HT2A receptor, with higher affinity for the 5-HT1A receptor subtype. GH001 is a vaporized 5-MeO-DMT formulation administered via a proprietary inhalation approach. Administration of GH001 was observed to be well tolerated in two completed Phase 1 healthy volunteer trials (GH001-HV-101 and GH001-HV-103). Here we report the results of a Phase 1/2 trial (GH001-TRD-102) to investigate the safety and potential anti-depressant effects of GH001 in adult patients with treatment-resistant depression (TRD).

Methods: The Phase 1 part (n=8) of the trial investigated two single dose levels of GH001 (12 mg, 18 mg) with a primary endpoint of safety, and the Phase 2 part (n=8) investigated an individualized dosing regimen (IDR) with up to three increasing doses of GH001 (6 mg, 12 mg and 18 mg) within a single day, with a primary endpoint of efficacy, as assessed by the proportion of patients in remission (MADRS ≤ 10) on day 7. In the IDR, the second and third doses were only administered if the patient did not achieve a peak experience (PE) at the previously administered dose. Occurrence of a PE was assessed using a novel PE scale, configured as a set of 3 visual analogue scales ranging from 0 to 100. Any prior psychoactive medication was discontinued, and a washout period observed before GH001 dosing. Patients were monitored on the dosing day, with additional follow-up visits on day 1 and day 7.

Results: In the Phase 1 part, 4 patients received 12 mg and 4 patients received 18 mg of GH001. The median age was 29 years and the median baseline MADRS was 33. In the Phase 2 part using the IDR, 6 patients received 6 mg and 12 mg of GH001 and 2 patients received 6 mg, 12 mg and 18 mg of GH001. The median age was 34 years and the median baseline MADRS was 32. All patients completed all visits. Administration of GH001 via inhalation was well tolerated in both parts of the trial with no severe or serious adverse events for the single dose levels and the IDR. Compared with the single dose results, the GH001 IDR increased the rate of PE and increased the mean PE score achieved. The proportion of patients with MADRS remission (MADRS≤10) at day 7 was 2/4 (50%) and 1/4 (25%) in the 12 mg and 18 mg groups of Phase 1, respectively, and 7/8 (87.5%) in the IDR group of Phase 2, meeting its primary endpoint ($p<0.0001$). All remissions were observed from day 1, with 7 of 10 remissions observed from 2 hours. The mean MADRS change from baseline to day 7 was -21.0 (-65%) and -12.8 (-41%) for the 12 and 18 mg groups, respectively, and -24.4 (-76%) for the IDR.

Conclusions: Administration of GH001 to a cohort of 16 patients with TRD was well tolerated and provided potent and ultra-rapid antidepressant effects. Individualized dosing with up to three doses on a single day was superior to single dose administration.

COMP360 PSILOCYBIN THERAPY IN TREATMENT-RESISTANT DEPRESSION: RESULTS OF A LARGE RANDOMIZED CONTROLLED PHASE IIB MONOTHERAPY STUDY AND AN EXPLORATORY UNCONTROLLED ADJUNCTIVE THERAPY STUDY

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Abstract: Background: COMP360 is a synthetic, purified form of psilocybin in development for treatment of patients with treatment-resistant depression (TRD). COMP360 psilocybin therapy is an integrated therapy that includes oral COMP360 administration with psychological support. It has received FDA designation as a breakthrough therapy.
Methods: COMPASS Pathways has completed two studies of COMP360 in participants with TRD. The first was a randomized double-blind controlled study that evaluated the efficacy and safety of a single treatment of COMP360 monotherapy at doses of 25 mg, 10 mg, and 1 mg. Participants were required to down-taper within 4 weeks and stop completely for 2 weeks any prior antidepressant treatments before COMP360 administration. The follow-up period was 12 weeks, with evaluations at Day 2 and Weeks 1, 3, 6, 9, and 12. The second study was an open-label trial that explored the effect of a single treatment of COMP360 25 mg adjunctive to an ongoing serotonergic antidepressant. The follow-up period was 3 weeks, with evaluations at Day 2 and Weeks 1, 2, and 3. In both studies, the primary endpoint was change from Baseline to Week 3 in Montgomery-Asberg Depression Rating Scale (MADRS) total score.

Results: The monotherapy study randomized 233 participants to 25 mg (n=79), 10 mg (n=75), and 1 mg (n=79) treatment groups. Dose-related improvements were evident at Day 2. At Week 3 primary endpoint, observed mean changes (standard deviation [SD]) from Baseline were -12.0 (12.98), -8.9 (10.94), and -6.8 (11.10) in the 25 mg, 10 mg, and 1 mg groups, respectively. The least-squares mean difference (LSMD) between 25 mg and 1 mg was statistically significant (LSMD=-6.6, $p<0.001$); the difference between 10 mg and 1 mg was not. At Week 3, protocol-compliant response (□50% reduction in MADRS) and remission (MADRS □10) rates were higher for COMP360 25 mg (response: 36.7%, n=29/79; remission: 29.1%, n=23/79) than for 1 mg (response: 17.7%, n=14/79; remission: 7.6%, n=6/79). At Week 12, sustained response (□50% reduction from baseline in MADRS at Weeks 3, 12, and either 6 or 9) was higher for 25 mg (24.1%, n=19/79) than for 1 mg (10.1%, n=8/79). The adjunctive therapy study treated 19 participants receiving escitalopram (n=6), sertraline (n=6), fluoxetine (n=3), vilazodone (n=2), paroxetine (n=1), and citalopram (n=1) with open-label COMP360 25 mg. Improvement was observed from Day 2. At Week 3 endpoint, participants had an observed mean change from Baseline of -14.9 (SD=11.97) points in MADRS; and 42.1% (n=8/19) of participants met criteria for response and for remission.

COMP360 25 mg was generally well-tolerated in both studies. In the monotherapy study, treatment-emergent adverse event (TEAE) rates were 83.5% (n=66), 74.7% (n=56), and 72.2%

(n=57) in the 25 mg, 10 mg, and 1mg groups, respectively. Over 90% of TEAEs were mild or moderate in severity. Treatment-emergent serious adverse event (TESAE) rates were 6.3% (n=5), 8.0% (n=6), and 1.3% (n=1) in the 25 mg, 10 mg, and 1 mg groups, respectively. In the adjunctive therapy study, the TEAE rate was 57.9% (n=11); and 82% of TEAEs were mild. No TESAEs were reported.

Conclusions: A single treatment with COMP360 25 mg psilocybin therapy appears to be a rapid, efficacious, and well tolerated monotherapy for patients with TRD, and may provide additional benefit as an adjunctive therapy to common antidepressant treatments. The efficacy and safety of COMP360 25 mg should be further evaluated in large, controlled, confirmatory studies.

MK-8189, A NOVEL PDE10A INHIBITOR FOR THE TREATMENT OF SCHIZOPHRENIA

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Abstract: Background: MK-8189 is an investigational selective PDE10A inhibitor for treating schizophrenia that reduces striatal D2 and increases D1 and NMDA signaling. In preclinical models, it has broad antipsychotic efficacy and a beneficial metabolic profile. Preclinical and phase 1 healthy volunteer enzyme occupancy studies with the specific PDE10A tracer [11C]MK-8193 established target engagement and guided dose selection for evaluation of MK-8189 in clinical trials. We report here on results from the initial proof-of-concept trial of MK-8189 for treating schizophrenia.

Methods: The trial was a randomized, double-blind, inpatient, Phase 2a study (NCT03055338) in adults experiencing an acute episode of schizophrenia. Participants were randomized 2:2:1 to once-daily MK-8189 12mg (controlled-release formulation), placebo, or risperidone 6mg (active-control) for 4-weeks. Efficacy was assessed by the PANSS.

Results: The number of treated patients was 90 for MK-8189, 89 for placebo, and 45 for risperidone. MK-8189 demonstrated a trend towards improvement versus placebo for change-from-baseline in PANSS total score after 4-weeks (difference = -4.7 [95% CI: -9.8,0.5], p=0.074), narrowly missing the superiority criterion of $p \leq 0.05$. MK-8189 had a more pronounced effect on PANSS positive subscale score (difference versus placebo = -2.2 [95% CI: -3.8,-0.5], $p<0.05$). The active-control risperidone was superior to placebo on PANNS total score (difference = -7.3 [95% CI: -14.0,-0.6], p=0.033), demonstrating assay sensitivity, while MK-8189 and risperidone did not significantly differ (difference = 2.6 [95% CI: -4.0,9.2], p=0.440). MK-8189 was generally well-tolerated and discontinuation of treatment due to an adverse event was low (<10%). Adverse events that occurred more often with MK-8189 than placebo included akathisia, nausea, dystonia, vomiting and back pain. MK-8189 was associated with improvements in metabolic parameters. Compared with placebo, MK-8189 reduced body weight (difference = -2.89kg [95% CI: -4.09,-1.69], $p<0.001$) while risperidone increased weight (difference = 3.44kg [95% CI: 1.67,5.21], $p<0.001$).

Conclusion: These findings suggest that PDE10A inhibition via MK-8189 could represent a new treatment approach for schizophrenia. Based on the signal detected in the phase 2a study, a phase 2b study (NCT04624243) is underway to evaluate a broader dose range of MK-8189.

DARIGABAT REDUCES ACUTE PANIC AND FEAR SYMPTOMS INDUCED BY CO2 INHALATION IN HEALTHY PARTICIPANTS

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Abstract: Background: There is substantial nonclinical evidence that α2/3 subunit–containing GABAA receptors are associated with the anxiolytic effects of benzodiazepines, and that the α1 subtype is responsible for sedative properties. Darigabat was rationally designed to selectively enhance the effect of GABA at α2/3/5 GABAA receptors, while sparing activity at α1, and is in development for the treatment of neurological and psychiatric disorders. To characterize the potential panicolytic effect of darigabat, CO2 inhalation was used as a model of panic and fear in healthy participants. The model is sensitive to pharmacological manipulation by anxiolytics, allowing investigation of pharmacodynamic effects of drugs in early clinical development.

Methods: This randomized, double-blind, placebo- and active-controlled trial assessed the panicolytic efficacy of multiple doses of darigabat on panic and fear symptoms evoked by CO2 inhalation in healthy participants. Only individuals sensitive to the anxiogenic effects of the 35% CO2 double-breath inhalation at screening were eligible for randomization. In this two-period, two-sequence partial crossover design, each eligible participant was randomized to receive either placebo and one of three active treatments in 3 separate cohorts (n=18-20/cohort) for 8 days: cohort 1 darigabat 25 mg BID, cohort 2 alprazolam 1 mg BID, and cohort 3 darigabat 7.5 mg BID. Darigabat was titrated to achieve the target maintenance dose on Day 5. On Day 8 of each crossover period, a CO2 challenge was performed at 3 hours after dosing. Alprazolam was used as a positive control to establish assay sensitivity. With each participant's placebo period serving as their own control, the change in panic and fear symptoms measured before and immediately after CO2 inhalation using the Panic Symptom List-IV total score (PSL-IV; primary endpoint) and fear visual analog scale (VAS Fear; secondary endpoint) were assessed. While the trial was not prospectively designed for formal hypothesis testing with statistical power, nominal P values for each comparison are presented. Pharmacokinetic samples were obtained at 2 and 4 hours after dosing.

Results: In the primary outcome measure PSL-IV total score on Day 8, the darigabat 7.5-mg and 25-mg BID treatment groups demonstrated a 3.9-point (P=0.036) and 4.5-point (P=0.008) improvement versus placebo, respectively. In the secondary outcome measure, VAS Fear, the 7.5-mg and 25-mg BID treatment groups demonstrated a 12.8-point (P=0.026) and 7.8-point (P=0.282) improvement versus placebo, respectively. Compared with placebo, alprazolam 1 mg BID exhibited outcomes in line with expectations, with placebo-adjusted improvements of 1.6-points (P=0.286) and 0.9-points (P=0.876) on PSL-IV total score and VAS Fear on Day 8, respectively. Plasma concentrations of darigabat were consistent with previous trials and estimated to achieve approximately 50% and 80% receptor occupancy at α2-containing GABAA receptors at 7.5 mg and 25 mg BID, respectively. Darigabat was generally well tolerated.

Conclusions: This trial demonstrated the panicolytic potential of darigabat, the rationally designed α2/3/5 receptor subtype-selective GABAA receptor positive allosteric modulator, based on reduction of acute panic and fear symptoms following 8 days of dosing in a validated, experimental clinical panic model in healthy participants. We believe these data warrant the further evaluation of darigabat in patients with anxiety disorders.

LUVADAXISTAT, AN INVESTIGATIONAL D-AMINO ACID OXIDASE INHIBITOR, WAS ASSOCIATED WITH SIGNALS OF EFFICACY IN COGNITIVE IMPAIRMENT ASSOCIATED WITH SCHIZOPHRENIA BUT NOT NEGATIVE SYMPTOMS: RESULTS FROM THE INTERACT STUDY

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Abstract: Background: Deficits in glutamatergic signalling are thought to play an important role in the negative symptoms and cognitive impairment associated with schizophrenia (CIAS). The D-amino acid oxidase inhibitor luvadaxistat may increase glutamatergic neurotransmission by elevating the levels of D-serine, an NMDA receptor co-agonist. Luvadaxistat has been shown to improve social interaction and cognition in rodent behavioral models. Here we report efficacy and safety results from INTERACT, a phase 2 study of adjunctive luvadaxistat in adults with schizophrenia (NCT03382639).

Methods: INTERACT was a randomized, placebo-controlled, dose range finding study that included participants with symptomatically stable schizophrenia, a baseline Brief Negative Symptom Scale score of ≥28 (items 1–3; 5–13), and who were receiving primary antipsychotic therapy. The study comprised a 28-day screening period, a 14-day single-blind placebo run-in period and a 12-week double-blind treatment period.

The primary endpoint was the 12-week change from baseline in the Positive and Negative Syndrome Scale – Negative Symptom Factor Score (PANSS NSFS). Secondary endpoints included the changes from baseline (CFB) to Week 12 in the Brief Assessment of Cognition in Schizophrenia (BACS) composite score and the Schizophrenia Cognition Rating Scale (SCoRS) score, a test battery and an interview-based tool that assess cognitive functioning. Safety endpoints included assessment of treatment-emergent adverse events (TEAEs).

Results: Of the 256 participants randomized 3:2:2:2 to receive placebo, luvadaxistat 50 mg, 125 mg and 500 mg, respectively, 228 (89.1%) completed the study. Baseline demographics and characteristics were similar across treatment groups.

No significant improvements in PANSS NSFS versus placebo were observed with luvadaxistat 50 mg, 125 mg or 500 mg at Week 12 (p = 0.426, p = 0.362 and p = 0.808, respectively). The least squares (LS) mean CFB to Week 12 in PANSS NSFS were –3.3 (95% confidence interval [CI]: –4.3, –2.2), –3.4 (95% CI: –4.4, –2.3) and –2.5 (95% CI: –3.6, –1.5) with luvadaxistat 50 mg, 125 mg and 500 mg, respectively, and –3.1 (95% CI: –4.0, –2.3) with placebo.

Significant improvements were observed with luvadaxistat 50 mg versus placebo in the BACS composite score and the SCoRS interviewer total score (nominal p = 0.031 and p = 0.011,

respectively), but not with luvadaxistat 125 mg or 500 mg. For the BACS composite score, LS mean CFB to Week 12 were 4.6 (95% CI: 2.7, 6.5) with luvadaxistat 50 mg and 2.3 (95% CI: 0.7, 3.9) with placebo. For the SCoRS interviewer total score, LS mean CFB to Week 12 were 3.8 (95% CI: –5.3, –2.3) with luvadaxistat 50 mg and –1.6 (95% CI: –2.9, –0.3) with placebo.

TEAEs occurring in ≥5 participants were headache, insomnia and weight gain, which occurred at similar frequencies in the four treatment groups. Two participants taking luvadaxistat had drug-related TEAEs of psychiatric disorders resulting in discontinuation.

Discussion: Luvadaxistat did not significantly improve negative symptoms of schizophrenia at the three doses studied. However, the 50 mg dose showed a signal of efficacy in the BACS composite score and the SCoRS interviewer total score vs placebo.

The efficacy signal seen with luvadaxistat 50 mg warrants further clinical research in participants diagnosed with CIAS. In line with past clinical experience, luvadaxistat was generally well tolerated.

EFFICACY AND SAFETY OF ZURANOLONE CO-INITIATED WITH AN ANTIDEPRESSANT IN ADULTS WITH MAJOR DEPRESSIVE DISORDER: RESULTS FROM THE PHASE 3, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED CORAL STUDY

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Abstract: Depression is a leading cause of disease burden and can lead to serious long-term adverse health effects (1, 2). Zuranolone is an oral neuroactive steroid and positive allosteric modulator of GABAA receptors under investigation as part of the LANDSCAPE clinical development program as a once-daily (QD), 2-week therapy for major depressive disorder (MDD). In previously completed studies, zuranolone was generally well tolerated in adults with MDD, either as monotherapy or concomitantly with antidepressant therapy (ADT), with a reduction in depressive symptoms as assessed by change from baseline (CFB) in the 17-item Hamilton Rating Scale for Depression total score (HAMD-17) observed as early as Day 3 and sustained at all measured time points through Day 42. The CORAL study was the first study to evaluate early (Day 3) efficacy and safety of zuranolone 50 mg co-initiated with a standard-of-care (SOC) ADT vs placebo co-initiated with a SOC ADT in adults with MDD.

This Phase 3 randomized, double-blind, placebo-controlled study (NCT04476030) enrolled patients (aged 18–64 years) with MDD and baseline HAMD-17 ≥24. Patients were randomized 1:1 to blinded zuranolone 50 mg:placebo QD, each co-initiated with an open-label SOC ADT for a 14-day treatment course; patients then continued on an ADT alone for another 28 days. SOC ADTs included selective serotonin reuptake inhibitors or serotonin-norepinephrine reuptake inhibitors. The primary endpoint was CFB in HAMD-17 at Day 3; the key secondary endpoint was treatment effect as measured by CFB in HAMD-17 over the blinded treatment period using equal weights for scheduled visits at Days 3, 8, 12, and 15. Safety, including treatment-emergent adverse events (TEAEs), was assessed.

A total of 425 patients received either zuranolone 50 mg co-initiated with ADT (210) or placebo co-initiated with ADT (215). Baseline demographics were balanced between treatment arms. The primary endpoint at Day 3 was met: patients who received zuranolone co-initiated with ADT showed a statistically significant reduction in depressive symptoms as assessed by CFB in the HAMD-17 (least squares [LS] mean standard error [SE]: −8.9 [0.39]; vs those who received placebo co-initiated with ADT (LS mean [SE]: −7.0 [0.38]; P=0.0004). The key secondary endpoint, the treatment effect over the treatment period, was also met; a statistically significant improvement in depressive symptoms as assessed by CFB in HAMD-17 over the blinded treatment period was observed for patients who received zuranolone co-initiated with ADT vs those who received placebo co-initiated with an ADT (−11.7 [0.40] vs −10.1 [0.39]; P=0.0054). Overall, TEAEs were reported in 157 (74.1%) patients in the zuranolone co-initiated with ADT group compared to 143 (65.6%) patients in the placebo co-initiated with ADT group. TEAEs that were ≥10% in either treatment group (zuranolone co-initiated with an ADT vs placebo co-initiated with an ADT) included somnolence (18.4% vs 8.3%), dizziness (13.2% vs 7.3%), headache (11.8% vs 14.7%), and nausea (9.0% vs 23.4%).

Consistent with previously completed studies of zuranolone, in which a reduction in depressive symptoms was observed as early as Day 3, zuranolone co-initiated with a SOC ADT resulted in a statistically significant improvement in depressive symptoms as assessed by HAMD-17 at Day 3 in adults with MDD compared with placebo co-initiated with a SOC ADT. Zuranolone 50 mg co-initiated with an ADT was generally well tolerated with no new safety signals.

Individual Research Reports: Brain Health Outcome Studies and Novel Potential Interventions

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

LONG-TERM SAFETY AND SUSTAINED EFFICACY OF ZYN002 CANNABIDIOL TRANSDERMAL GEL IN CHILDREN AND ADOLESCENTS WITH FRAGILE X SYNDROME (ZYN2-CL-017)

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Abstract: BACKGROUND: ZYN002 is a pharmaceutically produced transdermal cannabidiol gel in development for the behavioral symptoms in Fragile X syndrome (FXS). ZYN2-CL-017 is an ongoing, long-term, open-label extension (OLE) for trials of ZYN002 in FXS. CONNECT-FX was a randomized, double-blind trial assessing safety and efficacy of ZYN002 in children and adolescents with full FMR1 gene mutation. Patients with complete, 100% FMR1 gene methylation treated with ZYN002 had significant improvements as compared to placebo on multiple endpoints. FAB-C (ZYN2-CL-009) was the initial Phase 2, open-label trial which led to the conduct of CONNECT-FX.

OBJECTIVES: To assess the long-term safety and efficacy of ZYN002 in patients ages 3 through 17 years with FXS.

METHODS: Interim analyses were completed with data collected through 21-May-2021. Safety data for all patients, up to 30 months, and efficacy data through 6 months of treatment

for patients with 100% FMR1 gene methylation who completed CONNECT-FX are reported. Patients screened for CONNECT-FX were eligible for entry, including patients ineligible to continue in the trial, and patients who were randomized to receive 12-weeks of ZYN002 (250 mg or 500 mg daily [weight-based]) or placebo. Patients from FAB-C also entered the trial. Patients who completed CONNECT-FX remain blinded to the treatment received in CONNECT-FX. Safety assessments included adverse events, vital signs, laboratories, and electrocardiograms (ECGs). The primary efficacy endpoint was change in the Social Avoidance (SA) subscale of the Aberrant Behavior Checklist–Community FXS (ABC–CFXS).

RESULTS: 240 patients were enrolled; 197 who completed CONNECT-FX, 12 screen failures and 21 patients ineligible to continue from CONNECT-FX and 10 patients from FAB-C. 110 patients received ZYN002 prior to entry. Mean age was 9.7 years and 76.3% were male. 156 patients (70.3%) for whom methylation status was determined had 100% FMR1 methylation. 210 patients completed at least 6 months of open-label treatment (median of 21 months). 131 patients were continuing at this interim analysis. Treatment emergent adverse events (TEAEs) were reported by 62.2% of patients; 97.7% were mild to moderate severity. TEAEs reported by $\geq$ 5% of patients included: upper respiratory infection (15.4%) and application site pain (6.6%). 13.3% of patients reported a TEAE possibly related to treatment. Six patients experienced 7 serious adverse events; none were considered treatment-related. Seven patients discontinued due to an adverse event. No clinically significant changes in vital signs, laboratories or ECGs were reported. At the end of the CONNECT-FX trial, completely methylated patients treated with ZYN002 had a median improvement of 40% in SA verses 20% ($p=0.027$) in patients treated with placebo. After six months of treatment with ZYN002, patients reported a median improvement of 50% in SA whether originally treated with ZYN002 in CONNECT-FX (3 months active medication in CONNECT-FX plus 3 months in the OLE) or newly treated with ZYN002 in the OLE trial.

CONCLUSIONS: ZYN002 was safe and well tolerated when administered over a median of 21 months. In patients with complete FMR1 gene methylation, ZYN002 led to sustained improvement in Social Avoidance, a key behavioral symptom of FXS, following initial improvement seen after 12 weeks of double-blind therapy. The results from this OLE trial continues to support the effectiveness of ZYN002 in patients with complete FMR1 gene methylation.

Learning Objectives:

1. To describe the long-term safety profile of ZYN002 transdermal cannabidiol gel in children and adolescents with Fragile X Syndrome.
2. To describe the long-term efficacy profile of ZYN002 transdermal cannabidiol gel in children and adolescents with Fragile X Syndrome who have complete methylation of their FMR1 gene.

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REAL-WORLD CLINICAL PRACTICE AMONG PATIENTS WITH BIPOLAR DISORDER AND CHRONIC KIDNEY DISEASE ON LONG-TERM LITHIUM THERAPY

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Abstract: Background/Aims: Lithium (Li) is the gold standard therapy for bipolar disorders (BD). Long-term lithium therapy (LTLT) has been associated with chronic kidney disease (CKD) in BD. Inadequately treated medical comorbidities such as diabetes and hypertension, and concomitant medications such as NSAIDs and thiazides, can further increase the risk of CKD in patients on LTLT. 40%-50% of BD patients on LTLT discontinue Li after CKD diagnosis. The kidney dysfunction between patients who continue Li (continuers) compared with patients who discontinue Li (discontinuers) after CKD development may not necessarily differ. We aimed to investigate the changes in clinical characteristics, pharmacotherapeutic treatments for medical/psychiatric disorders, and outcomes among BD patients with CKD on LTLT in a 2-year mirror-image study design. We hypothesized that as compared to continuers, discontinuers would have more mood episodes with a shorter time to the first mood episode.
Methods: This is a historical cohort study of adult BD patients on LTLT (≥1 year) enrolled in the Mayo Clinic Bipolar Biobank, Rochester, Minnesota.1 In a cohort of 39 BD patients who developed CKD stage-3, 19 patients (49%) discontinued lithium (discontinuers), rest continued (n=20).2 Mirror periods were 2 years pre CKD and post CKD among BD patients on LTLT. We extracted demographic, clinical characteristics, medical comorbidities, treatment interventions (antihypertensive -ACE inhibitors [ACEI], angiotensin II receptor blockers [ARBs], beta-blockers, calcium channel blockers [CCB], diuretics; antidepressants, mood stabilizers, antipsychotics, stimulants, benzodiazepines, and other psychotropics) and treatment outcomes (mood episodes). Kruskal-Wallis and Chi-square/Fisher's exact test were used.

Our primary outcome was the time to the first mood episode after CKD diagnoses among the continuers and discontinuers. Cox proportional hazards models were used to estimating the time to the first mood episode among the continuers and discontinuers post-CKD diagnoses.

Results: The median age of the cohort was 56.1 years (IQR, 48.2-66.6 yrs.), 64.1% females, and 97.4% were Caucasian. There were no significant differences between the continuers and discontinuers in demographic variables (all $p>0.27$). In the 2-years pre-post analysis, there were no significant differences in the pharmacotherapeutic interventions between groups (continuers vs discontinuers) among those who did change (all $p>0.14$). Discontinuers had a decrease in the SSRIs prescription rate (43% to 6%) as compared to a slight increase in continuers (6% to 10%). In the antihypertensive medications (ACEIs/ARB, CCBs, diuretics, beta-blockers), only beta-blockers had a slight increase in the prescription rate among continuers post CKD diagnoses.

Discontinuers had more psychotropic medication trials (median, IQR, 6 (4-6) vs 3 (2-5), $p=0.016$) and mood episodes as compared to continuers (57.9% vs 10%, $p=0.002$) in the 2 years post-CKD diagnoses. As compared to discontinuers, continuers had a longer time to the first mood episode after CKD diagnoses, HR=0.13, 95% CI, 0.03-0.59 (log-rank $p= 0.002$).

Conclusion: Bipolar disorder patients with CKD on LTLT who discontinued lithium therapy had a higher risk for relapse and a shorter time to the first mood episode, suggesting a need for more thorough discussion and probably a higher threshold before lithium discontinuation after the CKD diagnosis. Further studies with a larger sample size are required to understand the intricacies of medication changes in this BD phenotype.

Learning Objectives:

1. To investigate the real-world clinical practice among patients with bipolar disorders and chronic kidney disease (CKD) on long-term lithium therapy.
2. To identify the differences in clinical characteristics, pharmacotherapeutic changes, and outcomes among bipolar disorder patients with CKD who continued lithium vs those who discontinued lithium after CKD diagnoses in a 2-year mirror-image study design.

Literature References:

1. Frye MA, McElroy SL, Fuentes M, et al. Development of a bipolar disorder biobank: differential phenotyping for subsequent biomarker analyses. Int J Bipolar Disord. 2015;3(1):30.
2. Pahwa M, Joseph B, Nunez NA, et al. Long-term lithium therapy and risk of chronic kidney disease in bipolar disorder: A historical cohort study. Bipolar Disord. 2021;23(7):715-723.

LOWER MORTALITY DUE TO ALL-CAUSE IN PATIENTS WITH MAJOR DEPRESSION TREATED WITH ECT COMPARED TO THOSE WHO DID NOT: A NATIONAL UNITED STATES STUDY

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Abstract: OBJECTIVE: The objective of this study is to examine the odds of in-hospital all-causes mortality among patients with Major Depressive Disorder (MDD) treated with ECT compared to those who did not, after controlling for demographic and impairment due to medical conditions.

METHODS: A national inpatient sample (NIS) data from 2012 to 2014 was utilized to include 949,394 adult inpatients across the US. Logistic regression was used to assess the odds ratio (OR) for in-hospital mortality for those with MDD treated with ECT (N = 25,535) vs. non-ECT (N = 923,859) groups after adjusting for demographics and medical conditions' functional impairment.

RESULTS: ECT use is significantly higher in older patients (mean age, 56.9±16.7), female (64%) and Caucasian (86.9%). A higher proportion of patients in the ECT group had major (37.1% vs. 4.9%) and extreme (62.9% vs. 0.2%) loss of body functions compared to non-ECT. Marked and extreme loss of function were highly and significantly associated with mortality. In-hospital mortality was significantly lower in the ECT group (OR 0.05, 95%CI 0.02-0.11, P <0.001) when adjusted for demographic and extreme loss of function due to medical conditions. In-hospital mortality was also significantly lower in the ECT group (OR 0.7, 95%CI 0.41-1.50, P <0.47) when adjusted for demographic and major loss of function.

CONCLUSION: All-cause mortality was less in MDD patients who had ECT compared to those who did not during hospitalization. Further studies are needed to replicate these findings.

Learning Objectives:

1. Learn the in-hospital all-causes mortality among patients with Major Depressive Disorder (MDD) treated with ECT compared to those who did not.
2. Learn the demographics of inpatients with Major Depressive Disorder (MDD) treated with ECT.

Literature References:

1. Philibert RA, Richards L, Lynch CF, Winokur G. Effect of ECT on mortality and clinical outcome in geriatric unipolar depression. J Clin Psychiatry. 1995;56(9):390-4. Epub 1995/09/01. PubMed PMID: 7665536.
2. Rhee TG, Sint K, Olfson M, Gerhard T, S HB, Wilkinson ST. Association of ECT With Risks of All-Cause Mortality and Suicide in Older Medicare Patients. Am J Psychiatry. 2021;178(12):1089-97. Epub 2021/09/11. doi: 10.1176/appi.ajp.2021.21040351. PubMed PMID: 34503341; PubMed Central PMCID: PMC8639649.

Individual Research Reports: Depression, Psychosis and Substance Use Disorders (SUD) on the Edge: Impacts on Brain Structures, Social Interactions Impact Outcomes Based on Neighborhoods, and Ketamine for Late-Life TRD to Boot

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

NEIGHBORHOOD POVERTY AND HIPPOCAMPAL VOLUME AMONG YOUTH AT CLINICAL HIGH RISK FOR PSYCHOSIS: THE MODERATING ROLE OF SOCIAL ENGAGEMENT

Benson Ku*[1], *Katrina Aberizk[2], Jean Addington[3], Carrie Bearden[4], Kristin Cadenhead[5], Tyrone Cannon[6], Ricardo Carrion[7], Michael Compton[8], Barbara Cornblatt[7], Benjamin Druss[2], Daniel Mathalon[9], Diana Perkins[10], Ming Tsuang[5], Scott Woods[6], Elaine Walker[2]*

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Abstract: Introduction: It is known that being raised in low-income homes is associated with decreased hippocampal volumes as well as increased risk of developing schizophrenia. The inverse relationship between poverty and hippocampal grey matter volume (GMV) has been shown to be mediated by social stress including lack of parental caregiving and stressful life events. More recent studies have shown that neighborhood poverty (NP) is also associated with lower hippocampal volumes (HV) even after controlling for parental household income among children. Perhaps, social engagement (SE) may serve as a moderator and buffer the deleterious effects of NP on brain areas involved with social stress, which would include HV. However, it is not known whether this association exists among youth at clinical high risk for psychosis (CHR-P). In this study, we explore the associations between NP, SE, and HV among youth at CHR-P.

Method: Data were collected at baseline as part of the North American Prodrome Longitudinal Study Phase 2. All available addresses where participants resided at baseline were geographically coded to poverty at the census tract level using the US Censuses. NP was

defined as the percentage of residents whose income was below the poverty level in the past year. SE was derived from the desirable events subscale items of the Life Events Scale. HV was obtained from structural magnetic resonance imaging (MRI) and were adjusted for study site, MRI manufacturer (GE versus Siemens), and estimated intracranial volume. Generalized linear mixed models tested associations between NP and bilateral HV using census tracts as the random intercept. Models controlled for age, sex, race/ethnicity, family history of mental illnesses, household poverty, educational level, and life events stress. Moderating effects of social engagement were tested using interaction term of NP x social engagement.

Results: This study included 174 CHR-P individuals, aged 12 to 33 years. NP was associated with reduced HV (unadjusted $\beta = -0.203$; 95% CI = -0.351 – -0.051) even after controlling for seven covariates (adjusted $\beta = -0.196$; 95% CI = -0.342 – -0.050). Interaction term NP x social engagement was significantly associated with HV ($p < 0.05$). Subgroup analyses show that among those with lower social engagement (3 or fewer social activities; n=77), NP was associated with reduced HV (adjusted $\beta = -0.341$; 95% CI = -0.551 – -0.131). However, among those with greater social engagement (4 or more social activities; n=97), NP was not significantly associated with HV (adjusted $\beta = -0.010$; 95% CI = -0.248 – 0.227).

Discussion: In this study, NP is associated with HV above and beyond individual-level risk factors including household poverty among youth at CHR-P. This association is moderated by social engagement. Among those with lower social engagement, NP may have a significantly negative impact on the hippocampus while the effect of NP on this brain region may be mitigated by greater social engagement. These preliminary findings suggest that social engagement may reduce the deleterious effect of poverty among youth at CHR-P, which has potential implications for early intervention and prevention in psychosis.

Learning Objectives:

1. Neighborhood poverty is associated with reduced hippocampal volume above and beyond individual-level risk factors including household poverty.
2. Social engagement may reduce the deleterious effect of poverty among youth at risk for psychosis, which has potential implications for early intervention and prevention.

Literature References:

1. Taylor RL, Cooper SR, Jackson JJ, Barch DM. Assessment of Neighborhood Poverty, Cognitive Function, and Prefrontal and Hippocampal Volumes in Children. JAMA Netw Open. 2020 Nov 2;3(11):e2023774.
2. Hakulinen C, Webb RT, Pedersen CB, Agerbo E, Mok PLH. Association Between Parental Income During Childhood and Risk of Schizophrenia Later in Life. JAMA Psychiatry. 2020 Jan 1;77(1):17–24.

ASSOCIATION BETWEEN DEPRESSION AND CHANGE IN NUCLEUS ACCUMBENS DRUG CUE-REACTIVITY DURING EXTENDED-RELEASE NALTREXONE TREATMENT FOR OPIOID USE DISORDER

Zhenhao Shi*[1], *Xinyi Li[1], Anna Rose Childress[1], Corinde E. Wiers[1], Daniel D. Langleben[1]*

[1]*University of Pennsylvania*

Abstract: Background: Patients with substance use disorders attribute high incentive value and display heightened dopaminergic responses to drug-related conditioned stimuli (i.e., cues),

which stimulate drug-seeking motivation and promote relapse. In patients with opioid use disorder (OUD), more severe drug use has been associated with greater nucleus accumbens (NAcc) response to drug cues. Once-monthly injectable, extended-release opioid antagonist naltrexone (XR-NTX) is an effective relapse prevention medication for OUD and significantly reduces NAcc cue-reactivity. Prior studies on opioid agonist treatments (e.g., methadone) have found poorer treatment outcomes in patients with more severe depression. However, it is unknown if depression influences the treatment effect of antagonist XR-NTX. The current study aims determine the relationship between depression severity and XR-NTX-induced change in NAcc cue-reactivity among OUD patients.

Methods: Fifteen detoxified adult patients with OUD (9 males, 6 females; 21–47 years old) participated in the study. Using functional magnetic resonance imaging (fMRI), we measured neural responses to four categories of visual stimuli: drug-related, sexual, aversive, and neutral. fMRI was performed before (pre-treatment) and two weeks after the first XR-NTX injection (on-treatment). Symptoms of depression were assessed approximately one week after the first XR-NTX injection using the Beck Depression Inventory (BDI). Preprocessed fMRI data were subjected to statistical analysis that modeled the effect of each stimulus category. The bilateral NAcc was treated as an a priori region of interest and anatomically defined using the Harvard-Oxford Atlas. XR-NTX-induced change in NAcc neural activity was calculated by subtracting pre-treatment from on-treatment responses to drug, sexual and aversive stimuli (vs. neutral stimuli). Pearson correlation was performed between BDI score and change in NAcc response to drug cues. We also tested the correlations of BDI with NAcc responses to sexual and aversive stimuli to explore specificity for drug-related cues.

Results: Participants' BDI scores ranged from 0 (no depression) to 26 (moderate depression). We found a significant correlation between BDI score and XR-NTX-induced change in NAcc response to drug cues, such that participants with a higher BDI score had a smaller reduction in NAcc cue-reactivity from pre-treatment to on-treatment ($r=0.56$, $p=0.030$). BDI score was not correlated with change in NAcc response to sexual or aversive stimuli, indicating specificity ($r=0.28$ and 0.30, $p=0.34$ and 0.27).

Conclusion: Our findings suggest that concurrent depression in OUD may hamper XR-NTX's ability to restore normal incentive salience processing in the dopaminergic system. Adjunct interventions targeting depressive symptoms may enhance XR-NTX treatment success in vulnerable individuals.

Learning Objectives:

1. Learners will be able to describe the effect of extended-release naltrexone on the neural correlates of drug cue-reactivity in patients with opioid use disorder.
2. Learners will be able to discuss the potential association between depression and the effect of extended-release naltrexone in the treatment of opioid use disorder.

Literature References:

1. Rounsaville BJ, Weissman MM, Crits-Christoph K, Wilber C, Kleber H. Diagnosis and symptoms of depression in opiate addicts. Course and relationship to treatment outcome. Arch Gen Psychiatry 1982; 39(2):151-156.
2. Shi Z, Wang AL, Jagannathan K, et al. Effects of extended-release naltrexone on the brain response to drug-related stimuli in patients with opioid use disorder. J Psychiatry Neurosci 2018; 43(4):254-261.

PRE-INFUSION NEURAL COMPLEXITY MODERATES CLINICAL RESPONSE TO INTRAVENOUS KETAMINE ACROSS 7 DAYS IN PATIENTS WITH LATE-LIFE TREATMENT RESISTANT DEPRESSION

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[1]Baylor College of Medicine, [2]Baylor College of Medicine and Michael E. DeBakey VA Medical Center

Abstract: Ketamine is a promising intervention for treatment-resistant depression (TRD) due to its rapid-acting effects. However, there are individual differences in treatment response to ketamine. Though there has been some advancement understanding ketamine treatment response, considerable study is still needed using inexpensive and low-clinic-burden measures such as EEG. Prior work has found that Lempel-Ziv complexity (LZC), an EEG measure of the number of distinct patterns present in the data, may provide one such biomarker of treatment response. LZC is of special importance as it has been previously used to predict rTMS treatment response with high accuracy. Furthermore, LZC is relevant to our variables of interest, given findings that LZC is increased in response to ketamine administration, and that depressed adults have altered LZC compared to healthy controls. Our purpose was to investigate LZC as a biomarker of ketamine response to improve predictive abilities for personalized treatment selection.

Twenty-eight medication-free military veterans (mean age=62, standard deviation=5.6, 36% female) with major depressive disorder resistant to at least two medication trials, were randomized to a single 40-minute infusion to one of three potential ketamine doses (0.1, 0.25, 0.5mg/kg) or midazolam (0.03 mg/kg) under double-blind conditions. This study was a secondary analysis of a Bayesian adaptive randomized trial [1]. Five minutes of eyes-open resting state EEG were collected prior to infusion using a 58-channel montage Brainproducts cap, digitized at 1000 Hz. Artifacts were removed using a combination of artifact sub-space reconstruction and independent components analysis. LZC was estimated using the L76 method described elsewhere [2]. A linear mixed model using scaled identity covariance structure was used to compare mean changes in depression (MADRS) score across time (-1, 1, 2, 3, 4, 5, and 7 days post-infusion) as a function of pre-infusion levels of LZC.

Our analyses revealed a drug-by-LZC interaction, suggesting that individuals had greater symptom reduction with ketamine than midazolam with increasing pre-infusion levels of LZC ($F(1,23)=6.86$, $p=0.015$). There was also a statistically significant drug-by-LZC-by-time interaction, with the difference between drug response by LZC level emerging at 24 hours post-administration ($F=2.68$, $p=0.04$).

Depressive symptoms are associated with maladaptive and rigid cognitive patterns, including repetitive rumination on negative information, passive acceptance, and self-blame. Such self-focused, inflexible methods of emotion regulation have previously been related with reduced complexity of EEG, whereas greater cognitive flexibility abilities correlate with increased neural complexity. Ketamine's mechanism of action is theorized to involve pro-cognitive effects, including positive effects on cognitive flexibility. Thus, we may speculate that having higher baseline neural complexity may provide individuals with the necessary neural architecture to be able to engage ketamine's mechanism of action. Our findings that treatment effect of ketamine was mediated by LZC may have practical implications in highlighting

unique profiles of patients who have differential treatment response to ketamine, contributing to treatment matching algorithms for this oft-detrimental disorder.

Ref.

1. Lijffijt M, Murphy N, Iqbal S, et al. Identification of an optimal dose of intravenous ketamine for late-life treatment-resistant depression: A bayesian adaptive randomization trial. Neuropsychopharmacology. 2021:1-8.

2. Lempel A, Ziv J. On the complexity of finite sequences. IEEE Transactions on information theory. 1976;22(1):75-81.

Learning Objectives:

1. Evaluate Lempel Ziv complexity as a non-linear EEG analysis.
2. Describe the relationship between neural complexity and the treatment response to ketamine.

Literature References:

1. Hasanzadeh F, Mohebbi M, Rostami R. Prediction of rTMS treatment response in major depressive disorder using machine learning techniques and nonlinear features of eeg signal. Journal of affective disorders. 2019; 256:132-142.
2. Lijffijt M, Murphy N, Iqbal S, et al. Identification of an optimal dose of intravenous ketamine for late-life treatment-resistant depression: A bayesian adaptive randomization trial. Neuropsychopharmacology. 2021:1-8.
3. Lempel A, Ziv J. On the complexity of finite sequences. IEEE Transactions on information theory. 1976;22(1):75-81.

GLIOVASCULAR PROTEIN CONCENTRATIONS IN THE PERIPHERY SHOW DIFFERENTIAL CHANGES DEPENDING ON CLINICAL OUTCOME OF TRANSCRANIAL MAGNETIC STIMULATION FOR TREATMENT RESISTANT DEPRESSION: NEW STAR OF THE SHOW

Andrew Fukuda*[1], *Lauren Hindley[2], Eric Tirrell[1], Linda Carpenter[3]*

[1]Brown University/Butler Hospital, [2]Butler Hospital, [3]Alpert Medical School, Brown University, Butler Hospital

Abstract: Background: Astrocytes have a diverse range of functions and peripheral astrocyte proteins show promise as a biomarker of either disease severity or treatment response in MDD but have not been explored in TMS. Our study examined serum levels of four astrocytic proteins: S100 Calcium Binding Protein B (S100B), Glial Fibrillary Acidic Protein (GFAP), Vascular endothelial growth factor (VEGF), and Aquaporin 4 (AQP4) before and after TMS in pharmacotherapy resistant MDD (TRD) to investigate their roles in the mechanism of TMS. Methods: Serum was collected from a naturalistic population of 35 patients with TRD approved to receive standard TMS therapy. Protein concentrations were determined via Enzyme-linked Immunosorbent Assay (ELISA) and all samples were run in duplicates. Inventory of Depressive Symptomatology Self Report (IDS-SR) was used as a measure of depression symptom severity, clinical response (≥50% improvement) and remission (end score≤14). Given non-normal distribution of data, non-parametric tests were used to examine relationship between astrocyte proteins and clinical outcomes.

Results: Mean concentration of the proteins did not change significantly from baseline to post overall, however there was evidence that successful treatment with TMS was associated with change in GFAP and VEGF. There was a positive correlation between improvement in depressive symptom severity and increase in concentrations of GFAP ($r = .561$, $p<0.05$), and VEGF ($r =.358$, $p<0.05$). VEGF increased from pre to post TMS in remitters but decreased in nonremitters (12.30±10.47 vs -9.24 ±5.78%; $p<0.05$). This same pattern was observed when comparing VEGF changes between responders and non-responders (+9.35 ±7.40% vs -12.42±6.82%; $p<0.05$). Similarly, GFAP also increased in responders but decreased in non-responders (+151.18 ± 29.28% vs -41.10 ±12.21%, $p<0.05$). S100B did not correlate with depression severity changes, nor did they differ between those with different clinical outcomes. AQP4 was also measured in a subset of the population (n=16, 25% male, 75% female; baseline AQP4 level had a positive correlation with the degree of depressive symptomatic improvement measured ($r = .410$, $p<0.05$). The protein levels did not differ by sex or with age.

Conclusions: Patients who responded or remitted following a course of TMS had significantly greater increases in VEGF and GFAP over time, and a larger increase in VEGF and GFAP was associated with greater improvement in depressive symptoms. These patterns were not seen in S100B. Although the functional implications of the differential changes in these astrocytic proteins are yet to be elucidated, data from basic science hint at a variety of possibilities including reduced neuroinflammation, increased neurogenesis/angiogenesis or synaptic remodeling. This is the first study examining GFAP, S100B, and AQP4 levels in depressed patients receiving TMS and suggests their potential role in the mechanism of action of TMS for TRD.

Learning Objectives:

1. Gliovascular cells such as astrocytes may play an important role in depression pathophysiology.
2. Astrocytic proteins may be promising biomarkers for depression treatment response.

Literature References:

1. Fukuda, A.M., et al., Peripheral vascular endothelial growth factor changes after transcranial magnetic stimulation in treatment-resistant depression. Neuroreport, 2020. 31(16): p. 1121-1127.
2. O'Leary, L.A. and N. Mechawar, Implication of cerebral astrocytes in major depression: A review of fine neuroanatomical evidence in humans. Glia, 2021. 69(9): p. 2077-2099.

Individual Research Reports: Imaging, Pregnancy Registry and AI: Different Approaches in Mental Health

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

USING MACHINE LEARNING TO PREDICT DEPRESSION CARE QUALITY AT COMMUNITY HEALTH CENTERS DURING THE COVID-19 PANDEMIC

Evan Goldstein*[1], *Fernando Wilson*[1]

[1]*University of Utah School of Medicine*

Abstract: Background: The pandemic brought new attention to the comorbidity of general health conditions and mental disorders. Recent studies have documented a connection between COVID-19 diagnosis and symptoms of depression. These findings are particularly concerning for lower-income patients, as low socioeconomic status can increase the risk for incident mood and anxiety disorders. Community health centers (CHCs) work to improve access to primary mental health services for low-income persons in the US. Preliminary evidence suggests COVID-19 disrupted depression care delivery at CHCs. However, little is known about which factors best predict whether CHCs provide high- or low-quality depression care during the pandemic.

Objective: To use machine learning (ML) models to identify predictors of CHCs providing low-quality depression care rather than high-quality depression care.

Methods: This cross-sectional study examined Uniform Data System (UDS) data from 2020. UDS is a standardized, mandatory reporting system for all federally-funded CHCs. Our analytic sample included 270 CHCs, representing CHCs that provided the lowest and highest-quality depression care in 2020. We used data-driven ML approaches to perform pattern recognition and compare the predictive results of classification tree and random forest classifier ML models. We randomly split the data into 80% training and 20% test sets to account for overfitting.

Our outcome variable was a binary measure equal to 1 for CHCs that provided the lowest-quality depression care in 2020 (i.e., the lowest-decile CHCs ranked by their depression care quality scores) and 0 for CHCs that provided the highest-quality depression care (i.e., highest-decile CHCs). We constructed this variable using National Quality Forum process of care metric #0418, which measures the percentage of CHC patients who screened positive for depression and had documented follow-up care (e.g., with a clinician to provide pharmacological intervention). The ML models used 80 independent features to predict whether a CHC provided low- or high-quality depression care. These variables measured organizational characteristics and demographic and health characteristics of each CHC's patient population. Geographic indicators and variables measuring state-level characteristics were also included from other data sources. Feature importance was computed using the mean decrease in impurity method. ML modeling was conducted using the scikit-learn package in Python 3.9.

Results: The random forest classifier model had the best accuracy (83.3%) and precision (83.2%) in predicting low-quality depression care at CHCs. The percentage of CHC patients diagnosed with obesity was the most important feature for predicting low-quality depression care selected by the random forest classifier model. The remaining top-5 important predictors were the percentages of female patients, patients living below poverty, patients diagnosed with COVID-19, and uninsured patients, respectively.

Compared to CHCs providing higher-quality depression care, CHCs providing low-quality depression care had relatively fewer patients diagnosed with obesity ($P<0.001$) and female patients ($P<0.001$), but more patients diagnosed with COVID-19 ($P=0.04$) in 2020.

Conclusions: This is the first study to use a data-driven ML approach to identify variables associated with CHCs providing low-quality depression care during the pandemic. Additional policy support will likely be needed to stem the comorbid health risks caused by the pandemic. Applying our predictive models may help advocates better characterize and identify which types of CHCs would benefit the most from additional mental health services support.

Learning Objectives:

1. Identify how organization- and area-level factors can impede access to depression care and worsen outcomes for follow-up depression care for low-income patients during the pandemic. Andersen et al.'s Behavioral Model for Health Services Use will provide conceptual framework for this Learning Objective.

2. Discuss how safety-net mental health care organizations and clinicians can use machine learning to (a) improve follow-up care for depression and (b) advocate for policymaker support.

Literature References:

1. Perlis RH, Ognyanova K, Santillana M, et al.: Association of Acute Symptoms of COVID-19 and Symptoms of Depression in Adults. JAMA Netw Open 2021; 4(3).
2. Goldstein E V.: Examining the Relationship Between COVID-19 Prevalence and Depression Care at Community Health Centers: Assessing 2020 Data. Psychiatr Serv 2021; 72. Available from: https://ps.psychiatryonline.org/doi/full/10.1176/appi.ps.202100478

RISK OF MAJOR MALFORMATIONS IN INFANTS AFTER FIRST-TRIMESTER EXPOSURE TO BENZODIAZEPINES: RESULTS FROM THE MASSACHUSETTS GENERAL HOSPITAL NATIONAL PREGNANCY REGISTRY FOR PSYCHIATRIC MEDICATIONS

Mercedes Szpunar*[1], *Marlene Freeman[1], Lauren Kobylski[1], Phoebe Caplin[1], Peter Gaccione[1], Adele Viguera[2], David Chitayat[3], Sonia Hernandez-Diaz[4], Lee Cohen[1]*

[1]Massachusetts General Hospital, Center for Women's Mental Health, [2]Massachusetts General Hospital, Center for Women's Mental Health; Cleveland Clinical Neurological Institute, [3]Mount Sinai Hospital, [4]Harvard T.H. Chan School of Public Health

Abstract: Introduction: Perinatal anxiety affects up to 20% of women, and untreated maternal mental illness can cause deleterious effects for women and their children, including poor obstetrical and neonatal outcomes. Benzodiazepines are commonly used to treat anxiety disorders and prescribed to approximately 4% of women during pregnancy. The reported risk of congenital malformations after in utero benzodiazepine exposure has been inconsistent.
Methods: The Massachusetts General Hospital (MGH) National Pregnancy Registry for Psychiatric Medications (NPRPM) was established to prospectively gather reproductive safety information of psychiatric medications. Enrollment is ongoing and includes pregnant women diagnosed with a psychiatric disorder. Participants are interviewed three times during the perinatal period: 1) enrollment; 2) 7 months gestation; and 3) 3 months postpartum. The exposed group for this analysis included women taking any benzodiazepine during the first trimester of pregnancy, and the comparison group was composed of women with psychiatric illness taking psychiatric medication(s) other than benzodiazepines during pregnancy. Information regarding major malformations is provided by participant interview and abstracted from medical records, and subsequently reviewed by a dysmorphologist blinded to medication exposure.

Results: For this analysis, a total of 1,053 women were eligible. N=151 women who had taken a benzodiazepine during the first trimester, and the comparison group was N=902 women. There were 5 major malformations in the exposure group: 3 with exposure to clonazepam and

2 to lorazepam. There were 32 major malformations in the control group. The absolute risk of major malformations in the exposure group was 3.21% and 3.46% in the control group. The odds ratio for major malformations after benzodiazepine exposure was 0.92 (95% CI 0.35-2.41).

Conclusion: This preliminary analysis of an ongoing pregnancy registry offers reassurance that benzodiazepines as a class do not appear to increase teratogenic risk. Greater numbers of participants are required to better estimate risk. The MGH NPRPM and other pregnancy registries will better inform the reproductive safety of benzodiazepines.

Learning Objectives:

1. Assess the relative risk of major malformations in infants after first trimester exposure to benzodiazepines.
2. Contrast gestational risks of in utero exposure to a benzodiazepine medication versus untreated psychiatric illness.

Literature References:

1. Freeman MP, Góez-Mogollón L, McInerney KA, et al: Obstetrical and neonatal outcomes after benzodiazepine exposure during pregnancy: Results from a prospective registry of women with psychiatric illness. General Hospital Psychiatry. 2018;53:73-79.
2. Grigoriadis S, Graves L, Peer M, et al: Maternal anxiety during pregnancy and the association with adverse perinatal outcomes. J Clin Psychiatry. 2018; 79:17r12011.

FUNCTIONAL CONNECTIVITY BETWEEN THE ORBITOFRONTAL CORTEX AND PUTAMEN IN OPIOID USE DISORDER

Mario Montelongo*[1], *Ramiro Salas[2], Michelle Patriquin[2], Hyuntaek Oh[1]*

[1]The Menninger Clinic, [2]Baylor College of Medicine

Abstract: Over the last 20 years, opioid overdose deaths and the incidence of opioid use disorder has continued increasing. The ventral tegmental area, substantia nigra, and the ventral and dorsal striatum have long been highlighted as being involved in the development and maintenance of addiction. However, imaging studies have begun showing that the prefrontal cortex also plays an important role in this process (Goldstein and Volkow, 2011). One study showed differences in the resting state functional connectivity (RSFC) of the orbital frontal cortex (OFC), dorsal striatum, and habenula between patients with high and low risk of addiction (Oh et al., 2020). In this study, we compared the RSFC of the OFC and dorsal striatum, and the amygdala of patients with high risk of opioid use disorder to that of healthy controls.

Psychiatric patients (N = 33) were recruited from The Menninger Clinic in Houston, Texas as a part of the McNair Initiative for Neuroscience Discovery – Menninger/Baylor (MIND-MB) research study. Problematic opioid use was determined using the World Health Organization (WHO) ASSIST questionnaire. Patients were matched to healthy controls (N = 33) using demographic characteristics (age and sex). Participants were scanned in a 3T Siemens Trio MR scanner in the Center for Advanced MR Imaging at Baylor College of Medicine. A 4.5 min structural MPRAGE sequence (TR = 2.66 ms, TR = 1200 ms, flip angle = 12o, 256 x 256 matrix, 1 mm isotropic voxels) was collected, followed by a 5 min resting state scan (TE = 40ms, TR = 2S, flip angle = 90o, 3.4x3.4x4 mm voxels). RSFC data were pre-processed using

the CONN Functional Connectivity Toolbox. The preprocessing pipeline included realignment, slice-timing correction, structural normalization to the MINI template, functional normalization, ART-based outlier detection and smoothing with an 8 mm full width at half maximum Gaussian smoothing kernel.

We compared functional connectivity between the OFC and the dorsal striatum and the amygdala between psychiatric patients with high risk of opioid addiction and healthy controls. Patients with a WHO-ASSIST score for opioid use of 4 or more were included in the analysis (average WHO-ASSIST Opioids = 25.1). Those with a WHO-ASSIST score for other substances, excluding alcohol and tobacco, greater than opioids were excluded. We observed that the opioid user group had lower RSFC between the left OFC and left putamen ($p = 0.009$), and left OFC and the right amygdala ($p = 0.05$).

These findings suggest that the OFC may be a target for neurostimulation and psychopharmacological intervention for patients with opioid use disorder. To gain further insight into reward-related brain connectivity in the opioid use disorder group, future steps will include assessing the OFC, striatum, and amygdala in a reward/disappointment processing paradigm- a reward is promised and delivered (juice delivery) or promised and withheld (juice expected but not delivered). The future study will provide a better understanding of how reward/disappointment processing may alter in patients with opioid use disorder.

Learning Objectives:

1. Patients with opioid use disorder have lower resting state functional connectivity between the left orbital frontal cortex and left putamen when compared to healthy controls.
2. Patients with opioid use disorder have lower resting state functional connectivity between the left orbital frontal cortex and right amygdala when compared to healthy controls.

Literature References:

1. Goldstein, R.Z., Volkow, N.D., 2011. Dysfunction of the prefrontal cortex in addiction: neuroimaging findings and clinical implications. Nat Rev Neurosci 12, 652–669. https://doi.org/10.1038/nrn3119
2. Oh, H., Lee, J., Gosnell, S.N., Patriquin, M., Kosten, T., Salas, R., 2020. Orbitofrontal, dorsal striatum, and habenula functional connectivity in psychiatric patients with substance use problems. Addictive Behaviors 108, 106457. https://doi.org/10.1016/j.addbeh.2020.106457

Individual Research Reports: Tracking Molecular, Physiological, and Behavioral Outcomes in Clinical Studies: Implications for Personalized Therapies and Trial Design

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

APPLICATION OF A BAYESIAN ADAPTIVE RANDOMIZATION DESIGN TO OPTIMIZE INTRAVENOUS KETAMINE DOSING FOR LATE-LIFE TREATMENT RESISTANT DEPRESSION

Nicholas Murphy*[1], *Marijn Lijffijt[2], Sidra Iqbal[3], Charles Green[4], Tabish Iqbal[2], Lee Chang[1], Lorna Hirsch[5], Nithya Ramakrishnan[6], Dylan Fall[7], Alan Swann[1], Rayan Al Jurdi[1], Sanjay Mathew[1]*

[1]Baylor College of Medicine, [2]Baylor College of Medicine/Micahel E DeBakey VA Medical Center, [3]Baylor College of Medicine/Baylor College of Medicine/Micahel E DeBakey VA Medical Center, [4]UTHealth, [5]UT Southwestern, [6]Baylor College of Medicine, [7]Micahel E DeBakey VA Medical Center

Abstract: The use of rapid onset glutamate modulating drugs to treat depression has grown in recent years due to the clinical efficacy of the the non-competitive N-methyl-D-aspartate receptor (NMDAR) antagonist ketamine (and its S-enantiomer). However, their use for treating late-life treatment resistant depression (LL-TRD) has not been investigated, acting as a barrier to safe treatment for a growing population of geriatric patients. The aim of our investigation was to clarify the dose-related effects of ketamine on clinical ratings and how these might be related to high-level change in synaptic transmission at a primary endpoint of 7 days post-infusion relative to a placebo infusion. N = 33 veteran patients (55-72 years, mean age: 62.9 ± 5.86, 30.3% female), were enrolled in a Bayesian adaptive randomized (BAR), double-blind, placebo-controlled design, and randomized to either a single infusion of IV ketamine (0.1, 0.25, or 0.5 mg/kg) or midazolam (0.03 mg/kg) condition. Patients completed clinical (Montgomery-Åsberg Depression Rating Scale (MADRS)) and electroencephalography (EEG) evaluations on six visits to assess the clinical effectiveness and durability of the intervention (baseline and 1, 2, 3, 7, and 28 days post infusion). Data were analyzed using Bayesian adaptations of the generalized linear model to study the effects of time, drug condition, and time*drug interaction. All analyses controlled for data values at the baseline time point. Kendall's tau correlations were performed to draw inferences on the relationship between gamma power and change in MADRS. Infusions in all conditions were safe and well tolerated. Randomization to the 0.1 (N=4) and 0.25 (N=5) mg/kg KET conditions was terminated by the BAR stopping rules due to significantly inferior clinical performance. N = 16 patients (48.5%) achieved a clinical response at day 7 (KET 0.5 = 8, KET 0.25 = 2, MID = 6). KET 0.5 mg/kg demonstrated a strong absolute probability (ap) of achieving a response at 7 days (ap = 0.7) and was consistent with a higher response at 7 days than MID (Posterior Probability (pp) [KET 0.5 > MID] = 0.89). Probability of a clinical response was lower for KET 0.25 (ap = 0.42) and 0.1 mg/kg (ap = 0.13). Response durability at 28 days among responders at 7 days was greatest for KET 0.5 (N = 7, ap = 0.82), and reduced proportionally with lower doses; KET 0.25 (N = 1, ap = 0.5), MID (N = 2, ap = 0.37). Our data showed evidence of a significant time*condition interaction amounting to divergent effects of drug on gamma power over the course of metabolism (pp [KET 0.5 > MID] = 0.92) [0-4 hours]. There were no detectable effects on gamma power between 24 hours and 7 days. Peak gamma power during infusion was associated with greater change in MADRS score at 7 days for KET 0.5 (τ = -0.5, p = .08), but not for MID (τ = 0.05, p = 0.84). Our results suggest that IV ketamine at 0.5 mg/kg is clinically effective in LL-TRD. Our EEG findings provide preliminary evidence that the reactivity of gamma power might reflect susceptibility to enhanced clinical effects; precision medicine optimization of ketamine therapy will require further study.

Learning Objectives:

1. Be able to discuss the biophysical challenges associated with treating depression in elderly patients.
2. Appreciate and describe the utility of Bayesian adaptive randomized clinical trial designs.

Literature References:

1. Lijffijt, M., Murphy, N., Iqbal, S. et al. Identification of an optimal dose of intravenous ketamine for late-life treatment-resistant depression: a Bayesian adaptive

randomization trial. Neuropsychopharmacol. (2021). https://doi.org/10.1038/s41386-021-01242-9.

2. Nelson JC, Delucchi K, Schneider LS. Efficacy of second generation antidepressants in late-life depression: a meta-analysis of the evidence. Am J Geriatr Psychiatry. 2008; 16:558–67.

USING ECOLOGICAL MOMENTARY ASSESSMENT TO IDENTIFY POTENTIALLY NON ADHERENT CLINICAL TRIALS PARTICIPANTS

Philip Harvey*[1], *Amy Pinkham[2], Colin Depp[3], Raaeanne Moore[3]*

[1]University of Miami Miller School of Medicine, [2]University of Texas at Dallas, [3]UCSD Medical Center

Abstract: Technology-based assessments offer the opportunity to collect momentary information with increased validity, as well as sampling relevant behavior that may be critical to successful completion of clinical trials. In specific, ecological momentary assessment (EMA) offers the opportunity to repeatedly sample potential clinical trials participants in order to assess their adherence prior to randomization. However, it is important to determine whether pre-randomization sampling is itself valid, both in terms of modeling later adherence during the trial and not excluding participants whose symptoms are in the range required by the clinical trial design

In this study, we collected EMA survey data on participants with schizophrenia (n=147) who were sampled 3 time per day for 30 days with a survey that queried location (home vs away) social context (alone vs. with someone), psychotic symptoms, and activities. Immediately prior to the EMA survey period, participants were rated with the PANSS. We examined the correlation between EMA adherence in the first 7 days as a predictor of adherence over the entire protocol and examined whether nonadherent patients differed from those who were adherent in their symptom severity.

We evaluated a common adherence threshold of >33% responses (i.e., at least one response per day). We found that 13% (19) of the 147 participants had lower than 33% adherence over the 30-day sampling period. Of those participants, 9 participants were non adherent in the first 7 days. Further, day 1-7 adherence of less than 33% excluded only 3 (2%) eventually adherent participants. The correlation between number of surveys answered in days 1-7 and over the entire protocol was r= .77 (R2=.60) and the correlation between baseline PANSS scores and adherence over the 30 days (90 total surveys) was r=.01 (R2=.0001).

Early nonadherence identified more than half of eventually non adherent participants with very few false positives. Non adherent patients did not differ in their symptom status compared to patients with acceptable levels of adherence. EMA surveys have the potential of identifying potentially non adherent participants with apparently limited risk of exclusion based on symptom severity.

Learning Objectives:

1. Describe the importance of adherence sampling prior to randomization in clinical trials.
2. Develop sampling procedures to identify potentially non adherent participants before they enter active treatment in clinical trials.

Literature References:

1. Jones SE, Moore RC, Pinkham AE, Depp CA, Granholm E, Harvey PD. A cross-diagnostic study of Adherence to Ecological Momentary Assessment: Comparisons across study length and daily survey frequency find that early adherence is a potent predictor of study-long adherence. Pers Med Psychiatry. 2021;29-30:100085. doi: 10.1016/j.pmip.2021.100085.
2. Vachon H, Viechtbauer W, Rintala A, Myin-Germeys I. Compliance and Retention With the Experience Sampling Method Over the Continuum of Severe Mental Disorders: Meta-Analysis and Recommendations. J Med Internet Res. 2019;21(12):e14475. Published 2019 Dec 6. doi:10.2196/14475.

ASSOCIATION BETWEEN THE EPIGENETIC LIFESPAN PREDICTOR GRIMAGE AND HISTORY OF SUICIDE ATTEMPT IN BIPOLAR DISORDER

Camila Nayane de Carvalho Lima*[1], *Alexandra Del Favero-Campbell[2], Alexandre Paim Diaz[2], Christopher Busby[2], Jair C. Soares[2], Consuelo Walss-Bass[2], Joao Quevedo[2], Gabriel R. Fries[2]*

[1]The University of Texas Health Science Center at Houston, [2]Louis A. Faillace, MD, McGovern Medical School

Abstract: Background: Bipolar Disorder (BD) has been previously associated with accelerated epigenetic aging and premature mortality. Suicide is a major cause of mortality in BD patients and a previous history of suicide attempt has been associated with worse clinical outcomes. We hypothesize that a history of suicide attempts may be associated with accelerated aging in patients.

Methods: Study participants were divided into three groups: 1) BD patients with no history of suicide attempt (BD/non-SA, n=75); 2) BD patients with lifetime history of suicide attempt (BD/SA, n=68); and 3) matched healthy controls (n=45). Whole blood genome-wide DNA methylation levels were measured with the Infinium EPIC BeadChip (Illumina), and the epigenetic lifespan predictor GrimAge and its acceleration index (GrimAgeAccel) were estimated using an online tool. We tested for group differences in GrimAgeAccel with one-way ANOVA followed by Tukey's post-hoc testing. We then ran linear regression models to identify differences in GrimAgeAccel while controlling for multiple covariates (model 1 - minimally-adjusted for age, sex, GWAS principal components (PCs), and body mass index (BMI); model 2 – same as model 1 plus white blood cell count estimates; model 3 – same as model 2 with addition of smoking score index; model 4 - adjusted for smoking score only; and model 5 - adjusted for smoking score, age, sex, GWAS PCs, and BMI).

Results: Groups significantly differed for GrimAgeAccel ($F(2,185) = 5.167$, $p=0.006$) in the unadjusted model. Post-hoc comparisons showed significantly greater GrimAgeAccel in participants with BD/SA than controls, with a mean of 3 years of excess epigenetic aging (BD/SA vs. Control, $p=0.004$), and a nominal difference between BD/SA vs. BD/non-SA ($p=0.058$, with BD/SA aging faster with a mean of 1.3 years). Adjusted regression models showed that BD/SA was significantly associated with a 1.64-year greater GrimAgeAccel after adjusting for age, sex, GWAS PCs, and BMI ($p=0.001$, model 1). This association remained significant after further adjustment for white blood cell proportions ($\beta=1.06$, $p=0.012$, model 2), but did not remain significant with further adjustment for smoking score in model 3 ($\beta=0.58$,

p=0.127). When covarying for smoking, we still found excess of GrimAgeAccel among those with BD/SA when adjusting for smoking score only (β=1.56, p<0.001, model 4), and with full adjustment for smoking score, age, sex, GWAS PCs, and BMI (β=1.64, p=0.001, model 5). In order to determine whether differences in GrimAgeAccel between groups were due to residual cofounding by differences in smoking status, we repeated our analysis in a subsample of current non-smokers. Among current non-smokers, we found excess GrimAgeAccel among those with BD/SA in adjusted analysis (β=1.28, p=0.010, model 1) although this was attenuated after further adjustment for white blood cell proportions (β=0.34, p=0.384, model 2). Finally, when analyzing a subset of patients who were not on lithium at the time of enrollment, GrimAgeAccel was 2.1 years higher in BD/SA compared with BD/non-SA (p=0.033). No association remained significant after further adjusting for age, sex, GWAS PCs, and BMI in this smaller sample (β=1.98, p=0.060 in model 1).

Conclusions: Accelerated GrimAge epigenetic aging may contribute to premature morbidity and mortality in BD patients with a history of lifetime suicide attempts.

Funding: This study was funded by the National Institute of Mental Health (NIMH, K01MH121580-01A1) and the Faillace Department of Psychiatry and Behavioral Sciences, UTHealth.

Learning Objectives:

1. Discuss epigenetic mechanisms of accelerated aging in patients with bipolar disorder with lifetime history of suicide attempt.
2. Discuss how accelerated aging in bipolar disorder may be associated with high morbidity and early mortality in these patients.

Literature References:

1. Caspi and Moffit: Gene–environment interactions in psychiatry: joining forces with neuroscience. Nat Rev Neurosci 2006; 7(7):583-90.
2. Gordoves and McMahon. The genetics of bipolar disorder. Molecular Psychiatry 2020; 25:544-559.
3. Fries GR, Zamzow MJ, Andrews T, Pink O, Scaini G, Quevedo J. Accelerated aging in bipolar disorder: A comprehensive review of molecular findings and their clinical implications. Neurosci Biobehav Rev.2020;112:107-116

OLANZAPINE/SAMIDORPHAN IN YOUNG ADULTS WITH SCHIZOPHRENIA, SCHIZOPHRENIFORM DISORDER, OR BIPOLAR I DISORDER WHO ARE EARLY IN THEIR ILLNESS: RESULTS OF THE ENLIGHTEN-EARLY STUDY

Rene Kahn[1], Christoph U. Correll[2], John Kane[3], Christina Arevalo[4], Adam Simmons[4], Christine Graham[4], Sergey Yagoda[4], Beibei Hu[4], David McDonnell[5]*

[1]Icahn School of Medicine at Mount Sinai, [2]Zucker Hillside Hospital, Glen Oaks; Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Hempstead, Charité Universitätsmedizin, Berlin, Germany, [3]The Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, [4]Alkermes, Inc., [5]Alkermes Pharma Ireland Ltd.

Abstract: Background: Early intervention in schizophrenia (SZ) or bipolar I disorder (BD-I) is critical to potentially improve disease trajectory. Olanzapine is effective at reducing symptoms but is often associated with clinically significant weight gain and cardiometabolic

sequelae. Weight gain may be particularly problematic for antipsychotic-naive patients, leading to treatment discontinuation. Combination olanzapine and samidorphan (OLZ/SAM; Lybalvi, Alkermes, Inc.) is approved for treatment of adults with SZ or BD-I. In clinical studies in adults with SZ, OLZ/SAM treatment had similar antipsychotic efficacy to olanzapine, with significantly less weight gain. This phase 3,
12-week, multicenter, randomized double-blind study (NCT03187769) evaluated the effect of OLZ/SAM on body weight in patients with recent onset SZ, schizophreniform disorder, or BD-I.

Methods: In total, 428 patients aged ≥16 and <40 years with a BMI <30 kg/m2 who were early in the course of illness (<24 weeks of cumulative antipsychotic exposure; <4 years since initial onset of active phase symptoms) and met DSM-5 criteria for SZ, schizophreniform disorder, or manic episode of BD-I were enrolled. Patients were stratified by diagnosis, region, and baseline BMI (<25 or ≥25 kg/m2) and randomized 1:1 to receive daily OLZ/SAM (olanzapine 5–20 mg + samidorphan 10 mg) or olanzapine (5–20 mg), with the dose determined by the investigator, for up to 12 weeks. Primary endpoint was percent change from baseline in body weight at week 12 (ANCOVA, with multiple imputation [MI] for missing values). Key secondary endpoints included the proportion of patients with ≥10% or ≥7% weight gain (logistic regression, MI) and change from baseline in waist circumference (ANCOVA, MI). Efficacy in controlling disease symptoms was assessed by the Clinical Global Impression of Severity (CGI-S) scale.

Results: Of 428 patients randomized (OLZ/SAM, n=213; olanzapine, n=215), 408 (95.3%) provided ≥1 postbaseline weight measure. At week 12, OLZ/SAM treatment was associated with a significantly lower percent weight change from baseline (4.91%) vs olanzapine (6.77%): least squares (LS) mean (SE) difference=−1.87% (0.745), P=0.012. Fewer patients in the OLZ/SAM vs the olanzapine group gained ≥10% of baseline body weight (21.9% vs 30.4%; OR=0.64, 95% CI=0.39, 1.05) or ≥7% of baseline body weight (33.1% vs 44.8%; OR=0.61, 95% CI=0.39, 0.94). Change from baseline in waist circumference was lower with OLZ/SAM (2.99 cm) vs olanzapine (3.90 cm): LS mean (SE) difference=−0.92 cm (0.582), 95% CI=−2.06, 0.22. Treatment with OLZ/SAM was associated with clinical symptom improvement over 12 weeks: LS mean (SE) change from baseline in CGI-S=−0.82 (0.06). Overall, 63.5% of patients in the OLZ/SAM group and 63.3% in the olanzapine group reported AEs. The most frequent AEs (OLZ/SAM vs olanzapine) were weight increase (21.8% vs 25.6%), somnolence (10.9% vs 9.3%), and alanine aminotransferase increase (7.6% vs 6.5%).

Discussion: In this study of patients early in the illness course of SZ, schizophreniform disorder, or BD-I, treatment with OLZ/SAM resulted in significantly less weight gain vs olanzapine. The safety profile was similar between OLZ/SAM and olanzapine and was consistent with that in prior studies. These results support the findings from the phase 3, 24-week pivotal weight study in patients with chronic schizophrenia and reiterate the clinical benefit observed with OLZ/SAM in mitigating olanzapine-associated weight gain.**Learning Objectives:**

1. Convey that OLZ/SAM and olanzapine have similar efficacy profiles, but OLZ/SAM is associated with less weight gain and a lower risk of clinically significant weight gain in patients with schizophrenia, schizophreniform disorder, or bipolar I disorder who were early in their illness.
2. Describe how the results of this study in patients who were early in their illness are consistent with previous comparisons of OLZ/SAM versus olanzapine in patients with chronic schizophrenia.

Literature References:

1. Manu P, Dima L, Shulman M, Vancampfort D, De Hert M, Correll CU: Weight gain and obesity in schizophrenia: epidemiology, pathobiology, and management. Acta Psychiatr Scand 2015; 132:97-108
2. Meyer JM, Davis VG, Goff DC, et al: Change in metabolic syndrome parameters with antipsychotic treatment in the CATIE schizophrenia trial: prospective data from phase 1. Schizophr Res 2008; 101:273-286.

Wednesday, June 1, 2022

Regulatory Plenary

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

REGULATORY PLENARY: PSYCHEDELIC DRUG DEVELOPMENT: PERSPECTIVES FROM THE FDA AND EMA

Charles Grob, Harbor-UCLA Medical Center

Overall Abstract: This year's Regulatory Plenary will focus on psychedelic drug development. There is growing interest in the development of psychedelic drugs as potential treatments for psychiatric disorders. The psychoactive effects of psychedelic agents present considerations and challenges for the design, conduct, and interpretation of clinical trials. Representatives from both FDA and EMA will discuss their agencies' approaches to these development programs.

PSYCHEDELIC DRUG DEVELOPMENT: REGULATORY PERSPECTIVES FROM THE US FOOD AND DRUG ADMINISTRATION AND EUROPEAN MEDICINES AGENCY

Tiffany Farchione, US Food and Drug Administration

Abstract: This year's Regulatory Plenary will focus on psychedelic drug development. There is growing interest in the development of psychedelic drugs as potential treatments for psychiatric disorders. The psychoactive effects of psychedelic agents present considerations and challenges for the design, conduct, and interpretation of clinical trials. Representatives from both FDA and EMA will discuss their agencies' approaches to these development programs.

Learning Objectives:

1. Understand FDA's approach to psychedelic drug development programs.
2. Understand EMA's approach to psychedelic drug development programs.

Literature References:

1. Draft Guidance for Industry: Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products; https://www.fda.gov/media/133660/download.
2. Swanson L.R. "Unifying Theories of Psychedelic Drug Effects", Front. Pharmacol., 02 March 2018 | https://doi.org/10.3389/fphar.2018.00172.

3. Vollenweider, F.X., Preller, K.H. Psychedelic drugs: neurobiology and potential for treatment of psychiatric disorders. Nat Rev Neurosci 21, 611–624 (2020). https://doi.org/10.1038/s41583-020-0367-2.
4. McClure-Begley T.D. and Roth B.L., "The promises and perils of psychedelic pharmacology for psychiatry", Nat Rev Drug Discov (2022). https://doi.org/10.1038/s41573-022-00421-7.
5. Amirah Al Idrus, "Psychedelics are getting closer to approval, but the market may not be ready", Aug 17, 2021, https://www.fiercebiotech.com/biotech/psychedelics-are-getting-closer-to-approval-but-market-may-not-be-ready.

PSYCHEDELIC DRUG DEVELOPMENT: REGULATORY PERSPECTIVES FROM THE US FOOD AND DRUG ADMINISTRATION AND EUROPEAN MEDICINES AGENCY

Maria Tome, European Medicines Agency

Abstract: This year's Regulatory Plenary will focus on psychedelic drug development. There is growing interest in the development of psychedelic drugs as potential treatments for psychiatric disorders. The psychoactive effects of psychedelic agents present considerations and challenges for the design, conduct, and interpretation of clinical trials. Representatives from both FDA and EMA will discuss their agencies' approaches to these development programs.

Learning Objectives:

1. Understand FDA's approach to psychedelic drug development programs.
2. Understand EMA's approach to psychedelic drug development programs.

PSYCHEDELIC DRUG DEVELOPMENT: REGULATORY PERSPECTIVES FROM THE US FOOD AND DRUG ADMINISTRATION AND EUROPEAN MEDICINES AGENCY

Dominic Chiapperino, U.S. Food and Drug Administration, Center for Drug Evaluation and Research

Abstract: This year's Regulatory Plenary will focus on psychedelic drug development. There is growing interest in the development of psychedelic drugs as potential treatments for psychiatric disorders. The psychoactive effects of psychedelic agents present considerations and challenges for the design, conduct, and interpretation of clinical trials. Representatives from both FDA and EMA will discuss their agencies' approaches to these development programs.

Learning Objectives:

1. Understand FDA's approach to psychedelic drug development programs.
2. Understand EMA's approach to psychedelic drug development programs.

Literature References: N/A

PSYCHEDELIC DRUG DEVELOPMENT: REGULATORY PERSPECTIVE FROM THE US FOOD AND DRUG ADMINISTRATION AND EUROPEAN MEDICINES AGENCY

Cynthia LaCivita, FDA

Abstract: This year's Regulatory Plenary will focus on psychedelic drug development. There is growing interest in the development of psychedelic drugs as potential treatments for psychiatric disorders. The psychoactive effects of psychedelic agents present considerations and challenges for the design, conduct, and interpretation of clinical trials. Representatives from both FDA and EMA will discuss their agencies' approaches to these development programs.

Learning Objectives:

1. Understand FDA's approach to psychedelic drug development programs.
2. Understand EMA's approach to psychedelic drug development programs.

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1. Draft Guidance for Industry: Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products; https://www.fda.gov/media/133660/download.
2. Swanson L.R. "Unifying Theories of Psychedelic Drug Effects", Front. Pharmacol., 02 March 2018 |https://doi.org/10.3389/fphar.2018.00172.
3. Vollenweider, F.X., Preller, K.H. Psychedelic drugs: neurobiology and potential for treatment of psychiatric disorders. Nat Rev Neurosci 21, 611–624 (2020). https://doi.org/10.1038/s41583-020-0367-2.
4. McClure-Begley T.D. and Roth B.L., "The promises and perils of psychedelic pharmacology for psychiatry", Nat Rev Drug Discov (2022). https://doi.org/10.1038/s41573-022-00421-7.
5. Amirah Al Idrus, "Psychedelics are getting closer to approval, but the market may not be ready", Aug 17, 2021, https://www.fiercebiotech.com/biotech/psychedelics-are-getting-closer-to-approval-but-market-may -not-be-ready

PSYCHEDELIC DRUGS FOR THE TREATMENT OF NEUROPSYCHIATRIC DISEASES - A EUROPEAN REGULATORY VIEW

Georgios Aislaitner, Federal Institute for Drugs and Medical Devices

Abstract: Effects to investigate and understand the effects of psychedelic drugs date back more than a century. Recently, substantial interest has been developed for psychedelics which are getting closer to approval, but the market may not be ready yet. A number of companies are currently exploring opportunities for psychedelics in treating neuropsychiatric diseases. There is growing evidence that psychedelics drugs can be effective treatments of neuropsychiatric disorders and the efficacy of psychedelic-assisted therapies is being investigated in various clinical trials. However, they are currently undergoing procedures with recommendations for their development programs and in some cases rigorous regulatory review by the EMA and National Competent Authorities in Europe. Specific requirements and difficulties are highlighted on the basis of concrete examples by EMA and BfArM representatives.

Learning Objectives:

1. Regulatory processes and requirements.
2. Psychedelic drugs as monotherapy or in assisted therapies.

Literature References:

1. Swanson L.R. "Unifying Theories of Psychedelic Drug Effects", Front. Pharmacol., 02 March 2018 | https://doi.org/10.3389/fphar.2018.00172.

2. Vollenweider, F.X., Preller, K.H. Psychedelic drugs: neurobiology and potential for treatment of psychiatric disorders. Nat Rev Neurosci 21, 611–624 (2020). https://doi.org/10.1038/s41583-020-0367-2.
3. McClure-Begley T.D. and Roth B.L., "The promises and perils of psychedelic pharmacology for psychiatry", Nat Rev Drug Discov (2022). https://doi.org/10.1038/s41573-022-00421-7.
4. Amirah Al Idrus, "Psychedelics are getting closer to approval, but the market may not be ready", Aug 17, 2021, https://www.fiercebiotech.com/biotech/psychedelics-are-getting-closer-to-approval-but-market-may-not-be-ready.

ASCP Awards Ceremony and ASCP Lifetime Awardee Talk

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

LIFETIME AWARDEE TALK

Madhukar Trivedi, UT Southwestern Medical Center

Overall Abstract: I am honored to present the 2022 Donald Klein Lifetime Achievement Award to Dr. Charles Reynolds. This talk will provide a history of the award in addition to Dr. Reynolds's significant contributions to the field of Clinical Psychopharmacology.

LOOKING BACK, GIVING THANKS, AND MOVING FORWARD: REFLECTIONS ON 50 YEARS AS PHYSICIAN/SCIENTIST/MENTOR IN GERIATRIC PSYCHIATRY

Charles Reynolds, University of Pittsburgh Medical Center, Western Psychiatric Institute and Clinic

Abstract: My journey has been grounded in relationships with those who mentored me, with those whom I have mentored, and with my patients, making it possible to pass the torch to new generations… The Don Klein award is much less a tribute to me than it is to my mentors, mentees, team, and patients.

My scientific work has been and remains at the interface of old-age psychiatry, primary care medicine, and behavioral neurology of aging. I will briefly summarize the contributions of my research team in three areas:

(1) Using the tools of clinical psychopharmacology and psychotherapy for preventing the recurrence of major depressive episodes in older adults and for enhancing neurocognitive functioning and independence in instrumental activities of daily living (published in JAMA 1999, NEJM 2006, and Arch Gen Psychiatry 2011);

(2) Understanding the moderators of response variability in late-life depression in order to further personalize care, with respect to both medical comorbidity (NEJM 2006) and neurocognition (JAMA Psychiatry 2016), in the context of difficult-to-treat depression in older adults (Lancet 2015);

(3) Modeling improved care of older adults for (a) successfully reducing suicide risk (JAMA 2004), (b) effectively preventing depression in low- and middle-income countries through the use of lay counselors (JAMA Psychiatry 2019), (c) prolonging life and health-span

in depressed primary-care elderly via long-term care orchestrated by on-site depression care managers (JAMA 2004; British Medical Journal 2013), and (d) diffusing stronger behavioral health homes in real-world rural and urban settings in Pennsylvania (Health Affairs 2018).

I will conclude my talk with transdisciplinary recommendations for future clinical practice and research in late-life depression, arising out of work with the Lancet/World Psychiatric Association Commission: "Time for United Action on Depression" (Lancet 2022).

Learning Objectives:

Following this presentation, participants will be able to identify and discuss:

1. Effective strategies for preventing recurrence of major depressive episodes in older adults.
2. The benefits to health of collaborative care models for preventing or treating late-life depression in primary care.
3. Moderators of response to depression treatment in older adults.

Literature References:

1. Reynolds C.F., Dew MA, Pollock et al. Maintenance treatment of major depression in old age. New England Journal of Medicine 354 (11): 1130-1138, 2006
2. Bruce ML, Ten Have TR, Reynolds CF 3rd, Katz II, Schulberg HC, et al. Reducing suicidal ideation and depressive symptoms in depressed older primary care patients: a randomized controlled trial. Journal of the American Medical Association. 2004 Mar 3;291(9):1081-91. PMID: 14996777.
3. Gallo JJ, Morales KH, Bogner HR, Raue PJ, Zee J, et al. Long term effect of depression care management on mortality in older adults: follow-up of cluster randomized clinical trial in primary care. British Medical Journal. 2013 Jun 5;346:f2570. PMID: 23738992; PMCID: PMC3673762.
4. Dias A, Azariah F,...Reynolds CF: Effect of a lay counselor- led intervention on the prevention of major depression in older adults living in low- and middle-income countries: a randomized clinical trial. JAMA Psychiatry 2019; 76(1): 13-20. Doi. 10/1001. Jama Psychiatry 2018.3048
5. Lenze EJ, Mulsant BH, Blumberger DM, Karp JF, Newcomer JW, Anderson SJ, Dew MA, Butters MA, Stack JA, Begley AE, Reynolds CF III: Efficacy, safety, and tolerability of augmentation pharmacotherapy with aripiprazole for treatment-resistant depression in late life: a randomized placebo- controlled trial. Lancet. 2015, 2;386(10011)2404-12. PMCID: PMC4690746
6. Lenze E., et al. Lancet 2016
7. Dias A et al., JAMA Psychiatry 2019

Panel Sessions

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

RACIAL AND ETHNIC DISPARITIES IN MENTAL HEALTH AND CLINICAL TRIALS: WHAT CAN BE DONE TO ENHANCE DIVERSITY AND ELIMINATE DISPARITIES?

Francisco Moreno, University of Arizona

Overall Abstract: Mental health disparity refers to a discrepancy in health outcomes, health services, and health determinants. Multiple studies have reported that racial/ethnic populations face numerous barriers to mental health treatment, services, and quality of care. There is also lack of diversity in clinical research and in clinical trial practices. The lack of diversity in clinical research implies that outcomes and interventions may not be generalized to all populations. This lack of diversity in mental health research has been an issue for decades and has drawn the attention of advocacy groups, pharmaceutical organizations, federal agencies, and academia due to its moral and scientific implications.

The objective of the panel is to educate the mental health community on the current state of mental health for minority populations, identify factors that contribute to mental health disparities and how these persistent disparities lead to poor health outcomes. The panel will also identify opportunities to enhance diversity, equity, and inclusion in clinical trials and research. In this peri-pandemic era, it has never been more important to address barriers or disruptions to mental health treatment and research, as minority populations have been disproportionately impacted by the pandemic.

This panel will include clinicians from academia and pharma, patient advocacy leaders, and clinical trials consulting groups that help network minority communities with pharmaceutical companies and medical societies. The panel will address:

- Mental health care disparities regarding diagnosis and treatment
- Disparities in Predictive models
- Disparities in Mental Health Literacy and Awareness
- Principals and strategies that will help eliminate/minimize mental health disparities within racial/ethnic sub-populations
- Specific interventions implemented in clinical trials programs across industry and academia to enhance and promote diversity of patients and culture competency.

After the presentation, attendees will have up-to-date information regarding the best practices, opinions, and solutions to address challenges related to mental health disparities within racial/ethnic populations.

Learning Objectives:

1. To educate the mental health community on the current state of mental health for minority populations, identify factors that contribute to mental health disparities and how these persistent disparities lead to poor health outcomes.
2. Identify opportunities to enhance diversity, equity, and inclusion in clinical trials and research.

RACIAL AND ETHNIC DISPARITIES IN MENTAL HEALTH AND CLINICAL TRIALS: WHAT CAN BE DONE TO ENHANCE DIVERSITY AND ELIMINATE DISPARITIES?

Luke Kramer, Evolution Research Group

Individual Abstract: Mental health disparity refers to a discrepancy in health outcomes, health services, and health determinants. Multiple studies have reported that racial/ethnic populations face numerous barriers to mental health treatment, services, and quality of care. There is also lack of diversity in clinical research and in clinical trial practices. The lack of diversity in clinical research implies that outcomes and interventions may not be generalized to all populations. This lack of diversity in mental health research has been an issue for decades and has drawn the attention of advocacy groups, pharmaceutical organizations, federal agencies, and academia due to its moral and scientific implications.

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• Specific interventions implemented in clinical trials programs across industry and academia to enhance and promote diversity of patients and culture competency. After the presentation, attendees will have up-to-date information regarding the best practices, opinions, and solutions to address challenges related to mental health disparities within racial/ethnic populations.

RACIAL AND ETHNIC DISPARITIES IN MENTAL HEALTH AND CLINICAL TRIALS: WHAT CAN BE DONE TO ENHANCE DIVERSITY AND ELIMINATE DISPARITIES?

John Kraus, Otsuka (OPDC)

Individual Abstract: Mental health disparity refers to a discrepancy in health outcomes, health services, and health determinants. Multiple studies have reported that racial/ethnic populations face numerous barriers to mental health treatment, services, and quality of care. There is also lack of diversity in clinical research and in clinical trial practices. The lack of diversity in clinical research implies that outcomes and interventions may not be generalized to all

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Learning Objectives:

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- Specific interventions implemented in clinical trials programs across industry and academia to enhance and promote diversity of patients and culture competency.

After the presentation, attendees will have up-to-date information regarding the best practices, opinions, and solutions to address challenges related to mental health disparities within racial/ethnic populations.

Literature References:

1. https://link.springer.com/article/10.1007%2Fs40596-020-01276-z
2. Acad Psychiatry. 2020 Oct;44(5):523-530. doi: 10.1007/s40596-020-01276-z. Epub 2020 Jul 23.

N/A

Lionel Philips, Inside Edge Consulting Group

Individual Abstract: N/A
Learning Objectives: N/A
Literature References: N/A

DEPRESSION, ATTENTIONAL BIAS AND EMERGING ROLE OF THYROID FUNCTION AND PHARMACOGENOMIC TESTING IN MOOD DISORDERS

Mark Frye, Mayo Clinic

Overall Abstract: Thyroid hormones (TH) regulate all aspects of ontological neurodevelopment and in adults this regenerative process is maintained by neural stem cell rich brain areas. Physiologically, TH enters the central nervous system via blood-brain or blood-cerebrospinal-fluid barriers whereby T4 binds to transthyretin releasing the hormone into cerebral spinal fluid. Once in the neural cell, T3 availability is tightly regulated between the

deiodinase enzymes, DIO2 (converting T4 to T3) and DIO3 (converting T4 to reverse or RT3) (Luongo et al., 2019).
The administration of TH prior to treatment has been associated with reduced overall illness severity (Liu et al., 2014). Thus, as an example, the ongoing presence of subventricular and subgranular hippocampal neurogenesis and the critical role of TH in mitigating CNS injuries, are in part the rational to consider TH as repair cues in regenerative medicine (Vancamp et al. ,2020). Furthermore, a population-based study reported that an elevated TSH was associated with significantly lower total brain volume, white matter volume, and hippocampal volume (Ittermann et al., 2018).

In studies with depressed patients, elevated TSH has been shown to significantly correlate with depressive symptom severity (Cleare 1995), treatment-resistant depression (Cohen et al., 2018), and inversely correlate to dorsal lateral prefrontal cortex cerebral blood flow metabolism (Marangell et al,1997), a brain region implicated in depression. Further, sustained low TH levels (i.e. low free T3) can be associated with depression recurrence (Joffe et al., 2000). Treatment with thyroid hormone, liothyronine (i.e. synthetic triiodothyronine) has a clinical evidence base for antidepressant acceleration (i.e. concurrent treatment with faster response time), particularly in women. (Altshuler et al., 2001).

Cognitive models of depression conceptualize negative cognitions drive negatively biased automatic thinking and attention (Beck 2008). A cognitive neuropsychological hypothesis put forward suggests that antidepressant treatment reduces negative, relative to positive, emotional material, absent any significant mood change early in treatment (Harmer et al., 2004; Harmer et al., 2009). Serum-free T3 levels have also been significantly associated with a greater implicit attentional bias toward happy stimuli (N=149, r=0.18, age-adjusted p=0.03, Burdick unpublished observations).

T4 is a pro-hormone that is released from the thyroid gland and is converted to metabolically active T3 by thyroid deiodinase type I (DI01) in the liver and deiodinase type II (DI02) in the central nervous system (CNS). Single nucleotide polymorphisms (SNPs) in the DI01-C785T gene functionally change serum thyroid parameters. For example, carriers of the SNP, rs11206244, in the DI01- C785T gene, have impaired conversion of T4 to T3, T4 to rT3, and lower T3/rT3 ratio, suggesting a lower DI01- C785T activity. Our pilot right unilateral (RUL) ECT survival analysis showed a faster time to response (50% reduction Hamilton Depression Rating Scale or HDRS) for depressed patients randomized to T3 compared to placebo ($\chi 2$=6.07, df=1, p=0.01) with a commensurate reduced number of ECT treatments (5.3±1.0 vs. 7.4±0.9, p=0.03). There was an association between T3+RUL ECT and rs11206244 (p=0.03) where minor allele carriers (i.e. impaired T4 to T3 conversion), vs. non-carriers, received fewer ECT treatments in the T3 group, compared to placebo (5.3±1.0 vs. 8.3±2.1, p=0.04) suggesting genetic variation may clinically contribute to accelerating mood response in ECT.

Learning Objectives:

1. To highlight and the effects of liothyronine in neuronal regeneration
2. To review the interface between thyroid and mood disorders.
3. Review thyroid hormone regulation and therapeutic outcomes of thyroid augmentation and acceleration in patients with depression
4. Review attentional bias in major depressive disorder and as a target for depression treatment
5. Emerging role and recent research studying genetic variations and their implications in treatment outcomes.

EFFECTS OF LIOTHYRONINE (T3) IN NEURONAL REGENERATION AND ITS IMPLICATIONS IN MOOD DISORDERS

Mark Frye, Mayo Clinic

Individual Abstract: Thyroid hormones (TH) regulate all aspects of ontological neurodevelopment and in adults this regenerative process is maintained by neural stem cell rich brain areas. Physiologically, TH enters the central nervous system via blood-brain or blood-cerebrospinal-fluid barriers whereby T4 binds to transthyretin releasing the hormone into cerebral spinal fluid. Once in the neural cell, T3 availability is tightly regulated between the deiodinase enzymes, DIO2 (converting T4 to T3) and DIO3 (converting T4 to reverse or RT3) (Luongo et al., 2019). Preclinical studies estimate 80% of intracellular brain T3 is from local T4 deiodination. By binding to nuclear thyroid hormone receptors, T3 can activate gene transcription in TH targeted cell types.

Epidemiological studies have identified that sustained low TH levels (i.e. low free T3) can be associated with depression recurrence (Joffe et al., 2000) as well as an overall delay in medical illnesses recovery (Bunevicius et al., 2015). Moreover, the administration of TH prior to treatment has been associated with reduced overall illness severity (Liu et al., 2014). Thus, as an example, the ongoing presence of subventricular and subgranular hippocampal neurogenesis and the critical role of TH in mitigating CNS injuries, are in part the rational to consider TH as repair cues in regenerative medicine (Vancamp et al. ,2020).Furthermore, a population-based study reported that an elevated TSH was associated with significantly lower total brain volume, white matter volume, and hippocampal volume (Ittermann et al., 2018). In studies with depressed patients, elevated TSH has been shown to significantly correlate with depressive symptom severity (Cleare 1995), treatment resistant depression (Cohen et al., 2018), and inversely correlate to dorsal lateral prefrontal cortex cerebral blood flow metabolism (Marangell et al,1997), a brain region implicated in depression.

Learning Objectives:

1. To highlight and the effects of liothyronine in neuronal regeneration and understand how do specific genetic variations on deiodinase enzymes regulation impact treatment response.
2. Discuss strategies aimed to better understand thyroid hormone regulation and its implications for therapeutic outcomes in patients with depression.

Literature References:

1. Bunevicius, A., Iervasi, G., and Bunevicius, R. (2015). Neuroprotective actions of thyroid hormones and low-T3 syndrome as a biomarker in acute cerebrovascular disorders. Expert review of neurotherapeutics, 15(3), 315–326. https://doi.org/10.1586/14737175.2015.1013465
2. Philibert, Robert A., et al. "The relationship of deiodinase 1 genotype and thyroid function to lifetime history of major depression in three independent populations." American Journal of Medical Genetics Part B: Neuropsychiatric Genetics 156.5 (2011): 593-599.

REVISITING TREATMENT IMPLICATIONS OF THE USE OF THYROID HORMONES IN MOOD DISORDERS

Michael Gitlin, UCLA Medical Center

Individual Abstract: Treatment with thyroid hormone, liothyronine (i.e. synthetic triiodothyronine) has a clinical evidence base for antidepressant acceleration (i.e. concurrent treatment with faster response time), particularly in women. The effect size (0.58) of a T3 acceleration of antidepressant response meta-analysis increased as the percentage of women in each study increased. Epidemiological studies have identified that sustained low thyroid hormone levels (i.e. low free T3) can be associated with depression recurrence (Joffe et al., 2000) as well as an overall delay in medical illnesses recovery (Bunevicius et al., 2015). Moreover, the administration of thyroid hormone prior to treatment has been associated with reduced overall illness severity (Liu et al., 2014) Serum free T3 levels have also been significantly associated with overall mood relapse with each 0.10 µg increase in T3 associated with 22% decrease in risk of recurrence.

Learning Objectives:

1. To highlight the interface between thyroid and mood disorders.
2. Review thyroid hormone regulation and therapeutic outcomes of thyroid augmentation and acceleration in patients with depression

Literature References:

1. Altshuler, Lori L., Mark A. Frye, and Michael J. Gitlin. "Acceleration and augmentation strategies for treating bipolar depression." Biological psychiatry 53.8 (2003): 691-700.
2. Stern, R. A., Nevels, C. T., Shelhorse, M. E., Prohaska, M. L., Mason, G. A., and Prange, A. J. (1991). Antidepressant and memory effects of combined thyroid hormone treatment and electroconvulsive therapy: preliminary findings. Biological Psychiatry.

THE RELATIONSHIP BETWEEN FREE TRIIODOTHYRONINE (FT3) AND EMOTIONAL PROCESSING IN BIPOLAR DISORDER

Katherine Burdick, Brigham and Women's Hospital/Harvard Medical School

Individual Abstract: Introduction: Thyroid dysfunction has been implicated in the pathophysiology of bipolar disorder (BD) because of the known effects on cognition and mood. Here we aimed to examine the effect of thyroid hormones and behavior using an emotional processing task in BD.

Methods: The study included 150 individuals with a diagnosis of BD. We administered the CANTAB Emotion Recognition Task (ERT faces) and assayed levels of free triiodothyronine (FT3) at the time of assessment. The ERT requires the accurate identification of both positive (happy) and negative (sad, angry, fearful, disgusted) valences and generates measures of implicit attentional affective bias. We conducted an analysis of covariance (ANCOVA) to compare ERT performance by FT3 status (groupings based upon a high-versus-low median split), with age and sex as covariates. Posthoc Pearson correlations were conducted to determine the direction and size of significant associations.

Results: We observed a significant main effect of FT3 group on ERT performance that was specific to the happy condition (all other valences were non-significant). We found that higher levels of serum free T3 were associated with greater implicit attentional bias toward happy stimuli (n=149, r=0.18, p=0.03).

Conclusions: These findings suggest that optimizing thyroid hormone levels in individuals with BD, even during affectively-stable phases of the illness may have a positive effect on emotional

processing. Specifically, higher levels of FT3 may contribute to an attentional bias toward positive stimuli, which may counter the trait-like negativity bias that is known to influence both risk and recurrence of depression.

Learning Objectives:

1. To discuss the role of thyroid hormones in brain-based measures of emotional processing.
2. To outline the clinical implications of thyroid hormones as a treatment target in mood disorders.

Literature References:

1. Beck AT. The evolution of the cognitive model of depression and its neurobiological correlates. Am J Psychiatry 2008;165:969-977. DOI: 10.1176/appi.ajp.2008.08050721
2. Harmer CJ, Shelley NC, Cowen PJ, Goodwin GM. Increased positive versus negative affective perception and memory in healthy volunteers following selective serotonin and norepinephrine reuptake inhibition. Am J Psychiatry. 2004 Jul;161(7):1256-63

DEIODINASE VARIATION AND LIOTHYRONINE TREATMENT INTERACTION TO ACCELERATE ECT RESPONSE IN MAJOR DEPRESSION: PILOT DATA AND IMPLICATIONS FOR THYROID PHARMACOGENOMIC TESTING IN MOOD DISORDERS

Nicolas Nunez, Mayo Clinic

Individual Abstract: T4 is a pro-hormone that is released from the thyroid gland and is converted to metabolically active T3 by thyroid deiodinase type I (DI01) in the liver and deiodinase type II (DI02) in the central nervous system (CNS). Single nucleotide polymorphisms (SNPs) in the DI01-C785T gene functionally change serum thyroid parameters. For example, carriers of the SNP, rs11206244, in the DI01- C785T gene, have impaired conversion of T4 to T3, T4 to rT3, and lower T3/rT3 ratio, suggesting a lower DI01-C785T activity.

Our pilot right unilateral (RUL) ECT survival analysis showed a faster time to response (50% reduction Hamilton Depression Rating Scale or HDRS) for depressed patients randomized to T3 compared to placebo ($\chi 2$=6.07, df=1, p=0.01) with a commensurate reduced number of ECT treatments (5.3±1.0 vs. 7.4±0.9, p=0.03). There was an association between T3+RUL ECT and rs11206244 (p=0.03) where minor allele carriers (i.e. impaired T4 to T3 conversion), vs. non-carriers, received fewer ECT treatments in the T3 group, compared to placebo (5.3±1.0 vs. 8.3±2.1, p=0.04) suggesting genetic variation may clinically contribute to accelerating mood response in ECT. This accelerating treatment response to RUL ECT is of note given a previous ECT lead placement study showed RUL to be less effective than BT lead placement in rapid symptom relief. Moreover, we demonstrated a significant interaction between liothyronine treatment and a functional SNP of the DI01- C785T gene with carriers of the minor allele vs. non-carriers, receiving fewer ECT treatments overall (p=0.045) and with RUL ECT alone (p=0.035).

Our study which reflects preliminary findings towards a proof of concept study design, suggests that exogenous liothyronine may attenuate the lower functional ability to convert peripheral T4 to T3 caused by genetic variation of rs11206244 gene DI0-C785T, and by doing so, may accelerate response time in patients receiving ECT.

Learning Objectives:

Review thyroid hormone regulation and therapeutic outcomes of thyroid augmentation and acceleration in patients with depression.

1. Emerging role and recent research studying genetic variations and their implications in treatment outcomes.

Literature References:

1. Nuñez, Nicolas A., et al. "Deiodinase variation and liothyronine treatment interaction to accelerate ECT response in major depression: Pilot data and implications for thyroid pharmacogenomic testing in mood disorders." Personalized Medicine in Psychiatry 29 (2021): 100089.
2. 2.Cooper-Kazaz, R. et al. (2007). Combined treatment with sertraline and liothyronine in major depression: a randomized, double-blind, placebo-controlled trial. Archives of general psychiatry, 64(6), 679–688.

EXPLORING POTENTIAL SYNERGIES BETWEEN KETAMINE'S PHARMACOLOGICAL PROPERTIES AND PSYCHOTHERAPEUTIC TREATMENT APPROACHES

Gerard Sanacora, Yale

Overall Abstract: Ketamine has emerged as a rapid-acting antidepressant, with the S-enantiomer of the drug (esketamine) receiving Food and Drug Administration approval for treatment-resistant depression (TRD) in 2019. Emerging evidence also suggests ketamine may provide benefit in the treatment of other neuropsychiatric treatments including substance use disorders. While evidence suggests ongoing treatment can prevent relapse, concerns exist regarding the risks, costs, and practicality of long-term, frequent treatments with the drug. In light of these concerns, there is great interest in identifying and developing possible means of enhancing the efficacy of the treatments and especially in extending the durability of the treatment to minimize the need and frequency of maintenance ketamine treatments.

Several mechanisms have been proposed as mediators of ketamine's antidepressant effect. Strong preclinical evidence suggests that NMDA receptor antagonism, as well as direct or indirect pharmacological effects on other receptor targets, serves as the proximal event in initiating a cascade of neurobiological mechanism that result in an enhancement in synaptic plasticity. Following this line of reasoning it is hypothesized that the ketamine treatment may create a unique window of opportunity during which cognitive and behavioral interventions may be used to harness a state of enhanced neuroplasticity that may confer a period of enhanced cognitive and behavioral flexibility. Furthermore, it is hypothesized that the use of behavioral and psychotherapeutic interventions may help to "lock in" more adaptive cognitive schemata through the processes of activity-dependent synaptic and circuit strengthening and survival. Others propose the possibility that the unique psychological experiences precipitated by ketamine allows patients to become more accepting of alternative thought processes and coping strategies that could enhance the efficacy of psychotherapeutic and motivational approaches in providing longer-term clinical benefits.

The presenters in this symposium will share recent and ongoing work from clinical trials and translational neuroscience studies specifically examining the potential effectiveness of ketamine combined psychosocial and behavioral interventions, as well as attempts to better understand the possible mechanisms of action underlying the synergistic nature of the

interaction if it is found to exist. Dr. Wilkinson will report on two early phase studies exploring the feasibility and efficacy of ketamine augmented with cognitive behavioral therapy (CBT) and discuss an ongoing NIMH funded study in this area. Dr. Price will share data on a study of 155 depressed patients suggesting that training positive self-representations could provide an efficient, low-cost, and highly dissemination-ready strategy for leveraging and extending ketamine's rapid antidepressant effects, and her ongoing NIMH trial using this approach. Dr. Dakwar will present his data exploring the potential use of ketamine combined with psychotherapeutic approaches including motivational enhancement therapy as a novel approach to provide longer-term benefits to individuals struggling with substance use disorders.

Overall, the panel will attempt to provide an up-to-date perspective of the previous work done in this area of inquiry, discuss ongoing work and highlight the major questions that remain to be addressed in this exciting area research. Dr. Sanacora, serving as panel chair, and Dr. Sanjay Mathew, serving as panel discussant, will attempt to provide context and perspective to the studies and highlight the potential importance of this work to neuroscience and clinical care.

Learning Objectives:

1. To review the potential mechanism underlying the proposed synergistic effects existing between ketamine and psychotherapeutic interventions.
2. To familiarize the attendees with the current data suggesting combined use of ketamine with psychotherapeutic interventions could enhance treatment response in patients with mood and substance use disorders.

COGNITIVE BEHAVIORAL THERAPY TO SUSTAIN THE ANTIDEPRESSANT EFFECTS OF KETAMINE IN TREATMENT-RESISTANT DEPRESSION: A RANDOMIZED CLINICAL TRIAL

Samuel Wilkinson, Yale School of Medicine

Individual Abstract: Introduction: Ketamine has emerged as a rapid-acting antidepressant. While ongoing treatment can prevent relapse, concerns exist regarding long-term exposure. We conducted a randomized trial to examine the feasibility and efficacy of cognitive behavioral therapy (CBT) following intravenous ketamine in treatment-resistant depression (TRD).

Methods: Subjects with TRD were recruited and treated with 6 intravenous infusions of ketamine over 3 weeks. Subjects who experienced clinical response (≥50% improvement in depression severity) were then randomized to receive CBT or treatment as usual (TAU) for an additional 14 weeks, using a sequential treatment model.

Results: Of 41 patients who signed consent, 28 patients achieved response and were randomized to CBT or TAU. When measured by the Montgomery-Asberg Depression Rating Scale (primary outcome measure), the effect size at end-of-study was moderate, Cohen's d=0.65 (95% CI, -0.55 – 1.82), though the group-by-time interaction effect was not significant. There was a significant group-by-time interaction as measured by the Quick Inventory of Depressive Symptomatology (F=4.58, p=0.033), favoring a greater sustained improvement in the CBT group. This corresponded to a moderate-to-large effect size of Cohen's d=0.71 (95% CI, -0.30 – 1.70) at end-of-study (14 weeks following last ketamine infusion). In a subset of patients (N=20) that underwent cognitive testing using the emotional N-back assessments pre-

and post-ketamine, ketamine responders showed improvement in accuracy of emotional N-back ($t(8)=2.33$, $p<.05$) whereas non-responders did not($t(10)<1$, p ns).

Conclusion: This proof-of-concept study provides preliminary data that CBT may sustain the antidepressant effects of ketamine in TRD. Further study and optimization of this treatment approach in well-powered clinical trials is recommended.

Learning Objectives:

1. To understand the state of the literature with respect to combining ketamine and psychotherapy.
2. To understand the rate of relapse following ketamine/esketamine without some form of long-term strategy.

Literature References:

1. Wilkinson ST*, Rhee TG, Joormann J, Webler R, Ortiz Lopez M, Kitay BM, Fasula M, Fenton L, Sanacora G. Cognitive behavioral therapy to sustain the antidepressant effects of ketamine in treatment-resistant depression: A randomized clinical trial. Psychother Psychosom, (in press).
2. Murrough JW, Perez AM, Pillemer S, Stern J, Parides MK, aan het Rot M, Collins KA, Mathew SJ, Charney DS, Iosifescu DV. Rapid and longer-term antidepressant effects of repeated ketamine infusions in treatment-resistant major depression. Biol Psychiatry 2013 Aug 15; 74(4):250-6.

A BRIEF, FULLY AUTOMATED NEUROCOGNITIVE TRAINING INTERVENTION EXTENDS THE ANTIDEPRESSANT EFFECT OF A SINGLE KETAMINE INFUSION

Rebecca Price, University of Pittsburgh

Individual Abstract: Background: Intravenous ketamine, which displays rapid antidepressant properties, is posited to reverse depression by rapidly enhancing neuroplasticity. We posited that ketamine would provide a clinical window of opportunity in which to introduce automated neurocognitive training techniques to consolidate adaptive forms of cognitive processing (specifically, positive implicit representations of self) while neuroplasticity remains high.
Methods: 154 unipolar depressed adults who failed at least one FDA-approved antidepressant medication were randomized to one of three intervention arms: (1) a single infusion of ketamine (0.5mg/kg over 40min) followed by 4 days (~2.5hours total) of active cognitive training, targeting self-worth through 'evaluative conditioning,' delivered by computer (ket+CT;n=53); (2) ketamine infusion followed by four days of sham computer training (ket+Sham;n=50); or (3) saline infusion followed by four days of cognitive training (saline+CT;n=51). The Montgomery-Asberg Depression Rating Scale quantified depression severity over a 30-day period. Patients are being followed in an ongoing 1-year naturalistic follow-up.

Results: Ketamine rapidly reduced depression scores at 24-hours post-infusion [$F(1,149)=24.2$, $p<.0001$; 52% responders (with ≥50% reduction in MADRS score) vs. 24% in saline arm]. In intent-to-treat, linear mixed models over the 30-day acute phase, ket+CT produced a stable, enduring decrease in depression relative to saline+CT ($t149=3.94$;$p=.0001$). By contrast, ket+Sham produced an initial decrease in depression that waned linearly over the 30-day window (group*time:$t568=-2.14$;$p=.03$), becoming non-significant by Day 12. In naturalistic

follow-up, the ket+CT arm showed continued benefits on self-reported depression 3-months post-infusion (t83=2.6;p=.01).

Conclusions: After priming brain plasticity with ketamine, training positive self-representations could provide an exceedingly efficient, low-cost, portable, non-invasive, and highly dissemination-ready strategy for leveraging and extending ketamine's rapid antidepressant effects.

Learning Objectives:

1. Discuss potential benefits of a synergistic pairing between ketamine's neuroplasticity-enhancing effects and mechanistic, targeted behavioral treatments deployed to leverage these effects during a post-infusion window of opportunity.
2. Understand pros and cons of utilizing a fully automated, computer-based intervention following ketamine infusion.

Literature References:

1. Wilkinson ST, Holtzheimer PE, Gao S, Kirwin DS, Price RB. Leveraging neuroplasticity to enhance adaptive learning: The potential for synergistic somatic-behavioral treatment combinations to improve clinical outcomes in depression. Biol Psychiatry. 2019; 85:454-465.
2. Price RB, Duman R. Neuroplasticity in cognitive and psychological mechanisms of depression: An integrative model. Mol Psychiatry. 2020; 25:530-543.

MIND, INTERRUPTED: HARNESSING THE EFFECTS OF KETAMINE IN ADDICTION TREATMENT

Elias Dakwar, College of Physicians and Surgeons Columbia University

Individual Abstract: Subanesthetic ketamine has shown preliminary transdiagnostic efficacy in psychiatric populations, with its rapid, robust, and enduring antidepressant effect attributed to a variety of proplastic and neuromodulatory mechanisms, which may also be relevant to its anxiolytic and anti-addiction effects. Its psychoactive properties may also have therapeutic potential; they sometimes involve the production of rich psychic content, shifts in perspective, meaningful insight, and abreaction (e.g., emotional release) experiences. Here I report on the rationale, methodology, and results of several published trials involving the coupling of ketamine infusions with behavioral treatment for a variety of substance use disorders. These data show that ketamine facilitates behavioral treatment, including mindfulness training and motivational enhancement therapy, to promote abstinence and reduce the risk of relapse. They also suggest that the behavioral treatment might produce the most salient initial impact if provided in the critical window after the infusion. Future directions and ongoing studies will also be discussed, especially insofar as they shed further light on the question of synergy.

Learning Objectives:

1. Understand the relevance of ketamine to addiction treatment.
2. Recognize the challenges involved in pairing ketamine with behavioral treatment in this population.

Literature References:

1. Dakwar, E., Levin, F., Hart, C. L., Basaraba, C., Choi, J., Pavlicova, M., and Nunes, E. V. (2020). A single ketamine infusion combined with motivational

enhancement therapy for alcohol use disorder: A randomized midazolam-controlled pilot trial. The American Journal of Psychiatry, 177(2), 125-133.
2. Dakwar, E., Nunes, E. V., Hart, C. L., Foltin, R. W., Mathew, S. J., Carpenter, K. M., "Jean" Choi, C. J., Basaraba, C. N., Pavlicova, M., and Levin, F. R. (2019). A single ketamine infusion combined with mindfulness-based behavioral modification to treat cocaine dependence: A randomized clinical trial. The American Journal of Psychiatry, 176(11), 923-930

*REAL-WORLD EVIDENCE OF LONG-TERM KETAMINE/ESKETAMINE THERAPY

Balwinder Singh, Mayo Clinic

Overall Abstract: Ketamine is a novel glutamatergic anesthetic agent, "repurposed" as a rapid-acting antidepressant for treatment-resistant depression (TRD). The enantiomer esketamine is now FDA approved, in conjunction with an oral antidepressant, for patients with TRD and major depressive disorder (MDD) with acute suicidal ideation or behavior. While there are numerous studies of the efficacy, safety, and tolerability of short-term off-label intravenous (IV) racemic ketamine and intranasal esketamine for TRD, the evidence base for long-term ketamine, especially IV ketamine is much less.

While ketamine's rapid antidepressant effect is revolutionary, the effect of a single infusion dissipates quickly. Hence, the natural response is to extend the number of treatments to prolong antidepressant effects. For TRD, studies have provided continuation infusions, for example up to 6, and then maintenance treatments every few weeks. However, the evidence base is limited regarding the duration and efficacy of long-term ketamine use, with the risk of ketamine tachyphylaxis/tolerance. There are also large gaps in the literature regarding the long-term side effects of using ketamine on a maintenance basis. Ketamine is considered a third-line treatment with Level 3 evidence for acute bipolar depression. Thus, highlighting a potential role of ketamine in acutely treating bipolar depression. Multicenter intranasal esketamine trials excluded patients with bipolar depression, thus limiting the generalizability of esketamine MDD trials' findings to bipolar depression.

Ketamine clinics providing off-label ketamine infusions to patients have flourished throughout the United States, with many being run by prescribers with limited to no mental health experience. Additionally, some of these clinics will treat a wide range of diagnoses including substance use disorder, at times with limited supervision. This symposium will discuss the real-world efficacy and challenges of a ketamine clinic that has been operating for 4 years.

This session will cover off-label use of IV ketamine and the FDA-approved esketamine for TRD. We will review the evidence base synthesis of ketamine/esketamine in treatment-resistant unipolar and bipolar depression, clinical pearls, and efficacy and outcomes of long-term ketamine use at Mayo Clinic. Presenters will be Dr. Jennifer Vande Voort (IV ketamine), Dr. Balwinder Singh (long-term ketamine use), and Dr. Simon Kung (esketamine and pitfalls).

Learning Objectives:

1. To understand the evidence, base of intravenous ketamine and intranasal esketamine in Treatment-Resistant Depression and review real-world evidence of long-term ketamine/esketamine therapy

2. To review the pitfalls of long-term ketamine/esketamine use and lessons learned.

EVIDENCE OF IV KETAMINE FOR TREATMENT-RESISTANT UNIPOLAR AND BIPOLAR DEPRESSION AND OBSERVATIONS FROM RUNNING A KETAMINE CLINIC

Jennifer Vande Voort, Mayo Clinic

Individual Abstract: Intravenous ketamine has been demonstrated to have robust, rapid-acting, antidepressant and antisuicidal properties. This novel approach to treatment resistant depression has led to the rapid growth of IV ketamine clinics nationally. However, the urgent need for rapidly acting antidepressant treatments should be balanced by a measured response and recognition that there are still gaps in our knowledge base, particularly regarding long-term efficacy and safety. Here, we review the evidence for acute and chronic use of IV ketamine for treatment resistant unipolar and bipolar depression and share observations from building and maintaining a clinical IV ketamine practice.

Learning Objectives:

1. Evaluate the evidence for acute, continuation, and maintenance phase IV ketamine for treatment resistant depression
2. Discuss building and maintaining a ketamine clinic

Literature References:

1. Wilkinson ST, Katz RB, Toprak M, et al: Acute and longer-term outcomes using ketamine as a clinical treatment at the Yale Psychiatric Hospital. J Clin Psychiatry 2018; 79:17m11731.
2. Joseph B, Parsaik AK, Ahmed AT, Erwin PJ, Singh B. A Systematic Review on the Efficacy of Intravenous Racemic Ketamine for Bipolar Depression. J Clin Psychopharmacol. 2021;41(1):71-75.
3. Parikh SV, Lopez D, Vande Voort JL, Rico J, Achtyes E, Coryell W, Goddard A, Goes F, Greden JF, Singh B, Kaplin A, Frye MA, Maixner D, Watson B, Drake K, Tarnal V, Riva-Posse P, Bobo WV, Bio-K Study Team. Developing an IV Ketamine Clinic for Treatment-Resistant Depression: a Primer. Psychopharmacol Bull. 2021 Jun 1;51(3):109-124.

EFFICACY AND SAFETY OF KETAMINE/ESKETAMINE CONTINUATION FOR TREATMENT-RESISTANT DEPRESSION IN LONG-TERM

Balwinder Singh, Mayo Clinic

Individual Abstract: A subanesthetic dose of intravenous (IV) racemic ketamine produces a rapid and robust antidepressant response, which is typically short-lived. Maintenance ketamine is provided to help maintain the antidepressant response for those with treatment-resistant depression (TRD). However, there is a paucity of literature on the long-term effects of the repeated use of subanesthetic ketamine for TRD. There are also large gaps in the literature regarding the long-term side effects of using IV ketamine on a maintenance basis.
In SUSTAIN-1 (Study 3003), TRD patients who responded to intranasal esketamine were randomized to receive intranasal esketamine or switched to intranasal placebo, and patients

continued to receive their oral antidepressant. The time to relapse was significantly longer in patients who continued esketamine treatment compared to patients who switched to placebo. However, there is limited data available on long-term esketamine for TRD in real-world scenarios.

Here, we will review the long-term effects of the repeated use of IV ketamine/intranasal esketamine for patients with TRD.

Learning Objectives:

1. Review the evidence on the long-term outcomes with continuing intravenous ketamine in a heterogeneous group of depressed patients.
2. Review the evidence on the long-term outcomes with continuing intranasal esketamine in a heterogeneous group of depressed patients.

Literature References:

1. Wilkinson ST, Katz RB, Toprak M, Webler R, Ostroff RB, Sanacora G. Acute and Longer-Term Outcomes Using Ketamine as a Clinical Treatment at the Yale Psychiatric Hospital. J Clin Psychiatry. 2018;79. 17m11731
2. Daly EJ, Trivedi MH, Janik A, et al. Efficacy of Esketamine Nasal Spray Plus Oral Antidepressant Treatment for Relapse Prevention in Patients with Treatment-Resistant Depression: A Randomized Clinical Trial. JAMA Psychiatry. 2019; 76:893-903.

LONG-TERM OUTCOMES AND CONSIDERATIONS OF INTRANASAL ESKETAMINE FOR TREATMENT RESISTANT DEPRESSION - IS THIS REALLY THE MIRACLE DRUG?

Simon Kung, Mayo Clinic

Individual Abstract: Background: Intranasal esketamine has been FDA-approved for treatment-resistant depression (TRD) since March 2019. We reviewed the evidence for intranasal esketamine, the outcomes of a small esketamine clinic, and the considerations of operating such a clinic longer-term.

Method: Retrospective review of patients with TRD receiving intranasal esketamine from June 2020 through October 2021. Depressive symptoms, measured by Quick Inventory of Depressive Symptoms Self-Rated 16 items (QIDS-16) were collected prior to each treatment and approximately 24 hours afterwards. Response (>50% improvement) and remission (QIDS<6) in the acute course, duration of maintenance treatment, and reason for leaving treatment were collected. Observations of patients and practical considerations of a clinic were reviewed.

Results: Of 14 patients, response rate was 71% (n=10) and remission rate was 21% (n=3). Duration of maintenance treatment in responders ranged from 1 month to 18.5 months. However, at long term follow-up, only 4 patients were still receiving maintenance ketamine (40% of 10 responders). Other than lack of sustained response, patients also left treatment because of logistical burden (taking time away from work, requiring a ride, distance to treatment center), the uncertainty of overall benefits after discussion with family, and insurance issues. From the provider standpoint, there were concerns about how to measure the functional benefits of esketamine, limited staff to expand treatments, the potential of iatrogenic dependency, and insurance issues.

Conclusions: While intranasal esketamine showed effect in the acute course, longer term treatment does not necessarily maintain response, and practical considerations also lead to patients discontinuing treatment.

Learning Objectives:

1. To recognize the long-term outcomes of an intranasal esketamine clinic and how those outcomes differ from the acute course of treatment.
2. To describe some of the barriers of long-term intranasal esketamine treatment from the patient and provider perspective.

Literature References:

1. Kasper S et al. Practical recommendations for the management of treatment-resistant depression with esketamine nasal spray therapy: Basic science, evidence-based knowledge and expert guidance. World J Biological Psychiatry 2021;22:468-82.
2. Sassano-Higgins S et al. A review of ketamine abuse and diversion. Depression and anxiety 2016;33:718-27.

Workshops

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

MID-CAREER WORKSHOP: HOW TO ADVANCE YOUR CAREER IN THE HYBRID/REMOTE WORK ENVIRONMENT

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

Overall Abstract: This workshop will be an interactive, engaging discussion on how to advance your career (and get promoted) in the hybrid/remote work environment. With more jobs relying on hybrid and remote work solutions, the panel will offer suggestions for ways to engage colleagues, communicate effectively and stay connected with your institution/organization and your industry in the post-pandemic environment. The panel will include experts from academia, industry, clinical research organizations and regulatory agencies to share perspectives on hybrid/remote work in different types of careers. After introductions, the majority of the session will focus on an interactive dialogue.

Learning Objectives:

1. Identify a new strategy for advancing a career goal.
2. Identify the skills needed to promote connection and collaboration in a hybrid/remote work environment.

ADVANCING YOUR CAREER IN THE HYBRID/REMOTE WORK ENVIRONMENT: AN INDUSTRY PERSPECTIVE

Carla Canuso, Janssen Research and Development

Individual Abstract: In the wake of the global COVID-19 pandemic, remote and hybrid work arrangements have become the norm within large pharmaceutical companies. While both

employers and employees are adjusting to the new normal, the current way of working requires creative and intentional efforts to engage colleagues, managers and mentors. This presentation will consider the challenges faced by mid-career industry clinicians/scientists aiming to advance professionally in the hybrid/remote environment, as well as offer some suggestions for those working on global and local teams.

Learning Objectives:

1. Identify some of the challenges faced by global and local teams.
2. Identify some of the best practices to engage colleagues, managers and mentors.

Literature References: None

HOW TO ADVANCE YOUR CAREER IN THE HYBRID/REMOTE WORK ENVIRONMENT

Kari Nations, Syneos Health

Individual Abstract: This workshop will be an interactive, engaging discussion on how to advance your career (and get promoted) in the hybrid/remote work environment. With more jobs relying on hybrid and remote work solutions, the panel will offer suggestions for ways to engage colleagues, communicate effectively and stay connected with your institution/organization and your industry in the post-pandemic environment. The panel will include experts from academia, industry, clinical research organizations and regulatory agencies to share perspectives on hybrid/remote work in different types of careers. After introductions, the majority of the session will focus on an interactive dialogue.

Learning Objectives:

1. Identify a new strategy for advancing a career goal.
2. Identify the skills needed to promote connection and collaboration in a hybrid/remote work environment.

HOW TO ADVANCE YOUR CAREER IN THE HYBRID/REMOTE WORK ENVIRONMENT

Michael Davis, US Food and Drug Administration

Individual Abstract: This workshop will be an interactive, engaging discussion on how to advance your career (and get promoted) in the hybrid/remote work environment. With more jobs relying on hybrid and remote work solutions, the panel will offer suggestions for ways to engage colleagues, communicate effectively and stay connected with your institution/organization and your industry in the post-pandemic environment. The panel will include experts from academia, industry, clinical research organizations and regulatory agencies to share perspectives on hybrid/remote work in different types of careers. After introductions, the majority of the session will focus on an interactive dialogue.

Learning Objectives:

1. Identify a new strategy for advancing a career goal.
2. Identify the skills needed to promote connection and collaboration in a hybrid/remote work environment.

CONTROVERSIES IN DEVELOPING PSYCHEDELIC TREATMENT IN PSYCHIATRY

Trisha Suppes, Stanford University

Overall Abstract: After decades of research hiatus, psychedelics have reemerged as a potential intervention for a wide variety of psychiatric conditions including mood disorders, anxiety disorders, substance abuse disorders and as an aid for patients experiencing medical illness related anxiety. We propose to address some of the emerging controversies around using psychedelics to treat mental disorders. There are many topics in this broad area of controversies. We've chosen to focus on four of these current issues with a speaker for each and a discussant allowing ample time for audience engagement and input. First, we will focus on how best to capture the unique perspective changes from psychedelics which don't resemble those from standard antidepressants, with a special focus on mood disorders and suicidality (proposed Dr. Scott Aaronson). Second, what should be the required training for therapist and is there a minimum psychotherapy needed for positive results (proposed Dr. Elizabeth Nielsen). Third, when should patients become eligible for psychedelic treatment, and will there be a need for a maintenance protocol? Will there be a need for repeat treatment and if so, what should the maintenance protocol look like (proposed Dr. Robin Carhart-Harris). Finally, we will consider how psychedelics may change the landscape of psychiatric diagnosis and treatment (proposed Dr. Trisha Suppes). We have a discussant who has a history of interest in alternative approaches to psychiatric treatment while maintaining rigor and scientific equipoise. He will address the broad and quickly changing arena of the use of psychedelics in psychiatry (proposed Dr. Mark Rapaport).

Learning Objectives:

1. Be able to discuss cutting edge issues in psychedelic therapies.
2. Understand the current state of research on psychedelic treatment and psychotherapies.

IMPROVEMENT FROM PSYCHEDELIC THERAPY IS DIFFERENT, HOW DO WE CAPTURE IT?

Scott Aaronson, Sheppard Pratt

Individual Abstract: Over six decades improvement, in depressive symptoms has been captured by several standardized scales that capture changes in somatic functioning, mood, anxiety and ability to get work done. These scales were developed to address the changes investigators found from treatment with tricyclic and serotonergic antidepressants. Early work with how psychedelic therapy is effective suggests that the key alteration may be in perception--how the patient views their life course, is less grounded in strict vegetative symptoms and is more likely to demonstrate efficacy across diagnoses where perception is impaired. Other illnesses which may see important gains besides depression are post-traumatic stress disorder, obsessive compulsive disorder, addictive behaviors including eating disorders and perhaps even autistic disorders. This talk will begin the discussion with how best to capture the changes investigators are seeing in the early phases of clinical investigation and how best to consider if these changes are meaningful, durable and lead to important alterations in the quality of life.

Learning Objectives:

1. Describe two changes in perception subjects given psychedelic therapy report.
2. Identify two important post-psychedelic outcomes not captured by currently used depression rating scales.

Literature References:

1. Carhart-Harris R, Giribaldi B, Watts R, Baker-Jones M, Murphy-Beiner A, Murphy R, Martell J, Blemings A, Erritzoe D, Nutt DJ (2021) Trial of Psilocybin versus

Escitalopram for Depression. NEJM 384(15):1402-1422 doi: 10.1056/NEJMoa2032994
2. Johnson MW, Hendricks PS, Barrett FS, Griffiths RR (2019) Classic psychedelics: An integrative review of epidemiology, therapeutics, mystical experience, and brain network function. Pharmacol Ther 197:83-102 DOI: 10.1016/j.pharmthera.2018.11.010

PSYCHEDELIC THERAPIST TRAINING FOR COMMUNITY PRACTICE

Elizabeth Nielson, Columbia University and New York State Psychiatric Institute

Individual Abstract: While research clearly acknowledges the therapist's indispensable role before, during, and after psychedelic therapy sessions, the unique process of training to become a psychedelic therapist is a relatively new endeavor, barely studied and largely unaddressed in the field. With psychedelic-assisted therapies on the verge of availability outside of research settings, training programs for research therapists may inform how educators train therapists for community-based practice, taking key differences into account. This talk will be based in part on the speaker's experience and publication on the development and evaluation of a training program for psilocybin therapists in clinical research and experience developing and running a postgraduate certificate program for community-based psychedelic therapists, Fluence. After providing an overview of what current training in the field looks like, what the needs and gaps are, ideas for how trainees, trainers, training institutes, and other key players might come together to ensure equitable access to high-quality training, in turn maintaining a high standard of care in psychedelic-assisted therapies will be discussed.

Learning Objectives:

At the end of this presentation, participants will be able to:

1. Describe how psychedelic therapist training in research differs from training for community practice
2. Identify gaps in their own training to provide psychedelic-assisted therapy.

Literature References:

1. Nielson, E. M. and J. Guss (2018). "The influence of therapists' first-hand experience with psychedelics on psychedelic-assisted psychotherapy research and therapist training." Journal of Psychedelic Studies.
2. Tai, S. J., et al. (2021). "Development and Evaluation of a Therapist Training Program for Psilocybin Therapy for Treatment-Resistant Depression in Clinical Research." Frontiers in Psychiatry 12(27).

Individual Abstract: A recently completed multi-site, randomized, controlled, double-blind psilocybin assisted therapy study showed rapid (within 2 days) and sustained (for as long as 3 months) response for patients with treatment resistant major depressive disorder (single or recurrent episode) receiving a single dose 25 mg psilocybin with psychological support. Important inclusion criteria were that if this was a single episode of MDD, the duration had to be at least 3-months, but not more than 2-years. All patients had failed at least 2, but no more than 4 adequate antidepressants treatments for the current episode and were off all antidepressants for at least 3 weeks before psilocybin therapy. At the primary endpoint, 3-weeks after dosing, 29% met study criteria for remission. This compares favorably to the 28% remission rate after 12-weeks treatment in Level1 (initial study treatment with SSRI monotherapy) in the STAR*D study and the 14% remission rates in Level 3 (after 2 failed trials

for the current episode). Also of note, 20% of the patients in the psilocybin therapy study experienced a sustained response during the 12-week trial. The first set of questions stemming from this (and most other psychedelic assisted therapy studies to date) is where this new treatment paradigm might best fit in out treatment algorithm for MDD. Since it compares so favorably with an initial treatment with daily SSRI monotherapy and appears safe and well tolerated, why reserve its use for TRD? Why not consider it as a first-line treatment for MDD? Why wait for weeks to months of multiple treatments to fail, exposing patients to the ravages of this often devastating and life-threatening disorder? The second set of questions relate to how often the treatment should be offered. The aforementioned study used a single dose; others have used 2 doses. Which is more effective and long lasting? While the 20% sustained response rate noted above is impressive, 80% didn't achieve a sustained response. Does that suggest that more frequent dosing may have led to both increased remission rates and increased sustainability of response? And when might booster doses enhance sustainability? What might be the role of psychedelic assisted therapy for relapse and recurrence prevention or intervention? These are some of the questions that will be raised during the presentation and discussion.

Learning Objectives:

1. Discuss where psychedelic assisted therapy best fits in the treatment algorithm for MDD and/or TRD.
2. Describe potential pros and cons of booster sessions and continuation/maintenance treatment with psychedelic assisted therapy

Literature References:

1. Davis, A. K., Barrett, F. S., May, D. G., Cosimano, M. P., Sepeda, N. D., Johnson, M. W., ... and Griffiths, R. R. (2021). Effects of psilocybin-assisted therapy on major depressive disorder: a randomized clinical trial. JAMA psychiatry, 78(5), 481-489.Carhart-Harris, R., Giribaldi, B., Watts, R., Baker-Jones, M., Murphy-Beiner, A., Murphy, R., ... and Nutt, D. J. (2021). Trial of psilocybin versus escitalopram for depression. New England Journal of Medicine, 384(15), 1402-1411.

WILL PSYCHEDELICS CHANGE PSYCHIATRIC PRACTICE AS WE KNOW IT?

Trisha Suppes, Stanford University

Individual Abstract: In this talk we will explore whether the current interest, media attention, and focus on psychedelics may lead to lasting change in the practice of psychiatry. It is currently an open question if the new surge of interest and clinical trials will lead to a significant change in the treatments we use for mental disorders. There are several assumptions in play. Generally, while the potential for fast acting treatments for severe mental conditions including depression, mania, and psychosis has been recognized since mid-20th century with the rise of electro convulsive therapy it was never seen as a cure per say. Recent anecdotal reports seem to suggest some psychedelics for some disorders in some people may in fact be a 'cure'. This remains to be seen but opens very interesting speculation including the possibility that psychedelics open up a window in brain plasticity allowing lasting brain change and a diminishment of psychiatric symptoms such as depression and anxiety. We will discuss various ways psychedelics may or may not change psychiatric practice.

Learning Objectives:

1. Understand the state of scientific clinical trials on the use of psychedelics to treat psychiatric disorders.

2. Be aware of how past changes in treatment have led to a change in clinical practice in psychiatry.

Literature References:

1. Pollen, M., How to Change Your Mind, Penguin Press, 2018
2. Raison, CL., Everything old is new again: are psychedelic medicines poised to take mental health by storm? Acta Psychiatr Scand. 2018 11;138(5):365-367.

EARLY CAREER WORKSHOP: PSYCHOPHARMACOLOGY "PRESCRIBERS' WORKSHOP" FOR TRAINEES AND EARLY CAREER CLINICIANS: THE DESIGN, IMPLEMENTATION, AND DISSEMINATION OF A MODEL CURRICULUM

Eileen Kavanagh, College of Physicians and Surgeons, Columbia University/New York State Psychiatry

Overall Abstract: Traditional psychopharmacology curricula tend to rely on lecture-based presentation of core knowledge. However, there are several limitations to this approach. First, there is a large body of literature demonstrating that lectures are a relatively ineffective means of transmitting content to adult learners (Zisook, et al., 2005). Second, the act of good prescribing requires more than acquired knowledge: psychiatrists must draw upon the confluence of communication skills, ethics, therapeutic process and professional identity. Lastly, the ability to recognize and process anxiety that is evoked by the experience of prescribing is vital to a trainee's development (Georgiopoulos, 2005 and Fann, 2003). However, as residents rotate to outpatient clinics they begin to function more independently, rarely seeing patients in concert with supervisors. These factors often serve as barriers to optimal acquisition and assessment of the full range of skills that encompass the act of good prescribing.

We designed a novel curriculum (Kavanagh et al. 2017) for teaching psychopharmacology that goes above and beyond basic knowledge. Our core learning objective is that residents will be safe and effective prescribers of psychotropic agents and one key skill is learning to obtain informed consent. To this end, we restructured classroom time so as to focus explicitly on behavioral proficiencies. To optimize active engagement with the material, each session incorporates self-directed learning, skills, role-play, peer feedback, group process and skills modeling. Furthermore, in developing this course, we specifically set out to create a frame that could be exported as a model curriculum and implemented at other sites.

In this Early Career Committee workshop, we will engage participants with an excerpt from our experiential, psychopharmacology "prescriber's workshop". We will then describe how the curriculum was adapted and customized for use at a second institution. At the second site, videos of expert faculty prescribing are an important part of the class. Finally, teaching faculty from both institutions will reflect on their experiences developing, adapting and implementing the curriculum, engaging participants in a discussion of how to optimize the value and accessibility of model curriculum resources.

This workshop is intended for faculty involved in core curriculum development and dissemination, particularly those interested in experiential learning techniques. It will require audience interaction and participation and will be structured as follows:

1. Introduction and overview (25 minutes);

2. Experiential learning exercise: group participation in a session excerpt from the "prescriber's workshop" course (25 minutes);

3. Report on the implementation at the secondary site with a demonstration of unique teaching resources developed – will include video; (25 minutes);

4. Group reflection on the presented educational materials and wider discussion on the process of design, implementation and dissemination of shared curriculum resources (25 minutes).; and

5. Discussion on challenges in incorporating evidence, such as those about choosing the right medication, and in applying this process of prescribing medications to new approved medications (20 minutes).

Learning Objectives:

1. Describe limitations of traditional approaches to teaching psychopharmacology;
2. Implement a novel, experiential workshop for teaching both psychopharmacology and therapeutic prescribing.

INVITED WORKSHOP: PSYCHOPHARMACOLOGY "PRESCRIBERS' WORKSHOP" FOR TRAINEES AND EARLY CAREER CLINICIANS: THE DESIGN, IMPLEMENTATION, AND DISSEMINATION OF A MODEL CURRICULUM

Catherine Lowenthal, College of Physicians and Surgeons, Columbia University

Individual Abstract: Traditional psychopharmacology curricula tend to rely on lecture-based presentation of core knowledge. However, there are several limitations to this approach. First, there is a large body of literature demonstrating that lectures are a relatively ineffective means of transmitting content to adult learners (Zisook, et al., 2005). Second, the act of good prescribing requires more than acquired knowledge: psychiatrists must draw upon the confluence of communication skills, ethics, therapeutic process and professional identity. Lastly, the ability to recognize and process anxiety that is evoked by the experience of prescribing is vital to a trainee's development (Georgiopoulos, 2005 and Fann, 2003). However, as residents rotate to outpatient clinics they begin to function more independently, rarely seeing patients in concert with supervisors. These factors often serve as barriers to optimal acquisition and assessment of the full range of skills that encompass the act of good prescribing.

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Literature References:

1. Zisook, S., Benjamin, S., Balon, R., Glick, I., Louie, A., Moutier, C., ... and Servis, M. (2005). Alternate methods of teaching psychopharmacology. Academic Psychiatry, 29(2), 141-154.
2. Kavanagh EP, Cahill J, Arbuckle MR, Lenet AE, Subramanyam K, Winchel RM, Nossel I, DeSilva R, Caravella RA, Ackerman M, Park HC, Ross DA (2017). Psychopharmacology Prescribing Workshops: A Novel Method for Teaching Psychiatry Residents How to Talk to Patients About Medications. Academic Psychiatry. 41(4):491-496.

INVITED WORKSHOP: PSYCHOPHARMACOLOGY "PRESCRIBERS' WORKSHOP" FOR TRAINEES AND EARLY CAREER CLINICIANS: THE DESIGN, IMPLEMENTATION, AND DISSEMINATION OF A MODEL CURRICULUM

David Ross, University of Alberta

Individual Abstract: Traditional psychopharmacology curricula tend to rely on lecture-based presentation of core knowledge. However, there are several limitations to this approach. First, there is a large body of literature demonstrating that lectures are a relatively ineffective means of transmitting content to adult learners (Zisook, et al., 2005). Second, the act of good prescribing requires more than acquired knowledge: psychiatrists must draw upon the confluence of communication skills, ethics, therapeutic process and professional identity. Lastly, the ability to recognize and process anxiety that is evoked by the experience of prescribing is vital to a trainee's development (Georgiopoulos, 2005 and Fann, 2003).

However, as residents rotate to outpatient clinics they begin to function more independently, rarely seeing patients in concert with supervisors. These factors often serve as barriers to optimal acquisition and assessment of the full range of skills that encompass the act of good prescribing.

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This workshop is intended for faculty involved in core curriculum development and dissemination, particularly those interested in experiential learning techniques. It will require audience interaction and participation and will be structured as follows:

1. Introduction and overview (25 minutes);
2. Experiential learning exercise: group participation in a session excerpt from the "prescriber's workshop" course (25 minutes);
3. Report on the implementation at the secondary site with a demonstration of unique teaching resources developed – will include video; (25 minutes);
4. Group reflection on the presented educational materials and wider discussion on the process of design, implementation, and dissemination of shared curriculum resources (25 minutes).; and
5. Discussion on challenges in incorporating evidence, such as those about choosing the right medication, and in applying this process of prescribing medications to new approved medications (20 minutes).

Learning Objectives:

1. Describe limitations of traditional approaches to teaching psychopharmacology.
2. Implement a novel, experiential workshop for teaching both psychopharmacology and therapeutic prescribing

Thursday, June 2, 2022

Keynote Plenary

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

KEYNOTE PLENARY: REASSESSING RESEARCH AND CLINICAL PRACTICE IN THE PERI-PANDEMIC ERA

Mark Rapaport, University of Utah Huntsman Mental Health Institute

Overall Abstract: The COVID-19 pandemic has created a second pandemic of mental health and substance use disorders. The prevalence of anxiety and depression symptoms have increased in both adults and children. Problems with alcohol and substance use disorders have markedly increased. The intent of this plenary session is to begin to discuss how the COVID-19 is modifying our field. In particular we will investigate potential factors leading to the startling increase in mood disorders. Then we will discuss the short- and long-term neuropsychiatric aspects of infection with COVID-19. Our third presenter will describe how his team successfully developed a strategy and implemented a clinical trail of Fluvoxamine treatment for patients of COVID-19. Thus, this session will serve as a basis for further retirements of how:

1. The neuropsychiatric squali of COVID-19
2. How COVID-19 pandemic is changing psychiatric research

"THIS SENSE OF BEING ABANDONED": COVID-19 AND MENTAL HEALTH

Roy Perlis, Massachusetts General Hospital

Abstract: Rates of major depressive symptoms among adults in the United States during COVID-19 reached levels 3 to 4 times greater than prepandemic norms on average, but not all groups were equally impacted. This presentation will describe differences between sociodemographic groups in terms of depression and anxiety during COVID-19 and explain some of the hypotheses for these differences. It will consider why, despite increases in suicidality, rates of suicide have not increased markedly among US adults. Then, it will address the contribution of neuropsychiatric symptoms to long covid and suggest potential longer-term consequences of the pandemic for mental health.

Learning Objectives:

1. Understand the increase in major depressive symptoms among adults during the COVID-19 pandemic, and which groups have experienced the greatest increases.
2. Understand the way in which the increases in depressive symptoms may have impacted efforts to contain the COVID-19 pandemic.

Literature References:

1. Perlis RH, Santillana M, Ognyanova K, Green J, Druckman J, Lazer D, Baum MA. Factors Associated With Self-reported Symptoms of Depression Among Adults With and Without a Previous COVID-19 Diagnosis. JAMA Netw Open. 2021 Jun 1;4(6):e2116612. doi: 10.1001/jamanetworkopen.2021.16612.

THE FUTURE OF CLINICAL TRIALS IS REMOTE: THE EXAMPLE OF FLUVOXAMINE DURING COVID-19

Eric Lenze, Washington University School of Medicine

Abstract: Clinical trials are critical for generating new and optimized mental health treatments, but this progress is impeded by challenges in efficiently conducting trials. A recent innovation called the full-remote trial has have emerged to meet this challenge. In a fully-remote trial, all study conduct occurs without face-to-face contact with participants, which has many benefits such as more rapid recruitment. In this talk, Dr. Lenze will describe a now-famous example during the pandemic, in which two psychiatrists created and conducted an innovative fully-remote trial to test and ultimately demonstrate the efficacy of fluvoxamine for the early treatment of COVID-19.

Learning Objectives:

1. Understand the features of fully-remote trials.
2. Understand the role of fluvoxamine in the treatment of COVID-19.

Literature References:

1. JAMA 2020 Dec 8;324(22):2292-2300. doi: 10.1001/jama.2020.22760.
2. Fluvoxamine vs Placebo and Clinical Deterioration in Outpatients With Symptomatic COVID-19: A Randomized Clinical Trial
3. Eric J Lenze, Caline Mattar, Charles F Zorumski, Angela Stevens, Julie Schweiger, Ginger E Nicol, J Philip Miller, Lei Yang, Michael Yingling, Michael S Avidan, Angela M Reiersen

NEUROPSYCHIATRIC SEQUELAE OF COVID-19

Scott Beach, Harvard Medical School, Massachusetts General Hospital

Abstract: Since March 2020, psychiatrists around the world have dedicated a large portion of their efforts towards caring for patients with COVID-19 and studying the neuropsychiatric effects of the illness. In the acute infection stage, rates of delirium approach 80% in some populations, and non-delirium psychosis is emerging as an important phenomenon as well. Novel presentations are also being described, including a cluster of symptoms that resembles akinetic mutism and other reports of catatonia successfully treated with benzodiazepines. As the pandemic has continued, survivors are being characterized as having high rates of depression, anxiety and PTSD. A phenomenon of Long COVID has also emerged, characterized by ongoing fatigue, subjective brain fog, and objective deficits in executive function on neuropsychological testing. Many of these patients initially only experienced mild illness not requiring hospitalization, but their symptoms have persisted for weeks or months, refractory to medication interventions.

Learning Objectives:

1. Describe acute and chronic neuropsychiatric sequelae of COVID-19
2. Recognize described imaging findings in COVID-19

Literature References:

1. Douaud G, Lee S, Alfaro-Almagro F, Arthofer C, Wang C, McCarthy P, Lange F, Andersson JLR, Griffanti L, Duff E, Jbabdi S, Taschler B, Keating P, Winkler AM, Collins R, Matthews PM, Allen N, Miller KL, Nichols TE, Smith SM. SARS-CoV-2 is associated with changes in brain structure in UK Biobank. Nature. 2022 Mar 7.

Update From Federal and Other Funding Agencies

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

UPDATE FROM FEDERAL AND OTHER FUNDING AGENCIES PLENARY

Leslie Citrome, New York Medical College

Overall Abstract: Continuing with long-standing tradiiton, this is the much-anticipated 2022 Update From Federal and Other Funding Agencies Plenary. Alphabet soup never tasted so good! Hear updates from NIMH, NIAAA, PCORI, NIDA, SAMSHA, and the VHA.

THE LATEST IN DRUG DEVELOPMENT FROM THE NIMH

Josh Gordon, National Institute of Mental Health

Abstract: The NIMH supports drug development through a translational pipeline beginning with basic neuroscience, continuing through target identification and proceeding through clinical trials. NIMH programs supporting this pipeline will be discussed.

Learning Objectives:

Attendees will learn about the AMP-Schizophrenia public-private partnership for drug development in the clinical high risk syndrome.

1. Attendees will become familiar with the NIMH grant portfolio balance

Literature References:

2. Brady LS, Potter WZ, Gordon JA. Redirecting the revolution: new developments in drug development for psychiatry. Expert Opin Drug Discov. 2019;14(12):1213-1219. doi:10.1080/17460441.2019.1666102

ALCOHOL USE DISORDER: CLOSING THE TREATMENT GAP

George Koob, National Institute of Health – NIAAA

Abstract: Alcohol misuse and alcohol use disorder (AUD) continues to be a major burden on society. For over 50 years, the National Institute on Alcohol Abuse and Alcoholism has been the leading funder of alcohol related research in the world. As a result, notable advances have been generated in the domains of genetics, development, fetal alcohol spectrum disorder, a heuristic neurobiological framework for AUD, and behavioral and pharmacological treatments for AUD. However, despite these advances, less that 10% of individuals with AUD receive any treatment for AUD. Efforts are being made to facilitate the implementation of the science advances into evidence-based practice in primary care, mental health, and other health care settings with a focus on closing the treatment gap. Successful implementation of this knowledge emanating from NIAAA directed at closing the treatment gap includes development of College Aim for prevention at the college and university level, Rethinking/Drinking website for evaluating one's relationship with alcohol, development of the NIAAA Treatment Navigator for treatment and development of screening and brief intervention for prevention, and development of programs to facilitate development of medications for treatment of AUD. Underway are programs for a Healthcare professional's Core Resource on Alcohol, development of a consensus definition of recovery from alcohol use disorder, and identification of social determinants and diversity as a driving forces for innovative science at all levels of such a science-based approach. Addressing such challenges will facilitate the implementation of evidence-based treatment for AUD in primary care, mental health, and other health care settings.

Learning Objectives:

3. To understand the challenges and efforts being made to close the alcohol use disorder treatment gap

Literature References:

4. White AM, Castle IJP, Powell PA, Hingson RW, Koob GF. Alcohol-related deaths during the COVID-19 pandemic. Journal of the American Medical Association, in press.

5. Hagman BT, Falk D, Litten R, Koob GF. Defining recovery from alcohol use disorder: development of an NIAAA research definition. American Journal of Psychiatry, in press.

A 2022 UPDATE ON PCORI RESEARCH PRIORITIES AND FUNDING OPPORTUNITIES IN MENTAL HEALTH

Holly Ramsawh, Patient-Centered Outcomes Research Institute

Abstract: Almost half of all Americans will experience a mental health disorder in their lifetime, yet a comparatively small amount will receive effective, evidence-based treatment. Patient-Centered Outcomes Research Institute (PCORI) funds a large portfolio of mental/behavioral health studies designed to help patients and caregivers make more informed decisions about mental health care. This presentation will discuss PCORI's mission to fund comparative clinical effectiveness research (CER), our patient-centered research focus, and challenges and opportunities that have arisen for PCORI-funded investigators during the COVID pandemic. PCORI's new national research priority relevant for psychiatric researchers, intellectual and developmental disabilities, will be described. Finally, the presentation will conclude with an overview of both targeted and broad research funding announcements that invite investigator-initiated CER topics in mental/behavioral health.

Learning Objectives:

1. To familiarize the audience with PCORI's mission to fund comparative clinical effectiveness research (CER).
2. To acquaint the audience with current mental/behavioral health funding opportunities at PCORI.

Literature References:

1. Frank L, Basch E, Selby JV, For the Patient-Centered Outcomes Research Institute. The PCORI Perspective on Patient-Centered Outcomes Research. JAMA. 2014;312(15): 1513–1514. doi:10.1001/jama.2014.11100

UPDATE OF THE MEDICATIONS DEVELOPMENT PROGRAM AT NIDA

Ivan Montoya, DHHS/National Institute on Drug Abuse

Abstract: The Medications Development Program (MDP) of the National Institute on Drug Abuse (NIDA) was created in 1990 by a mandate from the U.S. Congress to develop medications to treat cocaine use disorder. Over the years the mission of the MDP has expanded to include the development of medications to treat cocaine, methamphetamine and cannabis use disorders. Due to the national opioid crisis, in 2019 the MDP received significant support from the Helping to End Addiction Long Term (HEAL) Initiative, which is an NIH-wide initiative to reduce the use of opioids to treat pain and to improve the prevention and treatment opioid use disorder and overdose. The purpose of this presentation is to describe the MDP and

provide an update of the medications that are in the pipeline of development to prevent and treat substance use disorders and overdose. It will include the development of small molecules and biologics, new and repurposed medications, and new formulations of FDA-approved medications for opioid use disorder and overdose.

Learning Objectives:

At the end of the presentation, participants will:

1. Learn about the history, mission and implementation of the NIDA's Medications Development Program
2. Become familiar with the medications in the NIDA MDP pipeline to prevent and treat substance use disorders and overdose

Literature References:

1. Montoya, I. D. (2022). Medications against drugs: Development of medications to prevent and treat substance use disorders. Metode Science Studies Journal, (12), 87-93.

AN UPDATE FROM SUBSTANCE ABUSE AND MENTAL HEALTH SERVICES ADMINISTRATION

Miriam Delphin-Rittmon, Substance Abuse and Mental Health Services Administration

Abstract: Mental health and substance use disorders affect people from all walks of life and age groups. While serious behavioral health issues existed before the COVID-19 pandemic, the circumstances of the pandemic exacerbated these issues on a population level. These illnesses are common, recurrent, and often severe, but they are treatable, and many people do recover. The Substance Abuse and Mental Health Services Administration (SAMHSA) is the agency within the U.S. Department of Health and Human Services that leads public health efforts to advance the nation's behavioral health. SAMHSA's mission is to reduce the impact of substance abuse and mental illness on America's communities. The Assistant Secretary for Mental Health and Substance Use, Dr. Delphin-Rittmon, will highlight the President's national mental health strategy, share the agency's priorities, and highlight programs designed to enhance behavioral health access and treatment in a peri-pandemic era.

Learning Objectives:

1. Describe the current state of behavioral health in the United States
2. List three pillars in the President’s national mental health strategy
3. Identify SAMHSA’s priorities and recognize the various programs and opportunities that SAMHSA offers for behavioral health access and treatment

VA OFFICE OF RESEARCH & DEVELOPMENT RESEARCH ON SUBSTANCE USE DISORDERS

Jana Drgonova, Veteran's Administration

Abstract: Veterans Health Administration Healthcare System is the largest integrated health care system in the nation and the largest provider of graduate medical education. This combination creates a unique environment for translation of research findings. The intramural research program is focused on Veterans' needs and health issues disproportionately affecting Veterans. The research is managed by the Office of Research and Development and its four Services via grant funding mechanism. Funding for research on alcohol and substance use has been growing steadily; particularly, the investment in the research on opioid use disorder has increased dramatically over the past five years. Recent accomplishments include findings from

observational studies, some of which resulted in new clinical trials, new genome-wide association of smoking trajectories, and an implementation intervention at non-addiction clinics that increased access of Veterans to medications for opioid use disorder.

Learning Objectives:

1. Research structure and organization at the VA Office of Research and Development.
2. Latest accomplishments in addiction research and new, ongoing studies funded by the VA.

Literature References:

1. Mackey K, Anderson J, Bourne D, et al: Evidence Brief: Benefits and Harms of Long-term Opioid Dose Reduction or Discontinuation in Patients with Chronic Pain. Washington, DC: Evidence Synthesis Program, Health Services Research and Development Service, Office of Research and Development, Department of Veterans Affairs. VA ESP Project #09-199; 2019
2. Ke Xu 1 2, Boyang Li 2 3, Kathleen A McGinnis, et al: Genome-wide association study of smoking trajectory and meta-analysis of smoking status in 842,000 individuals. Nat Commun 2020; 151:5032-5043

***Clinical Updates in Psychopharmacology**

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

CLINICAL UPDATE IN PSYCHOPHARMACOLOGY

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

Overall Abstract: This session will feature three leading psychopharmacologists in reviewing the treatment of insomnia, psychosis and mood disorders. Dr. Andrew Krystal will describe the importance of using mechanism of action of insomnia medications to optimize the risk-benefit ratio of treatment when matching treatment to patient needs. Dr. Oliver Freudenreich will update the audience on schizophrenia care in the context of the healthcare system, the prevention of relapse of schizophrenia and managing antipsychotic-related medical morbidity. Dr. Michael Thase will provide an overview of the state of the art of combining and sequencing different forms of treatment for depression and prophylaxis of relapse/recurrence.

UPDATE ON INSOMNIA PHARMACOTHERAPY

Andrew Krystal, MD, UCSF

Abstract: The longstanding view of insomnia medications is that clinical effects are determined by pharmacokinetics (Tmax, dose, and half-life) and the mechanism of action doesn't really matter. An increasing number of medications with differing mechanisms of action have become available for the treatment of insomnia. The clinical effects of these medications have been well-characterized and indicate that mechanism of action actually does matter and has a significant impact on clinical effects. This talk reviews the clinical effects of the insomnia medications and elucidates how these effects differ as a function of mechanism of action. It then outlines how it is possible to optimize the risk-benefit ratio of treatment by selecting treatments for each patient based on mechanism of action such that the clinical effects best match the patient's needs.

Learning Objectives:

1. Review the data on the clinical effects of insomnia medications
2. Outline the evidence that mechanism of action matters and that awareness of how clinical effects depend on mechanism of action can serve as the basis for optimizing therapy.

Literature References:

1. Krystal AD. Optimizing Treatment for Insomnia. J Clin Psychiatry. 2021 Jul 13;82(4):EI20008BR4C.

PSYCHOSIS UPDATE

Oliver Freudenreich, Massachusetts General Hospital

Abstract: This update will review progress in the clinical management of patients with schizophrenia, focusing on two critical aspects of psychosis care: the prevention of relapse and managing antipsychotic-related medical morbidity. Newer medication classes like non-dopaminergic antipsychotics and glucagon-like peptide-1 receptor agonists will be discussed. The update will put schizophrenia care in the larger context of our healthcare system, including changes brought about by the COVID-19 pandemic.

Learning Objectives:

Upon completion of this educational activity, participants should be able to:

1. List three patient groups that should be prioritized for long-acting injectable antipsychotics.
2. Outline an algorithm to manage antipsychotic-associated weight gain.

Literature References:

1. Wadden TA, Bailey TS, Billings LK, et al: Effect of subcutaneous semaglutide vs placebo as an adjunct to intensive behavioral therapy on body weight in adults with overweight or obesity. The STEP 3 randomized clinical trial. JAMA 2021;325:1403-1413
2. Lim C, Van Alphen MU, MacLaurin S, et al: Increasing Covid-19 vaccination rates in patients with serious mental illness: a pilot intervention aimed at psychiatric providers. Psychiatr Serv (in press)

MAKING THE MOST WITH WHAT WE HAVE TO OFFER: COMBINED AND SEQUENTIAL THERAPIES FOR PATIENTS WITH DIFFICULT TO TREAT MOOD DISORDERS

Michael E. Thase, Perelman School of Medicine, University of Pennsylvania, and Corporal Michael J. Crescenz VAMC

Abstract: As many as one in five Americans will suffer from a mood disorder at some point in their life and, because these illnesses often begin in adolescence or young adult life and typically run chronic and/or recurrent courses, they are among the greatest causes of disability and loss of human capital to plague modern life. Although there are many types of medications with established efficacy, a number of well-established forms of psychotherapy and psychoeducational interventions and several neuromodulation therapies with FDA-approved indications for mood disorders, major depressive disorder and bipolar affective disorder remain two of the greatest public health problems. Although heuristically grouped together as related diagnoses, the conditions that comprise the mood disorders are heterogeneous in both

symptomatology and pathophysiology and are multifactorial in origin. As such, it is not a surprise that NO particular form of treatment is effective for more than 50-60% of those with mood disorders. This presentation will provide an overview of the state of the art of combining and sequencing different forms of treatment for depression and prophylaxis of relapse/recurrence. It is argued that matching treatments to take into account patient's preference, aptitudes, past treatment histories and select clinical characteristics can improve the "coverage" provided by treatment combinations and sequences. Examples of using Cognitive-Behavioral and Interpersonal Therapies to lessen the risk of relapse/recurrence following pharmacotherapy or to improve outcomes following electroconvulsive therapy or intravenous ketamine therapy. It is also suggested that the principles of Measurement Based Care can be adapted to treatment selection and ongoing monitoring to help keep track of how our patients are doing and to facilitate when in the ongoing course of therapy revisions in the treatment plan are indicated.

Learning Objectives:

At the end of this presentation, the participant will be able to describe:

1. The potential roles of psychotherapy and various "wellbeing" therapies may improve the outcome of patients with difficult-to-treat mood disorders
2. Identify the potential additive benefit of sequential therapies for patients with bipolar affective disorder
3. Identify the ways in which sequential focused therapies may reduce the risk of relapse and increase the chances for recovery in people with difficult to treat depressive disorders.

Literature References:

1. Brakemeier EL, Merkl A, Wilbertz G, Quante A, Regen F, Bührsch N, van Hall F, Kischkel E, Danker-Hopfe H, Anghelescu I, Heuser I, Kathmann N, Bajbouj M. Cognitive-behavioral therapy as continuation treatment to sustain response after electroconvulsive therapy in depression: a randomized controlled trial. Biol Psychiatry. 2014 Aug 1;76(3):194-202.
2. Miklowitz DJ, Efthimiou O, Furukawa TA, et al. Adjunctive Psychotherapy for Bipolar Disorder: A Systematic Review and Component Network Meta-analysis. JAMA Psychiatry. 2021;78(2):141–150.
3. van Bronswijk S, Moopen N, Beijers L, Ruhe HG, Peeters F. Effectiveness of psychotherapy for treatment-resistant depression: a meta-analysis and meta-regression. Psychol Med. 2019 Feb;49(3):366-379. doi: 10.1017/S003329171800199X. Epub 2018 Aug 24. PMID: 30139408.
4. Wilkinson ST, Rhee TG, Joormann J, Webler R, Ortiz Lopez M, Kitay B, Fasula M, Elder C, Fenton L, Sanacora G. Cognitive Behavioral Therapy to Sustain the Antidepressant Effects of Ketamine in Treatment-Resistant Depression: A Randomized Clinical Trial. Psychother Psychosom. 2021;90(5):318-327.

Panel Sessions

3:45 p.m. - 5:15 p.m.

ACHIEVING DIVERSITY IN CLINICAL TRIALS

Shishuka Malhotra, Neuro Behavioral Clinical Research

Overall Abstract: Diversity Equity and Inclusion are interconnected but certainly not interchangeable.
Only 5 % of African Americans and 1/% of the Hispanic population participate in clinical trials.

With recent initiatives by US Government and FDA to achieve diversity in clinical trials, it is time to move from philosophical to operational embracement of diversity.

Our panel will provide accountable solutions at the sponsor, CRO, and site level to improve diversity in clinical trials.

Learning Objectives:

1. Attendees will learn to identify their implicit biases.
2. Attendees will be able to take away tools to improve diversity at sites, CRO, and sponsor levels and recruit a diverse population.

PRACTICAL IMPLEMENTATION OF DE&I IN CLINICAL TRIALS

Alexandria Wise, Syneos Health

Individual Abstract: As there is increased emphasis on the inclusion of diverse patient populations in our clinical trials, the implementation of DE and I in the clinical trial setting has practical implications including considerations around trial design, clinical site geography, addressing minority populations within countries participating, and lesser understood aspects of diversity such as digital diversity. While regulatory guidance is present on the importance of DE and I in clinical trials, the implementation can require expense, time, and methods that call for active problem-solving and attention from our community. This presentation seeks to raise important practical aspects of implementing DE and I in clinical trials, including how to address the barriers in doing so, while also inviting dialogue from our collective community on how to address these opportunities.

Learning Objectives:

1. Understand the key challenges to including diverse populations in clinical trials.
2. Learn methods that help to reduce barriers to involving diverse populations in clinical trials.

Literature References:

1. U.S. Department of Health and Human Services, Food and Drug Administration
2. Enhancing the Diversity of Clinical Trial Populations-Eligibility Criteria, Enrollment Practices, and Trial Designs Guidance for Industry, 2021.

1) Kahn, JM, Gray, DM, Oliveri, JM, Washington, CM, DeGraffinreid, CR, Paskett, ED: Strategies to improve diversity, equity, and inclusion in clinical trials. ACS Journals 2021.

DIVERSITY, EQUITY, AND INCLUSION: GLOBALIZED INSIGHTS FOR LOCALIZED STRATEGIES

Charles Wilcox, Praxis Research Consulting

Individual Abstract: The explicit emphasis on the embracement of increasing ethnic diversity in clinical research was the primary focus of our NCDEU-now-ASCP conference as far back

as 1995 (1). Not only has the awareness of this important need been present for more than 25 years, but numerous well-intentioned initiatives have also been articulated and implemented over the past three decades. Moreover, throughout this same time period, a wide array of diversity, equity and inclusion endeavors have been a key focus throughout the rest-of-the-world (ROW). Paradoxically, when we examined and evaluated the proportional representation of ethnic minorities in clinical research both here in the United States and ROW, over this same time period, we see painfully little substantive progress.

While the terminology may be slightly different in terms of "discrimination" here in the U.S. versus "inequalities" in many foreign countries, the substantive challenges and overall phenomena are nearly identical all over the world. The African-American/Black and Latino/Hispanic underrepresentation in clinical trials here in the U.S. has remarkably similar underpinnings with the disproportionally small representation of the Pakistani population in Norwegian clinical trials and the Moroccan community in Belgian trials. In our panel, we will share compelling data illustrating the world-wide persistent prevalence of under-representation and the most commonly reported reasons. Feelings of "not being taken seriously," "treated with less respect" and spoken to in a "condescending" manner are just three of the six most frequently reported reasons. In terms of the elderly minority populations, many European minority citizens feel a "triple whammy" of ageism, language barriers and socioeconomic hurdles. Embedded within the common themes for the disproportionately low global representation of ethnic minorities are a number of both common and innovative solutions that we will share with the audience, in tandem with soliciting their experience, insights and suggested strategies for improvement.

Learning Objectives:

1. The audience will learn the most persistent global challenges impeding more proportional representation of ethnic minorities in clinical research today.
2. Suggested solutions from both here in the US and ROW will be presented.

Literature References:

1. Wilcox, C.S., Katz, B.B., Morgan, D.L., Schneider, A.L. and De Francisco, D.F. "Increasing Ethnic Diversity and Managed Care: How Will They Influence Research Patient Recruitment in the 1990's?", Psychopharmacology Bulletin, 32 (3) 335-342, 1996.
2. Alzheimer Europe: the development of intercultural care and support for people with dementia from ethnic minority groups; Dementia in Europe Ethics Report 2018, Robert Bosch Stiftung.

OPERATIONALIZING THE ENHANCEMENT OF DIVERSITY IN CLINICAL TRIALS

Stacey Versavel, Cerevel Therapeutics

Individual Abstract: Objective: Adequate representation of diverse participants remains a notable challenge in the design and execution of clinical trials. Investment in representing affected populations and encouraging clinical trial participation across socioeconomic status and demographics should not be rate limiting. Early engagement in the clinical trial lifecycle to incorporate Diversity, Equity and Inclusion (DEI) assists with gaining a precise understanding of a therapeutic intervention's effects prior to commercial availability.

Design: A DEI guidebook was developed for clinical trial teams to address potential barriers which may impact clinical trial participation. It contains suggested strategies to inform

feasibility while considering trial-specific objectives, operational parameters, phase of development, indication and therapeutic target population(s). This guidebook acts as a primary resource focused on enrolling clinically relevant populations to provide sufficient information pertaining to the safety and efficacy of the therapeutic intervention.

Results: The DEI guidebook is focused on the clinical trial lifecycle. Planning concentrates on eligibility and early engagement with participant and patient advocacy organizations. Start-up supports the informed selection of investigators and sites to ensure representation of geographically diverse populations and underrepresented businesses. Conduct strategies reflect consideration of cultural differences, provision of financial support and leveraging a visualization platform to track demographic representation. Closeout emphasized continued communication to share learnings and cultivate partnership with clinical trial participants and patient advocacy organizations.

Conclusion: Application of strategies in the DEI guidebook enables more effective, evidence-based recommendations. This tool champions improvements to the representation of population(s) who will ultimately utilize, if approved, the therapeutic intervention under study.

Learning Objectives:

1. Adequate representation of diverse participants in the design and execution of clinical trials.
2. Enrolling clinically relevant populations to provide sufficient information pertaining to the safety and efficacy of a therapeutic intervention.

Literature References:

1. Gray S: Andrew E: How To Build The World's Fastest Car [Internet]. ACRP 2021; [cited 2021 Nov 16] Available from: https://acrpnet.org/2021/04/20/diversity-in-clinical-trials-going-beyond-why-to-how/
2. Government Accountability Office: Food and Drug Administration: Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment Practices, and Trial Designs Guidance for Industry. Rockville, MD, U.S. Government Printing Office, 2020

*SWITCH VERSUS AUGMENTATION IN TREATMENT-RESISTANT DEPRESSION: LITERATURE AND NEW FINDINGS

George Papakostas, Massachusetts General Hospital

Overall Abstract: Major depressive disorder (MDD) is a serious, debilitating, life-shortening illness that affects many persons of all ages and backgrounds. The point prevalence of MDD is relatively high (2.3-3.2% in men; 4.5-9.3% in women) and the lifetime risk for MDD is 7-12% for men and 20-25% for women. To date, all U.S. Food and Drug Administration (FDA)-approved antidepressants used as monotherapies have shown only modest benefits in MDD. Treatment-resistant depression (TRD) typically refers to the occurrence of an inadequate response following at least two adequate antidepressant treatments among patients suffering from MDD. A particularly critical decision in everyday practice is choosing what to do next when patients with TRD present after antidepressant treatments have failed to produce a clinical response, especially with respect to the use of sequential monotherapies versus polypharmacy strategies such as augmentation, and, until recently, a large evidence gap existed with respect to this common clinical scenario. This evidence gap existed despite the

completion of the large, multi-center STAR*D study, since most patients in the trial were not assigned at random to augmentation versus switch as very few patients agreed to potentially accept either of these two broad treatment arms. Since the publication of STAR*D, three additional, large, multicenter trials have been completed specifically comparing augmentation versus switch as their primary outcome measure in TRD. The purpose of this proposed panel is to discuss the findings of these three large trials. In addition, the design of an ongoing study comparing electroconvulsive therapy (ECT) with ketamine for TRD will be discussed.

Learning Objectives:

1. By the end of this panel, the audience will be able to describe the relative efficacy of various augmentation versus switch strategies for treatment-resistant depression.
2. By the end of this panel, the audience will be able to describe the relative tolerbility of various augmentation versus switch strategies for treatment-resistant depression.

SWITCHING ANTIDEPRESSANTS AS A STRATEGY IN RESISTANT DEPRESSION

Maurizio Fava, Massachusetts General Hospital

Individual Abstract: The STAR*D study provided critical information on the usefulness of switching antidepressants among depressed patients who have not responded to antidepressant monotherapy. In Level 2 of STAR*D, approximately one fourth of citalopram responders remitted, with no differences between the within-class switch and the two switches to a different class of antidepressants. Levels 3 and 4 of STAR*D, however, showed that continuing to switch among monoamine-based antidepressants yielded fairly low remission rates, suggesting that switching may make more sense for patients who have failed only one antidepressant monotherapy. The STAR*D study, because of its unique study design involving an equipoise stratified randomization, did not allow for an adequately powered comparison of the switching strategy with the augmentation strategy. The VAST-D Randomized Clinical Trial, instead, did allow for such comparison and found that remission rates at 12 weeks were 22.3% (n = 114) for the switch group, 26.9% (n = 136)for the augment-bupropion group, and 28.9% (n = 146) for the augment-aripiprazole group. The augment-aripiprazole group exceeded the switch group in remission (relative risk [RR], 1.30 [95% CI, 1.05-1.60]; P = .02), but other remission comparisons were not significant. Another study by Han and Colleagues (Journal of Psychiatric Research 66-67 (2015) 84-94) confirmed the superiority of aripiprazole augmentation over switching. This presentation will review the major switching studies in resistant depression such as STAR*D and VAST-D, but also discuss the clinical implications of the findings of these studies. In addition, the role of tolerability issues in the decision to switch antidepressants will also be discussed.

Learning Objectives:

1. to familiarize with the major switching studies in resistant depression such as STAR*D and VAST-D,
2. to learn the most common approaches to switching antidepressants.

Literature References:

1. Rush AJ, Trivedi MH, Wisniewski SR, Stewart JW, Nierenberg AA, Thase ME, Ritz L, Biggs MM, Warden D, Luther JF, Shores-Wilson K, Niederehe G, Fava M; STAR*D Study Team. Bupropion-SR, sertraline, or venlafaxine-XR after failure of SSRIs for depression. N Engl J Med. 2006 Mar 23;354(12):1231-42. doi: 10.1056/NEJMoa052963. PMID: 16554525

2. Mohamed S, Johnson GR, Chen P, Hicks PB, Davis LL, Yoon J, Gleason TC, Vertrees JE, Weingart K, Tal I, Scrymgeour A, Lawrence DD, Planeta B, Thase ME, Huang GD, Zisook S; and the VAST-D Investigators, Rao SD, Pilkinton PD, Wilcox JA, Iranmanesh A, Sapra M, Jurjus G, Michalets JP, Aslam M, Beresford T, Anderson KD, Fernando R, Ramaswamy S, Kasckow J, Westermeyer J, Yoon G, D'Souza DC, Larson G, Anderson WG, Klatt M, Fareed A, Thompson SI, Carrera CJ, Williams SS, Juergens TM, Albers LJ, Nasdahl CS, Villarreal G, Winston JL, Nogues CA, Connolly KR, Tapp A, Jones KA, Khatkhate G, Marri S, Suppes T, LaMotte J, Hurley R, Mayeda AR, Niculescu AB 3rd, Fischer BA, Loreck DJ, Rosenlicht N, Lieske S, Finkel MS, Little JT. Effect of Antidepressant Switching vs Augmentation on Remission Among Patients With Major Depressive Disorder Unresponsive to Antidepressant Treatment: The VAST-D Randomized Clinical Trial. JAMA. 2017 Jul 11;318(2):132-145. doi: 10.1001/jama.2017.8036. PMID: 28697253

AUGMENTATION VERSUS SWITCH: RESULTS OF THE PCORI-FUNDED ASCERTAIN-TRD TRIAL

George Papakostas, Massachusetts General Hospital

Individual Abstract: Major depressive disorder (MDD) is a serious, debilitating, life-shortening illness that affects many persons of all ages and backgrounds. The point prevalence of MDD is relatively high (2.3-3.2% in men; 4.5-9.3% in women) and the lifetime risk for MDD is 7-12% for men and 20-25% for women. To date, all U.S. Food and Drug Administration (FDA)-approved antidepressants used as monotherapies have shown only modest benefits in MDD. Treatment-resistant depression (TRD) typically refers to the occurrence of an inadequate response following at least two adequate antidepressant treatments among patients suffering from MDD. A particularly critical decision in everyday practice is choosing what to do next when patients with TRD present after antidepressant treatments have failed to produce a clinical response, especially with respect to the use of sequential monotherapies versus polypharmacy strategies such as augmentation, and, until recently, a large evidence gap existed with respect to this common clinical scenario. This evidence gap existed despite the completion of the large, multi-center STAR*D study, since most patients in the trial were not assigned at random to augmentation versus switch as very few patients agreed to potentially accept either of these two broad treatment arms. The purpose of the current presentation is to describe the results of ASCERTAIN-TRD, a multicenter study comparing aripiprazole augmentaton and rTMS augmentation with switching to venlafaxine in TRD.

Learning Objectives:

1. By the end of this presentation the audience will be able to describe the relative effectiveness of switching to venlafaxine versus augmentation with rTMS or aripiprazole for TRD.
2. By the end of this presentation the audience will be able to describe the relative tolerability of switching to venlafaxine versus augmentation with rTMS or aripiprazole for TRD.

Literature References:

1. Papakostas GI. Managing partial response or nonresponse: switching, augmentation, and combination strategies for major depressive disorder. J Clin Psychiatry. 2009;70 Suppl 6:16-25.

2. Fava M. Management of nonresponse and intolerance: switching strategies. J Clin Psychiatry. 2000;61 Suppl 2:10-2.

AUGMENTATION VS. SWITCHING ANTIDEPRESSANTS FOR TREATMENT RESISTANT DEPRESSION IN OLDER ADULTS: WHAT PROVIDES THE MOST BENEFITS? WHAT IS SAFEST? RESULTS FROM THE OPTIMUM CLINICAL TRIAL

Eric Lenze, Washington University School of Medicine

Individual Abstract: Background: Treatment-resistant depression is common in older adults and depletes psychological well-being. Augmenting or switching antidepressants may benefit late-life treatment resistant depression (LLTRD). However, the relative benefits and risks of these strategies are unknown. Augmentation may improve remission rate but at the cost of greater adverse events such as falls which are common in depressed older adults and lead to high morbidity and costs.

Methods: This was a randomized, comparative effectiveness study of adults aged 60+ with treatment-resistant depression, defined as current major depression with current symptoms (PHQ9 10+) in spite of at least 2 adequate antidepressant trials within the current depressive episode. The study had two steps; each was a separate randomized trial. In Step 1, participants were randomized to aripiprazole augmentation, bupropion augmentation, or bupropion switch. Those who did not benefit or were ineligible were randomized into Step 2: lithium augmentation or nortriptyline switch. Both steps were 10 weeks. The two primary effectiveness outcomes were 1) depression remission and 2) psychological well-being. The two primary safety outcomes were 1) falls and 2) serious adverse events.

Results: A total of 619 patients were randomized into Step 1. Remission rates were 28.9% for aripiprazole augmentation, 28.2% for bupropion augmentation, and 19.3% for bupropion switch; reductions in the Montgomery Asberg Depression Rating Scale were 7.4, 7.3, and 4.0 points, and improvements in the NIH Toolbox Psychological Wellbeing were 4.1, 3.8, and 1.4 points, respectively. The augmentation arms experienced higher remission rates and greater reduction in depressive symptoms compared to the switch arm (both $p=0.001$), as well as greater improvements in psychological well-being ($p=0.01$). Fall rates were 6.4% for aripiprazole augmentation, 9.3% for bupropion augmentation, and 7.7% for bupropion switch, with a higher rate of falls for bupropion augmentation compared to aripiprazole augmentation arm ($p=0.04$). There were no differences in serious adverse events among the three arms. In Step 2 ($n=251$), there were no differences between the lithium augmentation and nortriptyline switch arms in remission rates, changes in depression or psychological well-being, falls, or serious adverse events.

Conclusions: Among older adults with TRD, augmentation with aripiprazole or bupropion was more effective than switching to bupropion; additionally, aripiprazole augmentation led to a lower rate of falls than bupropion augmentation. In addition to improving remission rates, augmentation strategies were associated with greater improvement in psychological well-being, an outcome of high relevance for patients. For more highly resistant depression, lithium augmentation and nortriptyline switch had similar effectiveness and safety. These findings provide patients, physicians, and other stakeholders with data to make informed decisions about the optimal care for late-life TRD.

Learning Objectives:

1. Learn about psychological wellbeing and falls in late-life depression.
2. Learn the comparative effectiveness and risks of commonly-used augmentation and switch approaches for late-life depression when it is treatment resistant.

Literature References:

1. Cristancho P, Lenard E, Lenze EJ, et al: Optimizing Outcomes of Treatment Resistant Depression in Older Adults (OPTIMUM): Study Design and Treatment Characteristics of the First 396 Participants Randomized. American Journal of Geriatric Psychiatry 2019 Oct;27(10):1138-1152.
2. Lenze EJ, Mulsant BH, Blumberger DM, et al: Efficacy, safety, and tolerability of augmentation pharmacotherapy with aripiprazole for treatment-resistant depression in late life: a randomised, double-blind, placebo-controlled trial. The Lancet 2015: 386(10011): 2404-12.

COMPARATIVE EFFECTIVENESS OF ELECTROCONVULSIVE THERAPY VS. INTRAVENOUS KETAMINE FOR TREATMENT RESISTANT DEPRESSION (ELEKT-D) TRIAL: UPDATE ON DESIGN AND IMPLEMENTATION

Amit Anand, MGH Brigham, Harvard Medical School

Individual Abstract: Background: Electroconvulsive therapy (ECT) is the gold-standard treatment for treatment resistant major depression (TRD). However, it remains underutilized due to the need for general anesthesia, social stigma, and concerns about cognitive side effects. Ketamine has emerged as an alternative to ECT for the treatment of TRD but there are concerns regarding efficacy, addictive potential and safety. There is no robust data available to clinicians regarding the relative effectiveness of ECT vs. ketamine for TRD. To address this gap, we are conducting the first comparative efficacy study of ECT vs. ketamine for TRD (ELEKT-D study). The study is funded by the Patient Centered Outcome Research Institute (PCORI) and sponsored by the Cleveland Clinic Foundation. This multisite study is being conducted at Baylor College of Medicine, Cleveland Clinic, Johns Hopkins Medical Institute, Mt. Sinai Hospital and Yale School of Medicine.

Method: the study is designed as a pragmatic open-label, non-inferiority, comparative effectiveness trial of ECT vs. intravenous ketamine for TRD. Patients with TRD referred for ECT treatment are randomized (1:1) to receive ECT (thrice weekly) or intravenous ketamine (twice weekly) for 3–5 weeks. The primary outcome is the proportion of responders in each group at the end of study visit, as measured by a patient-reported outcome measure (Quick Inventory of Depressive Symptomatology-Self Report). The study is powered for a non-inferiority margin that allows for ketamine to retain 90% of the ECT treatment effect, with a projected sample size of 400 patients (200 per group). Secondary outcomes include remission rates, depression severity, cognitive functioning, quality of life, adverse events, and tolerability. Responders to either treatment (>50% decreased in QIDS-SR score) are followed up for 6 months with periodic assessments.

Results: To date, we have screened 371 eligible TRD subjects referred to the ECT service and N = 342 subjects have been enrolled in the study. Subjects have tolerated the study well with a low incidence of serious adverse events related to the treatments. Responders have continued in the follow-up phase with low attrition. The study is in the last year of enrollment.

Discussion: we will discuss the study design in detail, particularly the elements which have contributed to the success of this large study of ECT and ketamine response. The advantages

and pitfalls of real-world pragmatic trials will be reviewed. Patient centeredness and stakeholders' participation will be described.

Learning Objectives:

1. Learn about ECT and Ketamine as treatments for Treatment Resistant Depression.
2. Learn about large pragmatic clinical trials designed to address real-world clinical treatment knowledge gaps.

Literature References:

1. Mathew SJ, Wilkinson ST, Altinay M, Asghar-Ali A, Chang LC, Collins KA, Dale RM, Hu B, Krishnan K, Kellner CH, Malone DA, Murrough JW, Ostroff RB, Sanacora G, Shao M, Anand A. ELEctroconvulsive therapy (ECT) vs. Ketamine in patients with Treatment-resistant Depression: The ELEKT-D study protocol. Contemp Clin Trials. 2019;77:19-26.
2. Berman RM, Cappiello A, Anand A, Oren DA, Heninger GR, Charney DS, Krystal JH. Antidepressant effects of ketamine in depressed patients. Biol Psychiatry. 2000;47:351-354.

DIGITAL MEASUREMENT AND THERAPEUTICS IN THE PERI-PANDEMIC ERA: CHALLENGES AND OPPORTUNITIES

Timothy Mariano, Woebot Health; Brown Medical School; Providence VAMC

Overall Abstract: The broad accessibility of the internet and sophisticated smartphone technology have created opportunities for approaches to measurement and intervention in psychiatric disorders that were unimaginable just 20 years ago. We can now use the ubiquitous smartphone to provide objective, 24/7 measurement of relevant patient behaviors while these same devices, along with tablets and home computers, can bring treatment to the patient rather than requiring the patient to come to treatment. The arrival of the COVID-19 pandemic has only served to catalyze interest in these new technologies.

A multiplicity of approaches to so-called digital phenotyping and outcomes prediction that benefit from the capacities of Machine Learning (ML) are finding their way into novel health system models for patient care as well as into pharmaceutical company trials. Some are dependent only on the sensors available on the patient's phone while others also involve wearable technology, all with the goal of achieving a more comprehensive and objective picture of patient behavior.

Digital therapeutics (DTx) had been steadily evolving since well before the pandemic made virtual care commonplace. The Digital Therapeutics Alliance defines* DTx as "deliver[ing] evidence-based therapeutic interventions that are driven by high quality software programs to prevent, manage, or treat a medical disorder or disease. They are used independently or in concert with medications, devices, or other therapies to optimize patient care and health outcomes." The technology supporting DTx can take multiple forms, ranging from standalone Software as a Medical Device (SaMD) utilizing ML to deliver therapeutic interventions directly to users to smartphone apps that integrate the kind of sensor data described above into a coherent framework. DTx can be prescribed or non-prescription.

With pandemic-initiated shifts in care paradigms likely to persist in some form, the behavioral monitoring and DTx field will mature even more rapidly. Against this backdrop, the assembled academic and industry expert panelists will discuss opportunities and challenges related to the

role of digital assessment, therapeutics, and related digital technology in pharmaceutical development, healthcare, and consumer-facing products. To generate as much discussion as possible, each of the four panelists will provide a brief presentation, followed by a formal discussant's commentary, and then panel discussion with audience participation.

*https://dtxalliance.org/wp-content/uploads/2021/01/DTA_DTx-Definition-and-Core-Principles.pdf

Learning Objectives:

1. Digital phenotyping uses software and sensors to characterize patient behavior objectively; digital therapeutics (DTx) utilize software to deliver evidence-based therapeutic interventions.
2. Both are already in clinical use and present challenges to integration into existing clinical workflows but also unique opportunities not available with traditional modalities.

NO LOOKING BACK: TECH-ENABLING THE PRACTICE OF PSYCHIATRY

Cynthia Epperson, University of Colorado Anschutz Medical Campus

Individual Abstract: Few counties in the United States have the recommended number (14/100,000) of psychiatrists to meet the mental health needs of its population. More than 60% of counties, including 80% of rural counties are without a single practicing psychiatrist. With the dearth of psychiatrists and other mental health care providers across the United States, the onus is upon leaders to focus on prevention and early intervention strategies.

One such strategy is to engage patients and providers with technology that utilizes evidence-based methods and biometrics to rapidly identify those with mental health needs and to provide micro-interventions aimed at preventing onset or relapse of depression, anxiety and other common psychiatric concerns. Smart phone applications (apps) that are based upon objective and informative biometrics and require little attention on the part of the user, are critical to the present and future of mental health care. They allow for a step-care approach of providing direct feedback to the app user regarding their current mental health, suggestions for health promoting behaviors, and referral to clinical resources if appropriate. App-based technologies hold promise to expand the supply of mental health interventions and providers in a system where the demands for services far out-pace the supply.

The University of Colorado (CU) Department of Psychiatry, CU Innovations and University of Colorado Health (UCHealth) are collaborating with an innovative digital health start-up to escalate the use of their evidence-based smart phone app throughout the entire health system. UCHealth provides care to more than half of adult Coloradans. With its flagship hospital University of Colorado Hospital (UCH) being named the number one hospital in Colorado for the past 9 years in a row, this academic-industry-health system partnership is poised to demonstrate to the entire state and greater Rocky Mountain Region, if not the nation, how evidence-based digital health products can improve the mental health of millions in a cost-effective manner that supports, not taxes, our currently overwhelmed mental health care system.

Learning Objectives:

1. Attendees will describe the shortage of mental healthcare providers across the US.

2. Attendees will be able to discuss the importance of digital technology in mental health care.

DIGITAL BIOMARKERS AND THEIR APPLICATION IN EVERYDAY MENTAL HEALTH CARE

Georgia Mitsi, Biogen

Individual Abstract: This talk will provide an overview of past and current efforts and the level of involvement and direction that pharmaceutical companies have and currently are taking in their efforts to incorporate digital health solutions in the Mental Health area. What technologies do they prefer and why? What business models are they willing to test? The level of readiness in incorporating digital measurements as part of clinical trials, other than exploratory ones, will be discussed. Analysis of the challenges that innovators are facing either as internal champions or as external partners will be explored, including what learnings we have so far to be used as a roadmap for success. Finally, we will discuss why now, more than ever before, we need to increase awareness about the value that these solutions bring and the tangible difference they can make in patients' lives.

DEVELOPING, TESTING, AND TAKING A DIGITAL INTERVENTION FOR DEPRESSION TO FDA INDICATION: CHALLENGES AND OPPORTUNITIES

Ellen Frank, University of Pittsburgh School of Medicine

Individual Abstract: In 2014, a group of academic researchers at the University of Pittsburgh, University College, Dublin and Cornell University recognized the potential of the commercial smartphone to provide something that had essentially been missing in psychiatry: continuous and objective measurement of patient behavior. The ubiquity and intimacy of the smartphone, already deeply embedded in people's lives made it the ideal technology for achieving that objective. Their initial efforts focused on the development of MoodRhythm, a self-monitoring tool for individuals with bipolar disorder based on social rhythm regulation principles; however, they soon realized that smartphone technology held the promise of much broader measurement and intervention application.

With SBIR funding from the National Institute of Mental Health, we set out to examine the feasibility and acceptability of Cue™, a platform that included continuous, objective measurement of patient behavior coupled with just-in-time suggestions for behavior change based on the individual patient's own sensed behavior that would be pushed to the patient through the phone. The Institute, however, thought the idea was ready for more than a feasibility and acceptability study. NIMH leadership accordingly encouraged us to carry out a randomized controlled trial to assess the efficacy of such a platform. Pivoting from our original, simpler proposal was the first of the challenges we faced.

The initial phase of our research involved the collaborative design of Cue™. We worked with outpatients receiving treatment at the University of Utah to understand what they thought would be most helpful to them and in what format. Once satisfied that we had incorporated the learning from the collaborative design phase into the Cue™ platform, we conducted a 16-week RCT in psychiatric outpatients with a lifetime diagnosis of a mood and/or anxiety disorder. Participants were randomly allocated to receive Cue ™ along with care-as-usual (primarily pharmacotherapy) by University of Utah faculty psychiatrists or digital monitoring

only plus care-as-usual. The intent-to-treat (ITT) sample consisted of 133 individuals; however, our primary interest was outcome for those individuals with major depression at study entry (baseline PHQ-8 score ≥15; N=28). We fit a mixed effects models to test for group differences in the slope of depressive symptoms over 16 weeks. In the depressed-at-entry sample, we found a large group difference in the slope of PHQ-8 (Cohen's d= -0.72), indicating a meaningfully more rapid rate of improvement in the intervention group.

Encouraged by the size of the intervention effect in those who were acutely ill at baseline, we applied for additional SBIR funding to take Cue™ to FDA indication for major depression. In the interim, we developed a library of over 1500 behavior change suggestions based on those sent to patients engaged in our initial trial and evolved a machine learning-based method for selection of the appropriate just-in-time behavior change suggestion to send to a patient throughout the course of the intervention. The process of defining a study protocol the meets the FDA's requirements has presented a series of interesting challenges that will be described as the final part of this presentation.

SOFTWARE AS A MEDICAL DEVICE FOR TREATMENT OF MENTAL HEALTH CONDITIONS: PROMISE AND CHALLENGE

Alison Darcy, Woebot Health

Individual Abstract: Using technology to deliver therapeutics - Software as Medical Devices (SaMD) - offer opportunities in health care that go beyond convenience and scalability. While these are important attributes, they are impactful only insofar as their underlying therapeutic modalities are clinically potent. While the field is nascent, some digital therapeutics create novel therapeutic mechanisms through interaction opportunities that are only made possible by the technology itself. The ability for virtual reality to engage opposing yet simultaneous neurocognitive processes - giving rise to both an emotional response and at the same time a rational one, for example, allows a person to retrain an emotional response to a feared event. In addition, digital therapeutics are well poised to be used in a moment of need, potentially heightening the clinical potency of the interaction if it leads to successful modulation of mood state. If these novel therapeutic mechanisms emerge as efficacious and safe, then their scalability could have a very positive influence on improving access to care - one of the key constraints of our health system today. An intriguing category of SaMD is that which conveys therapeutic content within a relational framing, such as Agent Guided Cognitive Behavior Therapy (AGCBT). Emerging evidence suggests that AGCBT can replicate some of the so-called "common factors" that have hitherto been considered to be the exclusive domain of human therapists, such as the creation of therapeutic bond. While the promise of these AI-based agents lies in unlocking therapeutic value, much confusion exists on this point, and there is a growing misperception that their intended use is to replace human clinicians. At the same time, some key challenges remain for all digital therapeutics. The ubiquitousness of untested and unvalidated apps that make health claims risk undermining public confidence in digital therapeutics as a whole which would in turn undermine what is potentially a key public health opportunity. Another challenge exists in the fact that our current clinical work flows and regulatory structures were not built for digital innovation and require leadership to illuminate the path based on a consideration of risk/benefit ratio.

AN ASCP/AFSP PANEL: USING TECHNOLOGY FOR SUICIDE PREVENTION

Jill Harkavy-Friedman, American Foundation for Suicide Prevention

Overall Abstract: Suicide risk is dynamic and difficult to address in real time with traditional methods. There is hope that technology can play a significant role in research and practice related to clinical trials research and suicide prevention. The use of technology in clinical trials and mental health research had been increasing, and the pandemic accelerated the use of technological devices. Devices are being employed for passive and active management as well as serving as a tool for providing treatment and this has the potential to change the conduct and impact of research and suicide prevention.

However, the jury is out about what technology and technical methods have to offer and when they will be most effect. Here we discuss the scope of practice for using technology in clinical research and practice. Strengths and limitations of using of technology for assessment, and intervention in clinical trials with a focus on suicide prevention will be provided using real world research examples.

Scott Langenecker will present his study of the SafeUT app, the role and implementation of the app in crisis response planning, and an in depth evaluation of active rescues in 2020. Matthew Nock will discuss consensus on the ethical considerations associated with the use of technology with practical suggestions for incorporating technology in clinical trials research and in clinical practice.

Learning Objectives:

1. Discuss at least two potential uses of technology in clinical trials.
2. Review the ethical issues related to the use of technology in clinical practice and research.

USING NEW TECHNOLOGY TO IMPROVE THE PREDICTION AND PREVENTION OF SUICIDAL BEHAVIOR

Matthew Nock, Harvard University

Individual Abstract: Suicide is a leading cause of death in the US and worldwide. Whereas the mortality rate associated with many leading causes of death (cancer, pneumonia, HIV/AIDS) has declined dramatically over the past decades, the suicide rate is the same now as it was 100 years ago. Recent advances in technology and computing are providing tools that have been used to advance the understanding, prediction, and prevention of suicidal behaviors in recent years. This presentation will review some of these advances and the ways in which they could be incorporated into clinical practice in a range of different hospital- and community-based settings.

Learning Objectives:

1. Describe how real-time monitoring has advanced the understanding of suicidal thoughts.
2. Explain how automated interventions can increase help-seeking among those at risk for suicide.

Literature References:

1. Wang, S. B., Coppersmith, D. D., Kleiman, E. M., Bentley, K. H., Millner, A. J., Fortgang, R., Mair, P., Dempsey, W., Huffman, J.C., and Nock, M. K. (2021). A pilot

study using frequent inpatient assessments of suicidal thinking to predict short-term post discharge suicidal behavior. JAMA Network Open, 4(3), e210591-e210591.
2. Jaroszewski, A.C., Morris, R., and Nock, M.K. (2019). Randomized Controlled Trial of an Online Machine Learning-Driven Risk Assessment and Intervention Platform for Increasing the Use of Crisis Services. Journal of Consulting and Clinical Psychology, 87, 370-379.

CHALLENGES AND OPPORTUNITIES FOR TEXT-BASED CRISIS RESPONSE - LESSONS LEARNED IN 2020 WITH SAFEUT

Scott Langenecker, University of Utah

Individual Abstract: Technology-based avenues for crisis intervention have proliferated in recent years, matching the generational switch to use of apps, including text-based crisis apps. SafeUT is a text based-crisis app developed by the University of Utah in partnership with Huntsman Mental Health Institute and University Information Technology, with support from multiple state stakeholders. SafeUT use has increased over time since the roll-out in 2017. Estimated usage now is at 200 users per semester for every 100000 students. For a high school of 2000 students, that is an estimated 12-15 users per year. There is still underutilization of SafeUT. For a given High School of 2000, we would expect about 600-800 students with mental health concerns. We specifically investigated crisis interventions in the calendar year of 2020, as it enabled us to determine benefits, challenges, and opportunities for future development. Of over 28,000 crisis text chats, which use a crisis assessment and intervention model, about 65% include text chats about suicide or self-harm. Two-hundred and ninety-eight of these interactions involved a crisis with an imminent risk of harm to self, in which a "break the glass" procedure was engaged by the licensed mental health professional at SafeUT. A significant minority were based from the "tip" function where a friend, family member or teacher could report a safety concern. A majority of active rescues (60%) involve a connection with emergency and rescue facilities in a matter of minutes. About 20% of the time, the user does not want to or doesn't feel comfortable engaging parents or others in the living space to organize help. 47% of active rescues have an "unknown" outcome for safety of the user. 40% of these active rescues include a mention of intent to harm in the initial chat or tip message. There are still some youth with mental health challenges who do not have access to SafeUT and many (35%) of youth have still not heard about SafeUT. There are still needs for closure to connect information on crisis response outcomes to improve SafeUT crisis interventions to as to better serve the youth users. Challenges to app-based crisis services include 1. Lack of awareness of services, 2. Lack of access to app devices during high risk periods (at night when devices may be in parent's rooms), 3. Lack of access to devices at any time (young children without access), 4. Lack of confidential access. Opportunities for future development include 1. creating more educational opportunities to increase parent and child awareness of availability, including for "lower" level concerns around worries and challenges, 2. Assessing strategies to work around access concerns in the context of confidentiality (working with older siblings, other trusted adults), 3., using machine learning strategies to identify lethality and facilitate more rapid triage, 4. Creating access opportunities in school tablet rentals (e.g., school chromebook access), 5. Trial access in health classes in middle school for kids screened as at risk. 6., creation of case numbers for active rescues to allow for safety disposition and outcome reporting from safety contacts (EMTs, mobile crisis teams, police departments, emergency departments) to allow for full 360 outcome analysis and quality improvement. There are

additional places to improve knowledge about crisis intervention opportunities that we will continue to pursue.

Learning Objectives:

1. For the learner to understand how often text-based contacts involve concerns about suicide or self harm.
2. For the learner to understand barriers to use of text-based crisis apps for youth.

Literature References:

1. Summers L., Meppen D., Ball S., Utah's Mental Health System A collaborative endeavor of the Kem C. Gardner Policy Institute and the Utah Hospital Association 2019.
2. https://gardner.utah.edu/wp-content/uploads/MentalHealthReportAug2019.pdf. Accessed June 18, 2021.
3. 2. SAMHSA Substance Abuse and Mental Health Services Administration. National Guidelines for Behavioral Health Crisis Care-A Best Practice Toolkit 2020.
4. https://www.samhsa.gov/sites/default/files/national-guidelines-for-behavioral-health-crisis-care-02242020.pdf. Accessed June 18, 2020.

TECHNOLOGY AS A TOOL AND OUTCOME IN CLINICAL TRIALS

Jill Harkavy-Friedman, American Foundation for Suicide Prevention

Individual Abstract: With advances in technology moving the field of assessment, there has been much discussion of implementing technology for monitoring and assessing outcome in clinical trials. Several options for active and passive assessment will be discussed with a focus on their use in clinical trials. Considerations for identifying optimal assessment measures will be provided. Specific attention will be paid towards rapidly changing outcomes such as suicidal ideation and behavior and how to have continuity of assessment can be made from rapid trial outcomes to longer-term outcomes such as ongoing symptom relief and recovery. Recent guidance such as that of the FDA will be considered.

Learning Objectives:

1. Identify at least two technological methods for assessing outcome in clinical trials.
2. Review indications and contraindications for using technology in clinical trials.

Literature References:

1. 1.Federal Drug Administration (2022) Digital Health Technologies for Remote Data Acquisition in Clinical Investigations; Draft Guidance for Industry, Investigators, and Other Stakeholders (Docket FDA-2021-D-1128). https://www.fda.gov/regulatory-information/search-fda-guidance-documents/digital-health-technologies-remote-data-acquisition-clinical-investigations Accessed May 10, 2022.

2. Inan, O.T., Tenaerts, P., Prindiville, S.A. et al. Digitizing clinical trials. npj Digit. Med. 3, 101 (2020). https://doi.org/10.1038/s41746-020-0302-y

Friday, June 3, 2022

Panel Sessions

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

*AUGMENTING VS. SWITCHING ANTIDEPRESSANT FOR TREATMENT RESISTANT DEPRESSION IN OLDER ADULTS: RESULTS FROM THE OPTIMUM STUDY

Helen Lavretsky, David Geffen School of Medicine at UCLA

Overall Abstract: Background: About 14% of older Americans are prescribed an antidepressant, but this broad use is not associated with a decrease in the burden of geriatric depression. Indeed, treatment resistance
is the norm, not the exception in older depressed adults, as most fail to remit with standard antidepressant pharmacotherapy, and persistent depression decreases older adults' quality of life more than any other illness. Effective use of antidepressants for TRD in real-world settings would address a leading cause of disability, excess mortality, and cognitive decline. While it is established that antidepressants are more efficacious than placebo, patients with TRD treated with active antidepressants should experience at least the improvement associated with the use of a placebo.

However, some published data suggest that patients whose depression is treated under usual care (nonstudy) conditions are actually less likely to respond to antidepressant treatment or to

experience remission of their depressive symptoms than depressed patients who receive a placebo in an RCT. Testing algorithmic, measurement-based antidepressant pharmacotherapy of TRD in real-world settings is needed to guide personalized and safe prescribing and advance clinical science beyond tightly controlled efficacy studies which may not translate to routine clinical care.

To address this, Dr. Karp will describe: 1) the characteristics of the patient sample from the multi-site OPTIMUM trial; 2) balancing the Pragmatic-Explanatory Continuum when planning

impactful pragmatic research; 3) the significance of engaging stakeholders in a pragmatic clinical trial, from inception to dissemination; and 4) some challenges and solutions to conducting a

successful pragmatic clinical trial.

Methods: In Step 1, participants were randomized to one of three strategies: augmentation with aripiprazole, augmentation with bupropion, or switch to bupropion. Treatment effectiveness was assessed using the Montgomery Asberg Depression Rating Scale (MADRS) after ten weeks of treatment. Those who did not remit proceeded to Step 2 where they were randomized to either lithium augmentation of an index antidepressant or switch to nortriptyline.

Results: Step 1 involved 621 participants, of which 212 were randomized to augmentation with aripiprazole, 206 to augmentation with bupropion, and 203 to a switch to bupropion. Step 2 involved 251 participants of which 127 were randomized to augmentation to augmentation with lithium and 124 to a switch to nortriptyline. Challenges which were successfully overcome in this pragmatic trial include sustaining engagement with primary care partners, minority recruitment, safe management of alcohol and occult benzodiazepine use and co-prescribed medications, adverse event reporting in a pragmatic design without a placebo condition in medically compromised older adults and planning for impactful dissemination.

Conclusions: OPTIMUM is the largest stakeholder-informed study of pharmacotherapy for late-life TRD. It is a model for balancing pragmatic and explanatory approaches for a successful clinical trial.

Listening to a variety of stakeholder voices during every six-month advisory board meetings makes OPTIMUM highly relevant and patient-centered.

Learning Objectives:

1. The participants will learn about the OPTIMUM algorithm of augmentation vs switching for treatment resistant Late-Life Depression.
2. The participants will learn about primary and secondary outcomes.

PRAGMATISM, CONTEXT, AND LESSONS LEARNED: PLANNING FOR IMPACTFUL DISSEMINATION

Jordan Karp, University of Arizona

Individual Abstract: About 14% of older Americans are prescribed an antidepressant, but this broad use is not associated with a decrease in the burden of geriatric depression. Indeed, treatment resistance is the norm, not the exception in older depressed adults, as most fail to remit with standard antidepressant pharmacotherapy, and persistent depression decreases older adults' quality of life more than any other illness. Effective use of antidepressants for TRD in real-world settings would address a leading cause of disability, excess mortality, and cognitive decline. While it is established that antidepressants are more efficacious than placebo, patients with TRD treated with active antidepressants should experience at least the improvement associated with the use of a placebo. However, some published data suggest that patients whose depression is treated under usual care (nonstudy) conditions are actually less likely to respond to antidepressant treatment or to experience remission of their depressive symptoms than depressed patients who receive a placebo in an RCT. Testing algorithmic, measurement-based antidepressant pharmacotherapy of TRD in real-world settings is needed to guide personalized and safe prescribing and advance clinical science beyond tightly controlled efficacy studies which may not translate to routine clinical care.

To address this, Dr. Karp will describe: 1) the characteristics of the patient sample from the multi-site OPTIMUM trial; 2) balancing the Pragmatic-Explanatory Continuum when planning impactful pragmatic research; 3) the significance of engaging stakeholders in a pragmatic clinical trial, from inception to dissemination; and 4) some challenges and solutions to conducting a successful pragmatic clinical trial.

Learning Objectives:

1. Appreciate pragmatic versus explanatory features of a clinical trial to aid meaningful interpretation.

2. Understand how clinical decision support tools in the electronic medical record may be used to guide best practice.

Literature References:

1. Thorpe KE, Zwarenstein M, Oxman AD, Treweek S, Furberg CD, Altman DG, Tunis S, Bergel E, Harvey I, Magid DJ, Chalkidou K. A pragmatic-explanatory continuum indicator summary (PRECIS): a tool to help trial designers. J Clin Epidemiol. 2009 May;62(5):464-75.

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WHAT TREATMENT CHOICES ARE EFFECTIVE? SAFE? FUTILE? RESULTS FROM THE OPTIMUM STUDY

Eric Lenze, Washington University School of Medicine

Individual Abstract: Background: The OPTIMUM trial was a pragmatic trial conducted in the community, testing treatments for treatment resistant depression in older adults for their effectiveness and safety.

Head-to-head tests of aripiprazole augmentation, bupropion augmentation, and bupropion switch in Step 1 and lithium augmentation and nortriptyline switch in Step 2 can identify treatments that are effective and safe, or futile and relatively unsafe, for older adults

Methods: The "Optimizing antidepressants for TRD in older adults" (OPTIMUM) study, funded by the Patient-Centered Outcomes Research Institute, is a 5-center collaboration that randomized depressed individuals aged 60+ with TRD. It is the largest-ever pragmatic clinical trial of TRD in older adults, with a similar design as the STAR*D and VAST-D studies that were conducted in younger adults. Participants were randomized into one of three arms: augmentation with aripiprazole, augmentation with bupropion, or switch to bupropion (n=619). Those who did not remit were then randomized into a second step with two arms: augmentation with lithium and switch to nortriptyline (n=248). Participants were measured at the beginning and end of these 10-week steps with a measure of remission (based on Montgomery Asberg Depression Rating Scale), and were measured throughout the steps for safety, including falls. Fidelity to the treatment assignment was also assessed.

Results: The study found that augmentation with aripiprazole and augmentation with bupropion had similar effectiveness (remission rates of 29% and 28% respectively) and were more effective than switch to bupropion (remission rate of 19%). In contrast, all three of these strategies were roughly equal in their risks such as falls and serious adverse events , and there were more reports of falls in the bupropion augmentation arm than the aripiprazole augmentation arm. In the second step of the trial, lithium augmentation and a switch to nortriptyline were roughly equivalent in both effectiveness (remission rates of 19% and 21% respectively) and with the similar tolerability and SAEs and falls. Overall, bupropion switch in Step 1 and lithium augmentation in Step 2 appeared to be futile treatments, with fewer than 10% of participants randomized to either of these treatment arms staying on the assigned treatment and remitting by the end of the acute step.

Conclusions: Aripiprazole augmentation appeared to be a superior treatment option in Step 1 when considering effectiveness and risks. In Step 2, there was no clearly superior treatment; however, lithium augmentation was unlikely to lead to remission.

Learning Objectives:

1. Learn effectiveness of treatment options for bringing about remission from late life depression when it is treatment resistant.
2. Learn comparative safety of different antidepressant options.

Literature References:

1. Antidepressant Treatment for Late-Life Depression: Considering Risks and Benefits.
2. Lenze EJ, Ajam Oughli H.
3. J Am Geriatr Soc. 2019 Aug;67(8):1555-1556. doi: 10.1111/jgs.15964. Epub 2019 May 29.
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6. Cristancho P, Lenard E, Lenze EJ, Miller JP, Brown PJ, Roose SP, Montes-Garcia C, Blumberger DM, Mulsant BH, Lavretsky H, Rollman BL, Reynolds CF 3rd, Karp JF.
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8. PMID: 31147244

OPTIMIZING OUTCOMES OF TREATMENT-RESISTANT DEPRESSION (TRD) IN OLDER ADULTS (OPTIMUM): EFFECTS ON PSYCHOLOGICAL WELL-BEING

Helen Lavretsky, David Geffen School of Medicine at UCLA

Individual Abstract: Background: The "Optimizing Antidepressants for Treatment Resistant Depression in Older Adults" (OPTIMUM) study, funded by the Patient-Centered Outcomes Research Institute, is a 5-center collaboration that randomized 621 depressed individuals aged 60+ with treatment resistant depression (TRD), the largest pharmacological study of late-life depression. A key goal of this pragmatic trial was measuring outcomes of interest to patients, which in this trial included psychological well-being. This construct is closely tied to physical and psychological functioning and can be measured by self-report. OPTIMUM is one of the first studies to measure antidepressant effects on psychological well-being.

Methods: Participants were recruited and randomized if they were 60 years and older, met the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria for Major Depressive Disorder, and had a score of 10 or higher on the Patient Health Questionnaire (PHQ-9), despite having been treated with at least two antidepressants with an adequate dosage and for at least four weeks (with previous antidepressants being different from the medications being tested in OPTIMUM). Upon study entry, participants were randomized into one of three strategies: augmentation with aripiprazole, augmentation with bupropion, or switch to bupropion. Treatment effectiveness was assessed using the Montgomery Asberg Rating Scale (MADRS) after ten weeks of treatment. Participants were also measured at the beginning and end of this 10-week step with the NIH Toolbox Psychological Well-being battery. Two well-being scales were measured: positive affect (34 items) and general life satisfaction (16 items). Positive affect is characterized as happiness, contentment, and interest in pleasurable or achievement –relevant activities. Each item administered has a 5 point scale with options ranging from “not at all” to “very much”. Meanwhile general life satisfaction is the cognitive evaluation of life experiences and items assessing this concept are usually phrased in a general or global way rather than having a momentary or recent recall period. Items administered include those with both 5-point and 7-point scales, with options in each case ranging from “strongly disagree” to “strongly agree”.

Results: Six hundred and twenty-one participants were included in the study of which 212 were randomized to augmentation with aripiprazole, 206 to augmentation with bupropion, and 203

to a switch to bupropion. The study found that augmentation with aripiprazole and augmentation with bupropion had similar effectiveness (remission rates of 34% per arm) and were more effective than switch to bupropion (remission rate of 24%). Participants randomized to either augmentation with aripiprazole or bupropion showed a statistically significant improvement in the general life satisfaction subscale estimated at the magnitude of 2.99 for aripiprazole ($p< 0.0001$) and 2.61 for bupropion ($p=0.0001$) while those switched to bupropion did not. Participants in either of the two augmentation arms, aripiprazole or bupropion, also showed an improvement in positive affect estimated at the magnitude of 5.35 ($p < 0.0001$) for aripiprazole and 5.02 ($p< 0.0001$) for bupropion as compared to those in the switching to bupropion arm.

Learning Objectives:

1. Present the effects of treatment on well-being, social engagement, and positive affect.
2. Present the results of qualitative analyses of patient and provider experience with the trial.

Literature References:

1. Hamm ME, Brown PJ, Karp JF, Lenard E, Cameron F, Dawdani A, Lavretsky H, Miller JP, Mulsant BH, Pham VT, Reynolds CF, Roose SP, Lenze EJ. Experiences of American Older Adults with Pre-existing Depression During the Beginnings of the COVID-19 Pandemic: A Multicity, Mixed-Methods Study. Am J Geriatr Psychiatry. 2020 Sep;28(9):924-932. doi: 10.1016/j.jagp.2020.06.013. Epub 2020 Jun 20. PMID: 32682619; PMCID: PMC7305766.
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*CHALLENGES AND OPPORTUNITIES IN THE USE OF REAL-WORLD EVIDENCE TO ADVANCE TREATMENT DEVELOPMENT IN BEHAVIORAL HEALTH

Scott Kollins, Holmusk

Overall Abstract: Fueled in part by the 21st Century Cures Act, there has been an increased emphasis from FDA and other stakeholders on the use of Real-World Data (RWD) and Real-World Evidence (RWE) in the treatment development process. There has been considerable progress incorporating RWE into the clinical evidence generation plans across a range of therapeutic areas (eg., oncology). Indeed, the COVID-19 pandemic has provided an important impetus to refine the way industry and regulatory stakeholders think about RWE.

In spite of these advances, there has been relatively less progress in the use of RWE in behavioral and mental health. There are few, if any, use cases of regulatory decisions in across psychiatric indications that have been influenced or informed by RWE. There are a number of potential reasons for this. First and foremost is the nature and quality of real-world data that are routinely gathered in behavioral health clinical settings and the relationship between these data and those gathered in randomized controlled trials. Across psychiatric indications, the primary outcomes that are routinely used in clinical trials are almost never collected in routine care. This makes it challenging to draw comparable conclusions regarding

efficacy/effectiveness from behavioral health RWD. A second limitation that is not unique to behavioral health is that the patients seen in clinical trials are not representative of those seen in routine care. Comorbid psychiatric (and medical) conditions are the norm, not the exception, and so comparability across settings is difficult to evaluate. Finally, data gathered in routine clinical care, is either subjective and largely unstructured (as is the case with data from electronic health records) or lacks depth and clinical richness (as is the case with insurance claims data).

Despite these myriad challenges, there are opportunities to innovate the ways that RWE can be used more effectively in behavioral health research. The continued development and refinement of data science methods such as natural language processing provide tools to help derive structure and clinical meaning from the traditionally variable and unstructured data captured in routine behavioral health care. In addition, the explosion of tools to gather, aggregate, and process vast amounts of patient generated health data holds great promise to augment the kinds of information gathered in clinical settings, which often do not capture the most important features of a patient's journey.

The overall objective of this panel is to take a critical and in-depth look at the challenges for using RWE in behavioral health and to explore opportunities for innovation. We aim to solicit input from diverse stakeholders across industry, academia, and regulatory bodies. We will also hear from experts in therapeutic areas that are farther ahead in the use of RWE than behavioral health. This panel will serve as an important point of departure for a journey to help define the field of RWE for behavioral health.

Learning Objectives:

1. Be familiar with the construct of RWE and why it is important to facilitate treatment development in general.
2. Characterize both the challenges and opportunities for using RWE in mental and behavioral health.

REAL-WORLD EVIDENCE DATA IN PHARMACEUTICAL PRODUCTS R&D FROM REGISTRATION TO REIMBURSEMENT: CHALLENGES AND OPPORTUNITIES

Luca Pani, University of Miami

Individual Abstract: Health real-world data (RWD) (1) are data derived from several sources and can be defined as data that are not captured in conventional randomised controlled trials [RCTs]. RWD are collected both prospectively and retrospectively and include clinical, economic, and patient-reported outcomes (PROs) such as health-related quality of life (HRQoL). Registries (patient drug/disease-based registries), electronic health records, practical or pragmatic clinical trials, administrative data, and observational studies (2) are all types of RWD. There is an increased interest in the use of real-world evidence (RWE) – which is derived from RWD -- to support regulatory decision-making for drug and biological products both in the EU (3) and in the US (4). The recent publication by the FDA of its new draft guidance (5) in this space is worth noticing and provides an important framework and data standards (6) for how researchers and sponsors can think about using RWE for regulatory purposes. According to the FDA, the use of computers, mobile devices, wearables, and other biosensors to gather and store huge amounts of health-related data has been rapidly accelerating. These data hold the potential to better design and conduct clinical trials and

studies in the health care setting to answer questions previously thought infeasible (4). In addition, with the development of sophisticated analytical capabilities, we can better analyze these data and apply the results to medical product development, approval (5), and reimbursement. It is expected for instance that RWD should enable the generation of additional evidence post-launch, inform dynamic price-setting in relation to the value of medicines, and may optimize appropriate use in daily practice. The situation seems to be, however, very different in Europe where, for the past three years, the limitations imposed by the General Data Protection Regulation (GDPR) (7) have added an unexpected layer of complication to the use of RWE data in health settings. Privacy protection is one of the several challenges that have emerged, others are on how to manage expectations about the use of such data, how to better understand their usefulness and their pitfalls throughout an entire medicine's lifecycle (and not just post-launch), and how to encourage their optimal use (8).

1) Real-world evidence (RWE) is the evidence derived from the analysis and/or synthesis of real-world data (RWD)

2) https://www.imi-getreal.eu/

3) https://www.getreal-institute.org/

4) https://www.nejm.org/doi/full/10.1056/NEJMsb1609216

5) https://www.fda.gov/media/152503/download

6) https://www.fda.gov/media/153341/download

7) https://gdpr.eu/

8) https://issuu.com/fipra/docs/real_world_data-5

Learning Objectives:

1. Learn the evolution of Real World Evidence Data and its possible use in Clinical Drug Development
2. Learn about the implications of the EU-GDPR for Clinical Trials
3. **Literature References:** Sherman RE, Anderson SA, Dal Pan GJ, Gray GW, Gross T, Hunter N, LaVange L, Marinac-Dabic D, Marks PW, Robb MA, Shuren J, Temple R, Woodcock J, Yue LQ, Califf RM, Real-World Evidence - What Is It and What Can It Tell Us? N Engl J Med 2016; 375:2293-2297
4. Martini N, Trifirò G, Capuano A, Corrao G, Pierini A, Racagni G, Pani L, Expert opinion on Real-World Evidence (RWE) in drug development and usage PharmAdvances 2020; 2:41-50

INDUSTRY PERSPECTIVE ON RWE FOR BEHAVIORAL HEALTH

Shuvayu Sen, Otsuka Pharmaceutical Companies

Individual Abstract: There are significant challenges with the use of RWE, particularly in behavioral health. One of the biggest barriers perceived by industry for investing into RWE is the current lack of guidance from the FDA and other regulatory bodies. The FDA's RWE Framework was published in 2018 but it was not until September of 2021 that more specific guidance to help industry frame RWE submissions specifically involving existing medical/ claims records was issued. Moreover, in terms of behavioral health RWD, there are unique challenges that industry faces including lack of standardized data elements, a high proportion of unstructured data without proper labels, and inconsistency of endpoint collection. This situation is further plagued by the disintegrated nature of the behavioral health eco system

where different sets of a patient records remain in different silos, often making it infeasible to merge. While industry is open to work with data vendors in addressing these challenges, the fact that industry does not own these types of data adds another layer of skepticism for investing into use of RWE. Furthermore, the influence of RWE on payers' decisions in this space is not clearly defined, leading to lower interest in RWE investment.

There are key areas where progress could be made. First, there needs to be an environment where industry can partner with data vendors to help augment the quality, validity and reliability of behavioral health RWD. Second, industry-academia partnership is critical to enable better access to RWD sources, thereby encouraging more investment in different types of data. Third, there needs to be a dedicated dialogue to develop registry data for behavioral health with adequate representation from industry, clinical and patient stakeholders. The recent digitalization of health care provides unique opportunities for industry to appropriately store and use the enormous amount of real-time data that are being generated every second to improve cost, access and quality to better behavioral health care. Finally, progress is needed to facilitate data linkage/tokenization. As noted, healthcare data are fragmented with variable follow-up, and do not allow for easy characterization of the full patient journey. Significant efforts are warranted to link the different existing databases to address this serious gap.

There are varying degrees of progress for the above referenced opportunities. External Control Arms (ECAs) represent a specific use case that has been gaining momentum for scenarios where there is a high unmet need. In some cases, it is unethical or practically infeasible to assign patients to placebo. ECAs, when developed appropriately, not only provide insights from real-world settings but also have the opportunity to expedite the regulatory approval timeline, consequently helping patients receive needed treatments faster.

I will present an ongoing study to develop an ECA for a mirror-image trial involving adults with schizophrenia. The external controls will be selected from a large RWD dataset. Findings from this study will support updating economic modeling to facilitate discussions with payers. Moreover, we will be able to evaluate how the healthcare resource utilization (HCRU) and clinical outcomes (e.g. – rate of psychiatric hospitalization during follow up care) among adults with schizophrenia in a real-world setting compare to those from our clinical trial. Thus, the insights from this study have the potential to augment findings from our mirror-image trial by assessing the comparability and validity of the trial findings when a RWD source is used as a comparator.

Learning Objectives:

1. Understanding of real world data and evidences derived from that.
2. Use of real world evidence and real world data from industry perspective.

Literature References:

1. Beaulieu-Jones BK, Finalayson SG, Yuan W, Altman RB, Kohane IS, Prasad B, Yu KH. " Examining the use of real world evidence in the regultory process." Clin Pharmacol Ther. 107: 843-852; 2020
2. Jarow JP, LaVange L, Woodcock J. "Multidimensional evidence generation and FDA decision making: definining and using real world data." JAMA. 318: 703-704; 2017

USING REAL WORLD DATA TO GENERATE HIGH QUALITY REAL WORLD EVIDENCE: LESSONS LEARNED FROM OPHTHALMOLOGY

Durga Borkar, Duke University Eye Center

Individual Abstract: The use of real world data (RWD) to generate high quality real world evidence (RWE) has gained significant traction in ophthalmology over the last decade with an ever expanding list of use cases. While initial research studies focused on insurance claims data, the limitation of not having visual acuity measurements, a crucial "vital sign" in ophthalmology, significantly limited the ability to generate RWE that could change clinical practice using this data alone. Currently, there is significant interest in generating high quality RWE from electronic health record (EHR) registries in ophthalmology, capitalizing on clinical data that is collected during routine clinical care. One of the most substantial ways RWE has been used to drive innovation is by emphasizing the need for longer acting therapeutics and sustained release drug delivery for retinal diseases that commonly require ongoing intravitreal injections at regular intervals. The therapeutic agents in our current treatment armamentarium have all demonstrated impressive treatment efficacy in randomized controlled trials for disease processes such as neovascular age related macular degeneration and diabetic retinopathy. However, studies using RWD have demonstrated repeatedly that treatment outcomes in the real world are not as good as what is seen in clinical trials. Factors such as undertreatment by physicians, prolonged periods of becoming lost to follow up, and differences between trial and real world populations have all surfaced as a result of RWD studies in ophthalmology. They have underscored the need for longer acting therapeutics and also helped drive clinical trial design. However, challenges remain in the use of RWD in ophthalmology and efforts are still underway to use RWE for regulatory decision making in ophthalmology. For one, disease processes, such as dry eye and uveitis, which rely heavily on unstructured data elements rather than diagnosis and procedure codes, to capture the true patient journey are more difficult to study using RWD without more advanced natural language processing (NLP) methodology. Additionally, imaging data plays a crucial role in understanding disease severity and treatment response in ophthalmology but difficulties with interoperability of different imaging platforms and image ingestion make this an ongoing area for improvement in the RWD space in ophthalmology. Overall, there are many lessons to be learned from the use of RWD in ophthalmology, particularly successful examples of studying retinal diseases using structured data, as well as opportunities for growth.

Learning Objectives:

1. To understand successful applications of real world data in ophthalmology.
2. To understand persistent limitations and opportunities for growth when using real world data for evidence generation in ophthalmolog.

Literature References:

1. Patel S, Sternberg P Jr. Real-World Data in Ophthalmology. Am J Ophthalmol. 2020 Jun;214:A1-A2. doi: 10.1016/j.ajo.2020.01.028. Epub 2020 Mar 10. PMID: 32169252.

2. US Food and Drug Administration. Framework for FDA's Real-World Evidence Program. Available at: 2018.https://www.fda.gov/downloads/ScienceResearch/SpecialTopics/RealWorldEvidence/UCM627769.pdf. Accessed November 6, 2021

NEUROPHYSIOLOGICAL BIOMARKERS IN THE CONTEXT OF EARLY PHASE CLINICAL TRIALS FOR MAJOR DEPRESSIVE DISORDER

Nicholas Murphy, Baylor College of Medicine

Overall Abstract: The clinical management of major depressive disorder (MDD) remains a considerable challenge due to a dearth in the understanding of pathophysiological mechanisms across the spectrum of depressive conditions. Attempts to unpack the diagnostic complexity of MDD have explored the variation in the psychological and biological factors which predict response outcome. However, in the clinical trial sphere these broad surface-level observations of response-gating factors are unhelpful due to their lack of biological specificity. To improve the development of therapeutic drugs and devices we need to map out the circuitry associated with the systems we are trying to target. Neurophysiological applications such as magneto/electroencephalography (M/EEG) present the researcher with the ability to dynamically assess the contributions of a drug or device to fluctuations in excitation/inhibition balance on a wide range of spatio-temporal scales that are not feasible with standard neuroimaging approaches. Monoaminergic and glutamatergic systems have been widely linked to established M/EEG paradigms such as the mismatch negativity (MMN), auditory steady state response (ASSR), and error related negativity (ERN), in human and animal models of depression, but remain under-utilized as drivers of therapeutic developments in clinical trials. In this symposium, three speakers will describe and evaluate neurophysiological original data providing insights to the treatment of different systems affected by MDD neuropathology. In the first presentation Dr. Murphy will discuss the application of gamma oscillations and the mismatch negativity for mapping the specificity of clinical engagement associated with variations in the pharmacological mechanism of N-methyl-D-aspartate receptor (NMDAR) blockade. In the second presentation Dr. Voineskos will describe the results of recent research using concurrent transcranial magnetic stimulation (TMS) and EEG to evaluate the contributions of cortical reactivity to therapeutic outcomes with clinical TMS. In the final presentation Dr. Gilbert will demonstrate the application of dynamic causal modeling to describe the parameters governing the stability and modulation of excitation/inhibition balance in patients with MDD and how these can be applied to the study of pharmacological interventions. The discussant will invite conversation around the conceptual links of these studies and how the modalities described can guide future research for the improvement of precision MDD treatment.

Learning Objectives:

1. To recognize how neurophysiological biomarkers can be implemented to clinical trials of major depressive order as a step to explain variability in clinical scales and other high level outcomes.
2. To be able to evaluate the choice of experimental design in targeting specific components of a circuit, and how this is driven by symptomatology.

APPLYING NEUROPHYSIOLOGICAL BIOMARKERS TO CLINICAL TRIALS OF NMDA RECEPTOR MODULATION FOR THE TREATMENT OF MOOD AND TRAUMA DISORDERS

Nicholas Murphy, Baylor College of Medicine

Individual Abstract: A critical problem facing the treatment of major depressive disorder (MDD) is the heterogeneity of symptom presentation. Williams et al (2016) demonstrated that the clinical presentation of MDD is indicative of the neural pathways and neurotransmitters

primarily affected by the neuropathology of depression, emphasizing the need to develop more precise batteries of clinical targets to aid with the process of drug development. Neurophysiological biomarkers capture important components of neural circuitry by measuring fluctuations in excitation and inhibition across user specified time scales. Through advances in digital signal processing the investigator can utilize this information to infer the interaction between medication and broad patterns of cellular activity implicated in the desired clinical and neural response (Murphy et al, 2021). In our research program we analyze electroencephalography (EEG) biomarkers of response to N-methyl-D-aspartate receptor (NMDAR) blockade, taken from early stage clinical trials for MDD. Our goal is to define accurate markers of dose-optimized clinical response in ketamine and functionally related alternatives including AV-101 (a NMDA receptor glycine site antagonist) and Lanicemine (a "low trapping" NMDAR channel blocker). Evidence of the antidepressant efficacy of sub-anesthetic doses of ketamine has prompted a paradigm shift concerning the neurochemical basis for treating MDD. The antidepressant effects of a single intravenous (IV) dose of ketamine (0.5 mg/kg) typically begin within 24 hours of infusion, and persist for up to two weeks. The presumed antidepressant effect associated with NMDAR blockade by drugs such as ketamine involves a complicated re-balancing of excitation and inhibition in the pre-frontal cortex that facilitates improved synaptic plasticity and the reorganization of distorted cortical connections. Attempts to replicate the rapid acting effects of ketamine, whilst bypassing the side effect profile, have validated the ability to induce rapid and meaningful reductions in depressive symptoms. However, the breadth of their clinical application is hindered by variation in response adoption and remission. In this talk I will outline and evaluate the use of sensory and cognitive EEG paradigms to map the circuitry engaged by these three NMDA receptor modulators. Using examples from our recent clinical trials research I will critically appraise the ability of EEG biomarkers to highlight signatures of successful clinical response, and illustrate their utility for the future of antidepressant drug development.

Learning Objectives:

1. To understand how sensory and cognitive engagement paradigms can be applied to study the effects of NMDA receptor blockade in clinical and pharmacological research.
2. Understand the reasons driving a need for high temporal resolution physiological markers of target engagement in the development of rapid acting antidepressants.

Literature References:

1. Williams, L. M. (2017). Defining biotypes for depression and anxiety based on large-scale circuit dysfunction: A theoretical review of the evidence and future directions for clinical translation. Depression and anxiety, 34(1), 9-24.
2. Murphy, N., Lijffijt, M., Ramakrishnan, N., Vo-Le, B., Vo-Le, B., Iqbal, S., ... and Mathew, S. J. (2021). Does mismatch negativity have utility for NMDA receptor drug development in depression?. Brazilian Journal of Psychiatry.

TMS-EEG INDICES AS HIGH POTENTIAL PREDICTIVE MARKERS OF BRAIN STIMULATION RESPONSE IN MAJOR DEPRESSIVE DISORDER

Daphne Voineskos, University of Toronto

Individual Abstract: There is substantial evidence that aberrant neurotransmission associated with glutamate and GABA underscores the pathophysiology of Major Depressive Disorder (MDD). Interestingly, Both GABA and glutamate appear to be more extensively dysfunctional in patients with treatment resistant depression (TRD) than MDD which is responsive to first line treatments. Transcranial magnetic stimulation combined with electroencephalography

(TMS-EEG) is a powerful method to assess cortical inhibition, excitability, connectivity and plasticity in non-motor cortical regions, including the dorsolateral prefrontal cortex (DLPFC). In TMS-EEG, the application of TMS pulses to prefrontal cortex results in the generation of specific cortical evoked potentials within the first 300ms of the TMS pulse, with pharmacological links to GABA receptor mediated inhibition and glutamate mediated excitation.

We have recently demonstrated that in TRD, abnormalities in TMS-EEG markers of cortical inhibition (N45, N100 amplitudes) and excitation (GMFA-AUC) accurately differentiate between healthy and depressed brains. Further, these same markers appear altered by effective brain stimulation, in multiple modalities of rTMS. 6 weeks of High frequency repetitive transcranial magnetic stimulation (rTMS) delivered over the DLPFC resulted in decreases in TMS-evoked cortical excitation ($F(1,29)=18.806$, $p<0.001$). The baseline N100 amplitude, associated with GABA-B inhibition, predicted improvement in depression symptoms in patients undergoing rTMS. This pilot data was consistent with a recent analysis of a large sample of patients with TRD undergoing intermittent theta burst stimulation (iTBS), a 3 minute version of rTMS, recently approved by the FDA for TRD. In 122 patients, baseline N100 amplitude predicted response ($F(1, 102.13) = 11.30$, $p = 0.001$). Our results suggest cortical inhibition has high potential in TRD as a biomarker of response across brain stimulation therapies. These findings suggest that stronger inhibitory neurotransmission at baseline reflects the integrity of interneuronal networks, optimal targets for brain stimulation therapy in TRD. Lastly, DLPFC heterogeneity has been shown to influence potential response to rTMS. Optimizing iTBS delivery via personalized approaches is an innovative way to improve response rates. In a pilot analysis, clinical response to iTBS appeared correlated to a more accurately delivered iTBS pulse (ie. closer to the intended DLPFC group-based targeting coordinates) ($r=0.638$, $p=0.006$). Therefore, while iTBS is a significant improvement in efficiency, an important explanation for high proportions of non-response may relate to suboptimal targeting of the DLPFC using methods developed for the motor cortex.

Learning Objectives:

1. Understand recent advances in brain stimulation for Treatment Refractory Depression
2. Understand novel markers of illness severity and treatment response.

Literature References:

1. Voineskos D, Blumberger DM, Rogasch NC, Zomorrodi R, Farzan F, Foussias G, Rajji TK, Daskalakis ZJ. Neurophysiological effects of repetitive transcranial magnetic stimulation (rTMS) in treatment resistant depression. Clin Neurophysiol. 2021;132:2306-2316.
2. Blumberger DM, Vila-Rodriguez F, Thorpe KE, Feffer K, Noda Y, Giacobbe P, Knyahnytska Y, Kennedy SH, Lam RW, Daskalakis ZJ, Downar J. Effectiveness of theta burst versus high-frequency repetitive transcranial magnetic stimulation in patients with depression (THREE-D): a randomised non-inferiority trial. Lancet. 2018;391:1683-1692.

ELECTROPHYSIOLOGICAL BIOMARKERS OF KETAMINE RESPONSE IN TREATMENT-RESISTANT MAJOR DEPRESSION

Jessica Gilbert, National Institute of Mental Health

Individual Abstract: A growing body of evidence suggests that alterations in the ratio of cortical excitation-inhibition balance could underlie a host of psychiatric disorders including depression. Short-lived gamma frequency oscillations have been shown to emerge from the coordinated interaction of glutamatergic excitation-GABAergic inhibition. Several studies now demonstrate alterations in gamma oscillations in both major depressive disorder (MDD) and bipolar disorder, potentially reflecting alterations in excitation-inhibition balance concomitant with depression. Thus, aberrant gamma oscillations might be a putative marker of mood disorders, including MDD. The glutamatergic modulator ketamine, which has been shown to rapidly reduce both depression and suicidal ideation, produces pyramidal cell disinhibition downstream of NMDA receptor antagonism. Thus, administration of ketamine should lead to robust changes in gamma oscillations. This finding has been well-replicated across species, perhaps driven by reduced NMDA receptor-mediated input to fast-spiking parvalbumin-expressing GABAergic interneurons. In addition, longer-term changes resulting from AMPA throughput following ketamine administration lead to activation of neuroplasticity-related signaling pathways, increasing synaptic potentiation and synaptogenesis. These longer-term changes in gamma power are associated with ketamine antidepressant response. Here, I will present work using magnetoencephalography (MEG) to measure differences in gamma power, a metric of synaptic potentiation, in individuals with treatment-resistant MDD, risk for suicide, and healthy participants. I will also discuss recent work looking at the impact of ketamine on antidepressant response, suicidal ideation, and delayed estimates of gamma power. Finally, I will present new modeling work using dynamic causal modeling in tandem with MEG to non-invasively characterize excitation-inhibition coupling in patients with treatment-resistant MDD and healthy participants, including discussing the utility of these metrics in characterizing ketamine-mediated antidepressant response in individuals with treatment-resistant MDD. These findings have important implications in future clinical trials of novel rapid-acting antidepressants as they could be used to move toward personalized medicine in the treatment of MDD.

Learning Objectives:

1. Describe the relationship between gamma power and ketamine antidepressant response in treatment-resistant major depression.
2. Understand the role of excitation-inhibition coupling and ketamine antidepressant response in treatment-resistant major depression.

Literature References:

1. Fagerholm ED, Leech R, Williams S, et al: Fine-tuning neural excitation-inhibition for tailored ketamine use in treatment-resistant depression. Transl Psychiatry 2021; 11:335
2. Gilbert JR, Yarrington JS, Wills KE, et al: Glutamatergic signaling drives ketamine-mediated response in depression: Evidence from dynamic causal modeling. Int J Neuropsychopharmacol 2018: 8:740-747

Regulatory Wrap-Up Plenary

10:15 a.m. - 11:45 a.m.

REGULATORY WRAP-UP

Trisha Suppes, Stanford University

Overall Abstract: Participants will be able to ask questions to a panel of EMA and FDA Representatives.

Maria Tome, European Medicines Agency

Tiffany Farchione, US Food and Drug Administration

Bernard Fischer, U.S. Food and Drug Administration

Marion Haberkamp, Federal Institute of Drugs and Medical Devices, BfArM, Germany

Wednesday, June 1, 2022

Poster Session I with Lunch

W1. EXTRAPOLATION OF EFFICACY OF A DEXTROAMPHETAMINE TRANSDERMAL SYSTEM FROM PEDIATRIC TO ADULT POPULATIONS USING PHARMACOKINETIC MODELING

Mariacristina Castelli[*1], Katsumi Suzuki[2], Brittney Starling[1], Kanan Balakrishnan[1], Suzanne Meeves[1], Marina Komaroff[1], Janelle Lennie[3], John T. Mondick[3], Stephen V. Faraone[4]*

[1]Noven Pharmaceuticals, Inc., [2]Hisamitsu Pharmaceutical Co., Inc., [3]Metrum Research Group, [4], SUNY Upstate Medical University

Abstract: Background: Similarities in pathophysiology and treatment outcomes between pediatric and adult ADHD patients have been demonstrated. Furthermore, post-marketing experience and published evidence support a tight link between the pharmacodynamic effects of amphetamines (AMP) and their pharmacokinetic (PK) profile in attention-deficit/hyperactivity disorder (ADHD).
In a pivotal efficacy and safety study, the dextroamphetamine transdermal system (d-ATS) met its primary and secondary efficacy endpoints for treatment of ADHD in children and adolescents, and d-ATS 15 mg was deemed optimal for the majority of pediatric patients. No PK data were collected in this study.

The scope of this work was to use PK data collected in children and adults to construct a model that would support extrapolation of efficacy and safety findings in pediatric patients to the adult population. Exposures at the doses tested in the pivotal pediatric study (5, 10, 15 and 20 mg) were then simulated and compared to adult exposures at the same doses.

Methods: A population PK (PopPK) data set was developed from data pooled across seven PK studies and used to develop a PopPK model to characterize exposures following d-ATS administration in pediatric and adult patients. Body weight was predefined as a covariate to account for body size effects on exposure. The model was evaluated via goodness-of-fit diagnostics and simulation-based predictive checks. Following model validation, simulations were performed to derive AMP exposures at the doses administered in the pivotal study. Body weights for 1000 individuals per age group (adults, adolescents, children) were sampled from the National Health and Nutrition Examination Survey database to supply covariates for model-predicted d-ATS exposures. The exposure metrics area under the concentration-time curve (AUC) and maximum concentration (Cmax) were compared between children, adolescents, and adults across the dose levels.

Results: A one-compartment model with sequential zero- and first-order absorption adequately described the AMP PK data. Visual predictive checks demonstrated that model-predicted AMP concentrations were in overall agreement with observed concentrations. Body weight was the only significant covariate. The simulated median (5th, 95th quantiles) AUC and Cmax values for adults administered 20 mg d-ATS were 1030 (701, 1520) ng·hr/mL and 46.2 (31.9, 66.0) ng/mL, respectively, comparable to simulated values for the pediatric group administered 15 mg d-ATS (AUC, 976 [624, 1560] ng·hr/mL; Cmax, 48.2 [29.4, 87.5] ng/mL). The shapes of

the observed PK profiles for d-ATS in adults and children were similar. One structural model was fit to pediatric and adult data simultaneously, and no other model refinement was needed after accounting for body size.

Conclusions: A PopPK model was developed to reasonably characterize AMP disposition across adult and pediatric ADHD populations. The only descriptor needed to differentiate the populations was body size. 20 mg d-ATS in adults produced exposures comparable to 15 mg in pediatric patients, demonstrated as efficacious and deemed optimal in the pivotal study. These comparable exposures in adults are likely to yield efficacy and safety results similar to those observed in the pivotal pediatric trial, thus supporting the extrapolation of efficacy findings in the pediatric population to the adult population.

Funding: Supported by Noven Pharmaceuticals, Inc.

W2. SINGLE CELL TRANSCRIPTOMICS REVEALS DISTINCT TRANSCRIPTIONAL RESPONSE TO OXYCODONE AND BUPRENORPHINE BY IPSC-DERIVED BRAIN ORGANOIDS FROM PATIENTS WITH OPIOID USE DISORDER

Ming-Fen Ho[*1], Cheng Zhang[1], Irene Moon[1], Coombes Brandon[1], Joanna Biernacka[1], Miclhelle Skime[1], Tyler Oesterle[2], Victor Karpyak[1], Kristen Schmidt[3], Kate Gliske[3], Quyen Ngo[3], Cedric Skillon[3], Marvin Seppala[3], Hu Li[1], Richard Weinshilboum[1]*

[1]Mayo Clinic, [2]Mayo Clinic, [3]Hazelden Betty Ford Foundation

Abstract: Background: The opioid epidemic represents a national crisis. Oxycodone is the most prescribed opioid medication in the United States, whereas buprenorphine is currently the most used drug for opioid use disorder (OUD) pharmacotherapy. Given the extensive use of prescription opioids and the global opioid epidemic, it is important to understand how these drugs modulate brain cell types at the single cell level.

Methods: We performed single nucleus RNA-seq (snRNA-seq) for iPSC-derived forebrain organoids from three male OUD subjects in response to oxycodone, buprenorphine or vehicle for seven days. The snRNA-seq data were utilized to identify differentially expressed genes following drug treatment using the Seurat integrative analysis pipeline.

Results: We used iPSC-derived forebrain organoids and single cell sequencing technology as an unbiased tool to study cell-type-specific and drug-specific transcriptional response. We analyzed 25787 cells after quality control filtering. Sixteen clusters were identified using unsupervised clustering analysis. Our results showed that oxycodone and buprenorphine displayed distinct gene expression profiles. Specifically, buprenorphine displayed significant influence on transcription regulation in astroglial cells. However, oxycodone induced type I interferon signalling in many cell types, including neural cells, in brain organoids. Finally, we used ELISA to confirm that oxycodone could induce interferon gamma concentrations in both iPSC-derived brain organoids and neurons. However, buprenorphine had no effect on interferon gamma concentrations.

Conclusions: Oxycodone induced type I interferon signalling was most pronounced in glutamatergic neurons, while buprenorphine affected transcriptional response primarily in glial cells. These results provide novel mechanistic insight into drug action at single cell resolution.

W3. COMPARATIVE EFFECTIVENESS OF BUPRENORPHINE AND NALTREXONE IN OPIOID USE DISORDER AND CO-OCCURRING POLYSUBSTANCE USE: A CASE-CROSSOVER ANALYSIS

Kevin Xu[*1], Carrie Mintz[1], Ned Presnall[1], Laura Bierut[1], Richard Grucza[2]*

[1]Washington University in St. Louis, [2]St. Louis University

Abstract: Purpose: Despite an epidemic of polysubstance use, individuals with opioid use disorder (OUD) and co-occurring substance use disorders (SUDs) are understudied. The goal of this presentation is to evaluate the distribution of buprenorphine and naltrexone use in individuals with OUD and polysubstance use, and analyze their comparative effectiveness in reducing acute SUD-related events.

Methodology: This case-crossover study evaluated 179,280 individuals with a primary diagnosis of OUD from a national dataset of commercial insurance and Medicaid enrollees (IBM MarketScan), of whom 29,508 persons experienced at least one drug-related poisoning and/or injury during admission. First, we assessed the association of poly-SUD diagnoses concurrent with or in the 6-months prior to treatment initiation with OUD treatment type (buprenorphine, naltrexone extended-release or oral, no medication) using multinomial logistic regression. Next, among medication recipients, we examined the association of admission for drug-related poisoning and/or injury, based on ICD-9/10 codes, with days covered with buprenorphine or naltrexone scripts, compared within individuals to days without prescriptions. Odds ratios from within-person fixed effects models were estimated as a function of OUD medication and stratified by co-occurring SUDs.

Results: Compared to treatment without medication, buprenorphine receipt was less likely among individuals with OUD and co-occurring SUDs than peers without polysubstance use (odds ratio [OR]=0.36, 95% CI: 0.35-0.36), whereas naltrexone receipt was more likely (OR=1.17, 1.10-1.25 and OR=2.23, 2.12-2.34 for naltrexone extended-release and oral respectively) in the poly-SUD group. Among individuals who received OUD medication and experienced an acute SUD-related event during insurance enrollment, buprenorphine receipt was associated with decreased admissions for acute drug-related poisoning and/or injury compared to non-treatment for both individuals with and without co-occurring SUDs (OR=0.66, 0.61-0.72 and OR=0.75, 0.73-0.78 respectively). Protective effects were observed in association with naltrexone ER treatment days for individuals with co-occurring SUDs (OR=0.57, 95% CI: 0.44-0.75) but not for individuals without co-occurring SUDs. No protective effect was observed for oral naltrexone. These findings were sustained in secondary analyses stratifying by event type (drug-related poisonings, non-poisoning injuries) and SUD type (alcohol-, stimulant-, and sedative use disorders).

Conclusion: Individuals with polysubstance use were less likely to receive buprenorphine and more likely to receive naltrexone than their peers without poly-SUDs. This is in spite of buprenorphine exhibiting a protective effect against acute SUD-related events across individuals both with and without polysubstance use.

W4. TRANSCRANIAL FOCUSED ULTRASOUND CAN ATTENUATE ANXIETY IN HEALTHY VOLUNTEERS

Norman Spivak[1], Bianca Dang[2], Andrew Swenson[2], Sabrina Halavi[2], Sergio Becerra[2], Luka Cvijanovic[2], Sonja Hiller[2], Nanthia Suthana[2], Martin Monti[2], Taylor Kuhn[2], Susan Bookheimer[2]*

[1]David Geffen School of Medicine at UCLA, [2]University of California, Los Angeles

Abstract: Objective: Until the advent of neuromodulation, psychopharmacology and psychotherapy were the primary options for treatment of psychiatric disorders. Now, transcranial magnetic stimulation (TMS) and deep brain stimulation (DBS) are frequently employed for treatment of disease. However, these advantages are not without their drawbacks. Many disorders involve dysfunction in regions that are not easily reached using TMS, and DBS requires invasive surgery. Low intensity, transcranial focused ultrasound (tFUS) is a non-invasive approach with an established safety record, with evidence in the literature that demonstrates it can both excite and disrupt neuronal activity in both animal models and in humans.

Participants and Methods: Anxiety disorders arise from dysregulated amygdalar circuits, which are known to play a critical role in the brain and the body's response to external stimuli. A randomized, double-blind within-subject crossover study was conducted to investigate whether tFUS can selectively downregulate emotional reactivity in the amygdala. The tFUS parameters were as follows: 650 kHz, 720 mW/cm2 ISPTA.3, 5% DC, with a PRF of 10 Hz for Amygdala (AG) and 100 Hz for the Entorhinal Cortex (ErC). Participants completed two tFUS sessions, two weeks apart, targeting either right AG or left ERc. Participants and statisticians were blinded to which brain region was targeted. ERc served as the control region for the AG and vice versa.

Subjects were asked to look at a series of images taken from the International Affective Picture Set, with instructions to WATCH (look at negative images), VIEW (look at neutral images), and REAPPRAISE (cognitively reappraise negative images). After each image, subjects were asked to rate levels of valence (higher more positive) and arousal. For each, we calculated the mean skin conductance level (SCL). We then generated indices of negative reactivity (WATCH-VIEW) and reappraisal (WATCH-REAPPRAISE) for valence, arousal, and SCL, and compared how these values changed after tFUS to AG and ErC.

Results: During this emotional reactivity and cognitive reappraisal task, there were significant main effects of image type on both self-reported valence and arousal: negative images were rated as less pleasant ($\eta 2$=.706, p=.000) and more arousing ($\eta 2$=.554, p=.001) than neutral images.

While no other findings were significant at Bonferroni-corrected α=.017, calculations of effect size reveal moderate to large effects. There was a large interaction effect between time, target, and prompt on self-reported arousal: cognitive reappraisal of negative images was more effective at reducing arousal after AG sonication than after ErC sonication ($\eta 2$=.180, p=.101).

Moreover, there was a moderate interaction effect between time and target on STAI-State scores, indicating greater attenuation of state anxiety after AG sonication than after ErC sonication ($\eta 2$=.125, p=.150).

Conclusions: These very preliminary data suggest that tFUS may be able to downregulate or disrupt amygdalar activity. While not yet definitive, this approach has the potential to be a future treatment for neuropsychiatric conditions with hyperactive amygdalae. Such conditions include anxiety disorders, phobias, and obsessive-compulsive disorders. Replication in larger samples is needed. Nevertheless, these early findings offer novel and exciting insight into the

potential future application of tFUS as an accessible, safe, and non-invasive therapeutic device for a wide variety of patient populations.

W5. GENETIC POLYMORPHISMS AND CLINICAL IMPLICATIONS OF THE USE OF STIMULANTS AGENTS IN ADULTS WITH MOOD AND ATTENTIONAL DEFICITS DISORDERS: A SYSTEMATIC REVIEW

Nicolas Nunez[1], Sofia Jezzini[2], Balwinder Singh[1], Manuel Gardea Resendez[1], Boney Joseph[1], Mark Frye[1], Alfredo Cuellar-Barboza[2]*

[1]Mayo Clinic, [2]Universidad Autonoma de Nuevo Leon

Abstract: Introduction: Stimulants are FDA approved for the treatment of attention deficit hyperactivity disorder (ADHD), and in mood disorders, their use as augmentation agents is controversial due to mixed findings 1-2. Moreover, there is a dearth of pharmacogenetic studies in this area. Our aim was to systematically explore the role of genetic variations on stimulants' action mechanisms and their clinical implications.

Methods: A comprehensive search was conducted from inception until May 2021; observational studies will include open-label, and randomized controlled studies in adults (≥18 years) with major depressive disorder (MDD) or bipolar disorder or ADHD, genotyping studies, and the use of stimulants (methylphenidate, lisdexamfetamine, dextroamphetamine, amphetamine/dextroamphetamine) or stimulant like compounds (modafinil, armodafinil). Our outcomes were an overall improvement in function, response, or remission, assessed by clinician-rated behavior scales and adverse events. We followed PRISMA guidelines.

Results: From 1,237 abstracts, we selected 11 articles for full-text review. Seven studies met the inclusion criteria for the systematic review. Five studies (N=498; mean age 37.13±12.26 years) analyzed polymorphisms in SLC64/5-HTTLPR, DAT1 VNTR (in the 3'-UTR) and DAT1 VNTR (hDAT1 5p15.3), one prospective (n=171,mean age 35±11 years) analyzed polymorphisms in DAT1/rs2652511, DAT1 In8 VNTR, DAT1/rs28363170 and two retrospective (n=206,mean age 36.5 ± 11.01 years) analyzed polymorphisms in DRD4 VNTR exon 3, DRD4 ins/del, SLC6A4/5-HTTLPR, SLC6A3/DAT1 VNTR, HTR1B/rs11568817, HTR1B/rs13212041 and HTR1B/rs6269.

In ADHD, there were no significant differences in allele or genotype frequencies between methylphenidate responders and non-responders. Only one study showed that a polymorphism in SCL6A3 may be associated with treatment response to methylphenidate in adults with ADHD. In MDD, the DAT 10/10 genotype was related to cognitive executive dysfunction at baseline and better response to methylphenidate added to citalopram. Most adverse events reported were moderate nausea, anxiety, polyuria, and, with highest percentages for headaches (38.1%), gastrointestinal complaints (21.2%), and decreased appetite (19.08%); none of these were associated with genetic polymorphisms. None of the included studies reported severe adverse events.

Conclusions: To date, the studied genetic polymorphisms appear to have no implications in the clinical response for adults with ADHD or MDD. Therefore, the development of studies focusing on the impact of genetic polymorphisms and treatment response in these specific populations are warranted.

W6. CENTRAL CORTISOL ALONE IS DIFFERENTIALLY REGULATED AS A FUNCTION OF AGE BUT NOT COGNITIVE IMPAIRMENT IN SIMULTANEOUS BASAL MEASUREMENTS OF HUMAN CEREBROSPINAL FLUID, SALIVA, AND TOTAL AND FREE PLASMA CORTISOL

*Katharine Liang**[1], Elizabeth Colasurdo[1], Ge Li[2], Jane Schofer[1], Elaine Peskind[1]*

[1]VA Northwest Network Mental Illness Research, Education and Clinical Center, VA Puget Sound Health Care System, [2]Geriatric Research, Education and Clinical Center, VA Puget Sound Health Care System

Abstract: Purpose:Dysfunction in the glucocorticoid system has been implicated in many diseases over the years, including mental health and neurodegenerative disorders. Robust changes in cortisol levels in response to many types of stress have made it a popular surrogate reporter of glucocorticoid homeostasis. Due to the difficulty of assessing central cortisol, measures of plasma and salivary cortisol are often used to approximate measures of central cortisol even in relation to disorders of the brain. While glucocorticoids can cross from the periphery to CNS by passive diffusion, active transport and protein binding dynamics are also thought to influence equilibrium and availability of free cortisol across compartments (1). Though the relationships between CSF, blood, and saliva have been examined to some degree, the relationships among basal morning concentrations of total plasma, free plasma, salivary, and cerebrospinal fluid (CSF) cortisol have not been systematically investigated as a function of age or mild cognitive impairment/Alzheimer's disease (MCI/AD). To determine the degree of correlation among these measures and to evaluate potential differential regulation of cortisol in different compartments, we measured basal morning cortisol concentrations in CSF and saliva, and total cortisol and corticosteroid-binding globulin (CBG) in plasma in healthy volunteers and patients with a diagnosis of MCI/AD.

Methods: Healthy volunteers (n=157) and patients with a diagnosis of MCI/AD (n=28), of both sexes, aged 20-85, were recruited for the study. Free plasma cortisol levels were calculated from total cortisol and CBG values as previously described (2). The association between cortisol concentration and age was assessed using linear regression with cortisol compartment as the dependent variable and age as the independent variable. The mean difference in cortisol compartment by cognitive status (AD/MCI vs. normal cognition) adjusted for age was estimated using linear regression with cortisol compartment as the dependent variable and cognitive status and age as independent covariates.

Results: A significant association was observed between CSF cortisol and age ($R2= 0.14$, $p<0.001$), with mean CSF cortisol concentration increasing approximately linearly with age. There was a borderline significant association between salivary cortisol and age ($R2 = 0.05$, $p=0.015$), with mean salivary cortisol concentration decreasing with increasing age from young to middle age, and then leveling off thereafter. There was no significant association between free or total plasma and age ($R2<0.01$, $p>0.25$), and no significant associations between cortisol in any compartment and AD/MCI diagnosis after adjustment for age ($p\geq0.30$).

Conclusion: These data suggest that basal cortisol levels in CSF, but not peripheral compartments, are differentially regulated as a function of age, and that these regulatory processes remain largely unaffected by MCI/AD.

W7. EXPLORING GENETIC VARIATION OF COMPLEX I AS POTENTIAL MARKER OF INCREASED MITOCHONDRIAL FUNCTION ASSOCIATED WITH ANTIDEPRESSANT-INDUCED MANIA

Manuel Gardea Resendez[*1], Coombes Brandon[1], Marin Veldic[1], Sussanah Tye[2], Alfredo Cuellar-Barboza[3], Francisco Romo- Nava[4], Ana Andreazza[5], Balwinder Singh[1], Nicolas Nunez[1], Miguel Prieto[6], Aysegul Ozerdem[1], Joanna Biernacka[1], Susan McElroy[7], Tamas Kozicz[1], Mark Frye[1]*

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Abstract: Background: Mechanistically, mitochondrial energetics may impact antidepressant (AD) response. In vitro and in vivo studies have shown that ADs can influence the electron transport chain (ETC) complex activity, either by increasing (Mito+) or decreasing (Mito-) energy production. Postmortem studies have reported decreased activity and expression of complex I (C-I) subunits in bipolar disorder (BD) patients1. C-I is the largest complex of the ETC, consisting of 45 subunits [38 encoded by nuclear DNA (nDNA) and 7 by mitochondrial DNA (mtDNA)] and the entry point of electron transfer for cellular respiration, generating ATP. We hypothesize that the rate of AD induced mania (AIM), a standardized biobank clinical phenotype, is higher for Mito+ ADs in comparison to Mito- ADs. We additionally sought to investigate whether genetic variants in nuclear genes that encode for complex I are associated with AIM+.

Methods: Mayo Clinic Bipolar Disorder Biobank participants were clinically phenotyped as AIM+ (n=129) or AIM- (n=597) and further classified based on whether the specific AD increases (Mito+ n= 481; includes venlafaxine, bupropion, paroxetine, nortriptyline) or decreases (Mito- n=245; escitalopram, amitriptyline) mitochondrial activity. We compared the rate of AIM between Mito+ and Mito- using generalized estimating equations (using a logit link) to account for patients that took both Mito+ and Mito- ADs during the course of treatment. We adjusted for sex and BD subtype in this model. For patients on Mito+ ADs that have been previously genotyped, we tested for association of genetic variations in 34 nuclear genes encoding for C-I with AIM while adjusting for the first principal component of ancestry. In addition to SNP-level analyses, we also performed gene-level tests of association using MAGMA.

Results: AIM+ was more frequent on Mito+ compared to on Mito- ADs (21.1% vs. 10.6%; OR=2.13; p= 0.00002) after accounting for the overlap between the two groups and adjusting for sex and BD subtype. Gene-level tests of association showed marginally significant associations with NDUFB9 (P= 0.005) after accounting for multiple testing (p = 0.05/34 = 0.002).

Conclusions: In our sample AIM+ was associated with use of ADs that increase mitochondrial activity. We did not find strong support for the hypothesis of variations in C-I related nDNA linking to an increase in mitochondrial bioenergetics and AIM. However, this genetic analysis was likely underpowered. Nevertheless, our preliminary data reconceptualizes AD classification based on mitochondrial energetics, and not only based on conventional mechanism of action (SSRI, TCA, etc.) which should be further investigated in larger clinical and pharmacogenomics studies of AIM.

W8. METABOLIC SYNDROME IN BIPOLAR DEPRESSION WITH LUMATEPERONE (ITI-007): A POST HOC ANALYSIS OF 2 RANDOMIZED, PLACEBO-CONTROLLED TRIALS

Christoph U Correll[1], Suresh Durgam[2], Susan G Kozauer[2], Jason Huo[2], Robert E Davis[2], Sharon Mates[2]*

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Abstract: Background: Treatments for bipolar disorder are often associated with increased rates of metabolic syndrome (MetSy). MetSy is defined as meeting 3 of the following 5 criteria: waist circumference >40in (men) or >35in (women), triglycerides ≥150mg/dL, high density lipoprotein cholesterol <40mg/dL (men) or <50mg/dL (women), systolic blood pressure (BP) ≥130mmHg or diastolic BP ≥85mmHg, fasting glucose ≥100mg/dL.
MetSy elevates the risk of developing type II diabetes, cardiovascular disease, and premature morbidity. Lumateperone, a mechanistically novel antipsychotic that simultaneously modulates serotonin, dopamine, and glutamate neurotransmission, is FDA-approved for the treatment of schizophrenia and for depressive episodes in adults with bipolar I or bipolar II disorder. This distinct pharmacological profile has been associated with favorable tolerability and a low risk of adverse metabolic effects in clinical trials.

Lumateperone 42-mg monotherapy was evaluated in 2 randomized, double-blind, placebo-controlled studies (Study 401 [NCT02600494]; Study 404 [NCT03249376]) in patients with a major depressive episode (MDE) associated with bipolar I or bipolar II disorder. This post hoc pooled analysis of these studies compares rates of MetSy with lumateperone 42 mg and placebo in the treatment of bipolar depression.

Methods: The incidence and shift in MetSy were analyzed in data pooled from 2 studies that recruited patients aged 18-75 years with a confirmed diagnosis of bipolar I or bipolar II disorder who were experiencing an MDE (Montgomery-Åsberg Depression Rating Scale [MADRS] Total score ≥20 and Clinical Global Impression Scale-Bipolar Version-Severity [CGI-BP-S] score ≥4). Patients in these studies were randomized 1:1 to lumateperone or placebo and treated for 6 weeks.

Results: The safety population comprised 746 patients (lumateperone, 372; placebo, 374). Rates of MetSy were similar between groups at baseline (lumateperone, 20.7%; placebo, 22.2%) and at the end of treatment (EOT, lumateperone, 21.8%; placebo, 23.8%). More lumateperone patients (36.4%) compared with placebo patients (30.1%) improved from having MetSy at baseline to no longer meeting MetSy criteria at EOT. The individual criteria that shifted the most from meeting MetSy criteria at baseline to no longer meeting criteria at EOT was BP for lumateperone (46.8%) and glucose for placebo (43.2%). The rate of MetSy developed during treatment was similar for lumateperone (10.8%) and placebo (10.7%) with approximately half of these patients (lumateperone, 43.8%; placebo, 45.2%) shifting due to a change in ≥2 criteria.

Conclusion: In this post hoc analysis of 2 randomized, placebo-controlled trials in patients with a MDE associated with bipolar I or bipolar II disorder, lumateperone 42 mg had similar rates of MetSy compared with placebo. These results support that lumateperone 42 mg is a promising treatment for bipolar depression with a favorable metabolic profile.

W9. EFFICACY OF ARIPIPRAZOLE ONCE-MONTHLY FOR THE MAINTENANCE TREATMENT OF PATIENTS WITH BIPOLAR I DISORDER: A POST-HOC ANALYSIS BY AGE

Pedro Such[1], Jessica Madera-McDonough[2], Maxine Chen[2], Heather Fitzgerald[3], Murat Yildirim[1], Jessica McDonough[4]*

[1]H. Lundbeck A/S, [2]Otsuka Pharmaceutical Development and Commercialization Inc, [3]Lundbeck LLC, [4]Otsuka Pharmaceutical Development and Commercialization, Inc. (OPDC)

Abstract: Background: Patients with bipolar I disorder experience a high risk of relapse and recurrence of mood episodes (1). The strongest predictor of relapse is non-adherence to treatment; non-adherence is common in patients with bipolar I disorder, particularly in younger patients. Thus, younger patients may be more likely to experience relapse than their older counterparts.

Aripiprazole once-monthly 400 mg (AOM 400), an atypical long-acting injectable antipsychotic, demonstrated efficacy and tolerability in a randomized, double-blind, placebo-controlled, 52-week study of maintenance treatment for patients with bipolar I disorder (NCT01567527) (2). This post-hoc analysis evaluated the efficacy of AOM 400 in preventing recurrence of mood episodes in patients with bipolar I disorder, grouped by age at baseline.

Methods: Patients with bipolar I disorder, currently experiencing a manic episode (DSM-IV-TR), were stabilized sequentially on oral aripiprazole and AOM 400, and then randomized to treatment with AOM 400 or placebo in a 52-week, double-blind, withdrawal phase. In this analysis, data were stratified according to patient's age at baseline (≤35 years; >35 years). Efficacy endpoints included the time from randomization to recurrence of any mood episode, and the proportion of patients with recurrence of any mood episode. The proportions of patients who were hospitalized due to mood episodes, and the change from baseline in Clinical Global Impressions for Bipolar Disorder (CGI-BP) severity score for mania, were also evaluated. Time to recurrence was analysed using the log-rank test, with hazard ratios (HRs) estimated using a Cox proportional hazards model with treatment as term. The proportion of patients with recurrence of any mood episode was evaluated using the Fisher's exact test. An MMRM approach was used to assess change from baseline in CGI-BP severity score.

Results: Data for patients ≤35 years (mean 28.3 years; n=93) and >35 years (mean 46.6 years; n=173) were analysed. For younger (≤35 years) and for older (>35 years) patients, AOM 400 treatment was associated with significantly longer time to recurrence of any mood episode vs placebo (≤35 years: HR=0.383 [95% confidence intervals {CI}: 0.185, 0.793], $p<0.01$; >35 years: HR=0.502 [95% CI: 0.306, 0.824], $p<0.01$). During 52 weeks of treatment, significantly lower proportions of AOM 400-treated vs placebo-treated patients experienced recurrence of any mood episode; younger patients: 23.4% vs 48.9%, $p<0.05$; older patients: 28.2% vs 52.3%, $p<0.01$. Similarly, significantly lower proportions of AOM 400-treated vs placebo-treated patients were hospitalized due to mood episodes; younger patients: 2.1% vs 13.3%; $p<0.05$; older patients: 2.4% vs 13.6%; $p<0.01$. In both age groups, least squares mean [standard error] change from baseline to Week 52 in CGI-BP scores indicated worsening of mania severity for placebo-treated patients (≤35 years: 0.23 [0.18]; >35 years: 0.34 [0.16]) but not for AOM 400-treated patients (≤35 years: -0.21 [0.08]; >35 years: -0.05 [0.08]). The difference in change from baseline to Week 52 in CGI-BP scores with AOM 400 vs placebo was statistically significant ($p<0.05$ for both age groups).

Conclusion: This analysis demonstrates that AOM 400 maintenance treatment delays the time to recurrence of mood episodes, and reduces the rate of recurrence, regardless of age. These findings support the use of AOM 400 maintenance treatment in younger, as well as older, patients with bipolar I disorder.

W10. EFFICACY AND SAFETY OF BREXPIPRAZOLE FOR THE TREATMENT OF BORDERLINE PERSONALITY DISORDER: A 12-WEEK, PHASE 2, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY

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Abstract: Background: Borderline personality disorder (BPD) is a mental disorder characterized by instability of interpersonal relationships and self-image, affective instability, and marked impulsivity (1). No drugs are currently approved for the treatment of BPD; however, pharmacotherapies are widely used to treat targeted symptoms (2). Evidence suggests that atypical antipsychotics may be efficacious in treating BPD. The aim of this study was to evaluate the efficacy and safety of brexpiprazole (a serotonin–dopamine activity modulator) for the treatment of patients with BPD.

Methods: This was a Phase 2, multicenter, randomized, double-blind, placebo-controlled study (NCT04100096). Following a 1-week double-blind placebo run-in phase, adults with BPD (DSM-5 criteria) were randomized (1:1) to brexpiprazole 2–3 mg/day (flexible dose) or placebo in an 11-week, double-blind treatment period. A modified intent to treat population was defined based on blinded criteria and used for the primary efficacy analyses. The primary endpoint was the change from baseline (Week 1) to Week 10 in the clinician-administered Zanarini Rating Scale for BPD (ZAN-BPD). Total score. The key secondary endpoint was the change from baseline to Week 10 in the Clinical Global Impression – Severity (CGI-S) score. A mixed model for repeated measures approach was used. Safety was assessed by standard variables including adverse events (AEs).

Results: A total of 324 patients were randomized (placebo: n=165; brexpiprazole: n=159). Patients had a mean age of 31.5 years (range: 18–64); 82.1% were female. At study entry, mean ZAN-BPD Total and CGI-S scores indicated moderate severity of BPD; scores were similar between treatment groups. Overall, 239 patients (73.8%) completed the study (placebo: n=127 [77.0%]; brexpiprazole: n=112 [70.4%]). No statistically significant difference between brexpiprazole and placebo was observed on the primary endpoint of mean change from baseline to Week 10 in the ZAN-BPD Total score (placebo: -6.25; brexpiprazole: -7.27; p=0.24). However, brexpiprazole was associated with nominally significant improvements versus placebo at Week 8 (p=0.029) and Week 12 (p=0.010). Similarly, mean change from baseline in CGI-S score was not statistically significantly different with brexpiprazole versus placebo at Week 10 (placebo: -1.09; brexpiprazole: -1.13; p=0.78); nominally significant separation was observed at Week 12 (p=0.031). The incidence of treatment-emergent AEs (TEAEs) was 60.5% with brexpiprazole and 47.9% with placebo. TEAEs with an incidence ≥5% in the brexpiprazole group and greater than placebo were: akathisia (14.0% vs 1.2%), insomnia (9.6% vs 6.1%), anxiety (8.3% vs 5.5%), fatigue (7.6% vs 3.6%), increased weight (6.4% vs 2.4%), restlessness (6.4% vs 1.2%), somnolence (5.1% vs 3.0%), and increased appetite (5.1% vs

2.4%). Serious TEAEs were reported by 3.2% of patients receiving brexpiprazole and 1.2% of patients receiving placebo; no patients died during the study.

Conclusion: In this sample of patients with BPD the efficacy of brexpiprazole was not statistically significantly different to placebo on the primary and key secondary endpoints. However, exploratory efficacy analyses demonstrated greater improvement with brexpiprazole versus placebo at other timepoints. Brexpiprazole was generally well tolerated, with a safety profile similar to that seen in other indications.

W11. RECONNECT (ZYN2-CL-033): DESIGN OF A PHASE 3 TRIAL OF ZYN002 CANNABIDIOL TRANSDERMAL GEL IN CHILDREN AND ADOLESCENTS WITH FRAGILE X SYNDROME BASED UPON LEARNINGS FROM CONNECT-FX (ZYN2-CL-016) COMPLETED DURING SARS-COV-2 PANDEMIC

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Abstract: Background: ZYN002 is a pharmaceutically manufactured transdermal cannabidiol gel in development for the treatment of behavioral symptoms in Fragile X syndrome (FXS). The endocannabinoid system (ECS) is dysfunctional in FXS due to silencing of the FRM1 gene and resulting absence of FMRP that facilitates functioning of the ECS. Exogenous administration of cannabidiol may help overcome ECS dysfunction and restore homeostatic function of the ECS in FXS which may lead to improvements in behavioral symptoms associated with FXS. RECONNECT (ZYN2-CL-033) is a pivotal, randomized, double-blind, Phase 3 trial to assess the efficacy and safety of ZYN002 in children/adolescents aged 3 through 17 years with a full FMR1 gene mutation. RECONNECT is designed based on learnings from CONNECT-FX (ZYN2-CL-016) which was completed during the SARS-COV-2 (COVID-19) pandemic in patients with FXS who were dependent upon their caregivers for assessments and support.

Methods: The results and conduct of CONNECT-FX were reviewed to identify key learnings to design RECONNECT.

Results: Lessons learned: 1) treatment response for ZYN002 was greatest in patients with ≥90% methylation of the FMR1 gene; 2) the Aberrant Behavior Checklist–Community FXS Specific (ABC–CFXS) was determined fit-for-purpose and meaningful within-patient change was determined for the Social Avoidance, Irritability and Socially Unresponsive/Lethargic subscales; 3) the Caregiver Global Impression of Severity/Change (CaGI-S/C) were highly responsive to change, with greatest change on the Social Interactions; 4) a FXS-specific Clinical Global Impression of Severity/Improvement (CGI-S/I) assessment was developed based upon outcomes in response to FDA guidance to use a disease-specific CGI; 5) virtual visits were successfully incorporated as a result of COVID-19.

Conclusion: RECONNECT will randomly assign approximately 200 patients 1:1 to receive 18-weeks of treatment with ZYN002 or placebo at approximately 25 sites in the USA, Australia, Europe. The primary endpoint is change from baseline in the ABC–CFXS Social Avoidance subscale at week 18 in patients with complete methylation of the FMR1 gene (100% by methylation PCR). Key secondary endpoints include change from baseline in ABC-CFXS Irritability, improvement in CaGI-C Social Interactions and FXS-specific CGI-I, and change from baseline in ABC-CFXS Social Avoidance in the full population (complete and partial

methylation). Four of 8 visits will be virtual to reduce family burden and minimize in-person visits given continuation of COVID-19. RECONNECT is also designed to confirm the impact of FRM1 gene methylation on treatment responsiveness to ZYN002 in patients with FXS. Results from RECONNECT may provide the data needed to support the potential approval of ZYN002 as the first treatment of the behavioral symptoms associated with FXS.

W12. COMBINING PHARMACOTHERAPY OF BI 425809 WITH COMPUTERIZED COGNITIVE TRAINING IN PATIENTS WITH SCHIZOPHRENIA: BASELINE DATA AND PATIENT DEMOGRAPHICS FROM AN ONGOING PHASE II TRIAL

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Abstract: Background: Despite the significant patient burden, there are no approved pharmacotherapies to treat cognitive impairment associated with schizophrenia (CIAS). BI 425809 is a novel glycine transporter-1 inhibitor that may improve glutamate transmission and neuroplasticity, currently under development for treatment of CIAS. A previous study demonstrated pro-cognitive effects of BI 425809 in patients with schizophrenia (1); however, concurrent cognitive stimulation could in theory enhance any pro-cognitive pharmacological effects on neuroplasticity. We present preliminary demographics and baseline data for a global multicenter trial exploring the efficacy of BI 425809 together with at-home computerized cognitive training (CCT) in patients with schizophrenia.

Methods: An ongoing Phase II, double-blind, placebo-controlled, parallel-group trial in patients with schizophrenia on stable antipsychotic therapy across ~50 centers in 6 countries (2). Patients aged 18–50 years, compliant with CCT during the run-in period (≥2 hours/week for 2 weeks), were randomized (1:1) to receive once-daily BI 425809 10 mg or placebo with CCT for 12 weeks. Thereafter, minimum compliance for at-home CCT is 1 hour/week, with a target of ~30 hours over 3–5 sessions totaling 2.5 hours/wk. Patients have been stratified to balance potential effects of age (18–40; 41–50 years). The primary endpoint is change from baseline (CFB) in neurocognitive composite T-score of the MATRICS Consensus Cognitive Battery (MCCB) at Week 12. Secondary endpoints include CFB in the Schizophrenia Cognition Rating Scale (SCoRS) total score, MCCB overall composite T-score, Positive and Negative Syndrome Scale (PANSS) total score and adverse events. Novel exploratory endpoints are the Virtual Reality Functional Capacity Assessment Tool to assess daily functioning and the Balloon Effort Task to assess motivation in cognitive performance.

Results: Of the planned sample of 200 randomized patients, the overall treated population currently includes 173; 68% (n=118) are male, and mean (standard deviation [SD]) age and time since first diagnosis are 38.3 (7.9) years and 13.5 (8.5) years. Overall, 47% (n=82) are White and 44% (n=76) are Black or African American; 81% (n=140) are from North America, 14% (n=25) from Europe, and 5% (n=8) from Australia/New Zealand. Mean (SD) baseline MCCB neurocognitive composite and overall T-scores (n=168) are 33.5 (11.7) and 32.2 (12.4). Mean (SD) baseline SCoRS total score (n=158) is 35.4 (8.6). Mean (SD) baseline PANSS total and negative symptom scale scores (n=173) are 65.4 (14.4) and 17.6 (5.3). The median (Q1, Q3) CCT compliance over the on-treatment period is 2.16 (1.33, 2.53) hours/week.

Conclusion: This trial is, to our knowledge, the first to combine novel pharmacotherapy for CIAS with at-home CCT and will indicate whether BI 425809 treatment together with

concurrent CCT provides an enhanced cognitive benefit. We also aim to demonstrate whether any observed improvements in neurocognition translate into improved measures of daily functioning. Preliminary baseline characteristics are as expected for a population of clinically stable patients with schizophrenia, with baseline MCCB scores consistent with marked CIAS. Preliminary CCT compliance exceeds the minimum and is close to the target, indicating the potential for at-home CCT to be implemented effectively in a multicenter clinical trial.

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W13. COULD SUDDEN DISCONTINUATION OF SUBOXONE INDUCE MANIA AND PSYCHOSIS?

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Abstract: Buprenorphine and Naloxone (Suboxone) is a combination medication-assisted treatment (MAT) for opioid addicted individuals. MAT withdrawal-induced psychosis is an uncommon clinical presentation. To our knowledge, few reports have summarized characteristic manifestations of buprenorphine withdrawal psychosis, and only in male patients. In this case report, we present a female patient, age 41 with previously diagnosed bipolar disorder and multiple substance use disorders, without personal or family history of psychosis, who developed acute psychotic symptoms following abrupt discontinuation of Bup/Nal. Manic and psychotic symptoms remitted after a short inpatient stay treated with an antipsychotic and a mood stabilizer. We also characterize the presentation, outline the approach to patient care, and discuss possible underlying mechanisms to enhance the understanding of this special phenomenon in clinical practice.

W14. WITHDRAWN

W15. CARIPRAZINE FOR THE ADJUNCTIVE TREATMENT OF MAJOR DEPRESSIVE DISORDER: RESULTS OF A RANDOMIZED PHASE 3 PLACEBO-CONTROLLED STUDY (STUDY 302)

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Abstract: Background: Inadequate response to antidepressant (ADT) monotherapy is common for patients with major depressive disorder (MDD); adjunctive treatment is often used to address this unmet need. Cariprazine, a dopamine D3-preferring D3/D2 and serotonin 5-HT1A receptor partial agonist approved to treat adults with bipolar I depression, is under investigation as adjunctive therapy for patients with MDD.

Methods: This randomized, double-blind, phase 3 placebo-controlled study assessed the efficacy, safety, and tolerability of cariprazine 1.5 mg/d and 3.0 mg/d versus placebo as an adjunct to ADT in adult patients (18-65 years) with MDD and inadequate response to

antidepressants alone (NCT03739203). The primary endpoint was change from baseline to week 6 in Montgomery-Åsberg Depression Rating Scale (MADRS) total score. Clinical Global Impressions-Severity of Illness (CGI-S) was also assessed. Treatment response was defined as at least 50% decrease in the MADRS total score.

Results: There were 752 randomized patients in the modified intent-to-treat population (cariprazine 1.5 mg/d + ADT=250; cariprazine 3 mg/d + ADT=251; placebo + ADT=251). Mean age was 45.7 years and 76.3% were female; mean baseline MADRS total score was 32.41. Overall, 92.4% of patients completed the study; rates of discontinuation due to adverse events (AEs) and lack of efficacy were 3.7% and 0.3%, respectively. The difference in MADRS total score change from baseline to week 6 (primary endpoint) was not statistically significant for cariprazine 1.5 mg/d vs placebo (-13.8 vs -13.4; P=.7156) or 3 mg/d (-14.8 vs -13.4; P=.2490). Differences in MADRS total score change from baseline were nominally significant vs placebo for cariprazine 1.5 mg/d at week 2 (P=.0411), and for cariprazine 3 mg/d at week 1 (P=.0154), week 2 (P=.0004), and week 4 (P=.0092). CGI-S change from baseline vs placebo reached nominal significance for cariprazine 1.5 mg/d at week 4 (P=.0448), and for 3 mg/d at weeks 2 (P=.0098) and 4 (P=.0138); at week 6, the least squares mean difference vs placebo did not reach statistical significance for cariprazine 1.5 mg/d (P=.5152) or 3 mg/d (P=.0573). Differences in MADRS response rates were nominally significant for cariprazine 1.5 mg/d and 3 mg/d vs placebo at weeks 2 (P=.0192 and P=.0005) and 4 (P=.0314 and 0.0022); at week 6, rates of response vs placebo (40.6%) were numerically higher but not significantly different for cariprazine 1.5 mg/d (46%; P=0.2874) or 3 mg/d (48.2%; P=.1176). The most common AEs for cariprazine (≥5% and twice placebo) were akathisia and insomnia.

Conclusion: In this phase 3 clinical study, some positive trends were observed for adjunctive cariprazine, although differences vs placebo did not reach statistical significance at week 6. The efficacy of cariprazine as adjunctive treatment for patients with MDD and inadequate response to antidepressants has been demonstrated in 2 other studies. This study was supported by AbbVie.

W16. IMPROVEMENT IN CLINICAL GLOBAL IMPRESSION SCORES WITH ZURANOLONE IN PATIENTS WITH MAJOR DEPRESSIVE DISORDER: RESULTS FROM THE LANDSCAPE CLINICAL DEVELOPMENT PROGRAM

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Abstract: Background: Zuranolone (ZRN) is an investigational, oral neuroactive steroid in clinical development for once-daily, 2-week treatment of major depressive disorder (MDD) as part of the LANDSCAPE clinical development program. In clinical practice, it is important to evaluate therapeutic response by multiple measures to capture various aspects of improvement. The Clinical Global Impression-Improvement (CGI-I) scale is a 7-point clinician-reported measure that assesses how the status of the patient's illness has changed from baseline. The clinician considers all available information, including patient history, psychosocial circumstances, symptoms, and behavior, as well as the impact of symptoms on the patient's ability to function. Here, we present CGI-I response rates across 4 clinical studies (3 placebo-controlled and 1 open-label) in the LANDSCAPE Program.

Methods: Completed, placebo-controlled studies in adult patients with MDD are:

1. MDD-201B (NCT03000530; Phase 2; ZRN 30 mg)
2. MOUNTAIN (NCT03672175; Phase 3; ZRN 20 mg or 30 mg; 30 mg data included here)
3. WATERFALL (NCT04442490; Phase 3; ZRN 50 mg)

For all 3 studies, the primary endpoint was change from baseline (CFB) in the 17-item Hamilton Rating Scale for Depression total score (HAMD-17) at Day 15. SHORELINE (NCT03864614; Phase 3; ZRN 30 mg or ZRN 50 mg) is an ongoing, open-label, safety study (data for patients with opportunity to complete 1 year reported here); CFB in HAMD-17 at Day 15 of treatment cycle 1 was a secondary endpoint. CGI-I response (defined as "much improved" or "very much improved") at Day 15 was a secondary endpoint in all studies.

Results: In the 3 placebo-controlled trials, patients who received ZRN demonstrated improvement in symptoms of depression as assessed by CFB in HAMD-17 at Day 15 vs patients receiving placebo (MDD-201B n = 45 vs 44: $p<0.0001$; MOUNTAIN n = 166 vs 157: $p=0.1158$; WATERFALL n = 266 vs 268: $p=0.0141$). In SHORELINE, mean CFB in HAMD-17 at Day 15 of treatment cycle 1 was −15.2 for the 30 mg Cohort (n = 725) and −16.0 for the 50 mg Cohort (n = 199). In the 3 placebo-controlled trials, a greater proportion of patients who received ZRN achieved CGI-I response at Day 15 vs patients receiving placebo (MDD-201B: 78.6% vs 45.2%, $p=0.0007$; MOUNTAIN: 55.3% vs 46.1%, $p=0.1107$; WATERFALL: 62.1% vs 51.0%, $p=0.0191$; all p values nominal). In SHORELINE, 533/725 (73.5%) patients in the 30 mg Cohort and 155/199 (77.9%) patients in the 50 mg Cohort achieved CGI-I response at Day 15 of treatment cycle 1. Across these 4 trials, the majority of patients (range across trials [Safety Sets]: 85.4%–100.0%) experiencing a treatment-emergent adverse event (TEAE) reported TEAEs that were mild or moderate in severity. The most common TEAEs (>5% occurrence) in ZRN arms (range across trials) were headache (6.3%–17.8%), somnolence (6.7%–16.1%), dizziness (5.7%–15.1%), nausea (3.6%–11.1%), sedation (4.4%–10.1%), upper respiratory infection (0%–7.9%), diarrhea (0%–7.4%), insomnia (1.1%–7.0%), fatigue (0%–6.8%), dry mouth (3.6%–5.9%), and tremor (0%–5.5%).

Conclusions: Patients treated with ZRN demonstrated clinical improvement as assessed by CGI-I response, consistent with HAMD-17 results. Rates ranged from 55% to 79% for patients receiving ZRN across various studies in the LANDSCAPE Program. The improvement in CGI-I observed across the LANDSCAPE Program potentially suggest that treatment with ZRN may provide improvements beyond core symptoms of depression.

W17. USE OF NONPARAMETRIC TESTING AND BAYESIAN ANALYSES TO ANALYZE MAJOR DEPRESSIVE DISORDER CLINICAL TRIAL RESULTS: POST-HOC SENSITIVITY ANALYSES OF TWO PHASE 3 CARIPRAZINE STUDIES

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Abstract: Introduction: Two recent phase 3 studies evaluated the safety and efficacy of cariprazine for the adjunctive treatment of major depressive disorder (MDD) in adults. In Study 1 (NCT03738215), cariprazine 1.5 mg/d demonstrated significant efficacy vs placebo and 3

mg/d demonstrated numerically higher efficacy than placebo at 6 weeks. In Study 2 (NCT03739203), positive trends for both doses were observed, but neither dose was statistically significant vs placebo at 6 weeks. Given the challenges of clinical trials in MDD and high placebo response variability, assessing results through additional statistical approaches may be useful for interpretation. To account for data variability, we conducted post-hoc sensitivity analyses of the phase 3 studies by excluding outliers and using nonparametric testing and Bayesian modeling.

Methods: In both Study 1 and Study 2, adults with MDD currently experiencing an inadequate response to antidepressants alone were randomized to receive cariprazine 1.5 mg/d, 3 mg/d, or placebo for 6 weeks. The primary outcome was change from baseline to week 6 in Montgomery-Åsberg Depression Rating Scale (MADRS) total score analyzed using mixed models for repeated measures (MMRM). Exploratory post-hoc analyses were conducted to evaluate the impact of different statistical methodologies on the primary results. Three alternative strategies were used to assess the change from baseline to week 6 in MADRS total score: 1) MMRM excluding outliers (eg, >95% placebo-responders), 2) nonparametric stratified van Elteren testing, and 3) Bayesian nonlinear mixed model with repeated measure (NLMMRM) analysis.

Results: In the primary MMRM analyses, between group differences were -2.5 for 1.5 mg/d and 1.5 for 3 mg/d in Study 1 and -0.4 for 1.5 mg/d and -1.4 for 3 mg/d in Study 2. Following the exclusion of responder outliers (n=3 in Study 1; n=5 in Study 2), least square mean difference vs placebo in change from baseline in MADRS total score at week 6 was -2.8 for cariprazine 1.5 mg/d (P=.0007) and 1.8 for 3 mg/d (P=.0295) in Study 1 and -0.7 for 1.5 mg/d (P=.4077) and -1.7 for 3 mg/d (P=.0510) in Study 2. Nonparametric testing showed that 6-week change from baseline in MADRS total score favored cariprazine over placebo in Study 1 with P<.025 for both doses; changes were similar among treatment and placebo groups in Study 2. Bayesian NLMMRM results favored cariprazine vs placebo, with posterior probability >98% for both doses vs placebo in Study 1 and 72.4% for 1.5 mg/d and 97.9% for 3 mg/d in Study 2. For the treatment effect compared with placebo, the 95% credible intervals for both doses in Study 1 excluded 0 (posterior means: -3.26 for 1.5 mg/d and -2.18 for 3 mg/d), indicating a high probability of greater change from baseline in MADRS total scores for both doses vs placebo. In Study 2, a high probability of 3 mg/d having greater effect than placebo was observed, with the 95% credible interval excluding 0 (posterior mean: -2.34); a trend of treatment effect was seen for cariprazine 1.5 mg/d vs placebo (posterior mean: -0.68).

Conclusions: In these post-hoc analyses, exclusion of responder outliers, use of nonparametric testing, and Bayesian analyses found greater differences between cariprazine and placebo on the primary outcome measure. Limitations included lack of multiplicity control. These findings suggest that due to high data variability and other challenges common to MDD clinical trials, additional statistical analyses may be useful for evaluating clinical trial data in MDD.

W18. ESTIMATING CHANGES IN WEIGHT AND METABOLIC PARAMETERS BEFORE AND AFTER TREATMENT WITH CARIPRAZINE: A RETROSPECTIVE STUDY OF ELECTRONIC HEALTH RECORDS

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Abstract: Introduction: Weight gain and cardiometabolic dysfunction are common in patients with bipolar I disorder (BP-I), major depressive disorder (MDD), and schizophrenia, and they frequently occur as medication-related side effects. We evaluated the effect of cariprazine on weight and metabolic parameters in a real-world, retrospective, observational dataset.

Methods: Analyses were based on Optum Humedica electronic health records data from October 1, 2014, through December 31, 2020. The primary objective was to estimate bodyweight trajectories in the overall patient cohort and in patient subgroups during a 12-month period before starting cariprazine (baseline) and for up to 12-months following cariprazine initiation. Secondary objectives were change in hemoglobin A1c (HbA1c), low density lipoprotein (LDL), high density lipoprotein (HDL), triglycerides, and discontinuation rates for metabolic regulating comedications. Weight and metabolic outcomes were estimated by linear mixed-effects regression models.

Results: Of 19,637 cases that had at least one cariprazine prescription, 2,301 patients met inclusion criteria and the average duration of follow-up was 133.7 days. When evaluated across timepoints, average weight increase for patients starting cariprazine was +0.8 kg (n=809), +1.13 kg (n=349), and +1.16 kg (n=73) at months 3, 6, and 12, respectively; the majority of patients did not experience clinically significant (≥7%) weight gain (82.8%). No differences in weight trajectories were observed by diagnosis (BP-I, MDD, schizophrenia), dose, or prior second-generation antipsychotic use. Average HbA1c levels (n=189) increased during the baseline period (+1.5%/year) and decreased after starting cariprazine (-0.21%/year). Average triglyceride levels (n=189) increased during baseline period (+14.98 mg/dL/year) and decreased after starting cariprazine (-0.69 mg/dL/year). LDL (n=247) and HDL (n=255) values decreased during the baseline period (-7.34 and -1.06 mg/dL/year, respectively); after starting cariprazine, LDL increased by +5.65 mg/dL/year and HDL decreased by -0.64 mg/dL/year relative to baseline values. During follow-up, shifts from normal/borderline to high levels of total cholesterol (<240 to ≥240 mg/dL) and fasting triglycerides (<200 to ≥200 mg/dL) did not occur in most patients (522 [90.2%] patients and 143 [88.8%] patients, respectively); shifts from high to normal/borderline levels occurred in 44 (61.1%) patients for total cholesterol and 33 (57.6%) patients for fasting triglycerides. After starting cariprazine, the discontinuation rate per 100 patient-years was 60.4 for antihyperglycemic medication and 87.4 for hyperlipidemia medication.

Conclusions: In this real-world analysis, cariprazine treatment was associated with <1.5 kg (<3.3 lb) weight gain across all timepoints and most patients did not have clinically significant increases. Changes in cardiometabolic risk factors were minimal, with net improvement versus baseline period seen in some cases. After starting cariprazine, discontinuation of antihyperglycemic and antihyperlipidemic medications suggest improved cardiometabolic functioning for some patients. These data confirm the safety profile that was observed during the cariprazine registration trials across indications.

W19. ZURANOLONE SAFETY AND EFFICACY IN PATIENTS WITH MAJOR DEPRESSIVE DISORDER (MDD): INTERIM 50 MG COHORT RESPONSE AND REMISSION OUTCOMES FROM THE OPEN-LABEL, PHASE 3, SHORELINE STUDY

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Abstract: Background: Zuranolone is an investigational, oral neuroactive steroid and gamma-aminobutyric acid type A (GABAA) receptor positive allosteric modulator in clinical development as a once-daily, 2-week therapy for MDD. The SHORELINE Study (NCT03864614) is an ongoing, open-label, Phase 3, longitudinal study evaluating the safety, tolerability, and need for additional treatment courses with zuranolone 30 mg or 50 mg through 1 year in adults with MDD. Data from the first treatment cycle (2-week treatment course + 2-week follow up) of the 50 mg Cohort with the opportunity to complete 1 year of study are reported here for the 17-item Hamilton Rating Scale for Depression total score (HAMD-17) response (≥50% reduction from baseline) and HAMD-17 remission (HAMD-17 ≤7) rates (Data for the 30 mg Cohort have been presented previously).

Methods: SHORELINE is enrolling patients aged 18–75 years with MDD, HAMD-17 ≥20, and a Montgomery–Åsberg Depression Rating Scale total score ≥28. Study design included a screening period (≤4 weeks), an initial 2-week treatment course, a 2-week follow up period, and an observational period (≤48 weeks). Patients who achieved a response at Day 15 (after the first treatment course) were eligible to continue in the study and receive repeat treatment courses during the observation period, with at least 8 weeks between consecutive treatment courses. Patients are assessed every 2 weeks for the need for additional treatment courses with zuranolone; a 9-item Patient Health Questionnaire score ≥10, followed by HAMD-17 ≥20 within approximately 1 week, is required for additional treatment courses. Zuranolone was taken orally, once nightly with food for 2 weeks. The primary endpoint was safety and tolerability, and secondary endpoints included change from baseline (CFB) in HAMD-17 total score, HAMD-17 response, and HAMD-17 remission rates through 1 year.

Results: As of November 2021, the SHORELINE Study enrolled 199 patients in the 50 mg Cohort who had the opportunity to complete 1 year of study. Demographic and baseline characteristics: mean (SD) age, 45.0 (14.1) years; female, 68.8%; and White, 87.9%; mean (SD) baseline HAMD-17, 25.1 (3.3); and antidepressant use at baseline, 41.2%. At least one treatment emergent adverse event (TEAE) was reported in 137/199 (68.8%) patients during the study. The majority of TEAEs were mild (32.1%) or moderate (53.3%) in severity. Serious adverse events were reported in 4.5% (9/199) of patients; 3 (1.5%) were treatment-related (confusional state, asthenia, and delirium). Discontinuation of study drug and withdrawal from the study due to TEAEs during the first treatment cycle were reported in 6.5% (13/199) and 6.0% (12/199) of patients, respectively. There was no increased incidence of suicidal ideation or suicidal behavior compared with baseline in any treatment course, as measured by Columbia Suicide Severity Rating Scale (C-SSRS). In the 50 mg Cohort at Day 15 of treatment cycle 1, the mean (SD) CFB in HAMD-17 was −16.0 (6.0), HAMD-17 response rate was 74.9% (149/199), and HAMD-17 remission rate was 40.2% (80/199).

Conclusions: In the SHORELINE Study, a once-daily, 2-week treatment with zuranolone 50 mg in patients with MDD resulted in a response rate of approximately 75% and a remission rate of approximately 40% at Day 15. Zuranolone 50 mg was generally well tolerated, with >85% of patients reporting TEAEs that were mild or moderate, which is consistent with the overall safety profile of zuranolone seen to date.

W20. HEAD-TO-HEAD COMPARISON OF VORTIOXETINE VS DESVENLAFAXINE IN PATIENTS WITH MAJOR DEPRESSIVE DISORDER WITH PARTIAL RESPONSE TO SELECTIVE SEROTONIN REUPTAKE INHIBITORS: PRELIMINARY BASELINE DATA FROM THE VIVRE STUDY

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Abstract: Introduction: Major depressive disorder (MDD) is a highly prevalent and burdensome psychiatric condition characterized by emotional, physical, and cognitive dysfunction. Many patients do not improve or show only a partial response to selective serotonin reuptake inhibitors (SSRIs), which are often prescribed as first-line therapy. Health care providers recommend switching to another class of antidepressants in cases of suboptimal response. Vortioxetine is a multimodal antidepressant that mediates its effects through modulation of receptor activity and serotonin transporter inhibition. VIVRE, a phase 4 international study (NCT04448431), compared the efficacy of vortioxetine with desvenlafaxine, a commonly prescribed serotonin and noradrenaline reuptake inhibitor, on depressive symptoms, cognitive performance, overall functioning, health-related quality of life, anhedonia, and reward motivation in patients with MDD who had a partial response to SSRI monotherapy.

Methods: This was a randomized, double-blind, multicenter, active-controlled, parallel-group study designed to compare the efficacy of vortioxetine (10 or 20 mg/day) vs desvenlafaxine (50 mg/day) in patients with MDD who had a partial response to SSRI monotherapy. Male and female patients aged 18-65 years with a Montgomery-Åsberg Depression Rating Scale (MADRS) score ≥24 were enrolled. At baseline, eligible patients were randomized (1:1) to vortioxetine or desvenlafaxine for 8 weeks, followed by a 4-week safety follow-up period. Primary endpoint was improvement in depressive symptoms as assessed by change from baseline to week 8 in MADRS total score. Secondary endpoints were MADRS anhedonia score at week 8 and change from baseline to week 8 in the following measures: Digit Symbol Substitution Test (DSST), elements in Effort Expenditure for Rewards Task (EEfRT), Clinical Global Impression–Severity (CGI-S), Functioning Assessment Short Test (FAST), and Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) scores. Here, we present preliminary baseline data; final results will be available at the time of poster presentation.

Results: A total of 606 patients with a mean (SD) age of 43.2 (12.8) years were enrolled; 71% were female and 92% were White. Sites in Russia (25%), Argentina (22%), and Ukraine (14%) enrolled the majority of patients. On average, patients experienced 2.5 (2.1) previous depressive episodes, and the mean duration of their current episode was 23.7 (9.2) weeks. Mean baseline MADRS total score was 30.7 (3.8), indicating, on average, a study population with moderate to severe depression. Mean baseline MADRS anhedonia, CGI-S, DSST, and FAST scores were 18.5 (2.5), 4.5 (0.6), 42.1 (13.1) and 41.5 (12.6), respectively, indicating moderate to severe mental illness with difficulty in functioning. Mean baseline EEfRT value for the proportion of hard choice was 32.0% (20.1%). Mean Q-LES-Q score at baseline was 30.1 (17.9). Mean subscale Q-LES-Q scores for physical health/activities, feelings, work, household duties, school/coursework, leisure time activities, social relations, general activities, and satisfaction with medication were 35.9 (12.5), 38.6 (14.5), 42.5 (24.0), 42.6 (19.8), 28.7 (25.1), 31.8 (22.1), 39.2 (17.0), 38.7 (12.7), and 40.3 (17.5), respectively.

Conclusions: The VIVRE study aims to establish noninferiority of vortioxetine vs desvenlafaxine on mood symptoms as well as superiority on other important clinical outcomes in patients with MDD.

W21. A MULTICENTRE, INTERNATIONAL PHASE IIB RANDOMISED CONTROLLED TRIAL OF COMP360 PSILOCYBIN THERAPY IN TREATMENT-RESISTANT DEPRESSION: RESPONSE AND REMISSION RATES

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Abstract: Background: Treatment-resistant depression (TRD) is a common and debilitating condition, affecting approximately 100 million people who are not helped by existing therapies. Safety and efficacy data from the largest randomised controlled, double-blind trial of psilocybin to date recently demonstrated rapid, significant and clinically meaningful reductions in depressive symptoms resulting from a 25 mg dose of COMP360 psilocybin, given in conjunction with psychological preparation and support from specially trained therapists. Here, we report further depression outcomes data including response and remission rates, and changes in self-reported depression scores.

Methods: This was a phase IIb, international, multicentre, randomised, fixed-dose, double-blind trial assessing the safety and efficacy of two doses (25 mg or 10 mg) of COMP360 (COMPASS Pathways' proprietary synthetic psilocybin formulation) compared with COMP360 1 mg in individuals with TRD. After psychological preparation with a specially trained therapist, participants received COMP360 in a therapist supported-session. Participants were followed up for 12 weeks post-administration. Depression severity was measured using the Montgomery-Åsberg Depression Rating Scale (MADRS) assessed by independent, blinded remote raters as well as via participant self-report using the Quick Inventory of Depressive Symptomatology (QIDS-SR-16). Response was defined as a 50% or greater reduction from baseline in MADRS total score. Remission was defined as a total MADRS score <=10. Sustained response was defined as meeting MADRS response criteria at weeks 3, 12, and at least one other visit out of weeks 6 and 9.

Results: 233 participants were randomised to 25 mg (n=79), 10 mg (n=75), or 1 mg (n=79) COMP360 (mean age 39.8 years; 121 female, 112 male; 94% had no prior psilocybin experience). At 3 weeks post-administration, 36.7% (n=29/79) of participants in the 25 mg group had responded compared with 17.7% (n=14/79) in the 1 mg group. Furthermore, 29.1% (n=23/79) in the 25 mg group had remitted at week 3 compared with 7.6% (n=6/79) in the 1 mg group. At 12 weeks post-administration, 24.1% (n=19/79) of participants in the 25 mg group were sustained responders compared with 10.1% (n=8/79) in the 1 mg group. Response and remission rates in the 10 mg group were comparable to those seen in the 1 mg group. Changes from baseline in the QIDS-SR-16 total score were greater in the 25 mg group at weeks 1, 2 and 3, compared with the 1 mg group with a least squares mean treatment difference of -2.8 (95% confidence interval = 4.6, -0.9) observed at week 3.

Conclusion: A single 25 mg dose of COMP360 psilocybin, given in conjunction with psychological preparation and support from specially trained therapists, generated a rapid antidepressant response which lasted up to 12 weeks for almost a quarter of participants. A long-term study is underway to further understand the durability of these effects.

W22. FACTORS ASSOCIATED WITH PATIENT ACTIVATION AMONG INDIVIDUALS WITH DEPRESSION WITHIN RACE/ETHNIC GROUPS

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Abstract: Background: Increasing patient activation, knowledge, skills, and confidence to manage one's own health, may be vital for improving quality of care for individuals with depression. However, little is known about the factors associated with patient activation among individuals with depression, and how patient activation may differ by severity, race/ethnicity, and household income.

Objective: To examine the association of depression severity, race/ethnicity, and household income with patient activation. Within race/ethnicity groups, identify factors associated with patient activation among individuals with depression.

Methods: Data from the 2020 US National Health and Wellness Survey, a cross-sectional general population survey, were used to identify White, Black/African American, Asian, and Hispanic respondents with diagnosed depression. Measures included the Patient Activation Measure (PAM), Patient Health Questionnaire-9 (PHQ-9), sociodemographic and health characteristics, and health-related outcomes. Generalized linear models were used to measure factors associated with PAM.

Results: Analyses included 8,216 respondents with self-reported physician-diagnosed depression (mean age = 44 years, 68% female; 5,964 White, 739 Black/African American, 282 Asian, and 1,231 Hispanic). Depression severity ($p=0.001$) and race/ethnicity ($p=0.002$) significantly predicted patient activation; household income did not ($p=0.062$). Specifically, for each unit increase in PHQ-9, PAM decreased by -0.11 points. Adjusted mean PAM scores were highest among Black respondents (61.1), followed by Hispanic (60.4), White (59.3), and Asian (59.0) respondents. Race/ethnicity did not moderate the relationship between depression severity and patient activation ($p=0.185$). The factors most strongly associated with patient activation differed by race/ethnicity. For White respondents, being female ($\beta=1.70$, $p<0.001$), household income above $100,000 ($\beta=1.40$, $p=0.012$), and prescription for depression ($\beta=-0.72$, $p=0.019$) were associated with greater patient activation. For Black respondents, undisclosed household income ($\beta=5.49$, $p=0.035$), uninsured ($\beta=4.73$, $p=0.002$), and younger age ($\beta=0.16$, $p<0.001$) were associated with lower patient activation. For Hispanic respondents, uninsured ($\beta=-2.72$, $p=0.01$), insurance other than Medicaid, Medicare, or Commercial ($\beta=-5.69$, $p<0.001$), and poorer physical ($\beta=0.20$, $p<0.001$) and mental health ($\beta=0.16$, $p=0.001$) were associated with lower patient activation. For Asian respondents, being female ($\beta=3.50$, $p=0.008$), better mental health ($\beta=0.37$, $p<0.001$), and higher anxiety ($\beta=0.37$, $p=0.019$) were associated with greater patient activation.

Some factors seemed to act as barriers toward patient activation for certain racial/ethnic groups, whereas those same factors acted as drivers toward patient activation for other racial/ethnic groups. More healthcare provider visits were associated with greater patient activation among White and Hispanic respondents but were associated with lower activation among Asian respondents. Greater activity impairment was associated with greater patient activation among White and Asian respondents but was associated with lower patient activation among Hispanic respondents.

Conclusions: These results indicate that the pathway to improving patient activation in individuals with depression may vary by race/ethnicity. Understanding the factors associated with patient activation can help inform the design and tailoring of interventions to increase patient activation in individuals with depression.

W23. SELTOREXANT REDUCES CORE DEPRESSIVE SYMPTOMS IN PATIENTS WITH MAJOR DEPRESSIVE DISORDER: ANALYSIS BASED ON MADRS-WOSI AND MADRS-6

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Abstract: Background: Seltorexant, a highly selective orexin-2 receptor antagonist, displayed antidepressant and sleep-promoting effects in patients with major depressive disorder (MDD) in a previous exploratory study (1). In a phase 2b study, seltorexant 20 mg demonstrated clinically meaningful improvement in Montgomery-Åsberg Depression Rating Scale (MADRS) total score from baseline to the end of week (W) 6 (the primary endpoint) (2). The current analysis evaluated the effect of seltorexant in improving depressive symptoms beyond sleep-related improvement in patients with MDD using the MADRS-WOSI (MADRS without the sleep item) and MADRS-6 (MADRS 6 core depression items).

Methods: This randomized, double-blind, multicenter, parallel-group, placebo (PBO)-controlled, adaptive dose-finding study (NCT03227224) was conducted in adults with MDD (DSM-5 criteria) who had an inadequate response to 1-3 selective serotonin/serotonin-norepinephrine reuptake inhibitors in the current episode (2). Patients were randomized 2:1:1 to receive PBO or seltorexant (20 or 40 mg) once-daily (QD). After an interim analysis, newly recruited patients were randomized 3:3:1 to receive PBO or seltorexant (10 or 20 mg QD; 40 mg dose was no longer assigned). Randomization was stratified for patients with (baseline Insomnia Severity Index [ISI] score ≥15) vs without clinically significant/subthreshold insomnia symptoms (ISI<15). Changes from baseline in MADRS-WOSI score (range: 0–54) and MADRS-6 score (range: 0-36) at W6, by treatment and baseline insomnia status, were assessed. Mixed model for repeated measures analysis was used to assess treatment effect by subgroups.

Results: Of 283 patients treated, 57.6% had baseline ISI ≥15 and 42.4% had ISI<15. In the overall sample, improvement in MADRS-WOSI score was observed in the seltorexant 20 mg group (n=61) at W3 and W6 with least squares mean (LSM) difference (90% CI) vs PBO (n=137): W3, −3.8 (−5.98; −1.57), P = 0.005; W6, −2.5 (−5.24; 0.15), P = 0.120, consistent

with the improvement in MADRS total score (W3, −4.5 [−6.96; −2.07], P = 0.003; W6, −3.1 [−6.13; −0.16], P = 0.083) (2). Seltorexant 20 mg dose was more effective when assessed using the MADRS-WOSI score in patients with ISI ≥15 (n=38) at W3 and W6, with LSM difference (90% CI) vs PBO (n= 81): W3, −4.7 (−7.53; −1.82), P = 0.008; W6, −4.2 (−7.86; −0.53), P = 0.060. Similarly, in the overall sample seltorexant 20 mg group showed improvement at W3 and W6 in the MADRS-6 score vs PBO, with LSM difference (90% CI): W3, −3.1 (−4.87; −1.41), P = 0.003; W6, −1.8 (−3.93; 0.26), P = 0.150. Seltorexant 20 mg was more effective for reducing MADRS-6 score in patients with ISI ≥15 at W3 and W6, with LSM difference (90% CI) vs PBO: W3, −4.0 (−6.19; −1.75), P = 0.004; W6, −3.7 (−6.57; −0.89), P = 0.032.

Conclusions: Seltorexant 20 mg demonstrated improvements in the MADRS-WOSI and MADRS-6 scores in patients with MDD, particularly in those with ISI ≥15, consistent with the improvement in the MADRS total score, suggesting that improvement in depression symptoms was not driven directly by the change in the MADRS sleep item. Seltorexant 20 mg was more effective for improving the MADRS-WOSI and MADRS-6 scores in MDD patients with significant insomnia symptoms. These data suggest seltorexant is more likely to reduce the severity of core depressive symptoms in MDD patients who manifest symptoms of insomnia.

W24. A MULTICENTRE, INTERNATIONAL PHASE IIB RANDOMISED CONTROLLED TRIAL OF COMP360 PSILOCYBIN THERAPY IN TREATMENT-RESISTANT DEPRESSION: CHANGES IN AFFECT, ANXIETY AND FURTHER EXPLORATORY ENDPOINTS

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Abstract: Background: In addition to its antidepressant effect, COMP360 psilocybin therapy has the potential to address symptoms and aspects of function which are important to patients suffering with treatment-resistant-depression (TRD). In the largest randomised controlled, double-blind trial of psilocybin therapy to date, a single 25 mg dose of COMP360 psilocybin (in conjunction with psychological preparation and support from specially trained therapists) resulted in rapid, significant, and clinically meaningful reductions in depression symptoms compared with a 1 mg dose. A 10 mg dose resulted in modest numerical reductions. Here, we report results for changes in positive and negative affect, anxiety, quality of life, functioning and cognition.

Methods: This was a phase IIb, international, multicentre, randomised, fixed-dose, double-blind trial assessing the safety and efficacy of two doses (25 mg or 10 mg) of COMP360 (COMPASS Pathways' proprietary synthetic psilocybin formulation) in individuals with TRD, compared with COMP360 1 mg. After psychological preparation with a specially trained therapist, participants received COMP360 in a therapist-supported session followed by post-administration integration sessions. Participants were followed up for 12 weeks post-administration.

Results: 233 participants were randomised to COMP360 25 mg (n=79), 10 mg (n=75), or 1 mg (n=79) (mean age 39.8 years; 121 female, 112 male; 94% had no prior psilocybin experience). At 3 weeks post-administration, the Positive Affect and Negative Affect Schedule (PANAS) showed a least squares mean (LSM) treatment difference favouring the 25 mg group for both positive (LSM 6.2; 95% Confidence Interval (CI) 3.5, 8.8) and negative (LSM 3.2; 95% CI 5.6, 0.8) affect compared with the 1 mg group. Similarly, changes from baseline in the Generalised Anxiety Disorder-7 item scale (GAD-7) total score were greater in the 25 mg group with a LSM treatment difference of 1.8 (95% CI 3.4, 0.2) compared with the 1 mg group at week 3. Changes from baseline in the Work and Social Adjustment Scale (WSAS) were also greater in the 25 mg group with a LSM treatment difference of 5.1 (95% CI 8.4, 1.8) compared with the 1 mg group at week 3. Changes from baseline in the Sheehan Disability Scale (SDS) were greater in both the 25 mg and 10 mg groups with LSM treatment differences of 6.5 (95% CI 9.5, 3.5) and -4.0 (95% CI -7.0, -1.0) respectively compared with the 1 mg group at week 3. No differences were seen between the treatment groups for quality of life (EQ-5D-3L), or for cognition (Digit Symbol Substitution Test) with all groups showing an improvement over time on these measures.

Conclusion: In combination with psychological preparation and support from specially trained therapists, 25 mg of COMP360 psilocybin demonstrates additional patient benefits beyond reduction in depressive symptoms. These exploratory results support further development of COMP360 psilocybin therapy for TRD.

W25. CHARACTERISTICS AND REAL-WORLD TREATMENT PATTERNS OF ADULTS WITH TREATMENT RESISTANT DEPRESSION COMPLETING ESKETAMINE INDUCTION TREATMENT PER DRUG LABEL IN UNITED STATES

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Abstract: Objective: To understand real world characteristics and treatment patterns among adults with treatment resistant depression (TRD) who complete induction treatment with esketamine in the United States.

METHODS: Adults with ≥1 esketamine claim (index date) on or after 03/05/2019 were selected from the IBM© MarketScan© Research Databases (01/01/2015-10/31/2020). Before the index date, patients had evidence of TRD (claims for ≥2 different antidepressants during the major depressive episode [MDE] in which esketamine was initiated), and ≥6 months of continuous insurance eligibility (baseline period). Additionally, patients had ≥6 weeks of follow-up period, spanning the index date through the earliest of end of continuous insurance eligibility or data availability. Finally, patients with ≥8 esketamine treatment sessions (per label, completed induction treatment) within the 6 weeks of follow-up period were included in the analysis.

Results: Overall, 124 patients with TRD were included in the analysis (mean [median] age 45.7 [47.8] years, 66.9% female). Patients filled claims for a mean [median] number of 2.2 [2.0] unique antidepressant agents; 79.0% of patients had ≥1 psychiatrist visit, 76.6% received psychotherapy and 9.7% received transcranial magnetic stimulation during the baseline period.

All patients had ≥1 outpatient visit, 28.2% had ≥1 emergency department visit and 14.5% had ≥1 inpatient admission during the baseline period.

The mean [median] number of esketamine treatment sessions was 21.9 [18.0] over a mean [median] of 9.3 [8.9] months of follow-up. The mean [median] time to completion of induction treatment (defined in this analysis as 8 treatment sessions within 6 weeks of esketamine treatment initiation) was 28.2 [27.5] days (per label, 28 days), with median time between consecutive sessions ranging from 3 to 5 days. Among these patients, 93.5% (N=116) had ≥9 esketamine sessions (per label, initiated maintenance phase) and 79.0% (N=98) completed >12 sessions; the mean [median] time between the 9th and 12th session was 23.8 [20.0] days (weekly dosing per label, 21 days) and median time between consecutive sessions ranged from 6 to 7 days. Further, 71.0% (N=88) completed ≥13 sessions; among these patients, the mean [median] number of esketamine treatment sessions was 26.8 [24.0] and the mean [median] time between consecutive sessions after the 12th session was 11.6 [9.7] days (per label, 7-14 days). Most patients initiated esketamine with 56mg dose (89.5%) and titrated to 84mg dose by the end of the induction treatment (82.3%).

Conclusion: Adult patients with TRD, who completed esketamine induction treatment within 6 weeks, received treatment consistent with the esketamine label, with the vast majority proceeding to maintenance treatment.

W26. REAL-WORLD TREATMENT PATTERNS, HEALTHCARE RESOURCE USE, AND COSTS OF PATIENTS WITH TREATMENT RESISTANT DEPRESSION AND A HISTORY OF COMORBID CARDIOVASCULAR OR METABOLIC CONDITION INITIATING ESKETAMINE IN UNITED STATES

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Abstract: Objective: To describe esketamine real world use, treatment patterns, healthcare resource utilization (HRU), and costs among adults with treatment resistant depression (TRD) and history of a comorbid cardiovascular (CV) or metabolic condition who initiate esketamine in the United States.

Methods: Adults with ≥1 esketamine claim (index date) on or after 03/05/2019 were selected from IBM© MarketScan© Research Databases (01/01/2015-10/31/2020). Before the index date, patients had evidence of TRD (claims for ≥2 different antidepressants during the same major depressive episode [MDE] in which esketamine was initiated) and ≥6 months of continuous insurance eligibility. Patients also had ≥1 claim with a diagnosis or procedure for a CV or metabolic condition during the 6-month period before the index date (baseline period). Treatment patterns, HRU, and costs (US $2020) were described during the baseline period and during the variable follow-up period, which spanned the index date until either end of continuous insurance eligibility or data availability.

Results: 185 patients with TRD and a history of either a CV or metabolic condition initiating esketamine were included (mean [median] age 48.4 [50.2] years, 65.9% female). The mean [median] length of follow-up was 8.3 [8.4] months. During the follow-up period, 56.8% of patients had ≥8 esketamine sessions (per label, completed induction treatment) with a mean [median] time from the index date to the 8th session of 68.8 [36.0] days (per label, 28 days).

49.2% of patients had ≥9 esketamine sessions (per label, initiated maintenance phase). Patients also filled claims for a mean and median number of 2.0 unique antidepressants; 71.9% of patients received psychotherapy and 78.4% of patients had a psychiatrist visit.

The mean monthly number of all-cause inpatient (IP) days decreased from 0.42 during the baseline period to 0.30 during the follow-up period, number of emergency department (ED) visits decreased from 0.14 to 0.10, while number of outpatient (OP) visits increased from 4.31 to 5.05. Similarly, mean monthly number of mental-health related IP days decreased from 0.41 during the baseline period to 0.28 during the follow-up period, number of ED visits decreased from 0.06 to 0.03, and number of OP visits increased from 2.85 to 3.67.

Mean monthly all-cause medical costs changed from $3,054 during the baseline period to $2,663 during the follow-up period. This was a result of a reduction in OP (baseline: $1,956; follow-up: $1,658), ED (baseline: $242; follow-up: $160), and IP costs (baseline: $850; follow-up: $827). During the baseline and follow-up periods, 57.4% and 52.7% of all-cause medical costs were related to mental health.

Conclusion: Approximately half of patients with TRD and history of a comorbid CV or metabolic condition completed the induction phase of esketamine. There appeared to be a lower mean number of monthly all-cause and mental-health related IP days and ED visits after esketamine initiation. Additionally, mean monthly all-cause medical costs appeared lower during the follow-up period compared to the baseline period.

W27. CONCURRENT PTSD AND THE MANAGEMENT OF DEPRESSIVE DISORDERS IN PRIMARY CARE CLINICS UTILIZING A PSYCHOPHARMACOLOGICAL CARE MANAGEMENT PROGRAM

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Abstract: Introduction: Depression and anxiety are two commonly diagnosed mental health disorders which are often treated in primary care settings.(1) Care management (CM) is a protocol based treatment approach to common mental health problems that present in primary care, with one example being pharmacological management of depression and anxiety. CM programs have been shown to improve patient functioning, engagement, adherence, and all-cause mortality,(2) however, pharmacological CM programs are typically reserved for the treatment of uncomplicated mild to moderate depression and anxiety, in the absence of other co-occurring MH disorders such as PTSD. The purpose of this study was to evaluate a pharmacological care management program for the treatment of Veterans with Major Depressive Disorder (MDD), which did not exclude individuals with concurrent PTSD, in an effort to evaluate the efficacy of this treatment modality in a sub-cohort of MDD patients with co-occurring trauma disorder symptoms.

Methods: A retrospective review was conducted on all patients enrolled in the Tampa VA's Antidepressant Monitoring Program (ADM; a pharmacological CM program) over the first 10 months of program implementation. 18 months of follow up data was obtained for analysis. Data collected included: sociodemographic data, symptomatic assessments, mental health medications, and co-occurring MH disorders, Descriptive and inferential analyses were conducted on patient characteristics in relation to outcomes measures of interest including symptomatic improvement and program adherence/completion.

Results: 433 patients were referred to the ADM program during the first 10 months of implementation. 112 (25.87%) of the cohort were identified as having active PTSD symptoms at the time of program enrollment as defined by PCL-5 scores >=33; an additional 43 had prior diagnoses of PTSD resulting in a total of 155 (35.80%) with current or past PTSD.

Program completion rates for the PTSD cohorts did not differ from that of individuals without PTSD, including when looking at any history of PTSD (27.74% vs 36.69%; x2 (1, N=433) = 3.5779, p= .058554), as well as when looking at only those individuals with active PTSD symptoms at time of ADM program enrollment (30.36% vs 36.69%, x2 (1, N=390) = 1.4101, p= .235044).

Of the Veterans who were referred, enrolled, and completed at least one ADM follow up, mean improvements in depression and anxiety symptoms, as evidenced by changes in PHQ-9 and GAD-7 scores were 43.90% and 42.83%, respectively. No differences in mean reduction in symptoms of depression were observed when comparing the cohort with no history of PTSD to to those with any history of PTSD (-6.16 vs -5.42; t(326)= 0.987, p= .3244, 95% CI -0.7349 to 2.2149) , nor to those with active PTSD symptoms (-6.16 vs -5.54; t(295)= 0.749, p= .4543, 95% CI -1.0086 to 2.2486). Similarly, for anxiety a mean reduction of -5.61 on GAD-7 scores were observed for the cohort without PTSD, compared to -4.99 and -5.35 in the any history of PTSD and active PTSD symptom cohorts, respectively. Again, these differences were non-significant (t(326)=0.892 p= .3728, 95% CI -0.7468 to 1.9868; t(295)=0.343 p= .7315, 95% CI -1.2297 to 1.7497).

Conclusions: No differences were observed in either program completion, nor symptomatic improvement of depression and anxiety, between Veterans with and without PTSD, demonstrating that individuals with depression and co-occurring trauma related disorders can achieve successful treatment for their depressive disorders utilizing a CM model in primary care. More research should be conducted on pharmacological CM programs including examining ADM programs for the initial treatment of individuals with a primary diagnoses of PTSD.

W28. AURICULAR TRANSCUTANEOUS HI-FREQUENCY E-MMUNOTHERAPY SEQUENCES (ATHENS) FOR MAJOR DEPRESSIVE DISORDER (MDD) WITH PERIPARTUM ONSET WITH AND WITHOUT CONCOMITANT ANTIDEPRESSANT USE: A MULTICENTER, OPEN-LABEL PILOT STUDY

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Abstract: Background: Peripartum depression (PPD) has a high prevalence in the U.S. (~13%) and often goes untreated/undertreated. Invasive vagus nerve stimulation is FDA-approved for treatment-resistant depression but carries the risks of surgery and stimulation of the vagus nerve efferent fibers. We conducted a multicenter, open-label, proof-of-concept trial to assess safety and preliminary efficacy of ATHENS, a non-invasive high frequency auricular vagus nerve therapy, for treatment of adult females with PPD.

Methods: Women (n=25), ages 18–45, within 9 months postpartum, diagnosed with PPD were enrolled at 3 sites. The study included 6 weeks of open-label therapy (15 minutes/day) and 2 weeks of observation (no treatment; Weeks 7 and 8). Safety and tolerability were assessed by adverse event (AE) reports. Efficacy outcomes included change from baseline (CFB) in Hamilton Rating Scale for Depression (HAM-D17) total scores, HAM-D17 response and remission, Hamilton Anxiety Rating Scale (HAM-A), Edinburgh Postnatal Depression Scale (EPDS), Generalized Anxiety Disorder Scale (GAD-7) total scores and patient and clinician global impression of change (PGIC, CGIC) scores. Baseline characteristics are reported as mean with standard deviation (SD). Efficacy outcomes were analyzed using mixed-effects models for repeated measures with CFB reported as least squares (LS) mean with standard error (SE).

Results: Of the 25 women who met eligibility criteria and were enrolled into the 6-week treatment phase, 24 completed the 8-week study and 1 discontinued due to noncompliance with the therapy. At baseline, mean (SD) age was 33.7 (3.9) years, mean (SD) HAM-D17 total score was 18.4 (5.3), and 10 (40%) were on a stable dose of antidepressant medication. Baseline HAM-D17 total score was similar for those on (17.8) vs off (18.9) antidepressants. For the 23 participants with data available at Week 6, LS mean (SE) CFB in HAM-D17 total score was 9.7 (0.87) overall, -8.7 (1.24) for those on antidepressants (n=8), and -10.3 (1.14) for those off antidepressants (n=15); response and remission were achieved by 74% and 61% of women overall respectively, 75% and 75% of women on antidepressants, and 73% and 53% of women off antidepressants. LS mean (SE) CFB in the overall population at Week 6 for the secondary outcome measures were 7.6 (0.88) for HAM-A, 6.6 (0.48) for GAD-7, and 7.9 (0.75) for EPDS. Of participants with PGIC/CGIC/satisfaction data available at Week 6, at least some improvement in condition was reported by 21/22 (95%) clinicians on CGIC and 22/23 (96%) participants on PGIC; 20/23 (87%) participants reported device satisfaction. A total of 21 AEs occurred in 13/25 (52%) participants, with 12 deemed treatment-related. None led to discontinuation, and all resolved without intervention. The most common AEs (≥5%) were discomfort (n=5), headache (n=3), and dizziness (n=2). No serious AEs or deaths occurred.

Conclusion: While further evaluation in larger sham-controlled studies is needed, results from this open-label proof-of-concept study suggest that the Nēsos ATHENS based therapy is well tolerated in postpartum women, with or without concomitant antidepressant use, and may be an effective non-invasive, nonpharmacological treatment option for MDD with peripartum onset.

W29. COVID-19 VACCINATION STATUS IN THE MAJOR DEPRESSIVE DISORDER CLINICAL TRIAL-SEEKING POPULATION

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Abstract: Introduction: Major Depressive Disorder (MDD) clinical trial recruitment and participation have historically been challenging given depression symptoms, and their impact upon attendance rates for screening visits.1,2 The COVID-19 pandemic has added complexity to clinical trials in a myriad of ways, from recruitment to retention. Vaccines hold great

promise, yet vaccine hesitancy has been a significant national obstacle. To better understand vaccination status and its relationship with other characteristics among the MDD clinical trial seeking population, we examined vaccination rates among a cohort of Massachusetts MDD trial seeking subjects and associated demographic and recruitment-related variables.

Methods: Between August 2019 and November 2021, 556 potential study participants responded to online trial advertisements and were called to complete a phone screening interview where vaccination status information was gathered. Fully vaccinated individuals who passed the initial phone screen were invited for an in-person prescreening visit with a clinician, where they completed self-report forms detailing their COVID-19 vaccine status and manufacturer. Being "fully vaccinated" was defined as either two doses of Pfizer/BioNTech or Moderna vaccines, or one of the Janssen vaccines. Unvaccinated and not fully vaccinated individuals were offered remote prescreen appointments with a clinician prior to in-person screening.

Results: COVID-19 vaccination status in the sample fell below the 82% Massachusetts adult vaccination rate, with nearly 76% of potential MDD study participants reporting being fully vaccinated. Both age and distance from site were significantly correlated with vaccination status, with older subjects being more likely to be fully vaccinated (β=.10, p=.02), and participants living further from the metropolitan Boston area less likely to be vaccinated (β=-.02, p=.008). Vaccination status was also significantly correlated with phone screen outcome, with fully vaccinated subjects being more likely to pass the initial phone screening (87% pass rate) than unvaccinated subjects (79% pass rate), even when controlling for age (β=1.8, p=.05). There were no significant differences between prescreening pass rates among vaccinated (58%) or unvaccinated (57%) participants. There were also no significant differences in screening rates for MDD studies between vaccinated (12.3%) or unvaccinated (9%) participants. Interestingly, vaccinated subjects were significantly more likely to decline screening for a study (18.7%), compared to unvaccinated subjects (11.1%), even when controlling for age (β=2.1, p=.02). While slightly more unvaccinated participants (21.6%) than vaccinated participants (17.2%) were lost to follow-up, the differences were not statistically significant.

Conclusion: COVID-19 vaccination rates among those with depression seeking help through clinical trials may be lower than the general population, even in a highly vaccinated state like Massachusetts. Vaccine status was predicted by age and distance to site (reflecting national trends in vaccine uptake in older adults and more urban versus rural areas). Unvaccinated participants were relatively overrepresented on some indicators of reduced participant quality, such as being ineligible or lost to follow-up. Future research should examine differences in vaccine status across indications in psychiatry studies.

W30. SUNSHINE INCREASED PLACEBO EFFECT IN ANTIDEPRESSANT STUDIES: A NEW GROUND TO BREAK

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Abstract: Background: Sex differences occur in human depressive symptoms and animal models of depression. Light therapy alleviates depression. Placebo effect should be increased by sunshine in depressed women.

Aims: To assess whether sunshine increases placebo effect in depressed women under 50 years.

Methods: Data from nine double-blind, randomized, placebo and reference compound controlled antidepressant studies were reviewed. Score changes between two consecutive visits were correlated to the median sunshine index at noon between theses visits.

Results: No correlation was found between sunshine and score changes for patients receiving the active compound. In the placebo group, no correlation was found in men, as well as in women exposed to cloudy/variable weather (<2000 Joules/cm²).

However, women exposed to sunny weather (>2000 Joules/cm²) elicit a significant correlation between score changes and sunshine index.

Conclusions: Research on placebo effect should include the assessment of sunshine index.

Declaration of interest No grant has been provided.

W31. RESULTS FROM A STUDY OF SELF-REPORTED EXPERIENCES ASSOCIATED WITH SLEEP ONSET WITH LEMBOREXANT VS ZOLPIDEM

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Abstract: Background: In clinical practice, patients managing their insomnia may need to change their insomnia medication for various reasons (i.e., side effects or inadequate response). Dosing paradigms when transitioning between insomnia medications are an important consideration, particularly when the medications are from different classes. Patients may ask how the medicines compare, particularly with respect to differences about how they may feel, especially as they are falling asleep (sleep onset) (Yang et al, 2010). Zolpidem tartrate (ZOL) is a GABAA-receptor agonist commonly prescribed for insomnia treatment. Lemborexant (LEM) is a dual orexin receptor antagonist approved in multiple countries for the treatment of adults with insomnia (Yardley et al, 2021). Study 312 (NCT04009577) was an open-label study that explored dosing paradigms for transitioning patients with insomnia from ZOL (immediate [IR] or extended-release [ER]) to LEM (5mg [LEM5] or 10mg [LEM10]). Information on subjects' experiences while taking ZOL or LEM was collected during the study.

Methods: Study 312 enrolled intermittent (3-4 nights/wk) or frequent (≥5 nights/wk) ZOL (-IR or -ER) users. The study included a 3-wk Screening Period (during which subjects remained on ZOL), a 2-wk Titration Period (TITR), a 12-wk Extension Phase (EXT), and a 4-wk Follow-up Period. Frequent ZOL users were assigned to Cohort-2 and randomized 1:1 to LEM5:LEM10. Subjects assigned to Cohort-1 (infrequent users) are not reported here. Subjects could change LEM dose during TITR (only once) or EXT. During the study, subjects completed the Sleep Drug Experience questionnaire, which included questions related to subjective experiences associated with falling asleep or returning to sleep after waking in the middle of the night (not reported here) with either drug. Subjects were asked "Did the sleep drug (ZOL or LEM) help you to fall asleep after taking it?" (possible responses: Yes or No). Subjects who answered "Yes" were then asked "If the sleep drug helped you to fall asleep after taking it, how did you know it was working?"; followed by a list of 25 possible experiences. For each applicable experience, subjects rated the intensity on a scale ranging from 1 to 5, with 1=low intensity and 5=high intensity. Subjects completed the Sleep Drug Experience questionnaire for ZOL at the end of Screening and for LEM at the end of TITR. Reported

percentages are for Cohort-2 subjects who endorsed that either or both drugs helped them to fall asleep.

Results: In Cohort-2, 38 subjects completed the questionnaire for ZOL, and 35 subjects completed it for LEM. Experiences endorsed by ≥50% during initial sleep onset with both ZOL and LEM, respectively, included: "drowsiness, grogginess, sleepiness" (76.3% vs 82.9%); "feeling relaxed/calm" (84.2% vs 85.7%); "falling asleep so quickly that you don't remember falling asleep" (68.4% vs 74.3%); "difficulty with remembering details of the night right before falling asleep" (60.5% vs 51.4%); "feeling sedated" (63.2% vs 60.0%); "having dreams" (76.3% vs 80.0%); and "feeling peaceful" (65.8% vs 85.7%). Two experiences were reported by ≥50% of LEM subjects only, with small differences between the drugs. These were "lightheadedness" (44.7% vs 51.4% for ZOL and LEM, respectively) and "feeling of floating" (47.4% vs 57.1% for ZOL and LEM, respectively).

Conclusions: These data suggest similarity in the most frequently endorsed falling asleep experiences between subjects while taking ZOL and during the initial two-week transition to LEM. These findings may be helpful in discussions with patients prior to initiating insomnia treatment with LEM.

Support: Eisai Inc.

W32. THE EFFECT OF LEMBOREXANT ON APNEA-HYPOPNEA INDEX AND PERIPHERAL OXYGEN SATURATION IN ADULT AND ELDERLY SUBJECTS WITH MODERATE OR SEVERE OBSTRUCTIVE SLEEP APNEA

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Abstract: Background: A safety risk of some regularly prescribed sleep-promoting drugs, like those targeting GABAA receptors, is central respiratory depression (Moline, 2021). Elderly individuals and/or those with a coexisting respiratory disorder, such as obstructive sleep apnea (OSA), are especially susceptible. Lemborexant (LEM) is a dual orexin receptor antagonist (DORA) approved in multiple countries for the treatment of adults with insomnia. In Study 102 (NCT03471871), no differences between LEM 10 mg (LEM10) and PBO were found on peripheral oxygen saturation (SpO2) and the apnea-hypopnea index (AHI: number of apneas/hypopneas per hour of sleep) in adult and elderly subjects with mild OSA following single and multiple doses (Cheng, 2020). Study 113 (NCT04647383) investigated the effect of LEM on respiratory safety in adult and elderly participants with moderate or severe OSA.
Methods: This was a multicenter, multiple-dose, randomized, double-blind, PBO-controlled, 2-period crossover study in adult (age ≥45 to <65y) and elderly (age ≥65 to ≤90y) participants with moderate (15≤AHI<30) or severe (AHI≥30) OSA. SpO2 for all participants was ≥94% at screening. Participants were randomized to two 8-night treatment periods (separated by a washout ≥14d) with either LEM10 or PBO. Overnight in-lab polysomnography (scoring AHI) and transmissive pulse oximetry (measuring SpO2) were performed at screening, on Day 1 (after a single dose before bedtime) and Day 8 (after multiple dosing before bedtime) of study drug during both treatment periods. On Days 2-7, participants were instructed to take the study drug before bedtime at home. Treatment-emergent adverse events (TEAEs) were recorded throughout the study.

Results: Forty-eight participants were screened; 33 (68.8%) were randomized; of these n=13 had moderate OSA and n=20 had severe OSA. Mean age was 60.6y; 22/33 participants (66.7%) were age ≥45 to <65y and 11/33 (33.3%) were ≥65 to ≤90y. During total sleep time, mean baseline SpO2 was 93.5% and mean AHI was 44.2. No significant difference was found in AHI (least squares mean [LSM]) after a single dose or multiple doses of LEM10 versus PBO in participants with moderate (single: LEM10, 31.49; PBO, 32.41, P=0.818; multiple: LEM10, 34.66; PBO, 37.16, P=0.442) or severe (single: LEM10, 48.22; PBO, 52.69, P=0.172; multiple: LEM10, 51.48; PBO, 51.15, P=0.902) OSA. Also, no significant difference was found in SpO2 (LSM) after a single dose or multiple doses of LEM10 versus PBO in participants with moderate (single: LEM10, 93.68%; PBO, 93.86%, P=0.696; multiple: LEM10, 93.74%; PBO, 93.86%, P=0.784) or severe (single: LEM10, 92.57%; PBO, 92.65%, P=0.841; multiple: LEM10, 92.63%; PBO, 93.02%, P=0.283) OSA. Furthermore, no significant difference was found in percentage of total sleep time during which SpO2 was below the thresholds of <90%, <85%, <80% for LEM10 vs PBO following a single dose (P=0.694, P=0.134, P=0.195, respectively) or multiple doses (P=0.481, P=0.711, P=0.699, respectively) in participants with moderate or severe OSA.

TEAEs were higher in LEM10- (18.2%) versus PBO- (9.1%) treated participants. One subject did not complete treatment due to an adverse event unrelated to LEM10 (COVID-19). Overall, LEM was well tolerated, and most TEAEs were mild in severity.

Conclusions: As objectively measured by AHI and SpO2 during TST, LEM, a DORA, demonstrated respiratory safety with single and multiple dosing in participants with moderate and severe OSA, and was well tolerated.

Support: Eisai Inc.

W33. SOCIAL DETERMINANTS OF HEALTH, HEALTHCARE RESOURCE UTILIZATION, AND COSTS AMONG PATIENTS WITH MAJOR DEPRESSIVE OR BIPOLAR I DISORDER BY PAYER TYPE

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Abstract: Background: Major depressive disorder (MDD) and Bipolar I disorder (BD) are serious mental health conditions associated with poor clinical outcomes, daily functional impairment, higher suicide rates, and an increased number of comorbidities. , Compared to the general population, patients with MDD or BD incur substantially higher healthcare utilization and costs. They also have a higher social determinants of health (SDOH) burden.
Objective: Describe SDOH characteristics, healthcare utilization, and costs in MDD/BD patients in a managed Medicaid (MM) or commercial insurance (CM) health plan.

Methodology: A retrospective study using claims data from 2016-2018 to identify patients age 18+ newly diagnosed with MDD or BD and continuously enrolled in MM or CM for ≥6m pre/post-index. SDOH were linked at the 9-digit ZIP level.

Results: 1,958,532 MDD (49.5% CM; 50.5% MM) and 243,286 BD (25.5% CM; 74.5% MM) patients were included. BD/MDD were more likely female (65%/71% MM; 60%/68% CM) but MDD were older than BD (mean age 43-44 vs 40). Medicaid insured BD/MDD were more

likely to be untreated (26%/29% MM vs 20%/19% CM) with much higher SDOH burden, including income <$30K (35%/33% MM vs 8%/7% CM), less likely to be married (40%/42% MM vs 52%/53% CM), live in areas with no shortage of primary care (5%/5% MM vs 10%/11% CM) or mental health professionals (5%/4% MM vs 9%/10% CM), own their home (53%/55% MM vs 75%/77% CM), more likely to live alone (70%/68% vs 52%/50%), have high school education or less (82%/81% MM vs 52%/50% CM), and no vehicle (15%/14% MM vs 6%/6% CM). Medicaid insured BD/MDD were more likely to have a hospitalization (35%/30% MM vs 22%/15% CM) and emergency room visit (64%/58% MM vs 40%/31% CM) and incurred 40-47% higher annual costs for both BD/MDD ($21,467/$21,474 MM vs $15,379/$14,531 CM).

Conclusion: This analysis found Medicaid insured BD/MDD patients had higher SDOH burden compared to commercially insured patients leading to significantly higher healthcare utilization and annual costs. It is important for physicians and payers to consider SDOH factors as well as clinical factors in treating patients with BD/MDD to achieve optimal and equitable outcomes and address unmet needs and lower healthcare costs.

W34. A REAL-WORLD COMPARISON OF PATIENTS PRESCRIBED ARIPIPRAZOLE TABLET WITH SENSOR AND PATIENTS PRESCRIBED ARIPIPRAZOLE ALONE IN THE US

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Abstract: Background: Aripiprazole tablet with sensor (AS) is a drug-device system comprised of aripiprazole tablets embedded with an Ingestible Event Marker sensor to track drug ingestion, mood, rest and physical activity, and is indicated for the treatment of adults with bipolar I disorder (BP I), schizophrenia (SCZ), and major depressive disorder (MDD). Real-world comparisons of patients using AS and aripiprazole without sensor (ari) are lacking. This study describes and compares real-world characteristics, treatment patterns and healthcare resource utilization (HRU) in patients prescribed AS versus a matched ari only cohort.
Methods: This was a retrospective observational study of patients prescribed AS or ari between 01-Jun-2018 and 31-Nov-2020 (first prescription date was the index date). Eligible AS patients were those with prescribed and shipped AS, were at least 18 years of age on the index date, linked to the IQVIA claims database, had ≥1 pharmacy claim in the claims database during both the 3-months pre- and post-index periods, and had a primary diagnosis of BP I, MDD, or SCZ. Up to 10 ari patients were direct matched to each AS patient on sex, 5-year age group, index month, indication, and duration of prior ari use. Clinical characteristics and resource utilization were assessed pre- and post-index, respectively.

Results: In total 381 patients had a prescription for AS, and 54 met all inclusion criteria; 531 patients with ari were included as matched controls. 52% of AS and 51% of ari patients were age 18-35; 56% of patients were female. More AS than ari patients were from the Northeast (20% vs. 17%) and West (39% vs. 21%) regions of the US. Alcohol/drug abuse was more common in ari patients (13% vs. 4%). The proportion of patients with ≥1 inpatient visit in the AS cohort decreased from 9% pre-index to 4% post-index, and 8% to 5% in the ari cohort. The proportion of patients with emergency department (ED) visits dropped from 13% pre-index to 6% post-index in the AS cohort and 14% to 11% in the ari cohort. Post-index, the average

psychiatric non-pharmacy medical charges in the AS cohort decreased by 70% compared to a 22% decrease in the ari cohort.

Conclusions: Results from this preliminary real-world comparative analysis suggest that AS may have clinical benefit resulting in a decrease in inpatient/ED visits and psychiatric medical charges. The study is limited to patients with a prescription and shipment of AS and matched controls, however actual use is not confirmed. Future analyses conducted among a larger sample, longer follow-up, and confirmed users of AS matched to non-users allowing for analysis separately for BP I, MDD and SCZ are warranted.

W35. PREVALENCE OF PSYCHIATRIC DISORDERS AND USE OF PSYCHOTROPIC MEDICATIONS IN PATIENTS WHO UNDERWENT PHARMACOGENOMICS TESTING: FINDINGS FROM A VERY LARGE SAMPLE AND "BIG DATA" ANALYSIS

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Abstract: Background: Over the years, variations in approximately 16 genes have been identified which could affect about 80 medications (1), leading to the increased use of pharmacogenomic testing in various specialty clinical practices. Mayo Clinic has a large number of patients who underwent pharmacogenomics testing clinically or through the Mayo-Baylor RIGHT 10K Pharmacogenomic Research Study. We investigated the proportion of patients with psychiatric diagnoses and receiving psychotropic medications.

Methods: An electronic search of the Mayo Clinic Database for patients who received pharmacogenetic testing for CYP2D6 and CYP2C19 between 1/1/2010 and 01/14/2022 was conducted. Given that different diagnostic classification systems were used over the years, we searched for keywords in their lifetime diagnoses to include schizophrenia and other psychotic disorders, bipolar and related disorders, depressive, anxiety, obsessive-compulsive, trauma and stressor related, somatic symptom and related, substance use, personality, and neurocognitive disorders. Descriptive statistics were used to report the results.

Results: We identified 30,294 patients who received pharmacogenomics testing. Of these patients, 18,791 (62.0%) had a psychiatric diagnosis listed above: 13,981 (74.4%) had depressive disorders, 13,507(71.9%) had anxiety disorders, 5,603 (29.8%) had stress- and trauma-related disorders, 2,258 (12.0%) had personality disorders, 1,736 (9.2%) had bipolar and related disorders, 892 (4.7%) had obsessive-compulsive disorders, 762 (4.1%) had dementia or major neurocognitive disorder, 311(1.7%) had schizophrenia spectrum disorders, and 80 (0.4%) had substance use and addictive disorders. Of these patients, only 5,430 (28.9%) were recorded to be taking psychotropic medications.

Discussion: A high rate of 62% of patients who received pharmacogenomic testing had at least one psychiatric diagnosis. Clinically, polymorphisms of CYP2CD6 and CYP2C19 have the most relevance to psychotropic medications, with more than 10 antidepressants and 4 antipsychotics having dosing recommendations for poor and ultrarapid metabolizers(2). However, we were unable to identify the reason for testing – whether it was for clinical concerns about drug-gene interactions or whether it was part of a research study (10,000 patients, or 1/3 of our sample). The high rate could represent the widespread use of pharmacogenomic testing, and/or the high prevalence of psychiatric diagnoses. Other factors

such as insurance coverage could also play a role in the prevalence of patients receiving clinical pharmacogenomic testing. The low rate of psychotropic medication prescriptions (28.9%) could reflect that patients may not be receiving testing primarily for their psychiatric diagnosis, or the use of non-medication treatments, or that the diagnoses were historical and the symptoms were not active.

Conclusion: There is a high prevalence of psychiatric diagnoses in a large sample of patients receiving pharmacogenomic testing. However, it is difficult to draw further conclusions unless we are able to "drill down" in this big data analysis.

W36. EARLY STABILIZATION OF WEIGHT CHANGES FOLLOWING TREATMENT WITH OLANZAPINE, RISPERIDONE AND ARIPIPRAZOLE: A 12-MONTH NATURALISTIC STUDY OF FIRST EPISODE PSYCHOSIS

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Abstract: Objective: Our objective was to examine whether and when antipsychotic-induced weight gain (AIWG) in first episode psychosis (FEP) stabilizes over a 12-month exposure to the same antipsychotic in a sample of previously untreated FEP patients.

Methods: In this prospective naturalistic outcome study, 109 patients, diagnosed with non-affective or affective psychosis (DSM-IV), were treated with the same antipsychotic medication (olanzapine n=45, risperidone n=39 or aripiprazole n=25) throughout the first year of treatment. Body weight (kg) was measured, and body mass index (BMI; kg/m2) calculated, at baseline and 1, 2, 3, 6, 9 and 12 months.. Additional weight data over the 2nd year were available making extending the comparison for a 2nd year possible.

Results: Linear mixed model analysis showed a significant main effect of time (Type III test $p<0.001$) after adjusting for baseline weight values. Post-hoc pairwise comparisons showed that incremental weight changes subsequent to month 6 were insignificant, suggesting weight stabilization by month 9. No significant difference ($p = 0.243$) between groups or time x group interaction ($p=0.111$) was observed. Similar findings were obtained with BMI. A follow-up analysis, of a sub-sample who continued treatment with the same antipsychotic for an additional 12 months (n=57), confirmed weight stabilization in the 2nd year. There was no significant main effect of time ($p = 0.641$), group ($p=0.539$) or time x group interaction ($p = 0.250$).

Conclusion: AIWG occurs mostly in the first few months of treatment. Preventive interventions concurrent to SGA treatment initiation in medication naïve FEP patients might be warranted.

W37. OPIOID PRESCRIPTION DISPENSING PATTERNS AMONG PATIENTS WITH SCHIZOPHRENIA OR BIPOLAR DISORDER

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Abstract: Background: Patients with schizophrenia (SZ) or bipolar disorder (BD) may have an increased risk of opioid-related complications. We compared prescription opioid dispensing among patients with SZ or BD vs controls over 5 years (2015–2019).
Methods: This retrospective, observational study analyzed claims data from the IBM® MarketScan® Commercial and Multi-State Medicaid Databases. Individuals aged 18–64 years with ≥1 inpatient or ≥2 outpatient claims for SZ or BD diagnoses during the year preceding the analysis years 2015-2019 were included, with age- and sex-matched controls. Baseline characteristics, comorbidities, and medication use were assessed. Opioid dispensing was defined as chronic (≥70 days over a 90-day period or ≥6 prescriptions annually) or nonchronic (≥1 prescription, chronic definition not met).

Results: In 2019, the Commercial and Medicaid databases contained 4773 and 30,179 patients with SZ and 52,780 and 63,455 patients with BD, respectively. Patients with SZ or BD had a higher prevalence of comorbidities, including pain, vs controls in each analysis year. From 2015–2019, among commercially insured patients with SZ, chronic opioid dispensing proportions decreased from 6% (controls: 3%) to 2% (controls: 1%), and, for patients with BD, from 11% (controls: 3%) to 6% (controls: 2%). Chronic opioid dispensing proportions declined in Medicaid-covered patients with SZ from 15% (controls: 15%) to 7% (controls: 6%), and, for patients with BD, from 27% (controls: 12%) to 12% (controls: 5%). Among commercially insured patients with SZ, nonchronic opioid dispensing proportions decreased from 15% (controls: 16%) to 11% (controls: 11%) and, for patients with BD, from 26% (controls: 17%) to 20% (controls: 12%). In Medicaid-covered patients with SZ, nonchronic opioid dispensing proportions declined from 23% (controls: 24%) to 15% (controls: 13%), and, for patients with BD, from 32% (controls: 26%) to 25% (controls: 14%).

Discussion: From 2015–2019, chronic or nonchronic prescription opioid dispensing decreased in all groups (for patients with SZ or BD and for controls in the Commercial and Medicaid databases). The proportion of individuals dispensed chronic or nonchronic opioids each year was similar between patients with SZ vs controls but was higher for patients with BD vs controls among both commercially and Medicaid-insured populations.

W38. PATIENT VERSUS CAREGIVER AND CLINICIAN REPORTS OF COGNITIVE DIFFICULTIES IN PATIENTS WITH SCHIZOPHRENIA SWITCHING TO LONG-ACTING INJECTABLE ANTIPSYCHOTIC ARIPIPRAZOLE LAUROXIL: A POST HOC ANALYSIS

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Abstract: Background: Discrepancies between patient- and clinician-perceived cognitive functioning in people with schizophrenia have been associated with functional impairment, which can be further confounded by side effects of treatment. Perceived cognitive impairment and level of agreement between patient, clinician, and caregiver responses on the New York Assessment of Adverse Cognitive Effects of Neuropsychiatric Treatment (NY-AACENT) were assessed for patients with schizophrenia switching to the long-acting injectable antipsychotic aripiprazole lauroxil (AL).

Methods: Clinically stable adults with schizophrenia with inadequate response or intolerability to paliperidone palmitate or risperidone LAI were switched to 6-month, open-label treatment with AL (441, 662, or 882 mg monthly or 882 mg q6wk). NY-AACENT patient, caregiver, and clinician forms were completed at baseline and month 6 or early termination. Level of agreement between groups in ratings of cognitive difficulty (not present, mild, moderate, severe, extreme) in NY-AACENT domains (Working Memory, Attention/Vigilance, Verbal Learning/Memory, Visual Learning/Memory, Reasoning and Problem Solving, Speed of Processing, Social Cognition) was evaluated at baseline and last assessment using weighted kappa coefficients.

Results: Fifty-one patients (mean age, 40.6 years) were enrolled; 35 completed the study. At baseline (n=50), cognitive difficulties were most commonly rated 'not present' or 'mild' in all NY-AACENT domains by patients (58%–86% across domains), clinicians (62%–94%), and caregivers (50%–92%). Percentages reporting cognitive difficulties 'not present' or 'mild' increased at last assessment for all reporters. Weighted kappa coefficients indicated fair to substantial agreement between patients and clinicians across domains at last assessment (0.32–0.64; baseline: 0.14–0.55); patient-caregiver agreement ranged from 0.07 to 0.50 at last assessment.

Discussion: In this analysis, clinician, caregiver, and patient reports indicate reduced cognitive impairment, on average, in all NY-AACENT domains after 6 months of AL treatment. Patient-clinician agreement on magnitude of improvement was higher than patient–caregiver agreement and increased from baseline to last assessment.

W39. SYNERGY BETWEEN VMAT2 INHIBITORS AND ANTIPSYCHOTICS IN ANIMAL MODELS OF SCHIZOPHRENIA

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Abstract: Background: Vesicular monoamine transporter 2 (VMAT2) inhibitors and antipsychotics have the potential to act synergistically, given that both target dopaminergic (DA) signaling in the central nervous system. While antipsychotics block postsynaptic DA receptors, VMAT2 inhibition lowers synaptic DA levels by preventing uptake into presynaptic secretory vesicles. The effects of a coadministered antipsychotic and VMAT2 inhibitor were evaluated using animal models of schizophrenia while also assessing potential for concomitant weight gain (primary side effect of antipsychotics).

Methods: In one animal model of schizophrenia (conditioned avoidance response [CAR]), rats were dosed with an antipsychotic (risperidone or olanzapine), [+]-alpha-dihydrotetrabenazine ([+]-α-HTBZ, a potent and selective inhibitor of VMAT2), and/or vehicle and tested in 20 trials of foot-shock avoidance. Antipsychotic effects were defined as CAR suppression or "escape" (failure to avoid foot shock despite prior conditioning). Synergy was defined as CAR suppression when antipsychotic and [+]-α-HTBZ were coadministered at subthreshold doses (ie, doses with no CAR suppression when administered individually). Synergy was also evaluated based on shifts in the antipsychotic plasma concentration-response (C-R) curve (with response defined as number of escapes) with [+]-α-HTBZ coadministration. Changes in weight were assessed for olanzapine, [+]-α-HTBZ, and both combined.

Results: In the CAR model, at subthreshold doses, the mean numbers of escapes for [+]-α-HTBZ alone (0.8 [0.15 mg/kg]) and risperidone alone (0.7 [0.1 mg/kg]) were comparable to vehicle (0.4). CAR suppression increased when subthreshold doses of [+]-α-HTBZ and risperidone were combined (range, 6.5-7.1 escapes), and the results were comparable to the effects at threshold doses for [+]-α-HTBZ alone (4.8-11.4 escapes [0.3 mg/kg]) and risperidone alone (7.2-8.0 escapes [0.3 mg/kg]). This synergistic effect was not due to a drug-drug interaction, as the combination of drugs did not significantly affect the plasma concentration of either agent. Subthreshold [+]-α-HTBZ also increased the potency of risperidone for CAR suppression, as evidenced by a leftward shift of the C-R curve. Similar CAR suppression and C-R curve results were observed with the coadministration of [+]-α-HTBZ and olanzapine. Weight gain was observed after administration of olanzapine for 14 days, but coadministration with [+]-α-HTBZ did not further increase weight.

Discussion: The observed synergistic effect is consistent with a reduction of presynaptic DA resulting from VMAT2 inhibition, which in turn decreases the level of postsynaptic DA receptor blockade required for an antipsychotic effect. VMAT2 inhibition therefore mitigates the counterproductive presynaptic stimulation of DA by antipsychotics. These results suggest that combining a VMAT2 inhibitor with antipsychotic treatment will provide favorable clinical outcomes for efficacy without potentiation of a side effect of weight gain.

W40. ACETYLCHOLINE AS A REGULATOR OF DOPAMINE PATHWAYS IMPLICATED IN PSYCHOSIS: RATIONALE FOR SELECTIVE MUSCARINIC RECEPTOR AGONISTS AS CANDIDATES FOR TREATMENT OF SCHIZOPHRENIA

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Abstract: Background: All currently approved antipsychotic drugs for the treatment of schizophrenia have direct affinity for dopamine (DA) D2 receptors. Developing antipsychotics with different mechanisms of action and devoid of these common problems remains an area of high unmet medical need. Clinical trials of muscarinic receptor agonists for schizophrenia with no direct DA D2-receptor blocking activity are ongoing and, if successful, hold the potential to change the current therapeutic landscape away from reliance on direct DA D2 receptor antagonists.

Methods: A literature search was performed to identify preclinical data on muscarinic acetylcholine receptor (mAChR) regulation of DA neural networks implicated in psychosis. Evidence gathered was reviewed to develop hypotheses about the role of mAChR involvement in the regulation of psychosis pathways.

Results: Acetylcholine (ACh) plays an important regulatory role on the mesocorticolimbic DA pathway. The muscarinic receptor agonists in development for psychotic disorders have preferential functional activity at M4 receptors, including dual functional activities at both M1 and M4 receptors. Antipsychotic efficacy observed with muscarinic receptor agonists in patients with schizophrenia and psychotic symptoms associated with dementia is consistent with preclinical findings identifying M1 and M4 receptors as regulators of DA circuits associated with psychosis. A “bottom-up” hypothesis is based on ACh regulation of DA neurons in the mesocorticolimbic pathway. These DA neurons originate in the ventral tegmental area (VTA) and end at the nucleus accumbens (NAc). At both the VTA and NAc,

the presence of ACh is an excitatory neurotransmitter for DA neurons. ACh-containing neurons are the main source of ACh release, and ACh in the synaptic spaces is excitatory for DA neurons. Presynaptic M4 receptors located on ACh-containing neurons are autoreceptors, such that activation of M4 receptors by ACh acts as a "brake" to inhibit further ACh release. An M4 receptor agonist would therefore decrease ACh release, which would reduce DA hyperactivity associated with psychosis through a "bottom-up" mechanism. A "top-down" hypothesis suggests that the role of M1 receptor agonists in antipsychotic activity involves M1 receptors on cortical GABAergic interneurons that terminate on cortical glutamatergic neurons. Activation of M1 receptors on GABA interneurons stimulates GABA release, which then dampens cortical excitatory glutamatergic pyramidal cells that terminate in the VTA. Stimulation of these M1 receptors by ACh (or an M1 agonist) may ultimately provide feedback inhibition for glutamatergic excitation of downstream targets, including midbrain DA neurons. Therefore, M1 receptor agonists may decrease top-down excitatory (glutamatergic) drive onto subcortical circuits.

Discussion: A growing body of evidence supports the development of muscarinic receptor agonists as potential treatments for schizophrenia and related psychotic disorders. Although the exact mechanism is unknown, ACh regulates DA signaling specifically within DA networks associated with psychosis. Muscarinic receptor agonists may represent a new therapeutic class that may extend beyond the limitations associated with direct DA D2-based antipsychotics.

W41. A SINGLE-DAY, TWO-INJECTION START REGIMEN FOR ARIPIPRAZOLE ONCE-MONTHLY IN PATIENTS WITH SCHIZOPHRENIA OR BIPOLAR I DISORDER WHO HAVE BEEN STABILIZED ON ORAL ARIPIPRAZOLE

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Abstract: Background: Long-acting injectable antipsychotic formulations, such as aripiprazole once-monthly 400 mg (AOM 400), can increase medication adherence, thereby improving long-term outcomes compared with oral formulations (1). In order to maintain therapeutic drug concentrations during the initiation of a long-acting injectable antipsychotic, start regimens may require that two injections be given on different days, or may consist of one injection with a period of concurrent oral antipsychotic. A one-injection start regimen for AOM 400 in patients with schizophrenia or bipolar I disorder requires 14 days of oral aripiprazole 10–20 mg, or other oral antipsychotic, to maintain therapeutic drug concentrations during initiation (2). Among patients at risk of non-adherence, it may be preferable to maintain therapeutic plasma concentrations from Day 1 without reliance on concurrent oral dosing. The aim of this study was to utilize population-pharmacokinetic (popPK) modeling to identify an alternative AOM start regimen that does not require 14 days of concurrent oral aripiprazole, for patients who are already stabilized on oral aripiprazole.

Methods: A previously developed and validated popPK model for characterizing aripiprazole plasma concentrations following oral or gluteal administration was expanded to include deltoid administration. The final model included 8,214 aripiprazole concentrations from 817 adults (765 patients with schizophrenia and 52 healthy participants). Various single-day initiation regimens were simulated with the goal of identifying a regimen that would a) reduce reliance on concurrent oral aripiprazole at initiation; b) maintain aripiprazole concentrations within the

established therapeutic window (94.0–534.0 ng/mL) (2); and c) achieve plasma concentrations (median, 25th–75th percentiles, and 5th–95th percentiles) similar to the one-injection start regimen. Simulations were performed for patients who were currently stabilized on oral aripiprazole.

Results: The alternative start regimen consisted of two AOM 400 injections at separate gluteal and/or deltoid injection sites, plus a single dose of oral aripiprazole 20 mg, all on Day 1. Among patients who were already stabilized on oral aripiprazole, this two-injection start regimen resulted in a simulated median aripiprazole plasma concentration that reached therapeutic levels on the first day and remained within the therapeutic window for the duration of the 28-day simulation. The simulated median, 25th–75th percentiles, and 5th–95th percentiles of aripiprazole plasma concentration for the two-injection start regimen were generally comparable to those of the one-injection start regimen (i.e., single injection plus 14 days of oral aripiprazole).

Conclusion: Among patients stabilized on oral aripiprazole, simulations using a popPK model indicate that a two-injection plus single dose of oral aripiprazole 20 mg start regimen for AOM achieves desired therapeutic aripiprazole plasma concentrations on the first day of treatment, which are maintained over the entire dosing interval and are similar to those of the one-injection start regimen. Thus, these data support the use of the two-injection start regimen in clinical practice to achieve similar clinical effectiveness and a comparable safety and tolerability profile to the one-injection start regimen, with reduced risk of non-adherence during initiation.

W42. MODELING REACTION TIME DISTRIBUTIONS INCREASES THE STATISTICAL POWER OF COGNITION TESTING

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Abstract: Background: Drug development clinical trials often include tests of cognition to assess participants' cognitive performance during individual testing sessions. The testing sessions, designed to measure cognitive domains (such as psychomotor function, attention, visual learning and working memory) collect subjects' response data as reaction time (RT) and accuracy, and report subject-level metrics (eg, mean log-RT) that are used to quantify cognition. We examined whether current approaches using mean log-RT to reduce an individual subject's performance data results in information loss relative to other approaches that more fully model individual subject's RT distributions, and thereby reduce the power to test specific hypotheses of cognition.

Methods: Reaction times were extracted from subject-level performance data during computerized cognitive tests (Cogstate tests of Detection, Identification, One Card Learning, One Back). Data from 7 drug development clinical trials (schizophrenia, bipolar depression, N=1,890 subjects) were compared to normative data obtained from healthy subjects (N=7,108). Parameters describing subject-level RT distributions were obtained by Bayesian estimation of population models using either ex-Gaussian or Wiener diffusion model residual likelihoods. Information loss was examined by comparing the ability of single parameter mean log RT to reject null hypotheses of cognition versus the parameters of RT distribution models (ex-Gaussian, Wiener Diffusion Model). Here we evaluated the sensitivity and specificity of the

discrimination (AUC) between subjects with schizophrenia or bipolar depression versus healthy subjects.

Results: An individual subject participating in a cognitive test session performed approximately 170-180 responses across the 4 tests. Subject-level RT distributions were well-described by ex-Gaussian and Wiener diffusion models, resulting in parameter estimates for each subject. The sensitivity/specificity of cognitive performance data alone to classify adults with schizophrenia or bipolar depression from healthy subjects was improved for each task. For example, correctly categorizing disease status was improved for the diffusion model versus mean log-RT, with AUC values of 81% vs. 77% for Identification, 78% vs. 69% for One Card Learning, and 74% vs. 62% for Detection.

Discussion: Analyzing subject-level responses during cognitive testing recovers information lost by mean log-RT, the latter being most typically used in analyses of cognitive performance data. The ability to separate individuals with schizophrenia or bipolar depression from healthy controls using cognitive domains was improved by 10-13% across cognition tasks. In conclusion, modeling subject-level RT distributions is superior to the typical use of single performance metrics and improved analysis methods may increase the statistical power to test specific hypotheses of cognition in clinical trials.

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W43. HEALTHCARE RESOURCE USE DECREASES FOLLOWING INITIATION OF ARIPIPRAZOLE 400MG LONG-ACTING INJECTABLE: A REAL-WORLD ELECTRONIC HEALTH RECORD DATABASE STUDY

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Abstract: Background: Prior clinical trial and claims database analyses have found healthcare resource use (HCRU) decreases following initiation of long-acting injectable aripiprazole 400mg (AOM400). This study examined changes in HCRU following initiation of AOM400 using real-world electronic health record (EHR) data from behavioral health practices in the US.

Methods: The NeuroBlu database (NeuroDB; 2014-2020) was used to identify adult (>18 years) patients with schizophrenia (SCZ) or bipolar I disorder (BP-I) with >1 prescription for AOM400. The index date was date of first AOM400 prescription in the dataset. Frequency of psychiatric-specific inpatient (IP) hospitalization and emergency department (ED) visits, average length of stay (LOS), and 30-day readmission rates were compared in a mirror-type analysis of 3, 6, 9 and 12 months pre- and post-index date. Pre/post HCRU was compared using a one-sided Wilcoxon signed-rank test for paired data. The 30-day readmission rate from the pre-index period was compared to the readmission rate from the post-index period using a paired t-test.

Results: A total of 222 patients with SCZ and 129 with BP-I taking AOM400 were identified. Among patients with SCZ (mean age 36.8; 37.8% female), monthly IP hospitalization rates per

1,000 patients were significantly lower in the post-AOM400 period than the pre-AOM period (116 vs. 215 at 3-months; 99 vs. 152 at 6-months; 82 vs. 126 at 9-months; 75 vs. 115 at 12-months; p<0.001 for all), as were monthly ED visit rates (23 vs. 42 at 3-months; 20 vs. 28 at 6-months; 15 vs. 23 at 9-months; 13 vs. 24 at 12-months; p<0.001 for all). LOS was also significantly lower at 3-, 9- and 12-months post-AOM400 than the same time periods pre-AOM400, but the 6-month LOS was not significant. The per-patient 30-day readmission rate also decreased at 3 (2.8% vs. 7.3%, p=0.002), 6 (4.0% vs. 8.1%, p=0.006), 9 (4.1% vs. 9.2%, p=0.001) and 12 (4.8% vs. 9.9%, p=0.001) months.

Among patients with BP-I (mean age 37.5; 56.6% female), monthly IP hospitalization rates per 1,000 patients were significantly lower in the post-AOM400 period than the pre-AOM period (160 vs. 271 at 3-months; 121 vs. 189 at 6-months; 97 vs. 152 at 9-months; 89 vs. 135 at 12-months; p<0.001 for all), as were monthly ED visit rates (21 vs. 41 at 3-months; 10 vs. 25 at 6-months; 7 vs. 16 at 9-months; 5 vs. 14 at 12-months; p<0.001 for all). LOS was also significantly lower (p<0.001) at all time points post-AOM400 than the same time periods pre-AOM400. The per-patient 30-day readmission rate also decreased at 3 (4.0% vs. 8.7%, p=0.031), 6 (4.7% vs. 10.7%, p=0.007), 9 (6.2% vs. 11.7%, p=0.024) and 12 (6.9% vs. 12.8%, p=0.012) months.

Conclusions: Data from real-world behavioral health EHRs indicated that treatment with AOM400 in patients with either SCZ or BP-I had a positive effect on HCRU outcomes within 12 months after treatment initiation. These findings are supportive of earlier analyses from different data sources.

W44. HIPPOCAMPAL BLOOD-BRAIN BARRIER AND PERIPHERAL ENDOTHELIAL DYSFUNCTION IN SCHIZOPHRENIA PATHOPHYSIOLOGY AS A PUTATIVE VASCULAR DISEASE MECHANISM

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Abstract: Schizophrenia spectrum disorder (SSD) is one of the most severe forms of mental illness, yet mechanisms remain unclear. Epidemiological evidence suggests increased vascular complications in SSD independent of lifestyle and medication, pointing to disease-specific pathology. Endothelial cell contributions to blood-brain barrier (BBB) compromise may influence neurovascular unit and peripheral vascular function, and we hypothesize that downstream functional and structural abnormalities may be explained by endothelial deficits. Postmortem human hippocampus sections (n=27 controls, n=25 SSD) were obtained from the NIH NeuroBioBank and Maryland Brain Collection, that were age, gender, race, and postmortem interval (PMI) frequency-matched to interrogate BBB integrity. Leakage phenomena was observed using a secondary IgG-only (Vector Laboratories, 1:250) staining technique, to demonstrate endogenous IgG extravasation, a marker of BBB compromise. IgG leak was quantified using unbiased stereology (MBF Bioscience, VT) to measure the areas of IgG immunoreactivity under blinded analysis. A ratio was then calculated of fraction of leak in the tissue compared to overall tissue area. To translate findings to in vivo endothelial testing methods, gold standard clinical strategies were employed, using post-occlusive reactive

hyperemia with simultaneously administered ultrasonographic brachial artery reactivity testing (Philips iE33 Ultrasound, Germany) of the macrovascular endothelial cell response in n=31 community controls and n=34 SSD participants. Flow-mediated dilation was captured in the brachial artery by calculating the percent dilation at one-minute post-occlusion compared to baseline. Analyses was corrected for multiple comparisons using false discovery rate with $q<0.05$ where applicable, and age and sex covaried.

Analysis of our immunohistochemistry data demonstrated a significantly higher incidence of IgG leak in schizophrenia patients compared to controls ($t50=2.8$, $p<0.008$). Further, BBB permeability was significantly higher in old schizophrenia patients compared to controls ($t39=2.5$, $p<0.01$). Male schizophrenia patients also demonstrated a significant increase in IgG permeability compared to control males ($t51=2.7$, $p<0.009$). The extravasated IgGs also demonstrated selective immunoreactivity for neurons in distinct hippocampal compartments and neuronal subpopulations of cell types. Post-occlusive reactive hyperemia experiments were performed in the peripheral vascular compartments to translate the findings of central endothelial cell dysfunction in the context of BBB permeability. Group differences were significantly present amongst the peripheral endothelial vascular measures shown using flow-mediated dilation of the brachial artery, a gold-standard cardiovascular measurement. Flow-mediated dilation was significantly reduced in the SSD group compared to controls, indicated endothelial damage (12% vs 8%, $p=0.02$), after covarying age, sex, and body-mass index.

Psychoneuropathology within SSD may be mediated by endothelial function within the various vascular compartments, including that of the brain. These results provide evidence for robust explorations of how endothelial dysfunction underserves impairments in neural correlates of SSD. The two-hit hypothesis suggested from these experiments implicates aberrant immunologic profiles with neuron-specific binding properties in the context of endothelial deficits in cerebrovascular and blood-brain barrier compartments. Moreover, this hypothesis may also account for vascular comorbidities unattributed to common confounds that exist in this population.

W45. THE MIND AFTER MIDNIGHT: NOCTURNAL WAKEFULNESS INCREASES RISK OF DEATH BY SUICIDE AND HOMICIDE

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Abstract: Introduction: During the night, elevated sleep propensity and circadian changes in brain function work together to suppress cognition and promote sleep. By contrast, interrupted sleep may lead to nocturnal wakefulness, in which sleep- and circadian-dependent disturbances in mood, reward processing, and executive function combine to produce the Mind after Midnight, a hypothetical state which increases an individuals' risk for dysregulated and violent behaviors. Evidence for the Mind after Midnight was first presented as a wakefulness-adjusted nocturnal peak in population suicide risk, but these results have not yet been replicated or extended to other behaviors.

Methods: A total of 77,784 suicides and 48,486 homicides with known time of fatal injury were extracted from the National Violent Death Reporting System (NVDRS) for the years 2003 to 2017. These data were then weighted by the estimated proportion of the population that was awake at each hour as derived from the American Time Use Survey (ATUS) for the same years. Suicides and homicides were tabulated by clock hours, age, sex, race, and ethnicity, and counts were modeled using robust Poisson regression with hourly population wakefulness entered as an offset term, thus producing hourly incident risk ratios.

Results: A comparison of analyses between previously reported data (2003 to 2010) and new data (2011 to 2017) showed a consistently elevated risk of suicide at night (midnight to 6AM). After combining all years and adjusting for population wakefulness, a significant increased risk for suicide emerged between 11PM and 5AM, with a 4.61-fold peak at 3AM (IRR: 4.61 [4.11-5.16]). Adjusting for age, sex, race, and ethnicity attenuated, but did not alter these results. This nocturnal risk for suicide was further elevated for those with bipolar disorder or a blood alcohol level greater than 0. Similarly, the incident risk for death by homicide was elevated between 10PM and 5AM compared to the 24-hour average, with the highest risk between 2AM (IRR: 8.25 [6.62-10.3]) and 3AM (IRR: 7.22 [6.04-8.64]). Moreover, the adjusted risk of dying by homicide was significantly greater at night for those with a BAL≥80mg/dl, such that the risk at 2AM was 13.8-fold greater than the 24-hour average (IRR: 13.8 [10.6-18.1]).

Conclusion: Fifteen years of data from across the United States show an increased nocturnal risk for death by suicide or homicide that peaks at 2-3AM. Nocturnal wakefulness remains a significant time-of-day risk factor for suicide, and suicide prevention efforts may benefit from interventions to reduce nocturnal wakefulness and/or an increase in prevention resources at this time. Unlike suicide victims, homicide victims do not choose when to die, but neurophysiological changes consistent with the Mind after Midnight may promote risky behaviors or put victims in more dangerous circumstances than they would be otherwise. Future research should examine sociodemographic, clinical, and circadian risk factors for death by homicide, as well as examine time-of-day patterns in other violent crimes.

W46. PREGNANCY OUTCOMES AFTER FIRST TRIMESTER EXPOSURE TO BUSPIRONE: PROSPECTIVE LONGITUDINAL OUTCOMES FROM THE MGH NATIONAL PREGNANCY REGISTRY FOR PSYCHIATRIC MEDICATIONS

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Abstract: Purpose: Anxiety disorders are prevalent among women of reproductive age. Buspirone is commonly utilized to treat anxiety disorders, although to date, systematic evidence pertaining to the reproductive safety of buspirone in humans has been lacking. Therefore, we sought to provide preliminary data from the MGH National Pregnancy Registry for Psychiatric Medications about the risk of first trimester use of buspirone and major malformations after in utero exposure.

Methodology: The Massachusetts General Hospital National Pregnancy Registry for Psychiatric Medications (NPRPM) enrolls pregnant women with psychiatric disorders and ascertains pregnancy and neonatal outcomes prospectively with longitudinal follow-up, with

the primary outcome being major congenital malformations after first trimester medication exposure. Women are interviewed twice during pregnancy and at 12 weeks postpartum. Cases of first trimester buspirone use were extracted from the database of women enrolled in the registry. Data were assessed as a rigorously ascertained case series to determine whether there appeared to be a signal for teratogenicity among those exposed to buspirone. The primary outcome was ascertained by maternal postpartum interview and medical record review. In the registry, all malformations are reviewed by a dysmorphologist blinded to medication exposure.

Results: As of January 6, 2022, N=97 women with first trimester use of buspirone had been enrolled in the MGH Pregnancy Registry. Of these women, 68 were evaluable and eligible for analysis (with known outcomes pertaining to the presence or absence of major congenital malformations among infants). Four women had twins, resulting in 72 infants. Among these, there were no malformations present among the sample.

Importance: Despite a small sample size, these preliminary data represent the only prospectively ascertained sample of infant outcomes after first trimester exposure to buspirone, and where outcomes were verified with original source materials. No major malformations were observed among N=72 infants from 68 pregnancies. The rigorous prospective ascertainment of outcomes is a strength of the study. Future analyses are planned that will include larger numbers of women with exposures to buspirone and comparison with control groups matched for demographic and diagnostic variables.

W47. ZURANOLONE SAFETY AND EFFICACY IN PATIENTS WITH MAJOR DEPRESSIVE DISORDER (MDD) AND METABOLIC COMORBIDITIES: RESULTS FROM THE PHASE 3 SHORELINE STUDY

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Abstract: Background: Patients with major depressive disorder (MDD) and metabolic comorbidities may face additional treatment challenges. Metabolic adverse events (e.g. weight gain, hyperglycemia, hyperlipidemia) associated with most standard-of-care antidepressants (ADTs) can be treatment-limiting for patients with pre-existing metabolic disease. Zuranolone (ZRN) is an investigational, oral, neuroactive steroid and GABAA receptor positive allosteric modulator in clinical development as a once daily, 2-week treatment of MDD. SHORELINE (NCT03864614) is an ongoing, open-label study evaluating the safety, tolerability, and need for repeat treatment courses with ZRN through 1 year in adults with MDD.

Methods: Adults with MDD (aged 18–75 y; 17-item Hamilton Rating Scale for Depression total score [HAMD-17] ≥20) were enrolled in 1 of 2 cohorts: ZRN 30 mg (ZRN30) or 50 mg (ZRN50). HAMD-17 responders (≥50% reduction from baseline) at Day 15 are eligible to continue in study and are assessed every 2 weeks for the need of repeat treatment courses. Primary endpoint is safety/tolerability; secondary endpoints include HAMD-17 response, HAMD-17 remission (HAMD-17 ≤7), and need for repeat treatment courses. Metabolic comorbidity was identified by coded terms in patient history: hyperlipidemia, hypercholesterolemia, type 1 or 2 diabetes, glucose tolerance impaired, hypertriglyceridemia, dyslipidemia, metabolic syndrome, and/or diabetic dyslipidemia.

Results: Of 924 patients (ZRN30 725; ZRN50 199) with an opportunity to complete 1-year follow-up in SHORELINE by the Nov 2021 data cut, 253 (27.4%) had ≥1 metabolic comorbidity (ZRN30 197/725 [27.2%]; ZRN50 56/199 [28.1%]). Baseline demographics (ZRN30/ZRN50 vs overall population): mean age 52.2/52.4 vs 45.0/45.0 y; Hispanic 30.5%/30.4% vs 24.3%/22.1%; ADT use 54.3%/53.6% vs 41.9%/41.2%; mean kg/m2 BMI 34.0/31.3 vs 30.2/29.3. At Day 15 of treatment cycle 1 (Days 1–28), mean change from baseline in HAMD-17 (ZRN30/ZRN50) was −14.4/−16.2 in metabolic comorbidity subgroup vs −15.2/−16.0 overall; HAMD-17 response rate was 64.5%/67.9% vs 69.7%/74.9%; and HAMD-17 remission rate was 35.0%/39.3% vs 38.1%/40.2%. Of patients with metabolic comorbidities who responded to and completed treatment cycle 1 (ZRN30/ZRN50 n = 123/38), 55.3%/57.9% (vs 42.9%/54.8% overall) did not need repeat treatment courses during their time in the study (up to 1 year). Of patients with metabolic comorbidities, 54.8% (108/197; ZRN30)/57.1% (32/56; ZRN50) had ≥1 treatment-emergent adverse event (TEAE) in treatment cycle 1 vs 50.8%/59.3% overall; most (95.4% [103/108]/93.8% [30/32]) had mild/moderate TEAEs (vs 95.4%/89.0% overall). In this subgroup, common (>5%) TEAEs included headache, somnolence, dizziness, diarrhea, upper respiratory infection, dry mouth, and sedation (similar to overall); TEAEs of interest during treatment cycle 1 included hyperglycemia (n = 1), elevated blood triglycerides (n = 1), and weight gain (n = 0). TEAEs starting in treatment cycle 1 (ZRN30/ZRN50) led to study drug discontinuation in 1.0%/7.1% of patients (vs 2.2%/6.5% overall) and to study withdrawal in 2.0%/5.4% (vs 2.6%/6.0%).

Conclusions: ZRN was generally well tolerated in adults with MDD and metabolic comorbidities in SHORELINE, to date, with similar safety and efficacy outcomes vs the overall study population. The data support further development of ZRN as a potential treatment for adults with MDD, including those with metabolic comorbidities.

W48. EFFICACY AND SAFETY OF ZURANOLONE CO-INITIATED WITH AN ANTIDEPRESSANT IN ADULTS WITH MAJOR DEPRESSIVE DISORDER: RESULTS FROM THE PHASE 3, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED CORAL STUDY

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Abstract: Depression is a leading cause of disease burden and can lead to serious long-term adverse health effects (1, 2). Zuranolone is an oral neuroactive steroid and positive allosteric modulator of GABAA receptors under investigation as part of the LANDSCAPE clinical development program as a once-daily (QD), 2-week therapy for major depressive disorder (MDD). In previously completed studies, zuranolone was generally well tolerated in adults with MDD, either as monotherapy or concomitantly with antidepressant therapy (ADT), with a reduction in depressive symptoms as assessed by change from baseline (CFB) in the 17-item Hamilton Rating Scale for Depression total score (HAMD-17) observed as early as Day 3 and sustained at all measured time points through Day 42. The CORAL study was the first study

to evaluate early (Day 3) efficacy and safety of zuranolone 50 mg co-initiated with a standard-of-care (SOC) ADT vs placebo co-initiated with a SOC ADT in adults with MDD.
This Phase 3 randomized, double-blind, placebo-controlled study (NCT04476030) enrolled patients (aged 18–64 years) with MDD and baseline HAMD-17 ≥24. Patients were randomized 1:1 to blinded zuranolone 50 mg:placebo QD, each co-initiated with an open-label SOC ADT for a 14-day treatment course; patients then continued on an ADT alone for another 28 days. SOC ADTs included selective serotonin reuptake inhibitors or serotonin-norepinephrine reuptake inhibitors. The primary endpoint was CFB in HAMD-17 at Day 3; the key secondary endpoint was treatment effect as measured by CFB in HAMD-17 over the blinded treatment period using equal weights for scheduled visits at Days 3, 8, 12, and 15. Safety, including treatment-emergent adverse events (TEAEs), was assessed.

A total of 425 patients received either zuranolone 50 mg co-initiated with ADT (210) or placebo co-initiated with ADT (215). Baseline demographics were balanced between treatment arms. The primary endpoint at Day 3 was met: patients who received zuranolone co-initiated with ADT showed a statistically significant reduction in depressive symptoms as assessed by CFB in the HAMD-17 (least squares [LS] mean standard error [SE]: −8.9 [0.39]; vs those who received placebo co-initiated with ADT (LS mean [SE]: −7.0 [0.38]; P=0.0004). The key secondary endpoint, the treatment effect over the treatment period, was also met; a statistically significant improvement in depressive symptoms as assessed by CFB in HAMD-17 over the blinded treatment period was observed for patients who received zuranolone co-initiated with ADT vs those who received placebo co-initiated with an ADT (−11.7 [0.40] vs −10.1 [0.39]; P=0.0054). Overall, TEAEs were reported in 157 (74.1%) patients in the zuranolone co-initiated with ADT group compared to 143 (65.6%) patients in the placebo co-initiated with ADT group. TEAEs that were ≥10% in either treatment group (zuranolone co-initiated with an ADT vs placebo co-initiated with an ADT) included somnolence (18.4% vs 8.3%), dizziness (13.2% vs 7.3%), headache (11.8% vs 14.7%), and nausea (9.0% vs 23.4%).

Consistent with previously completed studies of zuranolone, in which a reduction in depressive symptoms was observed as early as Day 3, zuranolone co-initiated with a SOC ADT resulted in a statistically significant improvement in depressive symptoms as assessed by HAMD-17 at Day 3 in adults with MDD compared with placebo co-initiated with a SOC ADT. Zuranolone 50 mg co-initiated with an ADT was generally well tolerated with no new safety signals.

W49. LUVADAXISTAT, AN INVESTIGATIONAL D-AMINO ACID OXIDASE INHIBITOR, WAS ASSOCIATED WITH SIGNALS OF EFFICACY IN COGNITIVE IMPAIRMENT ASSOCIATED WITH SCHIZOPHRENIA BUT NOT NEGATIVE SYMPTOMS: RESULTS FROM THE INTERACT STUDY

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Abstract: Background: Deficits in glutamatergic signalling are thought to play an important role in the negative symptoms and cognitive impairment associated with schizophrenia (CIAS). The D-amino acid oxidase inhibitor luvadaxistat may increase glutamatergic

neurotransmission by elevating the levels of D-serine, an NMDA receptor co-agonist. Luvadaxistat has been shown to improve social interaction and cognition in rodent behavioral models. Here we report efficacy and safety results from INTERACT, a phase 2 study of adjunctive luvadaxistat in adults with schizophrenia (NCT03382639).
Methods

INTERACT was a randomized, placebo-controlled, dose range finding study that included participants with symptomatically stable schizophrenia, a baseline Brief Negative Symptom Scale score of ≥28 (items 1–3; 5–13), and who were receiving primary antipsychotic therapy. The study comprised a 28-day screening period, a 14-day single-blind placebo run-in period and a 12-week double-blind treatment period.

The primary endpoint was the 12-week change from baseline in the Positive and Negative Syndrome Scale – Negative Symptom Factor Score (PANSS NSFS). Secondary endpoints included the changes from baseline (CFB) to Week 12 in the Brief Assessment of Cognition in Schizophrenia (BACS) composite score and the Schizophrenia Cognition Rating Scale (SCoRS) score, a test battery and an interview-based tool that assess cognitive functioning. Safety endpoints included assessment of treatment-emergent adverse events (TEAEs).

Results: Of the 256 participants randomized 3:2:2:2 to receive placebo, luvadaxistat 50 mg, 125 mg and 500 mg, respectively, 228 (89.1%) completed the study. Baseline demographics and characteristics were similar across treatment groups.

No significant improvements in PANSS NSFS versus placebo were observed with luvadaxistat 50 mg, 125 mg or 500 mg at Week 12 ($p = 0.426$, $p = 0.362$ and $p = 0.808$, respectively). The least squares (LS) mean CFB to Week 12 in PANSS NSFS were –3.3 (95% confidence interval [CI]: –4.3, –2.2), –3.4 (95% CI: –4.4, –2.3) and –2.5 (95% CI: –3.6, –1.5) with luvadaxistat 50 mg, 125 mg and 500 mg, respectively, and –3.1 (95% CI: –4.0, –2.3) with placebo.

Significant improvements were observed with luvadaxistat 50 mg versus placebo in the BACS composite score and the SCoRS interviewer total score (nominal $p = 0.031$ and $p = 0.011$, respectively), but not with luvadaxistat 125 mg or 500 mg. For the BACS composite score, LS mean CFB to Week 12 were 4.6 (95% CI: 2.7, 6.5) with luvadaxistat 50 mg and 2.3 (95% CI: 0.7, 3.9) with placebo. For the SCoRS interviewer total score, LS mean CFB to Week 12 were 3.8 (95% CI: –5.3, –2.3) with luvadaxistat 50 mg and –1.6 (95% CI: –2.9, –0.3) with placebo.

TEAEs occurring in ≥5 participants were headache, insomnia and weight gain, which occurred at similar frequencies in the four treatment groups. Two participants taking luvadaxistat had drug-related TEAEs of psychiatric disorders resulting in discontinuation.

Discussion: Luvadaxistat did not significantly improve negative symptoms of schizophrenia at the three doses studied. However, the 50 mg dose showed a signal of efficacy in the BACS composite score and the SCoRS interviewer total score vs placebo.

The efficacy signal seen with luvadaxistat 50 mg warrants further clinical research in participants diagnosed with CIAS. In line with past clinical experience, luvadaxistat was generally well tolerated.

Study funded by Takeda Pharmaceutical Company, Ltd and Neurocrine Biosciences, Inc.

W50. DARIGABAT REDUCES ACUTE PANIC AND FEAR SYMPTOMS INDUCED BY CO2 INHALATION IN HEALTHY PARTICIPANTS

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Abstract: Background: There is substantial nonclinical evidence that α2/3 subunit–containing GABAA receptors are associated with the anxiolytic effects of benzodiazepines, and that the α1 subtype is responsible for sedative properties. Darigabat was rationally designed to selectively enhance the effect of GABA at α2/3/5 GABAA receptors, while sparing activity at α1, and is in development for the treatment of neurological and psychiatric disorders. To characterize the potential panicolytic effect of darigabat, CO2 inhalation was used as a model of panic and fear in healthy participants. The model is sensitive to pharmacological manipulation by anxiolytics, allowing investigation of pharmacodynamic effects of drugs in early clinical development.

Methods: This randomized, double-blind, placebo- and active-controlled trial assessed the panicolytic efficacy of multiple doses of darigabat on panic and fear symptoms evoked by CO2 inhalation in healthy participants. Only individuals sensitive to the anxiogenic effects of the 35% CO2 double-breath inhalation at screening were eligible for randomization. In this two-period, two-sequence partial crossover design, each eligible participant was randomized to receive either placebo and one of three active treatments in 3 separate cohorts (n=18-20/cohort) for 8 days: cohort 1 darigabat 25 mg BID, cohort 2 alprazolam 1 mg BID, and cohort 3 darigabat 7.5 mg BID. Darigabat was titrated to achieve the target maintenance dose on Day 5. On Day 8 of each crossover period, a CO2 challenge was performed at 3 hours after dosing. Alprazolam was used as a positive control to establish assay sensitivity. With each participant's placebo period serving as their own control, the change in panic and fear symptoms measured before and immediately after CO2 inhalation using the Panic Symptom List-IV total score (PSL-IV; primary endpoint) and fear visual analog scale (VAS Fear; secondary endpoint) were assessed. While the trial was not prospectively designed for formal hypothesis testing with statistical power, nominal P values for each comparison are presented. Pharmacokinetic samples were obtained at 2 and 4 hours after dosing.

Results: In the primary outcome measure PSL-IV total score on Day 8, the darigabat 7.5-mg and 25-mg BID treatment groups demonstrated a 3.9-point (P=0.036) and 4.5-point (P=0.008) improvement versus placebo, respectively. In the secondary outcome measure, VAS Fear, the 7.5-mg and 25-mg BID treatment groups demonstrated a 12.8-point (P=0.026) and 7.8-point (P=0.282) improvement versus placebo, respectively. Compared with placebo, alprazolam 1 mg BID exhibited outcomes in line with expectations, with placebo-adjusted improvements of 1.6-points (P=0.286) and 0.9-points (P=0.876) on PSL-IV total score and VAS Fear on Day 8, respectively. Plasma concentrations of darigabat were consistent with previous trials and estimated to achieve approximately 50% and 80% receptor occupancy at α2-containing GABAA receptors at 7.5 mg and 25 mg BID, respectively. Darigabat was generally well tolerated.

Conclusions: This trial demonstrated the panicolytic potential of darigabat, the rationally designed α2/3/5 receptor subtype-selective GABAA receptor positive allosteric modulator, based on reduction of acute panic and fear symptoms following 8 days of dosing in a validated,

experimental clinical panic model in healthy participants. We believe these data warrant the further evaluation of darigabat in patients with anxiety disorders.

W51. MK-8189, A NOVEL PDE10A INHIBITOR FOR THE TREATMENT OF SCHIZOPHRENIA

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Abstract: Background: MK-8189 is an investigational selective PDE10A inhibitor for treating schizophrenia that reduces striatal D2 and increases D1 and NMDA signaling. In preclinical models, it has broad antipsychotic efficacy and a beneficial metabolic profile. Preclinical and phase 1 healthy volunteer enzyme occupancy studies with the specific PDE10A tracer [11C]MK-8193 established target engagement and guided dose selection for evaluation of MK-8189 in clinical trials. We report here on results from the initial proof-of-concept trial of MK-8189 for treating schizophrenia.

Methods: The trial was a randomized, double-blind, inpatient, Phase 2a study (NCT03055338) in adults experiencing an acute episode of schizophrenia. Participants were randomized 2:2:1 to once-daily MK-8189 12mg (controlled-release formulation), placebo, or risperidone 6mg (active-control) for 4-weeks. Efficacy was assessed by the PANSS.

Results: The number of treated patients was 90 for MK-8189, 89 for placebo, and 45 for risperidone. MK-8189 demonstrated a trend towards improvement versus placebo for change-from-baseline in PANSS total score after 4-weeks (difference = -4.7 [95% CI: -9.8,0.5], p=0.074), narrowly missing the superiority criterion of $p \leq 0.05$. MK-8189 had a more pronounced effect on PANSS positive subscale score (difference versus placebo = -2.2 [95% CI: -3.8,-0.5], $p<0.05$). The active-control risperidone was superior to placebo on PANNS total score (difference = -7.3 [95% CI: -14.0,-0.6], p=0.033), demonstrating assay sensitivity, while MK-8189 and risperidone did not significantly differ (difference = 2.6 [95% CI: -4.0,9.2], p=0.440). MK-8189 was generally well-tolerated and discontinuation of treatment due to an adverse event was low (<10%). Adverse events that occurred more often with MK-8189 than placebo included akathisia, nausea, dystonia, vomiting and back pain. MK-8189 was associated with improvements in metabolic parameters. Compared with placebo, MK-8189 reduced body weight (difference = -2.89kg [95% CI: -4.09,-1.69], $p<0.001$) while risperidone increased weight (difference = 3.44kg [95% CI: 1.67,5.21], $p<0.001$).

Conclusion: These findings suggest that PDE10A inhibition via MK-8189 could represent a new treatment approach for schizophrenia. Based on the signal detected in the phase 2a study, a phase 2b study (NCT04624243) is underway to evaluate a broader dose range of MK-8189.

W52. TREATMENT PATTERNS AND ECONOMIC BURDEN ASSOCIATED WITH FIRST VERSUS SUBSEQUENT ADJUNCTIVE ATYPICAL ANTIPSYCHOTIC USE IN PATIENTS WITH MAJOR DEPRESSIVE DISORDER

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Abstract: Introduction: Adjunctive therapy with atypical antipsychotics (AAs) is a treatment option for patients with major depressive disorder (MDD) who do not adequately respond to initial antidepressant monotherapy. Patients with MDD often cycle through multiple treatments prior to receiving an adjunctive AA; however, the patterns of treatment and healthcare costs associated with delayed adjunctive AA initiation for MDD are unknown. The study objectives were to compare treatment patterns and mental health (MH)-related healthcare resource utilization (HRU) and costs between patients with first versus subsequent initiation of AA adjunctive therapy for MDD.

Methods: This retrospective cohort study used claims data from the IBM® MarketScan® Commercial Database. Adults newly diagnosed with MDD (index date defined as the first MDD diagnosis) with ≥6 months of continuous enrollment pre-index (baseline) and ≥3 months post-index and initiated MDD therapy within 60 days post-index were selected. Patients who received AA adjunctive therapy were categorized as first AA initiator (ie, first adjunctive therapy included an AA) or subsequent AA initiator (ie, index AA initiated after other adjunctive regimen). Lines of therapy (LOTs) were defined as continuous treatment periods of monotherapy or adjunctive therapy regimens (AA or non-AA [antidepressant combination, other] adjunctive treatments) and compared using multivariable regression models. HRU was compared using rate ratios estimated from multivariable Poisson regression models. Mean healthcare cost differences were compared using multivariable regression models. HRU and costs were reported per patient per year (PPPY).

Results: A total of 508,830 patients with MDD met selection criteria; <5% (n=20,797; 13,824 first and 6,973 subsequent AA initiators) of patients with MDD received AA adjunctive therapy over a mean follow-up of 1.9 years (standard deviation=1.2). Baseline characteristics were generally similar between cohorts. Mean time to AA adjunctive therapy initiation was significantly longer for subsequent AA initiators compared with first AA initiators (362 days vs 151 days; P<.0.05). Of first AA initiators, 80% received their index AA in their first 2 LOTs while 90% of subsequent AA initiators received it in LOT3 or later (mean number of LOTs to index AA: 0.9 vs 3.9, respectively; P<.0.05). Antidepressant monotherapies were the most prescribed (LOT1: first AA, 63%; subsequent AA, 73%) but generally decreased with subsequent LOTs. In each LOT, ~40% of first AA initiators were receiving AA adjunctive therapy. For subsequent AA initiators, <10% of patients received AA adjunctive therapy in LOT2 but increased to ~30% in later LOTs. Subsequent AA initiators used significantly more MH-related resources than first AA initiators, with outpatient visits accounting for the largest difference in HRU between cohorts (38% higher, P<0.05). Subsequent AA initiators also incurred significantly higher MH-related healthcare costs PPPY than first AA initiators (cost difference=$1,762; P<0.05), mainly due to higher medical costs (cost difference=$1,656; P<0.05).

Conclusions: Patients with MDD who initiated an AA as subsequent adjunctive therapy versus first adjunctive therapy took significantly longer to initiate AA and used significantly more resources as well as incurred significantly higher healthcare costs. This suggests that initiating AA adjunctive therapy earlier may reduce the economic burden of MDD.

W53. REAL-WORLD PREDICTION AND ESTIMATED PREVALENCE OF BIPOLAR I DISORDER MISDIAGNOSIS AMONG PATIENTS WITH MAJOR DEPRESSIVE DISORDER

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Abstract: Introduction: Misdiagnosing bipolar I disorder (BP-I) as major depressive disorder (MDD) has significant clinical and economic impact. Prediction models that identify potentially misdiagnosed patients may allow for earlier detection of BP-I. To identify patients with BP-I misdiagnosed as MDD, we developed a claims-based prediction model assessing patients at the time of first BP-I diagnosis.

Methods: Claims data from IBM® MarketScan® Research Databases (Commercial, Medicaid, and Medicare) were used. Patients initially diagnosed with MDD and later with BP-I were included in the misdiagnosed BP-I cohort; the index date for this cohort was the date of the first BP-I diagnosis. Patients with MDD and no observed bipolar disorder diagnosis were included in the MDD-only cohort; the index date of this cohort was imputed based on the distribution of time between the MDD and BP-I diagnosis in the misdiagnosed BP-I cohort. Predictors of misdiagnosis were evaluated during the 12 months before the index date. LASSO logistic regression models were trained, tested, and validated in a 1:1 population of the misdiagnosed BP-I cohort and a random sample of patients in the MDD-only cohort with ≥36 months of post-index observation. Cross-validated performance metrics included the area under the receiver operating characteristic curve (AUC) and accuracy. Predictors of misdiagnosis were quantified using odds ratios (ORs), 95% confidence intervals, and P-values. The model was applied to patients in the MDD-only cohort with <36 months of follow-up (ie, at-risk population); predicted prevalence of misdiagnosis was evaluated among the at-risk and overall study population.

Results: The study included 30,354 patients in the misdiagnosed BP-I cohort and 320,464 patients in the MDD-only cohort with ≥36 months of post-index observation, of whom 30,354 were randomly selected for model development. The strongest predictor of misdiagnosis was having a mental healthcare provider specialty switch (ie, between categories of primary care, mental health specialist, and other) between the time of MDD diagnosis and the index date—these patients had 5.74 times the odds of being misdiagnosed versus those who did not switch provider specialty (P<.001). Misdiagnosis was more likely in patients who had used atypical antipsychotics or mood stabilizers/anticonvulsants, with ORs of 4.08 and 1.86, respectively (both P<.001). Patients with a history of suicidal ideation, drug abuse, post-traumatic stress disorder, or ≥1 mental health-related emergency room visit also had higher odds of misdiagnosis (ORs=2.91, 2.12, 2.07, and 1.99, respectively [all P<.001]). Antidepressant use was associated with lower odds of misdiagnosis (ie, correct diagnosis of MDD) when patients had ≥3 pharmacy fills (OR=0.60 [P<.001]) but not when patients only had 1–2 fills (OR=0.99 [P=.844]). The model was 77.8% accurate with an AUC of 0.864, indicating a strong ability to identify misdiagnosed patients. In this data source, 8.7% of patients diagnosed with MDD had a subsequent BP-I diagnosis (ie, observed misdiagnosis). However, when the model was applied to the at-risk population, the prevalence of predicted misdiagnosis was estimated at 25–29%.

Conclusions: This real-world prediction model identified several important predictors of BP-I misdiagnosis among patients diagnosed with MDD. Identification of these factors may support healthcare providers in the accurate and timely diagnosis of BP-I.

W54. THE EFFECT OF LURASIDONE ON ANHEDONIA IN ADULT PATIENTS WITH BIPOLAR DEPRESSION

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Abstract: Introduction: During the course of bipolar disorder, depression is the predominant symptomatology, ranging in severity from major depressive episodes to milder subsyndromal depression. One of the most common and disabling symptoms of bipolar depression is anhedonia, which has been reported to be associated with a worse prognosis, including impairment in quality of life and functioning. Lurasidone has demonstrated efficacy in the treatment of bipolar depression in adults and pediatric patients 10-17 years old. This post-hoc analysis evaluated the efficacy of lurasidone to improve anhedonia and determined the extent to which improvement in anhedonia was associated with improvement in quality of life and functioning.

Methods: Patients with bipolar I depression (Montgomery Åsberg Depression Rating Scale [MADRS]≥20) were randomized to 6 weeks of once-daily, double-blind treatment with lurasidone in doses of 20-60 mg/d and 80-120 mg/d (N=161 and N=162, respectively) or placebo (N=162). Anhedonia was measured using item-8 (inability to feel pleasure/reduced interest) on the MADRS. Anhedonia responder criteria consisted of a week 6 item-8 score ≤2 (mild-to-no anhedonia). A mediational analysis was performed to determine to what extent improvement in anhedonia mediated improvement in the Sheehan Disability Scale (SDS) and the Quality of Life, Enjoyment, and Satisfaction Questionnaire (Q-LES-Q).

Results: At baseline 276/485 (56.9%) of patients had moderate-to-severe anhedonia (item-8 ≥4). Lurasidone treatment significantly reduced mean MADRS total scores at week 6 for both the 20-60 mg/d group (-15.4; effect size=0.51) and the 80-120 mg/d group (-15.4; effect size=0.51) compared with placebo (-10.7). Lurasidone also significantly reduced item-8 anhedonia at week 6 for both the 20-60 mg/d group (-1.8; P=0.002; effect size=0.38) and the 80-120 mg/d group (-1.8; P=0.002; effect size=0.38) compared with placebo (-1.3). A mediational analysis showed that 56.9% (Wald 95% CI, 32.4, 81.4) of the total lurasidone effect on improvement in the Q-LES-Q total score was mediated by improvement in the item-8 anhedonia score (P<0.0001). A significant percent (48.4%; Wald 95% CI, 22.8, 74.0) of the lurasidone effect on improvement on the SDS total score was also mediated by improvement in the item-8 anhedonia score (P<0.0005).

Conclusion: The results of this post-hoc analysis suggests that lurasidone is an effective treatment for anhedonia in patients with a diagnosis of bipolar I disorder who present with moderate-to-severe major depressive episodes. Improvement in both quality of life and functioning appeared to be largely mediated by improvement in anhedonia, indicating that the amelioration of patients' pervasive inability to feel pleasure or take interest in their environment is an important therapeutic target.

Clinicaltrials.gov identifier: NCT00868699

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W55. HOSTILE INTERPRETATION BIAS AND AVOIDANCE RELATED TO CONCERN FOR RISK OF VIOLENCE TOWARDS OTHERS IN A PTSD PHARMACOTHERAPY TREATMENT TRIAL

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Abstract: Avoidance of situations where there is a risk of harm to self or others is a core feature of PTSD, and patients with PTSD expressing concern about the potential for them to engage in violent behavior, generally out of proportion to objective risk of this occurring, is a known component. One relatively under-explored potential contributor to this potential risk is that of hostile interpretation bias (HIB), where an encounter that others might consider neutral is experienced as conveying hostility or threat. Here, we describe initial results addressing HIB in a treatment trial of prazosin for PTSD in treatment-seeking Veterans (N=41).

Concern about HIB versus concern about the risk of harm to self was assessed using a custom questionnaire. A majority of participants expressed at least come concern about the risk of harming others based on their perception of hostility or threat, with >20% expressing significant or extreme concern about this risk. Concern about HIB was significantly related to PTSD symptom severity (CAPS-5 total score, R=0.56, p=.0019). Concern about HIB was also significantly related to degree of functional impairment on the Inventory of Psychosocial Functioning (IPF, R=0.42, p=.0042), which was in contrast to the lack of a significant relationship between concern about one's self being attacked or harmed (R=0.24, p=.12).

Overall, response to treatment was significant across the first 8 weeks of the trial, with significant improvement in PTSD symptom severity (CAPS-5 total score, p<.001), problems with psychosocial functioning (NIH PROMIS Social Roles and Activities 8-item short form, p<.001), and concern about the risk of threat from others (p=.016). However, there was not a significant decrease in concern HIB (p=.359). The degree of improvement in concern for HIB was significantly related to the degree of improvement in psychosocial functioning (R=.42, p=.019) and total PTSD symptom severity on the self-report PCL5 (p=4.6e-5). The degree of improvement in concern for risk to self was not significantly related to improvement in psychosocial functioning (R=.21, p=.25). Results on the word-sentence association task for hostile interpretation bias (Dillon et al, 2016) and their relationship the above measures are expected to be included and may provide additional clarification.

W56. AXS-05 (DEXTROMETHORPHAN-BUPROPION) IMPROVES DEPRESSIVE SYMPTOMS AND FUNCTIONING IN PATIENTS WITH ONE PRIOR TREATMENT FAILURE: RESULTS FROM THE EVOLVE LONG-TERM, OPEN-LABEL STUDY

Amanda Jones[*1], Caroline Streicher[1], Zachariah Thomas[1], Herriot Tabuteau[1]*

[1]Axsome Therapeutics

Abstract: Background: Major depressive disorder (MDD) is difficult to treat. Over 60% of MDD patients experience inadequate response to current first-line oral antidepressants and the majority of those patients also fail second-line treatment. Currently approved oral antidepressants act primarily via monoaminergic mechanisms and are associated with a prolonged time to clinically meaningful response and adverse effects can impact adherence to treatment. There is an urgent need for additional treatment options for MDD.

AXS-05 (dextromethorphan-bupropion) is a novel, oral, investigational, NMDA receptor antagonist with multimodal activity being developed for MDD. The dextromethorphan component of AXS-05 is an antagonist of the NMDA receptor, an ionotropic glutamate receptor, and a sigma-1 receptor agonist. The bupropion component of AXS-05 serves primarily to increase the bioavailability of dextromethorphan.

Objective: To evaluate the efficacy and safety of AXS-05 in patients who had been treated with one prior treatment in their current major depressive episode.

Methods: EVOLVE (Evaluation of NMDA Modulation for Depressive Episodes) was an open-label, US trial, in which patients were treated with AXS-05 (dextromethorphan HBr 45 mg-bupropion HCl 105 mg) twice daily for up to 15 months. Eligible patients had either rolled in following completion of a prior AXS-05 study, or were directly enrolled, and had a DSM-5 diagnosis of MDD, a MADRS score of ≥25, and had been treated with at least 1 prior antidepressant in the current major depressive episode. A total of 186 patients were enrolled, consisting of 35 roll-over and 146 directly enrolled. Efficacy endpoints included MADRS, CGI-S, and SDS. The primary efficacy analysis was the change from baseline to Week 6 (primary timepoint) and Weeks 1 and 2 (key secondary timepoints). Here we present the results for the directly enrolled patients.

Results: Depressive symptoms improved rapidly after treatment with AXS-05. Mean change in MADRS total score from a baseline of 32.2 were -9.1±7.64 ($p<0.001$), -13.3±8.58 ($p<0.001$), and -20.4±7.79 ($p<0.001$) points at Weeks 1, 2, and 6. Clinical response (≥50% improvement) was achieved by 17.7% of patients at Week 1, 39.0% at Week 2, and 74.2% at Week 6. Remission on the MADRS (≤10) was achieved by 5.7%, 16.2%, and 46.0% of patients at Weeks 1, 2, and 6, respectively. Antidepressant effects were durable and sustained through Month 12.

CGI-S scores correlated highly with MADRS changes over time. Response (≥2 category change) on the CGI-S was rapid, with 19.1% of patients responding at Week 1, 38.2% at Week 2, and 71.0% at Week 6. The CGI-S improvement was durable, with response by 77.9% of patients at Month 6 and 79.5% at Month 12.

Functioning, measured by the SDS, improved rapidly after treatment with AXS-05. Mean changes in SDS total score was -2.9±5.39 ($p<0.001$), -5.0±5.78 ($p<0.001$), and -8.3±6.71 ($p<0.001$) points at Weeks 1, 2, and 6, respectively. Remission on the SDS (≤6) was achieved by 8.5% of patients at Week 1, 18.4% at Week 2, and 39.5% at Week 6. Improvements on the SDS were durable and sustained through Month 12.

Long-term treatment with AXS-05 was well tolerated. The most commonly reported adverse events were COVID-19 infection (8.9%), nausea (8.9%), headache (7.5%), dry mouth (6.2%), insomnia (5.5%) and dizziness (5.5%).

Conclusions: AXS-05 resulted in rapid and sustained improvement in depressive symptoms and functioning in patients who failed one prior antidepressant in the current major depressive episode. These data support the long-term efficacy and safety of AXS-05 in this difficult-to-treat patient population.

This research was supported by Axsome Therapeutics.

W57. IMPROVEMENT IN ANXIETY SYMPTOMS IN DEPRESSED PATIENTS TREATED WITH AXS-05 (DEXTROMETHORPHAN-BUPROPION): RESULTS FROM THE EVOLVE OPEN-LABEL, LONG-TERM STUDY

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Abstract: Background: Approximately half of all patients with major depressive disorder (MDD) also experience significant levels of anxiety. Various studies, including STAR*D, have reported that comorbid anxiety is associated with worse clinical outcomes in patients with MDD, including lower response and remission rates, and reduced quality of life and functioning. There is an urgent need for innovative therapies to treat individuals with MDD, especially those with comorbid anxiety.

AXS-05 (dextromethorphan-bupropion) is a novel, oral, investigational, NMDA receptor antagonist with multimodal activity being developed for MDD. The dextromethorphan component of AXS-05 is an antagonist of the NMDA receptor, an ionotropic glutamate receptor, and a sigma-1 receptor agonist. The bupropion component of AXS-05 serves primarily to increase the bioavailability of dextromethorphan.

Objective: To evaluate the effects of AXS-05 on anxiety in MDD patients.

Methods: EVOLVE (Evaluation of NMDA Modulation for Depressive Episodes) was an open-label, US trial, in which patients were treated with AXS-05 (dextromethorphan HBr 45 mg-bupropion HCl 105 mg) twice daily for up to 15 months. Eligible patients had either rolled in following completion of a prior AXS-05 study or were directly enrolled and had a DSM-5 diagnosis of MDD, a MADRS score of ≥25, and had been treated with at least 1 prior antidepressant in the current major depressive episode. A total of 186 patients were enrolled, consisting of 35 roll-over and 146 directly enrolled. Efficacy endpoints included MADRS and HAM-A. The primary efficacy analysis was the change from baseline to Week 6 (primary timepoint) and Weeks 1 and 2 (key secondary timepoints). Here we present the results for the directly enrolled patients.

Results: Treatment with AXS-05 resulted in meaningful improvement in HAM-A. Mean baseline HAM-A scores were 15.6. Reductions from baseline to Weeks 1, 2, and 6 were 3.4±5.34 ($p<0.001$), 5.5±5.81 ($p<0.001$), and 8.6±5.75 ($p<0.001$), respectively. Improvements on the HAM-A were durable through Month 6 (-10.2±6.47; $p<0.001$) and Month 12 (-10.2±6.33; $p<0.001$). Response on the HAM-A (≥50% improvement) was achieved by 18.4%, 27.9%, and 62.1% of patients at Week 1, 2, and 6, respectively. Response rates continued to improve through Month 6 (73.7%) and Month 12 (77.1%). Remission (≤7) rates on the HAM-A at Weeks 1, 2, and 6 were 19.9%, 36.0%, and 58.1%, respectively. Remission was durable, with 74.7% of patients remitting at Month 6 and 78.3% at Month 12.

Long-term treatment with AXS-05 was well tolerated. The most commonly reported adverse events were COVID-19 infection (8.9%), nausea (8.9%), headache (7.5%), dry mouth (6.2%), insomnia (5.5%) and dizziness (5.5%).

Conclusions: Treatment with AXS-05 reduced anxiety in patients with MDD. Remission from anxiety was achieved starting at Week 1. These data support the use of AXS-05 in patients with comorbid depression and anxiety.

This research was supported by Axsome Therapeutics.

W58. A PILOT STUDY OF LOW-INTENSITY FOCUSED ULTRASOUND FOR TREATMENT-RESISTANT GENERALIZED ANXIETY DISORDER

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Abstract Objective: Low-intensity transcranial focused ultrasound (fUS) is a non-invasive deep-brain stimulation technique that demonstrates safety and potential for targeted neuromodulation of deeper brain structures. This study intended to evaluate the possible therapeutic effect among patients with treatment-refractory generalized anxiety disorder (trGAD) by using targeted fUS to disrupt amygdalar activity.

Methods: Eight participants with severe trGAD as outlined in the DSM-V were recruited from Los Angeles neurology and psychiatry clinics. All participants completed eight weekly 10-minute fUS sessions using the Brainsonix Pulsar 1002 device targeting the right amygdala. Functional and structural neuroimaging were used to navigate individual targets. Outcome measures including the Hamilton Anxiety Inventory (HAM-A), Hamilton Depression Inventory (HAM-D), Back Anxiety Inventory (BAI), and Beck Depression Inventory (BDI-II) were collected before and after every treatment session.

Results: All participants were able to tolerate treatment without notable side effects. No adverse events were reported. A Wilcoxon Signed-Rank Test was conducted to compare pre- and post-fUS measures of anxiety and depression. fUS resulted in a significant decrease in anxiety as measured by the HAM-A ($z = -2.52$, $p < 0.01$, pre-post-$\Delta = 7.56$) and the BAI ($z = -2.10$, $p < 0.05$, pre-post-$\Delta = 18.0$). fUS also resulted in a significant decrease in depression as measured by the BDI-II ($z = -2.38$, $p < 0.05$, pre-post-$\Delta = 13.0$).

Conclusion: This study provides preliminary evidence supporting the safety and efficacy of fUS as a clinical intervention. This study was performed on treatment-resistant subjects who had previously undergone many pharmacological, psychological, and brain stimulation treatments with minimal-to-no therapeutic response. This study group intends to report on at least 10 additional subjects through the next year. These results warrant further investigation of fUS as a therapeutic intervention for anxiety and other psychiatric and neurological disorders.

W59. UPDATED TREATMENT OF DEMENTIA WITH BOSUTINIB: AN OPEN-LABEL STUDY OF A TYROSINE KINASE INHIBITOR

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Abstract: Learning Objective: This study pursues and updates data on an effective therapeutic intervention for dementia using TKI's such as bosutinib.
Keywords: Tyrosine Kinase Inhibitors (TKI's), Neurodegenerative

Background: A 2020 publication from Mahdavi and colleagues reported on clinical status changes observed among a sample of 31 older adults with neurodegenerative conditions who completed 12 months of bosutinib therapy. This abstract provides updated results for an additional 21 patients who have completed the 12-month regimen since the time of the initial publication. This study pursues and updates data on an effective therapeutic intervention for dementia using TKI's such as bosutinib.

Method: 52 patients with probable Alzheimer's dementia (AD) or Parkinson's spectrum disorder with dementia (PDD) completed 12 months of bosutinib therapy. The Clinical Dementia Rating scale (CDR) as estimated by the Quick Dementia Rating System (QDRS) was the primary cognitive status outcome measure.

Results: For the updated sample size of 52 individuals who have completed the protocol, bosutinib was associated with improved CDR scores for 40% of participants (36% AD, and 46% PDD); bosutinib was also associated with clinically stable CDR scores for 38% of patients (36% AD, and 46% PDD). After completion of the protocol intervention, 29% of the AD population yielded decreased CDR scores while only 8% of PDD patients had decreased CDR scores.

Discussion: These results continue to warrant further investigation of bosutinib as a potential therapeutic agent for dementia. The data continue to suggest an overall positive or stable outcome among participants after a year of bosutinib, with a clinical improvement rate of approximately 40% and a 38% rate of clinical stabilization. This observation remains consistent regardless of severity of cognitive impairment at baseline. We expect to report on an update for an additional 30 participants in the next year.

W60. IDENTIFYING PATIENTS WITH HIGH BURDEN OF POSITIVE AND NEGATIVE SCHIZOPHRENIA SYMPTOMS IN ELECTRONIC HEALTH RECORD DATA USING NATURAL LANGUAGE PROCESSING

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Abstract: Background: Schizophrenia is a serious mental disorder characterized by the presence of positive and negative symptoms. Positive symptoms include paranoia, delusions and hallucinations whereas negative symptoms refer to features such as poor motivation, diminished emotional expression, and reduced social interaction. Increased symptom burden is thought to be associated with worse clinical outcomes. Electronic health records (EHRs) provide the opportunity to analyze data that are representative of real-world clinical practice. In this study, we applied natural language processing (NLP) models to unstructured EHR data to identify heavy positive or negative schizophrenia symptom burden and examined their associations with clinical outcomes.

Methods: Data were analyzed using NeuroBlu™, a HIPAA-compliant data assembly and analytic environment for de-identified data from the MindLinc EHR system. MindLinc includes data from over 560,000 patients receiving care from 25 U.S. mental healthcare

providers, including structured data on demographics and clinical outcomes, as well as NLP-derived data on mental disorder symptoms documented as part of the Mental State Examination (MSE). NeuroBlu™ was used to assemble a cohort of adults with schizophrenia (ICD-9: 295*; ICD-10: F20*). The index date for the analysis was defined as the first recorded clinical event. We analyzed the distribution of heavy positive and negative symptom burden (defined as 3 or more symptoms) by age, gender, and race. A multiple linear regression analysis was conducted to determine whether heavy positive or negative symptom burden was associated with disease severity measured using Clinical Global Impression - Severity (CGI-S) score and psychiatric hospitalization.

Results: Of the 4,400 individuals in the cohort, 1,267 (28.8%) had a heavy positive symptoms burden and 986 (22.4%) had a heavy negative symptom burden. The mean age of those with a heavy positive and heavy negative burden was 36.3 (SD: 14.7) years and 36.4 (SD: 14.7) years, respectively. Heavy positive symptom burden (β=0.15, 95% CI 0.13 to 0.18, $p<0.001$) and heavy negative symptom burden (β=0.11, 95% CI 0.09 to 0.14, $p<0.001$) were associated with greater CGI-S at diagnosis. Female gender (β=0.08, 95% CI 0.01 to 0.14, p=0.023) was also associated with greater CGI-S score. Increasing age (β=-0.004 years, 95% CI -0.006 to -0.001, p=0.002) and Black or African American race compared to White race (β=-0.22, 95% CI -0.30 to -0.14, $p<0.001$) were associated with lower CGI-S scores recorded at index date. Heavy positive symptom (β=2.74, 95% CI 2.31 to 3.18, $p<0.001$) and heavy negative symptom burden (β=3.13, 95% CI 2.70 to 3.60, $p<0.001$) were also associated with higher number of days spent in psychiatric hospital. In addition, increasing age (β=0.08 years, 95% CI 0.04 to 0.13, $p<0.001$) or a race of Native Hawaiian or Other Pacific Islander (β=11.3, 95% CI 7.23 to 15.3, $p<0.001$) or Other compared to White race (β=5.05, 95% CI 1.14 to 8.98, p=0.011) were associated with increased number of hospitalization days.

Discussion: We demonstrate that heavy positive or negative symptom burden (derived from EHR data using NLP) are associated with greater severity of illness and increased duration spent in psychiatric hospital in people with schizophrenia. Proactively identifying individuals with heavy positive or negative symptom burden could support the development of more targeted treatments for people with schizophrenia.

W61. ER VISITS AND HOSPITALIZATIONS AMONG PATIENTS TREATED WITH PIMAVANSERIN OR OTHER-AAPS FOR PARKINSON'S DISEASE PSYCHOSIS: ANALYSIS OF MEDICARE BENEFICIARIES

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Abstract: Objectives: Real-world analysis demonstrating pimavanserin (PIMA) benefits, the only FDA approved atypical antipsychotic (AAP) in 2016 for hallucinations and delusions associated with Parkinson's Disease Psychosis (PDP) is needed. This analysis examined health resource utilization (HRU) outcomes among PDP patients treated with PIMA vs. other AAPs. Methods: Analysis of Parts A, B, and D claims from 100% Medicare sample of PDP patients from 01/01/13-12/31/19 was conducted. Patients initiating (i.e., index date) continuous monotherapy of PIMA or other-AAP for ≥12-month during 01/01/14-12/31/18 without any prior-AAP use during 12-month pre-index were selected after 1:1 propensity score matching on 30 variables (sex, race, region and 27 Elixhauser comorbidity characteristics). HRU

outcomes included: annual all-cause and psychiatric-ER visit rates, annual all-cause and psychiatric (i.e., short-term stay, long-term stay, and SNF-stay [skilled nursing facility] hospitalization rates, mean per-patient-per-year (PPPY) hospitalizations and average length-of-stay (ALOS). Differences in PIMA vs other-AAPs were described using chi-square and t-tests. Generalized linear models (GLM) controlled for demographic characteristics, comorbidities, coexisting dementia, and coexisting insomnia were conducted to compare PIMA and other-AAPs.

Results: Of 12,164 PDP patients, approximately 48.41% (n=5,889) were female and mean age was >77 (±8.14) years. Among 1:1 matched PIMA (n=842) vs. other-AAP (n=842) patients, 37.8% (n=319) on PIMA vs. 49.8% (n=420) on other-AAPs ($p<0.05$) reported ≥1 all-cause hospitalizations. Specifically, short-term and SNF-stay among PIMA patients vs. other-AAPs were: 34% (n=286) vs. 46.2% (n=389) and 20.2% (n=170) vs. 31.8% (n=267) ($p<0.05$), respectively. Similarly, 9.6% (n=81) of PIMA vs. 14.6% (n=123) of other-AAPs patients had ≥1 psychiatric hospitalization ($p<0.05$). Furthermore, patients with ≥1 all-cause and psychiatric ER visit were: 61.6% (n=519) for PIMA vs.69.4% (n=584) for other-AAPs and 5.2% (n=43) for PIMA vs.10.2% (n=86) for other-AAPs ($p<0.05$), respectively. Mean PPPY short-term and SNF stays for patients on Pimavanserin vs. other-AAPs was: 0.59 (±1) vs. 0.89 (±1.35) and 0.28 (±0.66) vs. 0.5 (±0.9) ($p<0.05$), respectively. ALOS for short-term stay was 5.43 (±5.45) days for Pimavanserin vs. 6.48 (±6.65) days for other-AAPs ($p<0.05$). Adjusted GLM results demonstrated these results were significant.

Conclusions: In this analysis of PDP patients, PIMA monotherapy resulted in nearly 12% lower all-cause hospitalizations and 7% lower all-cause ER visits vs. other-AAPs. Mean PPPY short-term and SNF stays were also significantly lower for PIMA monotherapy vs. other-AAPs. These results analysis demonstrate the real-world HRU benefits of PIMA vs. other-AAPs among patients with PDP.

W62. THE USE OF DIGITAL HEALTH TECHNOLOGIES IN MENTAL HEALTHCARE DURING A GLOBAL PANDEMIC: RESULTS FROM A SURVEY OF HEALTHCARE PROFESSIONALS

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Abstract: Background: Digital mental health tools have vastly expanded in recent years, and demand for them has skyrocketed since the start of the COVID-19 pandemic.1 Many clinicians began using these tools for the first time during the pandemic and are learning to navigate them in a rapidly changing digital health landscape.1, 2 However, the evolving use of digital tools in mental healthcare is not well understood. Here, we surveyed mental healthcare professionals (HCPs) to assess which digital health technologies they are using, what implementation barriers they face, and how the pandemic has affected their practice.

Methods: Between July 28, 2021 and September 29, 2021, HCPs in the United States completed a digital health survey that recorded their occupations and types of digital health technologies currently used in their practice. The survey also captured how their technology

use has changed since the start of the pandemic, as well as any ethical concerns or barriers they have faced integrating new digital health tools into their clinical practice.

Results: The majority of respondents (78%) increased their use of telehealth since the start of the pandemic, and the percentage of providers averaging more than 20 hours of telehealth visits per week increased from 10% to 37%. Despite this sudden and substantive change, 81% of respondents believed that patient care quality has remained the same or improved, and 60% thought that after the pandemic, patients will decide whether they prefer face-to-face or virtual visits. The technologies most commonly recommended to patients were digital relaxation techniques (53%), online patient support groups (44%), and health-related apps (39%). Most providers (77%) expected to continue recommending these technologies even after the pandemic. Providers used a variety of digital health technologies in their clinical practice, the most popular being well-established digital tools: electronic health records (81%), telemedicine (81%), and patient portals (46%). Respondents learned about new technologies most often from their colleagues (30%), peer-reviewed publications (17%), and websites (15%), but they indicated a wider array of digital health resources they would like developed. Three-quarters of providers considered the patient's level of technical competence before recommending technology-based treatments, and they most often cited patient comfort with technology (43%) and privacy and security concerns (35%) as the biggest barriers to implementing new digital health tools. Privacy (30%) and equitable access (16%) were respondents' primary ethical concerns, although 21% had no ethical concerns about digital health tools. When asked which outcome could be most improved through digital health technology, 46% of respondents indicated expanded patient access to care.

Conclusions: The pandemic has changed the way HCPs incorporate technology into their clinical practice. While most surveyed respondents increased their use of telepsychiatry after the start of the pandemic, they believed that patient care has remained the same or improved in quality. Despite concerns about privacy and patient comfort with technology, providers recommended a range of digital health technologies to their patients and expected to do so even after the pandemic subsides, believing these tools may increase access to care.

W63. LONGER ISN'T ALWAYS BETTER: THE RELATIONSHIP BETWEEN PHONE SCREENING INTERVIEW DURATION AND MDD CLINICAL TRIAL ELIGIBILITY

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[1]*Adams Clinical*

Abstract: Background: Recruitment for major depressive disorder (MDD) trials is particularly challenging. The nature of MDD symptoms (e.g., fatigue, low motivation, anxiety) can result in high no-show rates for screening visits. Moreover, strict eligibility requirements for trials result in low eligibility rates among the MDD trial-seeking population. As a result, considerable time and effort is often spent on recruitment with little enrollment to show for it. Thus, identifying strategies to improve recruitment efficiency is of great interest. In this study we examined phone screening interview duration as a predictor of prescreening visit attendance and trial eligibility.

Methods: Our sample includes prospective MDD trial participants recruited by advertising on Facebook, Instagram, and Google. After submitting contact information online, subjects were called by a recruiter to complete a phone screening interview. These semi-structured interviews included questions on demographics, treatment history, medical history and current symptoms. Start and end times were recorded for each interview. Potentially eligible subjects were scheduled for a prescreening visit with a clinician (either in-person or remote depending on COVID-19 vaccination status and other factors) to assess their eligibility for a trial. Analyses focused on examining phone screening duration as a predictor of prescreening visit attendance and trial eligibility

Results: From January-October 2021, 2,084 prospective trial participants completed a phone screening interview. Of those, 1,340 (64%) were scheduled for a prescreening visit with a clinician. 943 (70%) attended their prescreening visit and of those, 606 (64%) were deemed eligible to screen for a trial. For subjects who passed their phone screening, interview duration ranged from 5-39 minutes (M=12, SD=5). Logistic regressions were conducted to examine phone screening duration as a predictor of prescreening visit attendance and trial eligibility. Phone screening duration was not a significant predictor of prescreening visit attendance (regardless of whether the visit was remote or in-person). Phone screening duration was, however, a significant predictor of prescreening outcome. Specifically, subjects who had longer phone interviews were less likely to be deemed eligible for a trial (β=-.001, $p<.01$). Age was also significantly correlated with both phone screening duration and prescreening outcome, with older age being associated with longer phone screenings (β=.15, $p<.001$) and lower likelihood of eligibility (β=-.20, $p<.001$). However, even when controlling for age, phone screening duration remained a significant predictor of prescreening outcome.

Conclusion: While it might seem prudent for recruiters to spend longer on the phone with potentially eligible participants in order to build rapport and improve attendance, this was not supported by the data. On the contrary, subjects with longer phone screening interviews were no more likely to show up for their prescreening visits and were ultimately less likely to be eligible for a trial. It may be that these subjects took longer to interview due to more complicated psychiatric and medical histories, as well as poor reporting – all factors that contribute to lengthier interviews, as well as a lower likelihood of eligibility. The findings suggest that keeping phone screening interviews as brief as possible may be one way to improve recruitment efficiency and speed up enrollment.

W64. SUPPORT: STUDYING THE IMPACT OF PATIENT TREATMENT EXPERIENCES ON PATIENT HOPE FOR FUTURE MAJOR DEPRESSIVE DISORDER PHARMACOTHERAPIES

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Abstract: Objectives: Individuals receiving pharmacologic treatment for major depressive disorder (MDD) continue to face multiple disease or treatment-related issues, including continued depression symptoms, productivity loss, medication non-adherence, bothersome

side effects, and perceived lack of treatment efficacy. The objective of this study was to characterize the perceptions and experiences of MDD patients across a variety of MDD-related issues and understand the effect of those issues on patient hope and complacency, across lines of therapy.

Methods: An online survey was conducted with adults who self-reported an MDD diagnosis recruited from the DBSA peer database and M3 Global Research general panel. The survey focused on depression history, demographics, and current disease and treatment-related issue categories: (1) depression symptoms, (2) productivity (3) adherence, (4) bothersome side effects, and (5) perceived treatment efficacy. Feelings of hope and complacency about current and future depression treatments were assessed by 11 "treatment expectations" statements. Depression symptom severity was calculated using Quick Inventory of Depression Symptomology (QIDS-SR-16) standard scoring. Presence of current disease and treatment-related issues and level of treatment expectations was calculated using standard Likert cutoffs based on responses. Logistic regression models were used to test the effect of current disease and treatment-related issues on low treatment expectations. Effect of line of therapy was assessed for all statistically significant models.

Results: Of 375 respondents, 81% were White, 9% were Black, 9% were Hispanic, and 80% were female. Over half (56%) reported being diagnosed ≥10 years ago, 31% reported ongoing issues with severe or very severe depression on the QIDS-SR-16, and 52% reported having productivity issues due to depression. The most reported prescription class for MDD was selective serotonin reuptake inhibitors (SSRIs) (40% current use, 93% lifetime use). Many reported having never used modified SSRIs (74%) or antipsychotics (42%). Among those who were currently taking a prescription for MDD (319, 85%), 21% reported being on 1st line of therapy (25% second; 48% ≥ third line), 19% reported that side effects were very or extremely bothersome, 46% were not fully satisfied with the efficacy of their medication, and 12% reported skipping a dose ≥6 times in the last 3 months.

Reported presence of disease or treatment-related issues was associated with low expectations on 6 treatment expectation statements (odds ratios ranged from 2.1 to 30.2). Those expectation statements were related to the following topics: perceptions of currently being on the best available treatment for MDD; possibility to achieve remission; possibility for MDD medications to have no side effects; complacency with side effects in exchange for efficacy; perceptions of MDD patients deserving better medications than what is available; and perceptions of how inevitable it is for MDD treatments to have side effects. Line of therapy was not significant in any of the models testing the effect of current disease or treatment-related issues on treatment expectations.

Conclusions: In this study, we found that MDD patients reported high rates of continued disease or treatment-related issues that are associated with low expectations for depression therapies. Line of therapy did not impact these associated expectations. These results highlight the need for improved treatment outcomes to address lack of hope and complacency in MDD patients. This need is especially pressing given that depressive disorders comprise the largest share of mental health-related disability burden worldwide.

Thursday, June 2, 2022

Poster Session II

TH1. GABAPENTIN IS AN EFFECTIVE ADJUNCT MEDICATION FOR BENZODIAZEPINE WITHDRAWAL

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Abstract: Benzodiazepine withdrawal is a widespread problem with potentially severe and deadly consequences. Currently, the only medication available for treating benzodiazepine withdrawal are short and long-acting benzodiazepines. Identifying other drugs to help in treating benzodiazepine withdrawal is necessary. Gabapentin, an anxiolytic drug also used off-label for treating alcohol withdrawal, is a potential candidate for modulating benzodiazepine withdrawal. Using electronic records from a large inpatient psychiatric facility, a retrospective study of 172 patients presenting with benzodiazepine withdrawal (N = 57 gabapentin, N = 115 no gabapentin) was conducted to determine if gabapentin as an adjunct was helpful in treating benzodiazepine withdrawal. Hospital length of stay and total amount of benzodiazepines given (lorazepam equivalent mg) were the primary outcomes. The results demonstrated that for patients given gabapentin there was a total reduction in the amount of benzodiazepines administered and a reduction in the hospital length of stay. These results point towards the potential use of gabapentin as an adjunct for treating benzodiazepine withdrawal. Limitations include small sample size and variability in medication management strategies across the sample.

TH2. AI-BASED ADHERENCE PREDICTION FOR PATIENTS: LEVERAGING A MOBILE APPLICATION TO IMPROVE CLINICAL TRIALS

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Abstract: Background: Medication nonadherence is a major public health concern and can impact the quality of data in clinical trials (1). Where traditional compliance collection methods (pill counts, diaries) have proven unreliable, pharmacokinetic sampling, adherence markers, and adherence technologies may provide more dependable and comprehensive datasets on participant adherence, thus improving trial outcomes (1). AiCure (LLC, NY, USA) is a medication-monitoring mobile application (app) that collects patient dosing data and connects patients to sites for ongoing dosing support. Phone-based computer vision algorithms confirm dosing steps, and secure transfer and storage of video to facilitate further artificial intelligence and human review. Boehringer Ingelheim is partnering with AiCure on several pilot trials to leverage AiCure adherence information to improve patient retention and data quality in clinical trials. Here we report initial findings.

Methods: In this pilot study, the AiCure mobile app was utilized to send medication reminders and record adherence of participants from two Phase II clinical trials studying the efficacy and safety of

BI 409306 in patients with schizophrenia (NCT03351244) or Attenuated Psychosis Syndrome (NCT03230097). Dose events were visually confirmed, providing a real-time view of adherence that allowed for targeted outreach and intervention. Data collected over the first 2 weeks was used to build quantitative, machine-learning models to predict individual adherence over the trial. Predictive modeling based on different monitoring periods (7-, 10-, 14-day), and adherence cut-off points (0.8, 0.7, 0.6) were explored.

Results: Initial AiCure assessment identified 45% of patients randomized in NCT03351244 as not meeting the traditional definition of compliance (>80% compliant). We also observed variance in adherence between electronic Case Report Form (78%) versus AiCure adherence (26%) in the highly compliant/adherent group randomized in NCT03230097. Based on the first 2 weeks of data (combined from both studies), the observation of a participant's adherence during this period predicted an individual's average adherence over the remainder of the trial. Furthermore, observation of a participant's adherence for the latest 4 weeks of a trial predicted an individual's probability of prematurely dropping-out (based on low adherence). There were further correlations of lower predicted adherence with actual disposition-based drop-outs. The early adherence predictive model (with 0.6 adherence cut-off) identified 22%, 20%, and 19% of patients for trial NCT03351244 (total n=235) as high-risk patients (low adherence prediction) across 7-, 10-, and 14-day monitoring periods, respectively. Of those high-risk patients, 81%, 90%, and 96%, respectively, were truly nonadherent patients based on their actual adherence data. The model utilizing the 14-day monitoring period provided the lowest false omission rate, indicative of a better performing model.

Conclusion: AiCure data provided deep insights into patient behavior and adherence patterns, which would not be available via traditional methods. The predictive models developed with AiCure adherence information can identify and predict future poor adherers. This creates numerous opportunities to plan possible intervention and mitigation strategies to improve patient adherence during trials, thereby providing test drugs the best opportunity to prove efficacy.

TH3. TRANSCRANIAL MAGNETIC STIMULATION FOR METHAMPHETAMINE USE DISORDER AND POTENTIAL USE DURING PREGNANCY

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Abstract: The prevalence of methamphetamine (MA) use during pregnancy ranges from 0.7% to 4.8% in endemic areas. In addition to negative health effects on the mother, the IDEAL study, which is the largest study to date on MA use during pregnancy, demonstrated an increased risk of adverse fetal and neonatal outcomes, including decreased body weight, head circumference, length, and admissions to intensive care unit. Despite these public health impacts, no FDA-approved therapies for MA use disorder are currently available. Development of effective pharmacotherapies is complicated for pregnant and postpartum women because most medications cross the blood-placenta barrier or are secreted in breast milk, and many

women would prefer a nonpharmacologic intervention to avoid fetal exposures. Transcranial magnetic stimulation (TMS) is a non-invasive, well tolerated intervention that is FDA-approved for depression. TMS has the potential to address neural circuit dysfunction that underlies key aspects of methamphetamine addiction, including loss of executive control, abnormal reward system response, and negative affect during drug withdrawal.

Methods: We reviewed the existing literature on the use of TMS during pregnancy and TMS targeting of prefrontal cortex to reduce MA craving in non-pregnant persons. In a recent completed feasibility trial (10 subjects enrolled) we implemented a 4-week, open-label, single-arm, dual-target TMS trial for MA use disorder. Intermittent theta burst stimulation was delivered to the left dorsolateral prefrontal cortex, and continuous theta burst stimulation to the medial prefrontal cortex. MRI-based neuro-navigation was used to visualize the stimulation sites and to adjust the intensity of stimulation to account for variation in the scalp-to-cortex distance.

Results: Our literature review yielded 17 original articles on the utilization of TMS in pregnant women. Three clinical trials, 10 case reports, and 4 addressed other aspects considered to be relevant to the topic. Only one sham-controlled study (Kim et al 2019,Brain Stimul 12(1):96–102. Twenty-six pregnant women with depression were enrolled. Depression severity, measured with the Hamilton Depression Rating Scale (HDRS-17), improved more for the active compared to the sham group ($p=0.003$). There was no increase of miscarriages or severe birth defects, in comparison to control group. Preterm delivery occurred in three women receiving active TMS, but this was not statistically significant when compared to the sham group.

In the clinical trial of non-pregnant participants with MA use disorder, six of ten enrolled subjects proceeded to receive at least one TMS treatment. Four participants completed the 4-week series of treatments. Self-reported drug craving was decreased ($p=0.008$, Brief Substance Craving Scale). Depression improved significantly ($p=0.0006$, 8-item Patient Health Questionnaire). Anxiety decreased during the trial ($p=0.02$, 7-item Generalized Anxiety Disorder scale). Overall sleep quality improved significantly over time ($p<0.001$, Pittsburgh Sleep Quality Index). Finally, overall life satisfaction improved significantly over the course of the study ($p=0.003$, Quality-of-Life Enjoyment and Satisfaction Questionnaire-Short Form). Barriers to participating in the study included problems securing reliable transportations and difficulties with scheduling.

Conclusions: TMS is likely to be safe during pregnancy as an adjunct to psychosocial treatments. We propose a future clinical trial of TMS for MA addiction during pregnancy. An effective TMS intervention that prevents or reduces MA use during pregnancy would have positive impact on both maternal and fetal well-being.

TH4. BRAIN AND PERIPHERAL DISTRIBUTION OF INTRANASAL RADIOLABELED PH94B IN LABORATORY RATS

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Abstract: Background: PH94B (3 beta-hydroxy-androsta-4,16-dien-ol) is a neuroactive steroid that engages olfactory chemosensory neurons which seem to activate subsets of olfactory bulb neurons that project directly to the limbic amygdala. PH94B treatment provides

rapid onset of efficacy in the treatment of social anxiety disorder (SAD)1, although the precise mechanism of action remains under active investigation. The objective of the present study was to determine the brain and peripheral tissue distribution following a single intranasal dose administration (10 μCi) of radiolabeled PH94B (14C-PH94B) to naïve male and female rats.
Methods: Male and Female Long Evans rats 10 to 13 weeks old and weighing between 231 to 325g at initiation of dosing were used. Animals were euthanized at 15 min, 60 min, 6 hours, 24, 72, 168, 336, and 504 hours after intranasal dosing of radiolabeled PH94B and subjected to whole body autoradiography. Whole-body sagittal plan sections approximately 30 μm thick were taken, exposed to phosphor imaging screens, and scanned. Quantification, relative to the calibration standards, was performed by image densitometry.

Results: One male and one female rat was used for autoradiographic analysis at each time point. A single intranasal administration of radiolabeled 14C-PH94B was largely confined to the nasal passages, with minimal or undetectable radiolabeled 14C-PH94B uptake in either peripheral (e.g. blood plasma, kidney, and liver) or central nervous system (CNS: olfactory lobes, cerebrum, cerebellum, and spinal cord) tissue at all time points- from 15 minutes to 504 hours after intranasal administration.

Discussion: Overall, the data further support the proposed mechanism of action whereby PH94B binds to peripheral sensory neuron receptors in the nasal passages, rather than neuronal receptors in the CNS, thereby limiting transport of molecules to the circulatory system, minimizing both blood brain barrier penetration and systemic exposure. When combined with preclinical electrophysiology data demonstrating that the mechanism of action of PH94B does not involve direct activation of GABA-A receptors2, there is a growing body of evidence suggesting that PH94B has potential to achieve anti-anxiety effects without requiring CNS penetration or systemic uptake, avoiding benzodiazepine- or antidepressant-associated side effects and safety concerns from traditional SAD therapies. We conclude that PH94B stimulates nasal chemosensory neurons which in turn activate neurons in the olfactory bulbs projecting to amygdala neurons regulating fear circuits. The efficacy, safety and tolerability of PH94B in human subjects suffering from SAD is currently being evaluated by VistaGen Therapeutics in the Palisade phase 3 program

TH5. NEGATIVE BIASES DURING THE PROCESSING OF FACES BASED ON EMOTION EXPRESSION IN MAJOR DEPRESSIVE DISORDER

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Abstract: Major depressive disorder is associated with negative processing biases including selection, encoding, perception, and interpretation of actual experiences. It demonstrated that negative schemata influence information processing by elevating the salience of negative events and by decreasing the salience of positive events. EEG data was acquired from patients with MDD who met DSM-IV or V diagnostic criteria and healthy volunteers during a novel memory task with emotional face stimuli. During acquisition happy (H), sad (S) and neutral (N) faces (n=36) were presented sequentially for 2 rounds and participants instructed to remember them. During the test phase, the 36 target acquisition stimuli were presented interspersed with 36 emotional distractor faces and subjects indicated whether the stimuli were target or nontarget. Raw EEG data were bandpass filtered (0.1 to 50 Hz), epoched (time-locked to each stimulus), separated by stimulus type, and averaged together to compute event related

potentials (ERP). Each epoch was defined from 1 second prior to stimulus onset until 2 seconds post stimulus onset. Baseline was removed from each epoch and trials with abnormal amplitude were filtered out using EEGLAB software. Amplitudes were measured for the ERP components of interest, separated by emotion (N, S, and H) and stimulus type (target or nontarget). Emotional processing biases (S vs H; S vs N; H vs N) were assessed in the N170 ERP components linked to stimulus processing. The amplitude of the N170 component was significantly higher for S stimuli than both H and N ($p<0.05$). The results suggest that the negative bias during the processing of faces based on emotion expression for MDD patients can be detected using N170 component measurements. EEG acquisition during the emotional faces task can be used as a biomarker for depression during investigational drug clinical trials.

TH6. ANTIDEPRESSANT RESPONSES OF ESKETAMINE NASAL SPRAY AND ATYPICAL ANTIPSYCHOTICS IN PIVOTAL PHASE 3 TRIALS: A META-ANALYSIS

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Abstract: Background: The US FDA has approved SPRAVATO™ (esketamine) nasal spray (ESK) as a conjunctive treatment with an oral antidepressant for treatment-resistant depression (TRD) and major depressive disorder (MDD) with acute suicidal ideation or behavior. Several atypical antipsychotics (AAPs) have also been approved as adjunctive treatments for MDD (1). This meta-analysis explored if these mechanistically different treatments differ in antidepressant outcomes in patients with MDD who experienced inadequate response to antidepressants.

Methods: The data retrieved included those fulfilling trial requirements similar to the specifications of a previous meta-analysis (2) and a sub-dataset from 12 phase 3 pivotal AAP trials on aripiprazole, brexpiprazole, quetiapine, olanzapine, and ESK. Trial outcome measures were Montgomery–Åsberg Depression Rating Scale (MADRS) total score changes from baseline to Week 1 (if available) and the end point, respectively, and response (≥50% decrease of MADRS total score from baseline) rates at the end point. Antidepressants, newly initiated or continuing, were used in both placebo and active arms of all trials analyzed. Linear mixed effect model from the R package "metafor" was used for statistical analysis on summary-level data.

Results: At the end point, the mean difference (95% CI) in MADRS score reduction between the model estimated means of placebo (from ESK studies) and ESK arms was -4.24 (-7.21, -1.37), $p=0.0038$; between the estimated means of placebo (from AAP studies) and AAP arms was -2.06 (-2.61, -1.51), $p<0.0001$ in the dataset of all included trials (all-dataset), and -2.37 (-3.16, -1.58), $p<0.0001$ in the sub-dataset of 12 pivotal phase 3 trials. The mean treatment differences (active versus placebo treatment) between the ESK and AAP trials were 2.18 points (all-dataset) and 1.87 points (sub-dataset) in favor of ESK but not statistically significant. In the sub-dataset, the mean treatment difference in response rates (versus their placebo arms) was bigger in ESK arms than that in AAP arms (ESK, +25%; AAP, +9%; difference between ESK and AAP, +16%; $p=0.0004$). At the Week 1 timepoint of pivotal phase 3 trials, the mean difference (95% CI) in MADRS score reduction between the placebo and active arms in ESK

trials (-2.95 [-4.50, -1.40], p=0.0002) were 1.71 and 2.06 points greater than those in aripiprazole trials (-1.24 [-2.09, - 0.39], p=0.0043) and brexpiprazole trials (-0.89 [-1.61, -0.18], p=0.0142), respectively.

Conclusions: At the end point, ESK arms displayed significantly greater response rates and numerically larger MADRS score reductions than the AAP arms compared to their respective control arms. Numerically larger MADRS score reductions with ESK were also observed at Week 1. Due to limitations of meta-analysis using studies with differing designs, a prospective study is needed to confirm these findings.

TH7. HARNESSING THE POWER OF SCIENTIFIC SURVEILLANCE IN CENTRALIZED MONITORING

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Abstract: The COVID-19 pandemic caused several significant challenges for clinical trials. On-site source data verification (SDV) in multicenter clinical trials became difficult due to travel ban and social distancing. These challenges resulted in a fundamental shift from the traditional on-site monitoring paradigm especially in indications such as Parkinson's disease to one that is more reliant on centralized statistical monitoring which will likely continue in a post-pandemic setting.

Commonly used on-site monitoring techniques are not optimal in finding data fabrication, tampering, non-random data distributions, scientific incompatibility between key measures of interest etc. that have the greatest potential for jeopardizing the validity of study results.

Scientific incompatibility can manifest as irregularities and inconsistencies in responses to efficacy questionnaires, diaries, and other outcomes of interest at subject level and site level. Furthermore, in case of placebo-controlled studies, variability introduced by patient or investigator factors, and placebo response rates can have a profound influence on the outcome.

Scientific surveillance is a component of centralized monitoring at PPD, part of Thermo Fisher Scientific, that includes statistical monitoring methods coupled with powerful visualizations to help detect scientific incompatibility, predict key risks and detect inflated placebo response using only the blinded data. Such tools can help improve scientific integrity and quality in clinical trials. Identifying these issues early with cross functional engagement in trials can drive targeted actions.

TH8. EFFECTS OF CARIPRAZINE ON REDUCING SYMPTOMS OF HOSTILITY AND AGITATION IN PATIENTS WITH MANIC OR MIXED EPISODES OF BIPOLAR I DISORDER

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Abstract Background: Bipolar mania and mixed episodes can be associated with hostility and agitated behavior. Effective management of these symptoms may prevent escalation into aggression or violence. Cariprazine, a dopamine D3-preferring D3/D2 and serotonin 5-HT1A

receptor partial agonist, has demonstrated efficacy in manic, mixed, or depressive episodes of bipolar I disorder. The effects of cariprazine on symptoms of hostility and agitation in patients with bipolar mania or mixed episodes were evaluated in post hoc analysis.

Methods: Data were pooled from 3 randomized, double-blind, placebo-controlled trials of cariprazine 3-12 mg/d in patients with manic/mixed episodes of bipolar I disorder (NCT00488618/NCT01058096/NCT01058668). Post hoc analyses were performed in subgroups of patients with hostility at baseline as defined by Young Mania Rating Scale (YMRS; baseline irritability and disruptive-aggressive behavior item scores ≥2) or the Positive and Negative Syndrome Scale (PANSS; baseline hostility item score ≥2); baseline agitation was defined by PANSS-excited component (PANSS-EC; total score ≥14 and score ≥4 on ≥1 item). Change from baseline to week 3 in YMRS irritability and disruptive-aggressive behavior item scores, PANSS hostility item and PANSS-EC response (≥40% decrease from baseline) were assessed.

Results: The pooled dataset included 1037 patients; at baseline, 950 and 856 patients had hostility as measured by the YMRS and PANSS (YMRS subgroup: placebo=385, cariprazine=565; PANSS subgroup: placebo=361, cariprazine=495), and 299 patients had agitation (placebo=106; cariprazine=193). Cariprazine significantly reduced hostility symptom scores vs placebo in patients with baseline hostility defined by either instrument (YMRS hostility subgroup: least squares mean difference [LSMD] YMRS total=-6.3; YMRS irritability=-1.1; YMRS disruptive-aggressive behavior=-0.96; PANSS hostility=-0.6 [P≤.001 each outcome]; PANSS hostility subgroup: LSMD YMRS total=-6.7; YMRS irritability=-1.1; YMRS disruptive-aggressive behavior=-0.99; PANSS hostility=-0.6; [P≤.001 each outcome]). Reduction of YMRS hostility-related symptoms remained significant after controlling for change in other YMRS items (P<.01, all comparisons), indicating an independent effect of cariprazine on this symptom domain. Cariprazine also significantly reduced symptoms of agitation vs placebo in patients with baseline agitation (LSMD in PANSS-EC total score=-2.7; P≤.001); PANSS-EC responder rates were significantly higher for cariprazine- vs placebo-treated patients (53.4% vs 32.1%; NNT = 5, P≤.001).

Conclusion: Cariprazine significantly reduced symptoms of hostility and agitation vs placebo in patients with bipolar mania and high levels of hostility or agitation at baseline. These post-hoc results suggest that cariprazine may be an effective treatment option for acutely manic bipolar I patients with hostility and agitation although further study is warranted. Supported by AbbVie.

TH9. MODIFIABLE BEHAVIORAL TARGETS ASSOCIATED WITH SUBSYNDROMAL SYMPTOMS OF DEPRESSION IN BIPOLAR DISORDER

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Abstract: Background: Bipolar disorder (BD) is a devastating chronic psychiatric illness. Historically, clinical outcomes have centered around treatment response and resolution of acute episodes with the expectation that patients return to normal/pre-morbid functioning. However, emerging evidence suggests that there is substantial individual variability with up to half of all patients with BD experiencing subthreshold symptoms of depression during remitted phases, accompanied by related functional disability. Subsyndromal symptoms of depression also increase an individual's risk for affective relapse and contribute to prolonged episode duration.

Subsyndromal symptoms suggest only partial recovery, despite the implementation of standard of care. If we can identify factors that are associated with this incomplete treatment response, we can direct therapeutic efforts toward these as targets for improving quality of life

Methods: We assessed 261 inter-episode individuals with BD for depressive symptoms, sleep quality, coping styles, and psychosocial functioning using standardized scales.

Results: As in prior work, we defined subsyndromal depression as a score on the Hamilton Rating Scale for Depression (HRSD) between 7-17; 40% (n=104) of the sample met this threshold and were compared with asymptomatic (HDRS < 6; n=130) patients and a smaller subset (n=27) who endorsed severe symptoms of depression (HDRS > 18). Compared to asymptomatic individuals, those with subsyndromal symptoms of depression endorsed significantly more functional disability across several domains (all ps < .001), higher levels of sleep disturbance ($F = 16.32$, $p < .001$), less emotional support coping, and more maladaptive and self-blaming coping ($F = 5.25$, $p < .05$; $F = 8.43$, $p < .001$; $F = 16.21$, $p < .001$, respectively). The only significant difference between the subsyndromal group and the severe group was the use of less self-blaming coping ($F = 16.21$, $p < .001$). There were no significant differences between individuals with subsyndromal depression and those with severe depression on functional disability, emotional support coping, or maladaptive coping between individuals with subsyndromal depression and those with severe depression.

Conclusion: In line with recent estimates, almost 40% of our sample endorsed subsyndromal symptoms of depression and exhibited functional impairment comparable to that seen in more severe depression. Traditional maintenance therapy focused solely on extending the time between acute episodes may not be enough to promote a full recovery and optimize psychosocial functioning for a substantial proportion of individuals with BD. Treating modifiable behavioral targets associated with subsyndromal symptoms of depression such as sleep, and coping behaviors may not only help prevent relapse but also improve psychosocial functioning and quality of life.

TH10. LONG-TERM LUMATEPERONE TREATMENT IN BIPOLAR DISORDER: SIX-MONTH OPEN-LABEL EXTENSION STUDY

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Abstract: Background: Approved therapeutics for bipolar depression are associated with a range of undesirable side effects. Lumateperone, a mechanistically novel antipsychotic that simultaneously modulates serotonin, dopamine, and glutamate neurotransmission, is FDA-approved for the treatment of schizophrenia and for depressive episodes in adults with bipolar I or bipolar II disorder. The efficacy of lumateperone in bipolar depression was previously established in 2 Phase 3 trials, as monotherapy (NCT03249376) and as adjunctive to lithium or valproate (NCT02600507).

A recent Phase 3 multi-center trial, Study 401 (NCT02600494) investigated the efficacy and safety of lumateperone in bipolar depression and comprised a 6-week, randomized, double-blind, placebo-controlled period and a 6-month open-label extension (OLE) period. Here, we report the results of the OLE period, examining the long-term safety of lumateperone in bipolar depression.

Methods: Patients, aged 18-75 years, with a clinical diagnosis of bipolar I or bipolar II disorder who were experiencing a major depressive episode (Montgomery-Åsberg Depression Rating Scale [MADRS] Total score ≥20 and Clinical Global Impression Scale-Bipolar Version, Severity [CGI-BP-S] score ≥4) were eligible for Study 401. Patients who completed the double-blind study were eligible for direct rollover into the OLE or were re-screened if completing the double-blind period prior to the initiation of the OLE. During the OLE, lumateperone 42 mg was administered once-daily in the evening for 25 weeks.

The primary objective was safety and tolerability of lumateperone as measured by incidences of adverse events (AEs) and changes in laboratory parameters, cardiometabolic measurements, and vital signs. The secondary objective was improvement/maintenance of symptoms of depression as measured by MADRS and CGI-BP-S Total scores.

Results: A total of 127 patients were enrolled in the OLE, with 74 (58.3%) completing the study. Treatment-emergent AEs (TEAEs) occurred in 73 patients (57.5%) with 54 (42.5%) experiencing a drug-related TEAE and 4 (3.1%) experiencing serious AEs. TEAEs that occurred in ≥5% of patients were headache, dry mouth, dizziness, nausea, somnolence, anxiety, and irritability. Most TEAEs were mild or moderate in severity. Extrapyramidal-symptom-related TEAEs were rare. Most patients who had normal metabolic laboratory values at baseline remained normal during the treatment period. Mean changes in blood pressure, pulse rate, respiratory rate, and body morphology were minimal. Symptoms of depression improved as measured by the mean change from baseline to Day 175 in MADRS Total score (−8.9) and CGI-BP-S Total score (−2.3).

Conclusion: In patients with bipolar depression, long-term lumateperone treatment was generally well tolerated with low risk of extrapyramidal symptoms, weight gain, and cardiometabolic effects. These data further support the safety, tolerability, and effectiveness of lumateperone in patients with bipolar depression.

TH11. EFFECT OF LUMATEPERONE (ITI-007) ON QUALITY OF LIFE AND FUNCTIONAL DISABILITY IN THE TREATMENT OF BIPOLAR DEPRESSION

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Abstract: Background: Amongst persons with bipolar disorder, depression symptoms are associated with greater reduction in function and quality of life than hypomania/mania symptoms. Lumateperone (lumateperone tosylate, ITI-007), a mechanistically novel antipsychotic that simultaneously modulates serotonin, dopamine, and glutamate neurotransmission, is FDA-approved for the treatment of schizophrenia and for depressive episodes in adults with bipolar I or bipolar II disorder.

In a recent phase 3 clinical trial (Study 404, NCT03249376), in people with bipolar I or bipolar II disorder experiencing a major depressive episode (MDE), lumateperone 42 mg monotherapy significantly improved symptoms of depression compared with placebo. This analysis of Study 404 investigated the effects of lumateperone on functional disability and quality of life as measured using the secondary outcome measure, the Quality-of-Life Enjoyment and Satisfaction Questionnaire-Short Form (Q-LES-Q-SF).

Methods: Patients (18-75 years) with bipolar I or bipolar II disorder experiencing an MDE (Montgomery-Åsberg Depression Rating Scale [MADRS] Total score ≥20 and Clinical Global Impression Scale-Bipolar Version-Severity [CGI-BP-S] score ≥4) were randomized to lumateperone 42 mg or placebo orally, once daily in the evening for 6 weeks. The primary endpoint was the change from baseline to Day 43 in MADRS Total score, analyzed using a mixed-effects model for repeated measures (MMRM) approach in the intent-to-treat population (ITT). This post hoc analysis evaluated the mean change from baseline to Day 43 in the Q-LES-Q-SF individual item scores using an analysis of covariance with last observation carried forward (ANCOVA-LOCF) in the ITT. Additional analyses were conducted to evaluate the effects of lumateperone across the dimensions of the Q-LES-Q-SF.

Results: The ITT comprised 376 patients (lumateperone 42 mg, 188; placebo, 188). Patients in the lumateperone 42-mg group had significantly greater improvement on MADRS Total score change from baseline to Day 43 compared with placebo (least squares mean difference vs placebo [LSMD], −4.585; 95% CI, −6.344 to −2.826; effect size vs placebo, −0.56; P<.0001). Lumateperone 42-mg treatment significantly improved Q-LES-Q-SF Total score from baseline to Day 43 compared with placebo (LSMD, 2.9; 95% CI, 1.15 to 4.59; P=.001).

The Q-LES-Q-SF items with the lowest mean scores at baseline in both groups were mood, leisure time activities, and sexual drive, interest, and/or performance. By Day 43, lumateperone 42 mg treatment significantly improved 8 of the 14 items in the Q-LES-Q-SF (P<0.05). Overall life satisfaction also significantly improved with lumateperone treatment (P=.0016). The largest improvements with lumateperone 42 mg compared with placebo (effect size >0.3,) were seen for the ability to function in daily life, family relationships, household activities, leisure time activities, mood, and overall life satisfaction (all LSMD=0.3; all P<.01).

Conclusion: In patients with bipolar depression, treatment with lumateperone 42 mg compared with placebo significantly improved patient reported quality of life and functional impairment. These results support lumateperone 42 mg as treatment of MDEs associated with bipolar I or bipolar II disorder in adults.

TH12. SAFETY AND TOLERABILITY OF BREXPIPRAZOLE FOR THE TREATMENT OF BORDERLINE PERSONALITY DISORDER: A 12-WEEK, FLEXIBLE-DOSE, OPEN-LABEL EXTENSION STUDY

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Abstract Background: Borderline personality disorder (BPD) mental disorder, characterized by instability of interpersonal relationships and self-image, affective instability, and marked impulsivity (1). No drugs are currently approved for the treatment of BPD. However, pharmacotherapies are widely used to treat targeted symptoms, and these drugs are also associated with clinically significant side effects (2), indicating the need for a well-tolerated treatment option. Evidence suggests that atypical antipsychotics may be efficacious in treating BPD. The efficacy and safety of brexpiprazole for the treatment of patients with BPD have previously been evaluated in a randomized, placebo-controlled study (NCT04100096). The

present study (NCT04186403) was an open-label extension of the randomized (parent) study, with the primary aim of assessing the safety and tolerability of brexpiprazole in patients with BPD. The efficacy of brexpiprazole was also evaluated.
Methods: This 12-week, Phase 2/3, multicenter, flexible-dose, open-label extension study enrolled patients with BPD (DSM-5 criteria) who had completed a previous 12-week, randomized, double-blind, placebo-controlled study of brexpiprazole 2–3 mg/day in BPD. In the extension study, all patients received brexpiprazole 2–3 mg/day (flexible dose, with titration) for up to 12 weeks. The primary endpoint was the frequency and severity of adverse events (AEs). Efficacy was assessed as an exploratory endpoint by changes in Zanarini Rating Scale for BPD (ZAN-BPD) Total score and Clinical Global Impression – Severity (CGI-S) score.

Results: A total of 199 patients were treated with open-label brexpiprazole, of whom 88 had previously received brexpiprazole in the parent study, and 111 had previously received placebo. Patients had a mean age of 32.7 years and were predominantly female (81.1%). Overall, 163 patients (81.1%) completed the extension study. The most common reasons for study discontinuation were withdrawal by the patient (n=15 [7.5%]), loss to follow-up (n=10 [5.0%]), and AEs (n=9 [4.5%]). Overall, 43.2% of patients reported treatment-emergent AEs (TEAEs). The most common TEAEs (≥5%) were insomnia (5.5%) and akathisia (5.0%). The incidence of TEAEs was lower among patients who had received brexpiprazole during the parent study (34.1%) compared with patients who had previously received placebo (50.5%). Three patients (1.5%) reported serious TEAEs; no patients died during the study. In exploratory efficacy analyses, open-label brexpiprazole was associated with further reductions from baseline to Week 12 in ZAN-BPD Total score and CGI-S score. Improvements from baseline were numerically greater among patients who received placebo during the parent study compared with patients who had previously received brexpiprazole.

Conclusion: Open-label treatment with brexpiprazole 2–3 mg/day for 12 weeks was generally well tolerated in patients with BPD, regardless of previous exposure to brexpiprazole. Open-label treatment with brexpiprazole was associated with continued improvement in symptoms of BPD.

TH13. STILL WORKING: PROFESSIONAL SUBJECTS BEFORE AND DURING THE PANDEMIC

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Abstract: Purpose: To compare the incidence of professional subjects in the two years of the pandemic compared to the two years prior to the pandemic.
Background: Duplicate and professional subjects present a significant challenge in the conduct of CNS clinical trials where complex Inclusion/Exclusion Criteria and subjective endpoints provide a competitive advantage to those subjects willing to present in a deceptive manner. The authors were interested to find out if the nature or frequency of subjects excluded from CNS trials due to their being duplicate subjects (participating in studies concurrently), professional subjects (being deceptive in order to receive stipends) or otherwise inappropriate (i.e. a subject with prior participation in multiple schizophrenia studies trying to enter an MDD study) varied in the 2 years preceding the pandemic and the two years during the pandemic.

Methods: All subjects entered into the CTSdatabase subject registry between March 2018 and March 2020 were considered in the "pre-pandemic" group. Subjects entered April 2020 to March 2022 were considered in the "pandemic" group. For each of these timeframes, the number of exclusionary matches that occurred and the number of subjects that were entered was collected. The Exclusionary Match Rate (matches / subjects) was then calculated for each timeframe for comparison. We also looked at this breakdown by indication (Migraine, Major Depressive Disorder, Alzheimer's Disease, and Schizophrenia).

Results: There was no significant difference overall in the groups entered into all CNS studies. (3.34% vs 3.18%, p=0.55). However, when we parsed the data by indication in the 4 most common CNS indications that used CTSdatabase (Schizophrenia, MDD, Alzheimer's Disease and Migraine), we found a trend for a higher percentage of MDD subjects excluded prior to the pandemic and a highly significant finding of more subjects in schizophrenia studies being excluded during the 2 years of the pandemic (7.2% during vs 4.0% prior, p<.0001).

Conclusion: Duplicate and Professional subjects continue to be a problem in CNS studies with a frequency of at least 3% of screened subjects. This has been consistent before and during the pandemic.

CNS studies, with their subjective endpoints are particularly vulnerable to the effective of deceptive subjects. Prior to the pandemic, subjects with schizophrenia have been found to have the highest rates of duplicate enrollment and this problem likely worsened during the pandemic.

Importance: Subject registries and other strategies that attempt to mitigate the adverse effects of duplicate and professional subjects remain crucial to data integrity and study success.

TH14. EFFICACY AND SAFETY OF BI 425809 IN PATIENTS WITH SCHIZOPHRENIA: CONNEX, A PHASE III RANDOMIZED CONTROLLED TRIAL PROGRAM

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Abstract: Background: Cognitive impairment, a core feature of schizophrenia, is a major determinant of poor functional outcome in schizophrenia and no pharmacological treatments are currently available. Deficits in glutamatergic signaling play a key role in the neuropathology of schizophrenia, particularly in cognitive symptoms (1). BI 425809, an inhibitor of glycine transporter-1, enhances N-methyl-D-aspartate receptor signaling in the brain by increasing synaptic levels of its co-agonist glycine (1).
A 12-week, Phase II, proof-of-clinical-concept trial (NCT02832037) that included 509 patients demonstrated BI 425809 was well tolerated and significantly improved cognition in patients with schizophrenia (2). The Phase III CONNEX program aims to confirm the efficacy, safety and tolerability of BI 425809 in improving cognition and functioning across a larger cohort of patients with schizophrenia.

Methods: The CONNEX program consists of three replicate randomized, double-blind, placebo-controlled parallel-group trials in patients diagnosed with schizophrenia (NCT04846868, NCT04846881, NCT04860830) on a stable phase of antipsychotic treatment.

To achieve adequate statistical power, each trial aims to recruit 586 patients, 18–50 years old, treated with 1–2 antipsychotic medications (≥12 weeks on current drug and ≥35 days on current dose prior to treatment), who have functional impairment in day-to-day activities, and interact ≥1 hour per week with a designated study partner. Patients with cognitive impairment due to developmental, neurological, or other disorders, with a current DSM-5 diagnosis other than schizophrenia or receiving cognitive remediation therapy within 12 weeks prior to screening, will be excluded. Patients will be recruited from multiple centers across 32 countries in Asia, North and South America, and Europe, and randomized 1:1 to receive either BI 425809 10 mg (oral administration; n=293), or placebo (n=293) once daily over a 26-week period. The primary efficacy endpoint is change from baseline in overall composite T-score of the Measurement and Treatment Research to Improve Cognition in Schizophrenia Consensus Cognitive Battery. The key secondary efficacy endpoints are change from baseline in total score on the Schizophrenia Cognition Rating Scale and change from baseline in the adjusted total time in the Virtual Reality Functional Capacity Assessment Tool. Long-term safety and tolerability data will be collected in an open-label safety extension study (CONNEX-X).

Results: The studies are currently recruiting (first patients enrolled Aug–Sept 2021), with completion expected in Q2 2024. As part of the presentation, an overview will be provided of the current study status, including any information relating to screening failures, and the experience of collecting these data as part of a large multi-country, multi-center study.

Conclusion: To date, most large, industry-sponsored studies testing various compounds to address cognitive function have failed to show proof-of-clinical-concept. Further demonstration of the efficacy of BI 425809 in treating cognitive impairment in schizophrenia in this Phase III program would provide important insight into the role of glutamate in cognitive symptoms, that may also have relevance for other cognitive disorders. BI 425809 may represent the first efficacious medication for cognitive impairment associated with schizophrenia.

TH15. ENHANCING PARTICIPANT RETENTION: LESSONS GAINED FROM ATTENTION-DEFICIT/HYPERACTIVITY AND ANXIETY DISORDERS CLINICAL TRIAL METHODOLOGIES

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Abstract: Introduction: Reducing study participant attrition is paramount to a clinical trial's success, as poor retention leads to biased study results, reduced power, lower internal validity, less generalizability, and higher study costs (Liu et al., 2018). However, a thorough search of attention-deficit/hyperactivity disorder (ADHD) and anxiety disorder publications yielded no overarching research of these indications' participant clinical trial dropout rates, with the exception of Lurie and Levine's (2010) meta-analysis of posttraumatic stress disorder (PTSD) trials which found a high average withdrawal rate of 30%. Single studies on adult ADHD and other anxiety disorders, namely generalized anxiety disorder (GAD) and obsessive-compulsive disorder (OCD), found post-baseline attrition concerns, ranging from 33% (Sutherland et al., 2012) for ADHD to 42% for OCD (Foa et al., 2005). As such, the goals of the current

investigation were to obtain a more comprehensive understanding of reasons ADHD and anxiety disorder participants withdrawal and recommend strategies to improve retention within these trails. This was accomplished by analyzing several Independent Variables theorized to be linked with participant attrition and some of which have not been previously empirically explored (e.g., number of study scales and participant compensation).
Methods: Across 5 US research sites in the midwest and east and west coasts, 24 outpatient placebo-control (PC; n=21; 148 participants) and open-label (OL; n=3; 13 participants) ADHD, GAD, PTSD, and OCD clinical trials were aggregately evaluated. Examining these disorders compositely is consistent with the ample research regarding their interrelatedness (e.g., Reimherr et al., 2017). Participant attrition post-baseline were collected from Closeout Report Forms submitted to Institutional Review Boards and sponsors at the completion of the analyzed trials. These data served as the Dependent Variable in this investigation, depicting participant's decisions or circumstances leading to their discontinuation (e.g., withdrew consent and lost to follow-up) rather than matters out of their control (e.g., investigator discretion due to labs or adverse events).
Results: Pearson correlation analyses revealed that regardless of site location, retention was significantly correlated with less study visits (r=-.52; p=.01), higher visit frequencies (r=.46; p=.03), and shorter study duration (r=-.62; p=.002), while dropout was significant associated with more assessment scales in the trial (r=.44; p=.04). When PC were separately analyzed, the above variables remained statistically significant. There were few OL trials to adequately independently analyze.
Conclusions: The results of the current investigation can be applied to developing protocols and implementing strategies with an eye toward managing attrition. For example, the finding regarding assessment scales suggests that sponsors should consider outcome data via tempering the over-use of psychometric measures. Additionally, visit frequencies can be enhanced by having remote (phone call) visits between onsite visits where suicidality and adverse events are evaluated while reminding participants of the trial's contraception and alcohol / illicit drug restrictions. Other applications from the current investigation's findings to protocol and study management aimed at reducing attrition as well as study limitations will be discussed in the poster.

TH16. ULOTARONT IMPROVES METABOLIC PARAMETERS IN RODENT MODELS OF WEIGHT GAIN AND HYPERGLYCEMIA

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Abstract Background: Ulotaront (SEP-363856) is a trace amine-associated receptor 1 (TAAR1) agonist with 5-HT1A agonist activity currently in Phase 3 clinical trials for the treatment of schizophrenia. Metabolic Syndrome, characterized by central obesity, dyslipidemia, hypertension, and hyperglycemia, is highly prevalent in patients with schizophrenia and can be induced or exacerbated by antipsychotic drugs (APDs). The need for novel treatments that lack APD class-specific metabolic side effects is therefore apparent. As a new pharmacological class, ulotaront has no significant activity at receptors commonly associated with APD-induced metabolic alterations (i.e. D2, 5-HT2C, H1 and M3). Recent preclinical evidence has identified TAAR1 as novel regulator of metabolic control and a promising target for treating obesity and type 2 diabetes. Here we evaluated the risk-benefit

profile of ulotaront for the treatment of schizophrenia by assessing its effects on metabolic parameters in rodent models of iatrogenic weight gain and hyperglycemia.
Methods: Effects of 15-day oral ulotaront treatment on body weight (BW), food intake and metabolic parameters were investigated in rats on a high-fat diet (HFD). In addition, body weight effects were determined in a rat (8-day treatment) and mouse (21-day treatment) model of olanzapine-, and corticosterone-induced BW gain, respectively. Glucose tolerance was assessed in C57Bl6 and diabetic db/db mice following acute oral dosing. The acetaminophen absorption test was used to evaluate effects on gastric emptying in C57Bl6 mice. To obtain insights into the neurocircuits modulated by ulotaront, whole-brain 3D c-fos imaging was performed in C57Bl6 mice.

Results: Administration of ulotaront to rats on a HFD resulted in a dose-dependent reduction in BW, food intake and liver triglyceride content compared to vehicle controls. A more rapid reversal of olanzapine-induced BW gain and food intake was observed in rats switched to ulotaront treatment compared to vehicle alone. Consistent with the BW-lowering effects in rats, chronic treatment with ulotaront normalized corticosterone-induced BW gain in mice. Acute ulotaront dosing dose-dependently reduced plasma glucose excursion in C57Bl6 and diabetic db/db mice during an oral glucose tolerance test (oGTT). Neither glucose nor insulin levels were changed in response to ulotaront during an ivGTT. Acute TAAR1 activation delayed gastric emptying in mice, which is likely the main mechanism driving reductions in glucose excursion during the oGTT. Ulotaront increased neuronal activity (c-fos expression) in several brain regions associated with the regulation of food intake and integration of peripheral metabolic signals, which was distinct from the signature produced by the APD haloperidol.

Conclusion: Our data indicate that ulotaront not only lacks APD-induced metabolic liabilities but can reduce BW and improve glucose tolerance in rodent models. The underlying mechanisms are not fully elucidated but may include TAAR1-mediated peripheral effects on glucose homeostasis and gastric emptying, and/or direct modulation of homeostatic and hedonic neurocircuits regulating energy balance. The beneficial metabolic effects of ulotaront suggest a substantially improved risk-benefit profile compared to established APDs. Thus, TAAR1 agonists may not only represent a novel therapeutic class for the treatment of schizophrenia, but potentially also for metabolic disorders.

TH17. THE PREDICTION OF SUICIDAL IDEATION AS A FUNCTION OF DAILY MOOD AND ANXIETY SCORES COLLECTED USING MOBILE HEALTH (MHEALTH) TECHNOLOGY IN PATIENTS UNDERGOING TREATMENT FOR DEPRESSION

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Abstract: Background: Suicides and suicidal attempts are one of the most common causes of death in the USA. The rates of suicide have increased by 33% in the period 1999-2019. Clinically, a previous history of suicide is the main the risk factor, as well as the presence of comorbid conditions like depression and anxiety. Accurate and real-time prediction of suicidal thoughts may lead to improved management of patients with depression. Prediction of suicidality is difficult due to its day to day variability in relation to mood and anxiety symptoms. This can be overcome with the advent of mobile health (mHealth) technology that can capture granular data at a higher frequency than conventional therapeutic visitations.

Methods: This study will utilize data from the 'DepWatch' study, a mHealth study that uses the DepWatch app developed by our research group. The objective of this longitudinal study is to develop a mHealth-based, personalized diagnostic prediction system for patients undergoing treatment for depression. Patients are followed over 12 weeks using electronic assessments conducted via the DepWatch app installed on their smart phones and automatic sensory data gathered by the app. The electronic assessments include the Quick Inventory of Depression Symptomatology-self report (QIDS-SR) conducted on a weekly basis and weekly medication adherence and medication safety and tolerability questionnaires. The assessments include brief mood and anxiety assessments conducted on a daily basis. Patients are interviewed on a monthly basis by a study clinician. Logistic regression analyses and analyses of the demographic and clinical characteristic collected at baseline is being conducted to predict the development of suicidal thoughts. The key explanatory variables are the daily mood and anxiety levels. The outcome variable is suicidal ideation (SI) as determined by the self-reported subject response to question 12 (about suicidal ideation) on the QIDS-SR scale.

Results: A total of 39 subjects are in the interim Analysis Set. The mean age is 35 years, 89.7% are females. A total of 60.5% of participants are White, 13.2% Asian, and 7.9% African American. 44.4% either have a college degree or graduate education, 41.6% have some college education or technical schooling. 23.08% had previous use of an illicit substance (excluding marijuana). A regression model is being designed and will be presented. The model will investigate if SI can be predicted using the daily mood and anxiety scores.

TH18. ZURANOLONE SAFETY AND EFFICACY IN POSTMENOPAUSAL WOMEN WITH MAJOR DEPRESSIVE DISORDER (MDD): RESULTS FROM THE PHASE 3 SHORELINE STUDY

Scott Aaronson[*1], Gregory Mattingly[2], Robert Lasser[3], Indrani Nandy[3], Nilanjana Rana[3], Colville Brown[3], Richard Hughes[4], Divya Narayanan[4], James Doherty[3], Andrew Cutler[5]*

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Abstract Background: Perimenopausal women are at increased risk of developing major depressive disorder (MDD). Hormonal changes due to menopause can affect the metabolism of standard-of-care antidepressant (SOC ADT) therapy. Consequently, postmenopausal women with MDD may not respond well to SOC ADTs. Zuranolone (ZRN) is an investigational, oral, neuroactive steroid and GABAA receptor positive allosteric modulator in clinical development for once-daily, 2-week treatment of MDD. SHORELINE (NCT03864614) is an ongoing, open-label study evaluating the safety, tolerability, and need for repeat treatment courses with ZRN through 1 year in adults with MDD. Here we present a post hoc analysis of postmenopausal women in SHORELINE.

Methods: Adults with MDD (aged 18–75 y; 17-item Hamilton Rating Scale for Depression total score [HAMD-17] ≥20) were enrolled to 1 of 2 cohorts: 30 mg Cohort (ZRN30) or 50 mg Cohort (ZRN50). HAMD-17 responders (≥50% reduction from baseline) at Day 15 are eligible to continue in the study and are assessed every 2 weeks for the need for additional treatment courses. Primary endpoint is safety/tolerability; secondary endpoints include HAMD-17 response, HAMD-17 remission (HAMD-17 ≤7) and need for repeat treatment courses.

Postmenopausal women were identified based on baseline follicle-stimulating hormone >40 mIU/mL and if medical history coded terms contained 'menopause.'

Results: Of 924 patients (ZRN30 725; ZRN50 199) who had the opportunity to complete 1 year of follow up in SHORELINE by the data cut (Nov 2021), 152 (16.5%) were postmenopausal women (ZRN30 110/725 [15.2%]; ZRN50 42/199 [21.1%]). Other than age, sex, and SOC ADT use, baseline demographics in this subgroup were generally consistent vs the overall study population (ZRN30/ZRN50): mean age 59.7/56.3 vs 45.0/45.0 y; mean baseline HAMD-17 25.6/25.8 vs 25.3/25.1; ADT use 52.7%/52.4% vs 41.9%/41.2%. At Day 15 of treatment cycle 1 (Days 1–28), mean change from baseline in HAMD-17 (ZRN30/ZRN50) was −16.2/−15.3 for postmenopausal women vs −15.2/−16.0 overall; HAMD-17 response rate was 74.5%/64.3% vs 69.7%/74.9%; and HAMD-17 remission rate was 42.7%/23.8% vs 38.1%/40.2%. Of the postmenopausal women who responded to and completed treatment cycle 1 (ZRN30/ZRN50 n = 80/n = 26), 43.8%/38.5% (vs 42.9%/54.8% overall) did not require additional treatment courses during their time in the study (up to 1 year). The number of postmenopausal women who had ≥1 treatment-emergent adverse event (TEAE) in treatment cycle 1 was 53/110 (48.2%) for ZRN30 and 25/42 (59.5%) for ZRN50 vs 50.8% and 59.3% overall; most (96.2% [51/53; ZRN30]/76.0% [19/25; ZRN50]) experienced mild/moderate TEAEs (vs 95.4%/89.0% overall). Common (>5%) TEAEs in postmenopausal women included headache, somnolence, dizziness, diarrhea, upper respiratory infection, dry mouth, sedation, and insomnia (similar to overall population). TEAEs starting in treatment cycle 1 (ZRN30/ZRN50) led to discontinuation of study drug in 1.8%/11.9% of postmenopausal women vs 2.2%/6.5% overall and to study withdrawal in 1.8%/9.5% vs 2.6%/6.0% overall.

Conclusions: In SHORELINE, to date, zuranolone was generally well tolerated in postmenopausal women, with a similar safety profile as observed in the overall study population. Improvements in depressive symptoms in postmenopausal women were similar to the overall population. These data support development of zuranolone as a potential treatment for adults with MDD, including postmenopausal women.

TH19. THE SAFETY, EFFICACY, AND NEED FOR ADDITIONAL TREATMENT COURSES OF ZURANOLONE 50 MG IN THE OPEN-LABEL, PHASE 3 SHORELINE STUDY OF PATIENTS WITH MAJOR DEPRESSIVE DISORDER

Andrew Cutler[1], Scott Aaronson[2], Gregory Mattingly[3], Robert Lasser[4], Indrani Nandy[4], Nilanjana Rana[4], Colville Brown[4], Catherine Miller[5], Fiona Forrestal[5], Mona Kotecha[5], James Doherty[4]*

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Abstract: Background: Zuranolone (ZRN) is an investigational, oral neuroactive steroid and GABAA receptor positive allosteric modulator under clinical development as a once-daily, 2-week therapy for adults with major depressive disorder (MDD) as part of the LANDSCAPE program. The SHORELINE Study (NCT03864614) is an ongoing, open-label, Phase 3 longitudinal trial evaluating the safety, tolerability, and need for additional treatment courses with ZRN 30 mg or 50 mg for up to 1 year in adults with MDD. Data on the 50 mg Cohort of patients who had the opportunity to complete up to 1 year are reported here (the 30 mg data are previously reported).

Methods: SHORELINE is enrolling adult patients (aged 18–75 years) with MDD, 17-item Hamilton Rating Scale for Depression total score (HAMD-17) ≥20, and a Montgomery–Åsberg Depression Rating Scale ≥28. The study initially enrolled a single, open-label cohort for treatment with ZRN 30 mg. The study protocol was later amended to enroll a 50 mg Cohort. ZRN is administered orally, once nightly with food for 2 weeks. Use of pre-existing antidepressant therapy is permitted. HAMD-17 responders (≥50% reduction from baseline) at Day 15 are eligible to continue in the study and are assessed every 2 weeks for the need of additional treatment courses. A 9-item Patient Health Questionnaire score ≥10, followed by HAMD-17 ≥20 within approximately 1 week, is required for additional treatment courses with ZRN. There is a minimum of 8 weeks between consecutive treatment courses, to allow for a maximum of 5 total treatment courses during the 1-year period, if needed. The primary endpoint is safety/tolerability; secondary endpoints include need for additional treatment courses, change from baseline (CFB) in HAMD-17, and HAMD-17 response rate at the end of each 2-week treatment course.

Results: As of November 2021, SHORELINE had enrolled 199 patients in the 50 mg Cohort who had the opportunity to complete up to 1 year of study. Demographic and baseline characteristics: mean (SD) age, 45.0 (14.1) years; female, 69.3%; White, 87.9%; patients on pre-existing antidepressant therapy, 41.2%; and mean (SD) HAMD-17, 25.1 (3.3). At least 1 treatment-emergent adverse event (TEAE) was reported in 137/199 (68.8%) patients. Most patients (117/137; 85.4%) reported mild or moderate TEAEs. No trend in incidence of TEAEs over different treatment cycles (up to 5 courses) was identified. Types and incidence of TEAEs was observed to be similar across treatment cycles; the most common (>5%) TEAEs in the 50 mg Cohort included headache, somnolence, dizziness, sedation, nausea, insomnia, and tremor. Among the 146 patients who responded to the first 2-week treatment course and completed treatment cycle 1 (Days 1–28), 116 (79.5%) received at most 2 treatment courses during their time in the study (up to 1 year), including 80 (54.8%) who only received an initial treatment course and 36 (24.7%) who received 2 treatment courses in total; the average (range) number of total treatment courses received was 1.8 (1-5).

Conclusions: In the SHORELINE Study, ZRN 50 mg was generally well tolerated, with an adverse event profile generally consistent with the overall safety profile of ZRN observed to date. The majority of TEAEs were mild to moderate in severity. Approximately 55% of patients who responded to the initial 2-week treatment course of ZRN 50 mg and were in study at Day 28 received 1 treatment course total, and approximately 80% received at most 2 treatment courses during their time of up to 1 year in the study.

TH20. CARIPRAZINE FOR THE ADJUNCTIVE TREATMENT OF MAJOR DEPRESSIVE DISORDER: RESULTS OF A RANDOMIZED PHASE 3 PLACEBO-CONTROLLED STUDY (STUDY 301)

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Abstract: Background: Patients with major depressive disorder (MDD) often do not respond to antidepressant (ADT) monotherapy; adjunctive treatment is often used to address this unmet

need. Cariprazine (CAR), a dopamine D3-preferring D3/D2 and serotonin 5-HT1A receptor partial agonist approved to treat adults with manic, mixed, or depressive episodes of bipolar I disorder, is under investigation as adjunctive therapy for patients with MDD.
Methods: This randomized, double-blind, phase 3 placebo (PBO)-controlled study assessed the efficacy, safety, and tolerability of CAR 1.5 and 3 mg/d as an adjunct to ADT in adult patients with MDD (18-65 years) and inadequate response to ADT alone (NCT03738215). The primary endpoint was change from baseline to week 6 in Montgomery-Åsberg Depression Rating Scale (MADRS) total score. Hamilton Depression Rating Scale (HAMD-17), Hamilton Anxiety Rating Scale (HAM-A), and Clinical Global Impressions (CGI) were also assessed. Treatment response was defined as at least 50% decrease in MADRS total score at week 6.

Results: Patients (n=751) in the modified intent-to-treat population were randomly assigned to CAR 1.5 mg/d+ADT (n=250), CAR 3 mg/d+ADT (n=252) or PBO+ADT (n=249). Mean age was 44.8 years and 73.4% were female; mean baseline total scores were: MADRS=32.5, HAMD-17=25.9, HAM-A= 21.4. Overall, 89.7% of patients completed the study; rates of discontinuation due to adverse events (AEs) and lack of efficacy were 3.6% and 0.5%, respectively. The difference in MADRS total score change from baseline to week 6 was statistically significant after multiplicity adjustment for CAR 1.5 mg/d vs PBO (-14.1 vs -11.5; adjusted P=.0050), but not for CAR 3 mg/d (-13.1; P=.0727). Differences for CAR 1.5 mg/d vs PBO were observed by week 2 (nominal P=.0453) and maintained at weeks 4 (nominal P<.0001) and 6 (nominal P=.0025). At week 6, more CAR 1.5 mg/d patients (44%) than PBO patients (34.9%) responded to treatment (nominal P=.0446). Greater improvement in the CGI-I scores was observed for CAR 1.5 (nominal P=.0026) and 3 mg/d (nominal P=.0076) vs PBO. At week 6, improvement in HAMD-17 total score reached nominal significance for CAR 1.5 mg/d vs PBO (-13.1 vs -11.1; nominal P=.0017), but not for CAR 3 mg/day (-12.2; P=.0783). HAM-A improvement was greater for CAR 1.5 mg/d vs PBO (nominal P=.0370). There were no deaths; 2 serious AEs occurred in each group (CAR: kidney infection, social stay hospitalization; PBO: depression; multiple sclerosis). The most common CAR AEs (≥5% and twice PBO) were akathisia and nausea.

Conclusion: Cariprazine 1.5 mg/d was effective as adjunctive treatment in adults with MDD and inadequate response to ADT. Cariprazine was generally well tolerated, with a safety profile that was consistent with other indications. Together with results from a prior flex-dose study, these results suggest that adjunctive cariprazine may be an effective option for patients with inadequate response to ADT alone. Supported by AbbVie.

TH21. SAFETY AND TOLERABILITY OF CARIPRAZINE FOR THE ADJUNCTIVE TREATMENT OF MAJOR DEPRESSIVE DISORDER: A POOLED ANALYSIS OF PHASE 2B AND 3 CLINICAL TRIALS

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Abstract Background: Cariprazine has been shown to be efficacious in placebo-controlled clinical trials. In this pooled analysis, the safety of cariprazine in patients with major depressive

disorder (MDD) with inadequate response to antidepressants was evaluated using data from placebo-controlled studies of up to 8 weeks' duration and a long-term open-label safety study. Methods: The safety, tolerability, and efficacy of cariprazine as an adjunctive treatment for patients with MDD with inadequate response to antidepressant alone was assessed in 5 placebo-controlled studies (two 6-week fixed-dose studies [NCT03738215; NCT03739203] and three 8-week flexible-dose studies [NCT00854100; NCT01715805; NCT01469377]) and one 26-week open-label flexible-dose study (NCT01838876). Fixed doses of cariprazine 1.5 and 3 mg/d and flexible doses of 0.1-4.5 mg/d were evaluated. Safety assessments included adverse event (AE) reporting, clinical laboratory tests, weight and other vital signs, and suicide evaluation with Columbia-Suicide Severity Rating Scale (C-SSRS). Pooled analyses of the incidence of safety endpoints overall and within each treatment arm were performed using the most frequent (modal) daily dose taken by patients during the study.

Results: A total of 2,222 MDD patients with an ongoing antidepressant received treatment with cariprazine, representing 370 patient-years of exposure in placebo-controlled and open-label studies. In the placebo-controlled studies, 1,969 patients were randomized to cariprazine (dose range, 0.1-4.5 mg/d) and 1,108 patients were randomized to placebo. Overall, treatment-emergent AEs occurred in 61% of cariprazine- and 48% of placebo-treated patients; discontinuation due to an AE occurred with 6% of cariprazine- and 2% of placebo-treated patients. The 2 AEs that occurred in at least 5% of cariprazine-treated patients and at a rate at least twice the rate in placebo-treated patients were akathisia (cariprazine=11%; placebo=2%) and restlessness (cariprazine=6%; placebo=2%). Changes in metabolic parameters, including shifts in fasting glucose and lipid parameters, were similar in cariprazine- and placebo-treated patients. In the long-term safety study, mean weight change was 1.6 kg over 6 months. In the placebo-controlled and long-term studies, other safety endpoints including laboratory and C-SSRS assessments of suicidality were generally consistent with the safety profile of cariprazine in approved indications of bipolar disorder and schizophrenia.

Conclusion: Cariprazine is generally safe and well-tolerated in MDD patients with inadequate response to antidepressant monotherapy. Safety analysis of 2,222 cariprazine-treated patients with MDD revealed no new safety signals, and the data is consistent with the currently approved prescribing information. This study was supported by AbbVie.

TH22. IMPACT OF AXS-05, AN ORAL NMDA RECEPTOR ANTAGONIST, ON ANHEDONIC SYMPTOMS IN MAJOR DEPRESSIVE DISORDER

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Abstract: Background: Anhedonia is one of the core features of major depressive disorder (MDD) and is present in up to 75% of individuals diagnosed with MDD. Anhedonia is considered among the most bothersome aspects of MDD by patients, has been associated with decreased functioning and is a risk factor for non-response to antidepressant therapy. Even among those who have responded to antidepressant therapy, anhedonic symptoms remain common residual symptoms. These observations demonstrate an urgent need for novel therapies for MDD that can improve both overall depressive and anhedonic symptoms.

AXS-05 (dextromethorphan-bupropion) is a novel, oral, investigational, NMDA receptor antagonist with multimodal activity being developed for MDD. The dextromethorphan component of AXS-05 is an antagonist of the NMDA receptor, an ionotropic glutamate receptor, and a sigma-1 receptor agonist. The bupropion component of AXS-05 serves primarily to increase the bioavailability of dextromethorphan, and is a norepinephrine and dopamine reuptake inhibitor.

Objective: To evaluate the effect of AXS-05 as compared to placebo in improving anhedonic symptoms in MDD as assessed by the MADRS anhedonia subscale.

Methods: GEMINI (N=327) was a randomized, double-blind, placebo-controlled, 6-week, U.S trial, which randomized (1:1) adults with MDD to AXS-05 (dextromethorphan 45 mg-bupropion 105 mg) or placebo, twice daily for 6 weeks. The primary endpoint was change from baseline in the MADRS total score at Week 6. A post-hoc analysis was conducted to determine the impact of AXS-05 as compared to placebo on the 5-item MADRS anhedonia subscale. The items included in the MADRS anhedonia subscale are: apparent sadness, reported sadness, concentration difficulties, lassitude, and inability to feel. Previous research has demonstrated that the MADRS anhedonia subscale is highly correlated to the to the Snaith-Hamilton Pleasure Scale (Cao et al. Front Psychiatry. 2019;10:17.), a validated measure of hedonic tone.

Results: Treatment with AXS-05 resulted in a statistically significant improvement in MADRS total score compared to placebo at Week 6, thus meeting the primary endpoint ($p=0.002$). At baseline, the MADRS anhedonia factor score was 19.8 and 19.6 in the AXS-05 and placebo group, respectively. Starting at Week 1, the first timepoint measured, treatment with AXS-05 resulted in a statistically significant mean reduction from baseline in the MADRS anhedonia subscale score of 4.44 versus 2.69 points for placebo ($p<0.001$). At Week 6, the mean reduction from baseline in the MADRS anhedonia subscale was 9.70 for AXS-05 compared to 7.22 for placebo ($p=0.001$). Rates of response ($\geq$ 50% MADRS anhedonia subscale improvement) were statistically significantly greater for AXS-05 compared to placebo at Week 1 ($p<0.001$) and at every time point thereafter, being achieved by 54% of AXS-05 patients versus 36% of placebo patients at Week 6 ($p<0.001$). Treatment with AXS-05 was generally safe and well tolerated.

Conclusions: Treatment with AXS-05 rapidly and significantly reduced anhedonic symptoms as well as overall depressive symptoms. These data support the efficacy of AXS-05 in a broad range of symptomatology in patients with MDD.

This research was supported by Axsome Therapeutics.

TH23. DECISIONS TO CONTINUE, SWITCH, OR DISCONTINUE ANTIDEPRESSANTS AMONG PATIENTS WITH MAJOR DEPRESSIVE DISORDER: OUTCOMES FROM A REAL-WORLD, EVIDENCE-BASED SURVEY WITH A FOCUS ON SEXUAL DYSFUNCTION

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Abstract: Background: Among patients with major depressive disorder (MDD), tolerability issues, including treatment-emergent sexual dysfunction (TESD), can lead to treatment discontinuation, worsening of a patient's condition, and failure to achieve treatment goals. In this real-world, evidence-based survey, we assessed the reasons why patients with MDD continued, switched, or discontinued oral antidepressants (ADs) and we evaluated the impact of sexual dysfunction.

Methods: Survey-eligible, commercially insured patients aged 18–64 years with ≥1 medical claim for MDD and treated with ADs between 12/1/2018 and 11/30/2019 were identified from the HealthCore Integrated Research Database. Consenting, qualified patients completed an online survey that categorized them as continuers, switchers, or discontinuers based on their current AD use and use of other ADs in the past 12 months. The survey included questions regarding reasons why patients continued, switched, or discontinued ADs; for example, effectiveness and treatment satisfaction, healthcare provider recommendations, comorbidities, cost, and tolerability (including side effects such as fatigue, weight gain, and sexual dysfunction).

Results: Overall, 900 patients completed the survey (554 [62%] continuers, 298 [33%] switchers, and 48 [5%] discontinuers). Among 852 patients currently using an AD (continuers and switchers), 1178 AD medications were reported as currently taken. The top 5 reasons for patients choosing their current AD were "healthcare provider recommendation" (95% major/minor), "prior antidepressant not working" (59% major/minor), "fewer side effects" (51% major/minor), "best medication considering other health problems" (48% major/minor), and "fewer drug interactions" (34% major/minor). Sexual problems since starting their current AD were reported with 31% of current ADs, yet respondents spoke with their healthcare providers for fewer than half (44%) of these occurrences. Among 346 patients who either switched or discontinued their AD, 534 prior ADs were reported as taken in the past 12 months. The top 5 reasons for discontinuing the medication were "not satisfied with it" (65% major/minor), "didn't feel it was working" (63% major/minor), "healthcare provider recommended another medication" (54% major/minor), "didn't like side effects" (49% major/minor), and "didn't like the way it made me feel" (46% major/minor). Sexual dysfunction was among the top 10 reasons for switched and discontinued ADs, with "sexual problems" reported as a major/minor reason for 24% of discontinued ADs. Overall, of 506 patients without any symptoms of sexual dysfunction prior to or as part of their MDD diagnosis, 94 (19%) were characterized as TESD positive.

Conclusions: From the patient perspective, healthcare provider recommendations and medication side effects play an important role in AD continuation, switch, and discontinuation for treatment of MDD. In this study, sexual problems were cited as a common reason for discontinuing treatment, yet often were not discussed with a healthcare provider. These findings may inform the importance of patient-physician shared decision-making for MDD management, including discussion, monitoring, and management of side effects.

TH24. THE SAFETY AND EFFICACY OF COMP360 PSILOCYBIN THERAPY AS ADJUNCTIVE TREATMENT IN TREATMENT- RESISTANT DEPRESSION

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Abstract: Background: COMP360 psilocybin therapy is under investigation as antidepressant monotherapy for treatment-resistant depression (TRD). In a recent phase IIb, randomised, double-blind clinical trial, a single 25 mg dose of COMP360 psilocybin given with psychological support from specially trained therapists, demonstrated a rapid and significantly greater decrease in depressive symptoms compared with 1 mg in medication free or withdrawn patients. These encouraging results raise the question of how COMP360 psilocybin therapy acts adjunctive to serotonergic antidepressants.

Aims: To explore the safety and efficacy of COMP360 psilocybin therapy administered adjunctive to selective serotonin reuptake inhibitors (SSRIs) for TRD.

Methods: Participants with TRD were recruited in this exploratory, phase II, open-label, multicentre trial. SSRI monotherapy was required for at least 6 weeks prior to entering the study. After preparation with a trained therapist, participants received COMP360 25 mg in a therapist-supported session and were followed for 3 weeks. The efficacy of COMP360 psilocybin therapy, adjunctive to SSRIs, was assessed by changes in the Montgomery-Asberg Depression Rating Scale (MADRS) total score at week 3 compared with baseline. The proportion of responders and remitters, clinical global impression - severity (CGI-S) scores, and safety outcomes were reported as secondary endpoints. The intensity of the psychedelic experience was assessed via the Five-Dimensions Altered State of Consciousness (5D-ASC) questionnaire at the end of the COMP360 administration day.

Results: 19 participants were administered 25 mg COMP360 psilocybin therapy adjunctive to their SSRI and all completed the study. Stable ongoing SSRI treatments included escitalopram (n=6), sertraline (n=6), fluoxetine (n=3), vilazodone (n=2), paroxetine (n=1), and citalopram (n=1). The majority of participants had failed 2 treatments during their current depressive episode (63.2%) prior to study entry. MADRS total scores at baseline indicated at least moderate depression (31.7, SD=5.77). After COMP360 administration participants had a mean change of -14.9 (SD=11.97) points improvement in MADRS total score at the week 3 visit compared with baseline. At week 3, 42.1% (n=8) participants were responders (defined as a ≥50% improvement in MADRS total score from baseline) and remitters (defined as a MADRS total score ≤10). Findings with the CGI-S were consistent with these results. COMP360 psilocybin therapy was well tolerated, with 11 (57.9%) participants reporting treatment emergent adverse events (TEAEs), the majority (81.2%) being of mild severity. On the day of COMP360 administration, average 5D-ASC scores of participants were consistent with a psychedelic experience according to the 5D-ASC scores (Oceanic Boundlessness=47.3 SD=30.37; Anxious Ego Dissolution=24.1, SD=20.30; Visual Restructuralization=51.7, SD=27.22; Auditory Alterations=17.5, SD=20.68; Reduction of Vigilance=43.7, SD=24.42).

Conclusions: COMP360 psilocybin therapy given at 25 mg dose adjunctive to an ongoing SSRI was well tolerated in this exploratory study. The encouraging efficacy and safety results support further investigation into COMP360 psilocybin therapy adjunctive to antidepressants as a treatment for TRD, especially in cases where antidepressant withdrawal may be challenging. This approach should be explored in future randomised control trials.

TH25. SOCIODEMOGRAPHIC CHARACTERISTICS, HEALTH-RELATED BEHAVIORS, AND CLINICAL CHARACTERISTICS BY DEPRESSION DIAGNOSIS STATUS: A NATIONAL HEALTH AND WELLNESS SURVEY ANALYSIS

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Abstract: Background: Depression is the leading cause of disability globally, costing $233 billion in the U.S. alone. It is estimated that in the U.S., roughly two-thirds of all cases of depression are undiagnosed. Few if any studies have reported the characteristics of individuals with undiagnosed depression (based on a clinically validated instrument) to assess similarities and differences with those with diagnosed depression.

Objective To describe sociodemographic and clinical characteristics, health-related behaviors, and outcomes for individuals with physician diagnosed depression compared to those with undiagnosed depression, but with Patient Health Questionnaire-9 (PHQ-9) indicative of depression.

Methods: This study used data from the 2020 US National Health and Wellness Survey, a self-administered, internet-based, cross-sectional questionnaire. The inclusion criteria were age >18 years, a PHQ-9 score, and a valid Patient Activation Measure (PAM). Two cohorts were identified; 1) individuals who self-reported a physician diagnosis of depression and who experienced depression in the past 12 months (depressed), and 2) individuals who did not self-report a physician diagnosis of depression but screened positive for depression (>10) on the PHQ-9 (depression-undiagnosed); this cohort was stratified by whether they self-reported experiencing depression in the past 12 months (depression undiagnosed-aware, depression undiagnosed -unaware). Sociodemographics (age, gender, race, marital status, education, income, insurance), clinical/health behaviors (body mass index, smoking status, alcohol, exercise, patient activation, comorbidities), healthcare utilization (healthcare use in past 6 months, direct and indirect medical costs), quality of life and work productivity are presented descriptively for each group.

Results: A total of 8216 individuals comprised the depression-diagnosed group, while 1794 individuals were depression-undiagnosed-aware and 4437 were depression-undiagnosed-unaware. Those in the depression-diagnosed group had a higher mean age (44) than the depression-undiagnosed-aware (35.6) and depression-undiagnosed-unaware (35.1) groups. Severity of depression based on PHQ-9 was substantial among both undiagnosed groups (14.7 “aware”; 14.3 “unaware”), indicative of mild major depressive disorder based on PHQ-9 scoring. Whites had higher representation among the depression-diagnosed group, with the percentage of Black, Hispanic, and Asian respondents overrepresented in the undiagnosed categories. Also notable were the increased frequency of uninsured among the undiagnosed respondents. Those with diagnosed depression exhibited greater patient activation than those with undiagnosed depression. Individuals in the depression-undiagnosed-unaware group had substantially higher annual indirect and direct medical costs, including greater use of acute care services and less frequent outpatient visits.

Conclusions: This exploratory descriptive analysis supports the high burden of illness of undiagnosed depression, while highlighting an even greater burden among those who lack self-awareness of their depression. Barriers to effective screening for depression are widespread and should be addressed at all levels of society and throughout the healthcare system to identify those individuals who may benefit from interventions.

TH26. FACTORS ASSOCIATED WITH ADHERENCE TO ESKETAMINE NASAL SPRAY AMONG MAJOR DEPRESSIVE DISORDER (MDD) SUBPOPULATIONS:

ROLE OF SOCIAL DETERMINANTS AND DISTANCE FROM TREATMENT CENTERS.

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Abstract: Background: Esketamine nasal spray CIII (esketamine) is indicated for adults with treatment-resistant depression (TRD) or depressive symptoms in adults with MDD and suicidal ideation or behavior (MDSI). All patients complete an induction phase, requiring twice weekly visits for 4 weeks. After induction, TRD patients (but not always MDSI patients) transition to maintenance phase (administration once per week or less). Esketamine must be administered under the supervision of a certified clinician at a treatment center in accordance with the approved Risk Evaluation and Mitigation Strategy (REMS).
Objective: To measure the association of social determinants and distance to treatment center with adherence and persistence to esketamine.

Methods: Using medical and pharmacy claims licensed from Clarivate and county-level social determinants data from the Area Health Resources File, a retrospective cohort study was conducted among U.S. adults who initiated esketamine between 10/11/2019 and 12/31/2020. The 12 months prior to initiation (baseline) was used to profile demographics, healthcare utilization, social determinants, and comorbidities (Charlson Comorbidity Index (CCI)). The six months following initiation were used to measure adherence (completing eight treatments in the first 45 days) and persistence, defined as continuation without ≥ 60-day gap between esketamine sessions. Distance (in geodesic miles) was derived from the individual's assigned zip code centroid to the esketamine treatment center, categorized by tertile. Multivariate analyses included logistic regression (adherent in the first 45 days: yes/no) and Cox proportional hazards model for time to discontinuation.

Results: Of 310 individuals with TRD or MDSI, 134 (43.2%) were adherent within the first 45 days. Adherent individuals had fewer comorbidities (CCI 0.3 vs. 0.7; $p<0.01$), were less likely to have substance disorders (5.2% vs. 15.9%; $p<0.01$) and were more likely to have a baseline psychiatry visit (82.8% vs. 55.1%; $p<0.01$), antidepressant use (51.5% vs. 33.5%; $p<0.01$), and oral antipsychotic use (29.1% vs. 17.0%; $p<0.01$). After adjustment, traveling farther than 7.3 miles to the treatment center was associated with non-adherence (OR: 0.6; 95%CI 0.3, 1.0), as was comorbid substance use disorder (OR: 0.4; 95%CI 0.2, 0.9) while baseline psychiatric medication use (OR 1.9; 95%CI: 1.1-3.0) and psychiatry visits (OR 1.8; 95%CI: 1.1-3.0) were associated with adherence.

Among the 277 individuals with TRD, 183 (66.1%) discontinued within 6 months. Individuals residing closer (≤7.3 miles) to the treatment center were less likely to discontinue esketamine (62.0% vs. 74.2%, $p<0.05$). After adjustment, residing farther (>7.3 miles) from a treatment center was associated with higher discontinuation rate (Hazard Ratio (HR) 1.6; 95%CI: 1.1, 2.2) as was Medicaid insurance (HR: 1.6, 95%CI 1.0, 2.5), and percent Asian (HR: 1.6; 95%CI: 1.0, 2.5) whereas baseline psychiatry visits (HR: 0.6; 95%CI: 0.4-0.8) was associated with higher persistence.

Conclusions: Our results suggest that race, Medicaid insurance, prior psychiatric care, prior psychiatric medication use, comorbid substance use disorder, and distance to treatment center are associated with esketamine use. Providers of esketamine treatment may need to consider social determinants and distance to treatment center when providing scheduling and support services.

TH27. REAL-WORLD HEALTHCARE RESOURCE UTILIZATION AND COSTS OF PATIENTS WITH MAJOR DEPRESSIVE DISORDER WITH ACUTE SUICIDAL IDEATION OR BEHAVIOR INITIATING ESKETAMINE IN UNITED STATES

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Abstract: Objective: To describe healthcare resource utilization (HRU) and costs during the 6-month periods before and after esketamine initiation among adults with major depressive disorder (MDD) with acute suicidal ideation or behavior (hereafter, MDSI) in the United States (US).

Methods: Adults with ≥1 esketamine claim were selected from Clarivate's Real World Data (RWD) Repository (01/2016-03/2021). Patients initiated esketamine (index date) from its first availability on 03/05/2019 (esketamine approval date for treatment resistant depression [TRD]) and had evidence of MDSI (≥1 diagnosis for MDD and ≥1 diagnosis for either suicidal ideation or behavior) on the index date or in the 12 months of clinical activity before it. Patients with diagnoses for schizophrenia spectrum or other psychotic disorders during the 12 months of clinical activity pre-index or without ≥6 months of clinical activity post-index were excluded. HRU and costs were described over the 6-month period before the index date and over the 6-month period after the index date, including the index date. Healthcare costs were reported in 2021 US dollars, as charged amounts (medical costs) or from a private payer's perspective (pharmacy costs).

Results: Overall, 115 patients were included in the analysis (mean [median] age 42.0 [42.5] years, 65.2% female). The proportion of patients with claims-based evidence of TRD before or on the index date was 13.9%. Among 63.5% of patients with ≥1 diagnosis for suicidal ideation or behavior during the 6 months pre-index period, 45.2% received their most recent diagnosis in an inpatient setting, 42.5% in an outpatient, 11.0% in an emergency department, and 1.4% in other unclassified setting. The mean [median] time from the most recent suicidal ideation or behavior diagnosis to index date was 2.3 [1.8] months. Among 67.8% of patients with ≥1 diagnosis for MDD during both the 6-month pre- and post-index periods, 76.9% and 60.3% had severe MDD based on the most recent diagnosis in each period, respectively. Proportions of patients with all-cause inpatient admissions were 37.4% and 19.1% during the 6-month pre- and post-index periods, respectively. Proportions of patients with emergency room visits were 42.6% and 33.9% during the 6-month pre- and post-index periods, and proportions of patients with outpatient visits were 92.2% and 81.7%, respectively. Mean [median] all-cause monthly total healthcare charges were $8,371 [$3,475] in the 6 months pre-index and $6,486 [$3,906] in the 6 months post-index. Mean [median] all-cause monthly medical charges comprised $8,252 [$3,188] pre-index and $4,733 [$1,652] post-index and were driven by outpatient (pre-index: $4,439 [$1,313], post-index: $2,570 [$1,006]) and inpatient charges (pre-index: $2,507 [$0], post-index: $1,188 [$0]). In the pre- and post-index periods, 65.9% and 65.8% of all-cause monthly medical charges were mental-health related, respectively.

Conclusions: Proportion of patients with MDSI with severe MDD diagnosis, as well as all-cause HRU and monthly medical charges trended lower in the 6-month period after patients were initiated on esketamine relative to the 6-month period prior to esketamine initiation.

TH28. ACCESS AND REAL-WORLD USE OF ESKETAMINE AMONG PATIENTS WITH MAJOR DEPRESSIVE DISORDER WITH ACUTE SUICIDAL IDEATION OR BEHAVIOR ACROSS VARIOUS HEALTH PLANS IN UNITED STATES

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Abstract Objective: To describe access to and real-world use of esketamine and other treatment patterns among adults with evidence of major depressive disorder (MDD) with acute suicidal ideation or behavior (MDSI) initiated on esketamine after its approval date for (1) treatment resistant depression (TRD; overall MDSI cohort) and (2) MDSI (MDSI indication cohort, subset of overall cohort).

Methods: Adults with ≥1 esketamine claim were selected from Clarivate's Real World Data (RWD) Repository (01/2016-03/2021). Patients had evidence of MDSI (≥1 diagnosis for MDD and ≥1 diagnosis for suicidal ideation or behavior) during the 12 months before (baseline period) or on the date of the first esketamine claim (index date). Patients with diagnoses for schizophrenia spectrum or other psychotic disorders during baseline were excluded. Patients with MDSI and an index date on or after 03/05/2019 (esketamine approval date for TRD) were included in the overall MDSI cohort, and those with an index date on or after 08/05/2020 (esketamine approval date for MDSI) were included in the MDSI indication cohort. Access to esketamine through pharmacy claims based on approval and rejection rates, esketamine use, and other treatment patterns were described over the follow-up period spanning the index date until the earliest of end of data or continuous clinical activity.

Results: 269 patients in the overall MDSI cohort and 78 in the MDSI indication cohort had esketamine pharmacy claims. When the 1st claim was a pharmacy claim, in the overall MDSI and MDSI indication cohorts, respectively, 46.8% and 39.7% had the claim approved, 38.7% and 47.4% had the claim rejected (most common reason: claim errors [52.9% and 54.1%], and 14.5% and 12.8% abandoned their claim. For the 8th esketamine treatment session (per label, completion of induction treatment), 90.7% and 81.3% of patients had their claim approved in the overall MDSI and MDSI indication cohorts, respectively.

A total of 169 patients initiated esketamine in the overall MDSI cohort (mean and median age 40.9 years, 62.1% female, 88.2% commercial insurance plan, 5.3% Medicaid, 3.6% Medicare) and 47 in the MDSI indication cohort (mean [median] age 37.7 [36.7] years, 63.8% female, 87.2% commercial insurance plan, 4.3% Medicaid, 4.3% Medicare). During the follow-up period, 39.6% and 36.2% of patients had ≥1 claim for an antidepressant other than esketamine in the overall MDSI and MDSI indication cohorts respectively. In the overall MDSI and MDSI indication cohorts, 37.9% and 27.7% received psychotherapy, 11.2% and 6.4% received care in a specialized mental health facility, 5.9% and 2.1% received electroconvulsive therapy, respectively. During the follow-up period, 45.0% of patients in the overall MDSI cohort and 38.3% in the MDSI indication cohort had ≥8 esketamine treatment sessions. The mean

[median] time from index date to the 8th session was 85.0 [58.5] days in the overall MDSI cohort and 50.8 [49.0] days in the MDSI indication cohort (per label, 28 days).

Conclusion: Accurate billing coding is needed to ensure access to esketamine as over a third of patients had their 1st esketamine pharmacy claim rejected. Access to esketamine based on the claim approval rate improved over the course of treatment. Patients who initiated esketamine after the approval date for MDSI indication had a shorter time to completion for induction treatment versus the overall MDSI cohort.

TH29. A POST HOC ANALYSIS OF PATIENTS WHO RECEIVED ESKETAMINE NASAL SPRAY MONOTHERAPY IN AN OPEN-LABEL SAFETY EXTENSION STUDY (SUSTAIN -3)

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Abstract: Background: Esketamine nasal spray (ESK) is indicated, in conjunction with an oral antidepressant, for treatment of adults with treatment-resistant depression (TRD) and for treatment of depressive symptoms in adults with MDD with acute suicidal ideation or behavior (1, 2). This post hoc analysis of SUSTAIN-3 characterized a subgroup of patients who received ESK without concurrent oral medication (OM [antidepressants, antipsychotics, or antiepileptics]; ie, ESK monotherapy) at the investigators' discretion.

Methods: Patients with TRD from an ongoing phase 3, open-label (OL) safety extension study, SUSTAIN-3 (NCT02782104), were included in the analysis. Included patients were aged 18-74 years and could have entered SUSTAIN-3 from 1 of 6 "parent" studies; during SUSTAIN-3, they either had never received concurrent OM with ESK or had stopped their OM but continued ESK as monotherapy for a period of ≥3 months. During the induction (IND) phase of SUSTAIN-3, OL ESK was flexibly dosed twice-weekly for 4 weeks. For patients who proceeded to the optimization/maintenance (OP/M) phase, ESK dosing frequency was individualized based on depression severity and tolerability. Most patients (n = 37) entered directly into the OP/M phase from their previous parent trial; too few patients had IND endpoint results for IND analyses. Therefore, efficacy outcomes included changes from baseline (ie, beginning of monotherapy in OP/M phase) in disease severity during the OP/M phase, based on the Montgomery-Åsberg Depression Rating Scale (MADRS) and the Patient Health Questionnaire 9-item (PHQ-9), and functional outcomes based on the Sheehan Disability Scale (SDS), which are summarized descriptively. The proportion of patients in remission (defined as MADRS score ≤12) and safety/tolerability data are also reported.

Results: 50 patients were included in this analysis (mean age, 48.0 years; White, 86.0%; female, 66.0%); 21 patients had never received any OM during SUSTAIN-3 and 29 patients had been receiving an OM in SUSTAIN-3 but stopped taking their OM and continued ESK as monotherapy for ≥3 months. Among patients who never received a concurrent OM in SUSTAIN-3, 16 (76.2%) had >1 year of ESK monotherapy exposure during the study; among patients who had previously received but discontinued (DC) OM and continued to receive ESK monotherapy for ≥3 months, 21 patients (72.4%) had >1 year of ESK monotherapy exposure. Throughout OP/M, most patients received ESK weekly or every other week; the median modal dose was 84.0 mg. The most common TEAEs (>20%) were headache, dizziness, nausea,

anxiety, and diarrhea. Rates of early DC due to AEs and lack of efficacy were 0 and 6.0% (n=3), respectively. Mean (SD) MADRS, PHQ-9, and SDS scores at OP/M baseline were 13.6 (11.1), 7.8 (6.4), and 8.9 (7.6), respectively. During OP/M, changes from monotherapy baseline to endpoint in MADRS, PHQ-9, and SDS scores were −1.1 (7.5), −0.1 (5.7), and 0.1 (5.4), respectively, suggesting that measures of depression severity and functioning remained stable throughout ESK monotherapy. The proportion of patients in remission was 50.0% (25/50 patients) at OP/M baseline and 53.1% (26/49 patients) at OP/M endpoint.

Conclusion: Overall, safety and tolerability were consistent with the established profile of ESK with no new safety signals identified. Patients in SUSTAIN-3 who received ESK monotherapy for ≥3 months continue to demonstrate stability of depressive symptoms and functioning.

TH30. THE IMPACT OF (2R,6R)-HNK AND REELIN ON IPSC-DERIVED NEURONS FROM TREATMENT-RESISTANT DEPRESSION PATIENTS

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Abstract: Introduction: Major Depressive Disorder (MDD) is the leading cause of disability worldwide, with a lifetime prevalence rate around 16%. Despite this ubiquity, traditional antidepressants have a substantial therapeutic time delay and low efficacy rates. Ketamine has been discovered to have rapid and robust antidepressant effects. Research suggests that the antidepressant effects of ketamine are mediated through a transient activation of the mammalian target of rapamycin (mTOR) which promotes a sustained elevation of proteins such as postsynaptic density-95 protein (PSD95). (2R,6R)-hydroxynorketamine (HNK) is a major metabolite of ketamine that appears to produce similar rapid antidepressant effects in animal models without the associated side effects of ketamine administration. Reelin, a large glycoprotein, is an important mediator of synaptic plasticity that is downregulated in depression and parallels some of the behavioural and biological effects of ketamine, warranting further investigation.

Methods: Inducible pluripotent stem cells (iPSCs) were programmed from peripheral mononuclear blood cells collected from 5 treatment-resistant depression patients and 2 healthy controls. The STEMdiffTM embryoid body protocol was followed for 19 days to develop single-cell neural progenitor cells. Cells were supplemented and cultured for 10 weeks, then divided into 5 different conditions (vehicle + DMSO; 5nM, 10nM, and 50nM reelin; 1μM (2R,6R)-HNK) at 2 timepoints (1 hour; 24 hours) to assess short and long-term effects of reelin and (2R,6R)-HNK. Western blotting analyses were used to quantify mTOR, phosphorylated-mTOR (p-mTOR), PSD95, Glutamate A1 (GluA1), Synapsin 1 (Syn-I), Disabled-1 (Dab1), tyrosine kinase receptor B (TrkB), extracellular signal-regulated kinase (ERK), and p-ERK.

Results: Baseline differences of GluA1 ($p<0.05$), TrkB ($p<0.05$), mTOR ($p<0.05$), ERK ($p<0.01$), and p-ERK ($p<0.001$) were observed between MDD cell lines and healthy controls. At 1 hour, reelin and (2R,6R)-HNK significantly increased levels of PSD-95 (R50nM, $p<0.05$; HNK1μM, $p<0.01$), Syn-I (R10nM, $p<0.05$; R50nM, $p<0.01$; HNK1μM, $p<0.01$), Dab1 (R10nM, $p<0.05$; R50nM, $p<0.01$; HNK1μM, $p<0.01$), and p-ERK (R50nM, $p<0.05$; HNK1μM, $p<0.05$). With 24 hour application, these effects were reversed, demonstrating a significant down-regulation of expression of PSD-95 (R10nM, $p<0.05$; R50nM, $p<0.01$) and Syn-I (R10nM, $p<0.05$; R50nM, $p<0.01$; HNK1μM, $p<0.01$).

Conclusions: Reelin and (2R,6R)-HNK have parallel effects both at 1 hour and 24 hours in iPSC-derived neurons from TRD patients, with reelin having a concentration-dependent impact on protein expression levels. This further cements reelin as a potential fast-acting depression therapeutic. Interestingly, the increased expression of various proteins were reversed at 24 hours, suggesting a mechanistic shift between time points. While mTOR has been hypothesized to mediate ketamine's antidepressant effects, our research found no significant upregulation in mTOR activity. However, a more transient activation of mTOR may have been missed. Further research should expand time points and use electrophysiological measures to assess functional synaptic communication after treatment.

Importance: Despite the ubiquity of MDD, traditional antidepressants often have long-term side effects, low efficacy rates, and a delay in therapeutic effects. These delays can have extremely detrimental effects on symptoms such as suicidal ideation. This study is a forward step towards the development of leading-edge antidepressant therapeutics and the use of novel methodologies to improve the translatability of pharmacological research.

TH31. INCIDENCE OF ABNORMAL DREAMS AND NIGHTMARES IN INSOMNIA PATIENTS TREATED WITH LEMBOREXANT

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Abstract: Background: Abnormal dreams and nightmares have been reported by patients with insomnia before and after treatment with sedative hypnotics such as benzodiazepine receptor agonist drugs. Lemborexant (LEM) is a dual-orexin-receptor-antagonist (DORA) approved in multiple countries for the treatment of adults with insomnia. DORAs, such as LEM, increase rapid eye movement (REM) sleep (Moline, 2021), during which dream content is more likely to be recalled (Ohayon, 1997). The purpose of this study was to analyze the frequency of reports of treatment-emergent adverse events (TEAEs) of nightmares/abnormal dreams in participants treated with LEM during two Phase 3 studies.

Methods: Study 303 (SUNRISE-2; NCT02952820) was a 12-month, randomized, double-blind, placebo (PBO)-controlled (first 6 months [Period 1]), phase 3 study that enrolled subjects ≥18 years with insomnia disorder and Insomnia Severity Index (ISI) scores ≥15. During Period 1, the safety analysis set (SAS) included: PBO, n=319; LEM 5 mg, (LEM5), n=314; LEM 10 mg (LEM10), n=314. Study 304 (SUNRISE-1; NCT02783729) was a 1-month, randomized, double-blind, PBO- and active-controlled (zolpidem tartrate extended-release 6.25 mg [ZOL-ER]) study of LEM5 and LEM10. The SAS included: PBO, n=209; ZOL-ER, n=263; LEM5, n=266; LEM10, n=268.

Results: In Study 303, Period 1, 28/947 subjects (3.0%) reported nightmares (n=12; PBO, 1; LEM5, 4; LEM10, 7) or abnormal dreams (n=17; PBO, 6; LEM5, 7; LEM10, 4) as TEAEs. In Study 304, 12/1006 subjects (1.2%) reported nightmares (n=4; PBO, 1; ZOL-ER, 0; LEM5, 2; LEM10, 1) or abnormal dreams (n=8; PBO, 1; ZOL-ER, 3; LEM5, 0; LEM10, 4). Overall, 32/40 subjects (80.0%) reporting these events were female, proportional to the total enrolled study population (% females in the studies: 303=67.9%; 304=86.4%). In the LEM groups,

11/28 subjects (39.3%) reported the TEAE within 3 days of treatment initiation. There were 2 TEAEs of nightmare/abnormal dreams during the PBO run-in prior to randomization.

Conclusions: Abnormal dreams/nightmares were not common events in either study, and there were no dose-related trends in incidence comparing LEM to PBO. Occurrence based on sex was proportional to enrollment with both studies.

Support: Eisai Inc.

TH32. ASSESSMENT OF NOCTURNAL WAKE BOUTS IN ADULTS WITH INSOMNIA TREATED WITH LEMBOREXANT VERSUS ZOLPIDEM

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Abstract: Background: Lemborexant (LEM) is a dual orexin receptor antagonist (DORA) approved in multiple countries for the treatment of adults with insomnia. DORAs, including lemborexant (LEM), are thought to promote sleep by inhibiting orexin-mediated wakefulness. In Study 304 (SUNRISE-1; NCT02783729; subjects age ≥55 years with insomnia disorder), LEM significantly improved sleep efficiency and wake after sleep onset (WASO) versus placebo (PBO) and versus zolpidem tartrate extended-release 6.25mg (ZOL) (Rosenberg R, et al., 2019). In this post hoc analysis, the precise effects of LEM on WASO dynamics were examined by evaluating the effect of LEM on frequency and duration of wake bouts.

Methods: Study 304 was a 1 month, randomized, double-blind, PBO (n=208)- and active-controlled (ZOL; n=263) study of LEM 5 mg (LEM5; n=266) and LEM 10 mg (LEM10; n=269). Polysomnographic data from Night (NT) 2 and NT31 of treatment were analyzed to determine the number and total duration of all wake bouts (any duration), short wake bouts (≤2 minutes) and long wake bouts (>2 minutes). P-values are based on differences in least squares mean changes from baseline, in the number and total duration of all, short, and long wake bouts among treatment groups.

Results: Wake bouts of any duration were more frequent in LEM-treated subjects during NT2, (LEM5, 35.1; LEM10, 37.8) versus PBO (32.7) or ZOL (31.5). Findings were similar during NT31: 37.9, 40.3, 31.7, and 31.0, respectively. LEM-treated subjects spent fewer total minutes in wake bouts during NT2 (LEM5, 62.2; LEM10, 55.2) versus PBO (93.0) or ZOL (72.7) and during NT31: 66.4, 67.3, 92.4, and 79.7, respectively. LEM-treated subjects had more short wake bouts during NT2 (LEM5, 30.4; LEM10, 33.4) versus PBO (26.9) or ZOL (26.3). Findings were similar during NT31: 32.8, 34.7, 26.1, and 25.9, respectively. LEM5- and LEM10-treated subjects spent significantly more minutes in short wake bouts than PBO- or ZOL-treated subjects during NT2 (LEM5, 22.0 [P<0.05 vs PBO and vs ZOL]; PBO, 20.1; and ZOL, 19.5; LEM10, 24.5 [P<0.0001 vs PBO and vs ZOL]). Findings were similar during NT31 (LEM5, 23.9; LEM10, 25.7 [both P<0.0001 vs PBO and vs ZOL]; PBO, 19.4; and ZOL, 19.3). ZOL did not differ from PBO for total time spent in short wake bouts at either NT2 or NT31.

LEM-treated subjects had fewer long wake bouts (LEM5, 4.7; LEM10, 4.4) versus PBO (5.9) or ZOL (5.2) during NT2 but experienced a similar frequency of long wake bouts during NT31: 5.1, 5.6, 5.5, and 5.2, respectively. LEM5- and LEM10-treated subjects spent significantly fewer minutes in long wake bouts than PBO- or ZOL-treated subjects during NT2 (LEM5, 40.3; LEM10, 30.8 [both P<0.0001 vs PBO and ZOL]; PBO, 73.0; and ZOL, 53.2). Findings were similar during NT31: LEM5, 42.5; LEM10, 41.6 (both P<0.0001 vs PBO and vs ZOL);

PBO, 73.0; and ZOL, 60.4. ZOL was significant versus PBO at NT2 (P<0.001) and NT31 (P<0.001).

Conclusions: Relative to PBO and ZOL, WASO decreased with LEM, mediated by a decrease in the number and time spent in long wake bouts, and an increase in the number and time spent in short wake bouts. These findings are generally consistent with the effects of the DORAs, suvorexant (Svetnik V, et al., 2018) and daridorexant on WASO and reflect differences between hypnotics with different mechanisms of action.

Support: Eisai Inc.

TH33. PREDICTORS OF PHARMACOTHERAPY OUTCOMES FOR BODY DYSMORPHIC DISORDER: A MACHINE LEARNING APPROACH

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Abstract: Background: Serotonin-reuptake inhibitors (SRIs) are first-line pharmacotherapy for treatment of body dysmorphic disorder (BDD), a common and severe disorder. However, prior research has not focused on or identified definitive predictors of SRI treatment outcome. Leveraging precision medicine techniques such as machine learning can facilitate prediction of treatment outcomes.

Methods: The study used 10-fold cross-validation support vector machine (SVM) learning models to predict three treatment outcomes (i.e., response, partial remission, and full remission) for 97 patients with BDD receiving up to 14-weeks of open-label treatment with the SRI escitalopram. SVM models used baseline clinical and demographic variables as predictors. Feature importance analyses complemented traditional SVM modelling to identify which variables most successfully predicted treatment response.

Results: SVM models indicated acceptable classification performance for predicting treatment response with an area under the curve (AUC) of 0.77 (sensitivity = 0.77 and specificity = 0.63), partial remission with an AUC of 0.75 (sensitivity = 0.67 and specificity = 0.73), and full remission with an AUC of 0.79 (sensitivity = 0.70 and specificity = 0.79). Feature importance analyses supported constructs such as better quality of life and less severe depression, general psychopathology symptoms, and hopelessness as more predictive of better treatment outcome; demographic variables were least predictive.

Conclusions: The current study is the first to demonstrate that machine learning algorithms can successfully predict treatment outcomes for pharmacotherapy for BDD. Consistent with precision medicine initiatives in psychiatry, the current study provides a foundation for personalized pharmacotherapy strategies for patients with BDD.

TH34. PHENOMENOLOGY OF POSTPARTUM PSYCHOSIS: PRELIMINARY RESULTS FROM MGH POSTPARTUM PSYCHOSIS PROJECT

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Abstract: Objective: Postpartum psychosis (PP) is a rare but severe psychiatric disorder, with historically few studies that have provided definitive data for consensus on diagnostic criteria, presentation, and definition. The Postpartum Psychosis Project at Massachusetts General Hospital (MGHP3) was established: 1) to describe the phenomenology of PP, and 2) to identify genomic and clinical predictors of PP in a large cohort of diverse women with histories of PP spanning a wide geographical range. In this presentation, we report on findings for the first aim; describing the phenomenology of PP.

Method: Data are retrospectively collected from women who experienced PP within 6 months of delivery within the past ten years from the time of interview. Recruitment methods include outreach to providers in perinatal health care, social media advertising, information and recruitment areas on websites including womensmentalhealth.org and MGHP3.org, partnership with advocacy groups, and digital partnerships. Study recruitment is ongoing. Subjects report data during a one-time structured clinical interview administered by phone, which includes the Mini International Neuropsychiatric Interview (M.I.N.I.) for Psychotic Disorders Studies, the MGHP3© Questionnaire (which includes assessment of the PP episode time of onset, duration, symptoms, and treatment received) and other relevant history. Descriptive statistics were conducted to report on mean values and frequency counts.

Preliminary Results: As of December 20, 2021, 283 subjects had enrolled in MGHP3. N=214 participants were included in this initial analysis, after excluding individuals who withdrew, were lost to follow-up, or who had incomplete responses to the MGHP3© Questionnaire or the MINI. The mean age of participants was 34.6 years (SD = 5.61) and most identified as White (88%) and non-Hispanic (91.1%). Using diagnostic criteria based on the MINI, most participants met criteria for Bipolar I disorder with psychotic features (73.1%). Nearly 50% reported suicidality and nearly 10% reported a suicide attempt during the postpartum. Participants reported experiencing persecutory delusions (73%), ideas of reference or receiving messages (55%), visual (49%) and/or auditory hallucinations (46%). On average, the time between delivery and the onset of symptoms was 33.46 (SD = 44.15) days. Over half (57%) of the PP episodes lasted between 1 day to 1 month, and 45% reported symptoms "waxed and waned" over time whereas 55% reported symptoms were consistent during the episode of PP. Nearly 75% were hospitalized for their PP episode with varying levels of access to their baby during their hospital stay. Most participants reported receiving medication (88%) and/or therapy (62%) as treatment, although 5% reported receiving no treatment. The most common type of medication received was an atypical antipsychotic (76.5%) or another type of mood stabilizer (47%).

Conclusions: This report describes the MGHP3 methods, cohort characteristics, and initial findings regarding PP phenomenology. The continuing goal of this research will be the provision of data in an understudied area in the aim of improving clinical care of women at risk for PP. MGHP3 gathers essential data on the clinical presentation of PP as well as genetic contributions, and the ongoing rigorous phenotyping and genetic sampling will contribute to our understanding of PP's phenomenology.

TH35. ATTENUATION OF OXYCODONE SEEKING IN RATS WITHOUT EFFECTS ON MOTOR OR COGNITIVE FUNCTION WITH M5 NEGATIVE ALLOSTERIC MODULATOR VU6008667

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Abstract: Mu opioid agonists are known to inhibit GABAergic interneurons within the ventral tegmental area (VTA) of the mesolimbic reward circuit resulting in decreased GABA inhibition of VTA dopamine (DA) cell firing, increased DA release in the nucleus accumbens (NAc), and enhanced opioid drug-seeking behaviors.

Recent evidence suggests that inhibition of M5 muscarinic acetylcholine receptors (mAChRs) located on VTA DA cells may provide a novel mechanism for decreasing opioid-induced disinhibition of VTA DA cell firing and associated addictive behaviors. We recently identified the selective M5 mAChR negative allosteric modulator VU6008667 with suitable pharmacokinetic properties to allow investigation of the effects of inhibiting M5 receptors in vivo in Sprague-Daley rats after both acute and chronic administration.

In the present studies, we examined the effects of acute VU6008667 in preclinical models of opioid drug seeking and relapse, including oxycodone self-administration and cue-reinstatement of extinguished oxycodone self-administration. In addition, we evaluated the effects of repeated daily 21-day administration of VU6008667 on the acquisition of oxycodone self-administration in opioid naïve rats. In order to interpret these effects of VU6008667, we also examined the effects of this compound on general locomotor activity, motivation and cognition after acute and repeated administration. We combined retrograde tracer (CTB-Alexa-Fluor 555) injections with fluorescent in situ hybridization in order to determine the localization of M5 on different circuits projecting from the VTA, including the prefrontal cortex and nucleus accumbens (NAc) core and shell.

After acute administration, VU6008667 produced a dose-dependent attenuation of sustained oxycodone self-administration and cue-induced reinstatement in rats. Repeated daily doses of VU6008667 also attenuated the acquisition of oxycodone self-administration in opioid naïve rats. Within the same dose range, VU6008667 had no effect on motor coordination or acquisition of cue-induced fear conditioning. However, while VU6008667 acutely had no effect on sucrose pellet maintained responding, it did delay acquisition after repeated administration. In situ hybridization studies showed that M5 is primarily expressed on dopamine neurons in lateral regions of the VTA, including the parabrachial pigmented nucleus, which projects primarily to the core and shell regions of the NAc. These findings provide likely neuronal projections through which VU6008667 is exerting effects.

Our results revealed that acute and repeated administration of a selective M5 inhibitor may block acquisition of opioid seeking behavior without a general impact on reward-mediated behavior, motor function or learning. This attenuation of oxycodone seeking behavior occurred in opioid naïve animals as well as in relapse models, providing rationale for the potential use of M5 inhibitors in multiple stages of treatment for opioid use disorder.

TH36. METABOLIC PARAMETERS, VITAL SIGNS, AND WEIGHT CHANGE IN PATIENTS WITH SCHIZOPHRENIA SWITCHED TO TREATMENT WITH ARIPIPRAZOLE LAUROXIL

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Abstract: Background: Long-acting injectable (LAI) antipsychotics are among the most effective treatments in psychiatry, but little data are available to inform clinician expectations when switching between LAIs. We assessed metabolic parameters, vital signs, and weight gain in patients with schizophrenia who switched to aripiprazole lauroxil because of efficacy or safety/tolerability limitations experienced with their current LAI antipsychotic treatment.

Methods: Clinically stable adults with schizophrenia and persistent positive or negative symptoms or intolerance to paliperidone palmitate or risperidone LAI were switched to open-label aripiprazole lauroxil (441, 662, or 882 mg q4weeks or 882 mg q6weeks) for 6 months (ClinicalTrials.gov identifier: NCT02634320). Metabolic parameters (blood glucose, hemoglobin A1c [HbA1c], total cholesterol, high-density and low-density lipoprotein [HDL and LDL] cholesterol, and triglycerides), vital signs (systolic and diastolic blood pressure [SBP and DBP] and heart rate), and body weight were recorded at baseline and 6 months; mean changes and standard deviations (SDs) were calculated. The proportion of patients with clinically significant weight gain (≥7%) from baseline at any assessment was also calculated. All analyses were descriptive.

Results: The study enrolled 51 patients, and all received ≥1 dose of aripiprazole lauroxil. Mean age was 40.6 years; most patients were male (72.5%) and Black (49.0%). Thirty-five patients completed the study. The most common reason for switching from the current LAI antipsychotic to aripiprazole lauroxil was persistent positive symptoms (n=34; 66.7%), followed by tolerability concerns (n=9; 17.6%) and persistent negative symptoms (n=8; 15.7%). At 6 months, the following mean (SD) changes from baseline in metabolic parameters were observed: glucose, +5.7 (30.3) mg/dL; HbA1c, +0.13% (0.5%); total cholesterol, −11.9 (36.2) mg/dL; HDL cholesterol, +0.4 (8.9) mg/dL; LDL cholesterol, −11.8 (32.7) mg/dL; and triglycerides, −14.9 (63.1) mg/dL. Mean (SD) vital sign parameter values decreased over the 6-month aripiprazole lauroxil treatment period: SBP, −4.0 (12.3) mm Hg; DBP, −0.5 (10.6) mm Hg; and heart rate, −2.3 (12.9) beats per minute. Mean (SD) weight at baseline was 95.4 (21.0) kg; mean (SD) weight change at 6 months was +0.04 (5.3) kg. Overall, 5/49 patients (10.2%) experienced clinically significant weight gain of ≥7% at any postbaseline assessment.

Discussion: Switching patients with schizophrenia to aripiprazole lauroxil was associated with minimal increases in glycemic indices, modest improvements in lipid measures, and reductions in blood pressure and heart rate. Mean weight gain was minimal over 6 months of treatment, and the rate of clinically significant (≥7%) weight gain observed was consistent with previous findings. Limitations include the small sample size, unconfirmed fasting status, and lack of placebo control due to the open-label study design. These data support the safety and feasibility of a switch to aripiprazole lauroxil in patients with schizophrenia who had persistent symptoms or tolerability issues with other LAI antipsychotics.

TH37. CHARACTERISTICS AND TREATMENT PATTERNS IN MEDICARE PATIENTS NEWLY DIAGNOSED WITH SCHIZOPHRENIA WITH TRADITIONAL FEE-FOR SERVICE VERSUS PRIVATE MEDICARE ADVANTAGE INSURANCE COVERAGE

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Abstract: Background: Schizophrenia is a serious mental disorder that requires lifelong treatment. Early treatment can help get symptoms under control before serious complications develop (e.g., suicide, anxiety disorder, aggressive behavior, depression, alcohol/drug abuse, inability to work, financial and health/medical problems).
Objective: This research evaluated demographic and clinical characteristics and treatment patterns in patients newly diagnosed with schizophrenia in two populations with traditional Medicare Fee-for-Service (FFS) versus private managed Medicare Advantage (MA) health insurance.

Methodology: A retrospective cohort analysis of adults age 18+ newly diagnosed with schizophrenia. Patients were continuously enrolled for ≥6 months pre-index diagnosis with no evidence of schizophrenia and a minimum of 12 months post-index. Patient characteristics were measured at baseline.

Results: A total of 81,683 FFS and 12,492 MA beneficiaries newly diagnosed with schizophrenia were identified from 2016-2019. FFS and MA beneficiaries were similar average age (mean 56.5 FFS; 57.1 MA) and both were more male (55.0%). MA members were more likely racial/ethnic minority (55.4% MA; 35.6% FFS) and both groups were much more likely to be dual eligible for Medicaid (82.3% MA; 83.1% FFS) compared to the overall Medicare population (37.3% MA; 25.7% FFS dual eligible in 2019). MA and FFS beneficiaries with schizophrenia were also more likely to be eligible for Medicare due to disability versus reaching age 65 (73.3% MA; 67.4% FFS) compared to the overall Medicare population (30.0% MA; 23.7% FFS in 2019) and were more likely to have Charlson Comorbidity Index scores ≥2.0 (33.1% MA; 39.8% FFS). Antipsychotic medication was the first treatment prescribed for 32.2% of FFS and 28.7% of MA beneficiaries patients, followed by dual therapy antipsychotic + antidepressant (20.3% FFS; 17.0% MA). Additional treatments include antipsychotic + antianxiety (10.8% FFS; 8.1% MA), and antidepressant + antianxiety (9.1% FFS; 8.9% MA). A small percentage were prescribed only an antidepressant (6.5% FFS; 6.9% MA) or antianxiety (5.4% FFS; 5.0% MA) as first treatment. Of those first prescribed an antipsychotic, 33.2% FFS and 27.2% MA patients remained on the treatment until end of follow-up (mean 354 days), while 34.3% FFS and 43.1% MA patients discontinued treatment after 143 and 134 days on average. Importantly, 15.6% of FFS and 25.5% of MA beneficiaries received no treatment during the 12-months follow-up.

Conclusions: Results show more than one in four MA patients newly diagnosed with schizophrenia receive no treatment in 12-months following diagnosis, and up to 43% of Medicare patients discontinue treatment after about 4 months. Steps to assure patients receive appropriate treatment can prevent worsening symptoms and adverse health outcomes in the vulnerable Medicare population with schizophrenia.

TH38. A SINGLE-DAY, TWO-INJECTION START REGIMEN FOR ARIPIPRAZOLE ONCE-MONTHLY IN PATIENTS WITH SCHIZOPHRENIA OR BIPOLAR I DISORDER WHO ARE NOT BEING TREATED WITH ORAL ARIPIPRAZOLE

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Abstract: Background: Non-adherence to antipsychotic medication is common among patients with schizophrenia and can be improved by use of long-acting injectable (LAI) antipsychotic formulations, such as aripiprazole once-monthly 400 mg (AOM 400) (1). In order to maintain therapeutic drug concentrations during initiation of an LAI antipsychotic, start regimens may entail two injections given on different days, or may comprise one injection with a period of concurrent oral antipsychotic. A one-injection start regimen for AOM 400 in patients with schizophrenia or bipolar I disorder requires 14 days of oral aripiprazole 10–20 mg, or other oral antipsychotic, to maintain therapeutic drug concentrations during initiation (2). Among patients at risk of non-adherence, it may be preferable to achieve therapeutic plasma concentrations from Day 1 without reliance on concurrent oral dosing. The aim of this study was to utilize population-pharmacokinetic (popPK) modeling to identify an alternative AOM start regimen that does not require 14 days of oral aripiprazole, for patients not being treated with oral aripiprazole.

Methods: A previously developed and validated popPK model for characterizing aripiprazole plasma concentrations following oral or gluteal administration was expanded to include deltoid administration. The final model included 8,214 aripiprazole concentrations from 817 adults (765 patients with schizophrenia and 52 healthy participants). Various single-day initiation regimens were simulated with the goal of identifying a regimen that would a) reduce reliance on concurrent oral aripiprazole at initiation; b) maintain aripiprazole concentrations within the established therapeutic window (94.0–534.0 ng/mL) (2); and c) achieve plasma concentrations (median and 5th–95th percentiles) similar to those of the one-injection start regimen. Simulations were performed for patients who were not being treated with oral aripiprazole.

Results: The alternative start regimen consisted of two AOM 400 injections at separate gluteal and/or deltoid injection sites, plus a single dose of oral aripiprazole 20 mg, all on Day 1. Among patients not treated with oral aripiprazole, this two-injection start regimen resulted in a simulated median aripiprazole plasma concentration that reached therapeutic levels on the first day and remained within the therapeutic window for the 140-day simulation (AOM 400 was administered every 28 days). There was no apparent impact of the two-injection start on steady-state maintenance concentration following multiple doses. The simulated median and 5th–95th percentiles of aripiprazole plasma concentration for the two-injection start regimen were generally comparable to those of the one-injection start regimen (i.e., single injection plus 14 days of oral aripiprazole).

Conclusion: Among patients not treated with oral aripiprazole, simulations using a popPK model indicate that a two-injection plus single dose of oral aripiprazole 20 mg start regimen for AOM achieves desired therapeutic aripiprazole plasma concentrations on the first day of treatment, which are maintained over the entire dosing interval and are similar to those of the one-injection start regimen. Thus, these data support the use of the AOM two-injection start regimen in clinical practice to achieve similar clinical effectiveness and a comparable safety and tolerability profile to the one-injection start regimen, with reduced risk of non-adherence during initiation.

TH39. EFFECT OF PALIPERIDONE PALMITATE VERSUS ORAL ANTIPSYCHOTICS ON TREATMENT FAILURE IN ADULTS WITH RECENT-

ONSET SCHIZOPHRENIFORM DISORDER: AN ANALYSIS OF THE DREAM STUDY

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Abstract: Background: Schizophreniform disorder shares features with schizophrenia but differs in the duration and degree of functional impairment. It is a temporizing diagnosis assigned in the first 1 to 6 months of symptoms; approximately two-thirds of patients with schizophreniform disorder will subsequently be diagnosed with schizophrenia. The Disease Recovery Evaluation and Modification (DREaM) study was conducted to evaluate the effectiveness of treatment with paliperidone palmitate (PP) versus oral antipsychotics (OAPs) in delaying time to first treatment failure (TtFTF) in subjects with recent-onset schizophrenia or schizophreniform disorder. This post hoc analysis of DREaM examined similarities and differences in baseline characteristics and treatment outcomes among subjects with schizophreniform disorder and subjects with schizophrenia.

Methods: DREaM (NCT02431702) was an open-label, double-randomized study with a 3-part design: Part I, 2-month oral run-in; Part II, 9-month disease progression (OAP or PP); Part III, 9 months of additional treatment (PP/PP; OAP rerandomized: OAP/OAP or OAP/PP). An extended disease progression (EDP) phase that spanned Parts II and III compared subjects remaining on the same treatment (PP/PP vs OAP/OAP) for the full 18 months. In this post hoc analysis, efficacy and safety outcomes were assessed by baseline diagnosis for the EDP intention-to-treat (ITT) analysis.

Results: Subjects diagnosed with schizophreniform disorder comprised ~20% of the total ITT population throughout the study (Part I: 63/273 [23.1%]; Part II: 54/235 [23.0%]; Part III: 36/169 [21.3%]; EDP: 22/112 pts [19.6%]). Within the EDP analysis set, subjects with schizophreniform disorder and schizophrenia demonstrated a consistent presentation of baseline demographic and disease characteristics. Mean (SD) age was 23.7 (4.72) years and 23.2 (4.40) years, respectively, and most subjects were male (72.7% vs 80.0%) and White (36.4% vs 43.3%) or Black/African American (36.4% vs 37.8%), with 1.1 (1.15) versus 1.2 (1.21) mean (SD) prior psychiatric hospitalizations and mean (SD) Clinical Global Impression of Severity scores of 3.1 (0.99) versus 3.3 (1.16). As expected, subjects with schizophreniform disorder had lower mean (SD) number of years since first psychotic episode versus subjects with schizophrenia (0.3 [0.27] vs 1.1 [0.58]).

In the EDP ITT analysis, the rates of TF were numerically lower with PP/PP versus OAP/OAP treatment across schizophreniform disorder (2/8 [25.0%; PP/PP]; 6/14 [42.9%; OAP/OAP]) and schizophrenia (12/41 [29.3%; PP/PP]; 22/49 [44.9%; OAP/OAP]) diagnoses, corresponding to a number-needed-to-treat of approximately 6 (both diagnoses). Rates of TEAEs in the EPD analysis were similar among treatments and diagnosis groups (≥1 TEAE; schizophreniform disorder: 7/8 (87.5%; PP/PP) and 13/14 (92.9%; OAP/OAP); schizophrenia: 38/41 (92.7%; PP/PP) and 44/49 (89.8%; OAP/OAP).

Conclusions: Subjects with schizophreniform disorder and schizophrenia in the DREaM study demonstrated a consistent presentation of baseline demographic and disease characteristics, effectiveness of PP versus OAPs in the rate of FTF, and safety of PP.

TH40. CLINICAL RATIONALE AND DESIGN OF THE ARISE STUDY: A PHASE 3 PLACEBO-CONTROLLED TRIAL EVALUATING THE SAFETY AND EFFICACY OF ADJUNCTIVE KARXT IN PATIENTS WITH INADEQUATELY CONTROLLED SCHIZOPHRENIA

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Abstract: Background: All currently approved antipsychotics share direct affinity for the dopamine (DA) D2 receptor, resulting in characteristic side effects ranging from movement disorders to behavioral toxicities. A significant unmet medical need remains for more effective, better tolerated therapies; this has served as the impetus for developing treatment approaches without any direct effects on DA receptors. One approach is through central muscarinic receptors involved in acetylcholine-mediated regulation of key neural circuits implicated in schizophrenia. KarXT (xanomeline-trospium), an M1/M4-preferring muscarinic receptor agonist, is currently in phase 3 development as monotherapy for treatment of schizophrenia after showing efficacy and tolerability in a phase 2 study. We describe a recently initiated adjunctive study where the goal is to assess adding KarXT to a current antipsychotic regimen when there continues to be inadequate response. KarXT has a different mechanism of action (MOA) than currently approved antipsychotics, and adjunctive KarXT may be one approach to improve clinical response over that achieved with currently available antipsychotics. Preclinical behavior models predicting antipsychotic activity show xanomeline can augment antipsychotic activity of current D2-receptor antipsychotics. At present, there are no treatments approved for adjunctive treatment of schizophrenia.

Methods: The ARISE study (NCT05145413) is a 6-week, phase 3, randomized, double-blind, placebo-controlled, multicenter outpatient study in up to 400 adult patients with a primary diagnosis of schizophrenia who have demonstrated an inadequate response to a therapeutic regimen of selected first-line (eg, non-clozapine) atypical antipsychotics. Eligible patients have received and taken therapeutic doses for ≥8 weeks of one of the first-line atypical antipsychotics aripiprazole, lurasidone, paliperidone, quetiapine, risperidone, or ziprasidone and, despite this, continued to experience clinically relevant positive symptoms. ARISE includes a 5-week screening period, 6-week double-blind treatment period, and safety follow-up visit at the end of week 7. Based on individual tolerability and clinical response, KarXT will be flexibly dosed (xanomeline/trospium) between 75 mg/20 mg twice daily and 125 mg/30 mg twice daily vs matched placebo twice daily. The primary endpoint is change from baseline in Positive and Negative Syndrome Scale total score at week 6 vs placebo. The key secondary endpoint is change from baseline in Personal and Social Performance Scale at week 6. Standard safety and tolerability assessments will be collected.

Results: This is a double-blind study for which results are not yet available. During the conference, we will present the rationale and study design. Recruitment has been initiated, and an update will be provided.

Discussion: To date, no adjunctive treatment approaches have been successful in fully powered, registrational studies in patients with schizophrenia who have inadequate control of their symptoms with antipsychotic treatment. KarXT has a different MOA (ie, muscarinic receptor agonism) from currently approved treatments and demonstrated efficacy in a phase 2, inpatient, monotherapy efficacy study, suggesting that adjunctive KarXT has reasonable probability of success as a treatment. We will describe some of the clinical trial design features that could enhance the probability of success in ARISE.

TH41. SEMAGLUTIDE FOR THE TREATMENT OF WEIGHT GAIN ASSOCIATED WITH ANTIPSYCHOTICS IN PATIENTS WITH SCHIZOPHRENIA: PROPOSED DESIGN FOR A RANDOMIZED CONTROLLED TRIAL

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Abstract: Semaglutide for the Treatment of Weight Gain Associated with Antipsychotics in Patients with Schizophrenia: Proposed Design for a Randomized Controlled Trial

Background and Aim: Patients with schizophrenia have 10 to 20 years shorter life span compared to general population, mostly due to a higher rate of cardiovascular disease. Obesity is a major contributor to the increased rate of cardiovascular disorders. It is estimated that more than 60% of patients with schizophrenia have obesity. Multiple factors including disease-specific factors, sedentary lifestyle, substance use, and antipsychotic medication are to be blamed for the increased rate of obesity. Antipsychotics, particularly second-generation ones, are highly associated with weight gain and metabolic syndrome.

To counter the weight, gain due to antipsychotics, several adjunctive agents have been studied. Metformin, topiramate, lorcaserin, orlistat, naltrexone, and samidorphan are among the most studied medications to prevent or reverse the weight gain associated with antipsychotics, which have shown to mildly attenuate the weight gain effect of antipsychotics and result in two-to-five-kilogram weight reduction compared to placebo.

Semaglutide is a glucagon-like peptide-1 receptor agonist (GLP-1RA) that has been recently approved for the treatment of type 2 diabetes mellitus, and obesity. Two recent, large randomized trials showed that once-weekly subcutaneous semaglutide resulted in more than 12 kg weight reduction in overweight and obese non-diabetic individuals compared to placebo. This medication has not been studied in patients with schizophrenia yet. In contrast to other medications currently in use in this population, semaglutide does not require daily oral administration. Its route of administration eliminates covert non-adherence. We hypothesize that administering weekly semaglutide as an adjunctive agent to antipsychotics in patients with schizophrenia can significantly attenuate the weight gain caused by antipsychotics and causes significant further weight reduction.

Methods: A double-blind, randomized, placebo-controlled trial to test the efficacy and safety of semaglutide in overweight and obese patients with schizophrenia could test this hypothesis. Eighty patients with schizophrenia, age > 18 years old, and BMI > 27 who are under treatment with antipsychotics in the outpatient setting would be recruited. Sample size was estimated based on previous studies on patients with schizophrenia. Inclusion criteria will be patients with any of the following psychiatric diagnoses: acute psychotic disorder, schizophreniform disorder, schizophrenia, or schizoaffective disorder, confirmed using the Structured Clinical Interview for DSM-5. Participants will be randomly assigned to once-weekly subcutaneous injection of semaglutide or placebo injection plus lifestyle modification for 24 weeks. To minimize potential gastrointestinal side effects, semaglutide will be initiated at 0.25 mg, with dose escalation every four weeks until the target dose of 2.4 mg is reached. No alterations will be made to patients' antipsychotic regimen. Assessments will include BMI, waist and hip circumference, CBC, CMP, Lipid profile, Hemoglobin A1C, EKG at baseline, and every four

weeks. Potential side effects will also be assessed and recorded after every four-week period. The co-primary outcomes will be the percentage change in body weight and weight reduction of at least 5% of the baseline body weight. The secondary outcomes will be the changes in waist and hip circumference, total cholesterol and Hemoglobin A1C level.

TH42. IMPACT OF TIMING OF INITIATION OF ARIPIPRAZOLE 400MG LONG-ACTING INJECTABLE ON HEALTHCARE RESOURCE USE AND COST IN PATIENTS WITH SCHIZOPHRENIA

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Abstract: Background: Research has indicated that early use of long-acting injectable antipsychotics (LAIs) decreases healthcare resource use (HCRU) and cost vs. use later in the disease state while use of LAIs in early phase schizophrenia (SCZ) has been shown to significantly delay time to hospitalization. Clinical trial and claims database analyses have found that HCRU and cost decreases following initiation of LAI aripiprazole 400mg (AOM400), but relation to timing of initiation of AOM400 in the disease course has not been assessed in the real-world setting.
Objective: To examine the impact of timing of AOM400 initiation on HCRU and cost in patients with SCZ taking AOM400.

Methods: A retrospective cohort study using IBM MarketScan® Medicaid data (01/01/2013 - 12/31/2019) was conducted. Included patients were >18 years and had >1 inpatient or >2 outpatient diagnoses for SCZ on different days during the study identification (ID) period (01/01/2014-12/31/2018). The index date was the first recorded prescription for AOM400 in the ID period, and patients were required to have the first diagnosis of SCZ prior to index date, no AOM400 use in the year prior to index date, and be continuously enrolled for >1 year both prior to (pre-index period) and after (follow-up period) index date. Patients were excluded if they were dual eligible, lacked pharmacy coverage, or had a prescription for clozapine during the study period. Patients were classified into 2 groups based on timing of first AOM400 claim after the first SCZ diagnosis identified in the dataset (≤12 months = Early cohort; >12 months = Late cohort). Descriptive statistics (means, standard deviations [SD], were calculated for each cohort and t-tests assessed differences between groups. Log link models with a Gamma distribution were conducted to examine the association between costs and timing of LAI initiation.

Results: A total of 945 patients with SCZ (525 Early; 420 Late) were identified. The Early cohort was statistically significantly younger (34.7 vs. 36.5 years; p=0.0207), less predominantly female (46.86% vs. 54.52%; p=0.0192) and had a lower mean Charlson Comorbidity Index (0.75 vs. 0.95; p=0.0386) at baseline than the Late cohort. During the 12-month follow-up period, the Early cohort had significantly lower unadjusted mean all-cause and psychiatric-related hospital admissions (0.47 vs. 0.76; p=0.0006 and 0.33 vs. 0.62; p<0.001) and inpatient days (2.74 vs. 4.83; p=0.0004 and 2.16 vs. 4.18; p=0.0002) than the Late cohort, as well as lower unadjusted psychiatric-related emergency department visits (0.41

vs. 0.75; p=0.0178). After controlling for baseline demographics and clinical characteristics, mean all-cause ($21,686 vs. $29,033; p=0.0002) and psychiatric-related ($24,413 vs. $32,461; p=0.0002) costs were significantly lower for the Early cohort.

Conclusions: This analysis supports prior literature showing that early initiation of AOM400 may lead to decreases in HCRU/cost in patients with SCZ.

TH43. UTILITY AND USABILITY OF ARIPIPRAZOLE TABLETS WITH SENSOR: AGGREGATED SURVEY DATA FROM 3 CLINICAL TRIALS OF PARTICIPANTS WITH SERIOUS MENTAL ILLNESS

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Abstract: Introduction: With the advent of new digital technologies to treat mental health disorders, usability and utility of these tools for patients with serious mental illness becomes an important concern.1 Aripiprazole tablets with sensor (AS, Abilify MyCite®, comprising an ingestible event-marker sensor embedded in aripiprazole tablets, wearable sensor patches, and a smartphone application) is a digital medicine approved for the treatment of schizophrenia and bipolar 1 disorder, and as adjunctive treatment for major depressive disorder.2 In this analysis, previously collected survey data on the utility and usability of the AS system for participants and healthcare providers (HCPs) were evaluated across 3 clinical trials of participants with schizophrenia, bipolar I disorder, or major depressive disorder.

Methods: Participant- and HCP-specific surveys were provided after 8 weeks (NCT02722967, NCT02219009) or 3 months (NCT03892889) of AS use, and users rated the AS system across multiple questions on a 7-point Likert scale, with higher scores indicating more favorable responses. Data were further analyzed by participant demographics, disease severity, and symptom profile. Continuous variables were assessed with regression-based P values and effect sizes; categorical variables were assessed with Mann-Whitney U tests and effect sizes.

Results: Most participants and HCPs responded positively across all survey questions. Overall, 65.8% to 80.8% of participants and 58.3% to 72.1% of HCPs were satisfied with the AS system across the 3 studies. The majority of participants (60.5% to 72.7%) and HCPs (58.3% to 74.0%) found the AS system easy to use. Additionally, most HCPs (79.8% to 81.7%) found the HCP dashboard easy to use. The AS system was helpful for 60.5% to 83.8% of participants in improving discussions with their doctor or treatment team. Similarly, most HCPs (68.8% to 75.0%) found the AS system helpful in improving conversations with their patients regarding treatment plan and progress, and the majority of HCP respondents rated the AS system as effective in aiding decision making (66.7% to 72.1%). Additional analyses of survey data found no impact of participant demographics, baseline disease severity, or symptom profile on survey responses.

Conclusions: Most participants and HCPs generally found the AS system easy to use and effective in improving discussions between HCPs and patients. HCPs also found the system useful to inform decision making.

TH44. BIOLOGICAL EMBEDDINGS OF EARLY TRAUMA: THE ROLE OF INCREASED PREFRONTAL GLUTAMATERGIC SYNAPTIC STRENGTH

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Abstract: Early life trauma can commence a toxic developmental cascade that continues into adulthood and impacts physical and mental wellbeing. The developing brain may calibrate to dangerous environments via aberrant synaptic processes that increase risk for psychiatric disorders. Glutamatergic synaptic alterations are particularly relevant to psychiatric disorders, given glutamate's ubiquity, its role in emotion, stress responsivity, learning, memory, and associations with trauma-related disorders. Trauma is believed to result in glutamatergic excitotoxicity, which reduces richness of synaptic connections, undermines neuroplasticity, and impairs cognitive processes like fear extinction with implications for psychiatric disorders. To date, no prior studies have directly examined the relationship between glutamatergic synaptic strength and early trauma in-vivo. To address this gap, we determined the association between early trauma inventory (ETI) severity and glutamatergic synaptic strength in patients with PTSD (n=16), as well as in healthy controls (n=18). Using dynamic Carbon-13 magnetic resonance spectroscopy, we computed prefrontal energy per cycle (EPC), a novel biomarker of synaptic strength. This study represents the first in-vivo examination of synaptic strength and early trauma in a relatively large human sample to undergo Carbon-13 imaging. Age, sex, race, height, and weight did not differ significantly between the two groups ($p>0.05$). We found a significant positive association in the PTSD group, such as increased childhood trauma predicted stronger synaptic connections ($r=0.71$, $n=15$, $p=0.003$). Age, medication status, PTSD severity, and sex did not account for the relation between early trauma and EPC. Our finding of a positive correlation between synaptic strength and early trauma was limited to the patient population. Healthy controls had no significant association between increased childhood trauma and synaptic strength ($r=-0.07$, $n=18$, $p=0.79$). A Fisher r-to-z transformation revealed that the correlation between total early trauma and EPC was significantly stronger in PTSD patients than healthy controls ($z=2.47$, $p=0.01$). Our results support our previous work in an independent sample showing that early trauma predicts greater occipital glutamate neurotransmission in depressed patients (1). Glutamatergic synaptic disturbances, regardless of their direction, have important implications given the neurotransmitter's critical roles in overall brain function, metabolism, emotions, and cognitive processes. Our findings highlight synaptic strength as one neurobiological variable that may be altered in individuals with PTSD and childhood trauma. Many therapies depend on extinction learning of feared cues (anxiety disorders) or rewarding cues (addiction/impulsivity disorders). Increased synaptic strength in childhood trauma may predict more intractable learning and explain findings of worse psychotherapy outcomes in exposed individuals. Our study has clinical implications for pharmacological treatments thought to target synaptic processes, e.g., ketamine (2).

TH45. COMP360 PSILOCYBIN THERAPY IN TREATMENT-RESISTANT DEPRESSION: RESULTS OF A LARGE RANDOMIZED CONTROLLED PHASE IIB MONOTHERAPY STUDY AND AN EXPLORATORY UNCONTROLLED ADJUNCTIVE THERAPY STUDY

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Abstract: Background: COMP360 is a synthetic, purified form of psilocybin in development for treatment of patients with treatment-resistant depression (TRD). COMP360 psilocybin

therapy is an integrated therapy that includes oral COMP360 administration with psychological support. It has received FDA designation as a breakthrough therapy.

Methods: COMPASS Pathways has completed two studies of COMP360 in participants with TRD. The first was a randomized double-blind controlled study that evaluated the efficacy and safety of a single treatment of COMP360 monotherapy at doses of 25 mg, 10 mg, and 1 mg. Participants were required to down-taper within 4 weeks and stop completely for 2 weeks any prior antidepressant treatments before COMP360 administration. The follow-up period was 12 weeks, with evaluations at Day 2 and Weeks 1, 3, 6, 9, and 12. The second study was an open-label trial that explored the effect of a single treatment of COMP360 25 mg adjunctive to an ongoing serotonergic antidepressant. The follow-up period was 3 weeks, with evaluations at Day 2 and Weeks 1, 2, and 3. In both studies, the primary endpoint was change from Baseline to Week 3 in Montgomery-Asberg Depression Rating Scale (MADRS) total score.

Results: The monotherapy study randomized 233 participants to 25 mg (n=79), 10 mg (n=75), and 1 mg (n=79) treatment groups. Dose-related improvements were evident at Day 2. At Week 3 primary endpoint, observed mean changes (standard deviation [SD]) from Baseline were -12.0 (12.98), -8.9 (10.94), and -6.8 (11.10) in the 25 mg, 10 mg, and 1 mg groups, respectively. The least-squares mean difference (LSMD) between 25 mg and 1 mg was statistically significant (LSMD=-6.6, $p<0.001$); the difference between 10 mg and 1 mg was not. At Week 3, protocol-compliant response (□50% reduction in MADRS) and remission (MADRS □10) rates were higher for COMP360 25 mg (response: 36.7%, n=29/79; remission: 29.1%, n=23/79) than for 1 mg (response: 17.7%, n=14/79; remission: 7.6%, n=6/79). At Week 12, sustained response (□50% reduction from baseline in MADRS at Weeks 3, 12, and either 6 or 9) was higher for 25 mg (24.1%, n=19/79) than for 1 mg (10.1%, n=8/79). The adjunctive therapy study treated 19 participants receiving escitalopram (n=6), sertraline (n=6), fluoxetine (n=3), vilazodone (n=2), paroxetine (n=1), and citalopram (n=1) with open-label COMP360 25 mg. Improvement was observed from Day 2. At Week 3 endpoint, participants had an observed mean change from Baseline of -14.9 (SD=11.97) points in MADRS; and 42.1% (n=8/19) of participants met criteria for response and for remission.

COMP360 25 mg was generally well-tolerated in both studies. In the monotherapy study, treatment-emergent adverse event (TEAE) rates were 83.5% (n=66), 74.7% (n=56), and 72.2% (n=57) in the 25 mg, 10 mg, and 1mg groups, respectively. Over 90% of TEAEs were mild or moderate in severity. Treatment-emergent serious adverse event (TESAE) rates were 6.3% (n=5), 8.0% (n=6), and 1.3% (n=1) in the 25 mg, 10 mg, and 1 mg groups, respectively. In the adjunctive therapy study, the TEAE rate was 57.9% (n=11); and 82% of TEAEs were mild. No TESAEs were reported.

Conclusions: A single treatment with COMP360 25 mg psilocybin therapy appears to be a rapid, efficacious, and well tolerated monotherapy for patients with TRD, and may provide additional benefit as an adjunctive therapy to common antidepressant treatments. The efficacy and safety of COMP360 25 mg should be further evaluated in large, controlled, confirmatory studies.

TH46. EMERGING PROFILE OF TAAR1 AGONIST ULOTARONT: PRECLINICAL AND CLINICAL EVIDENCE FOR AN EMERGING PHARMACOLOGICAL CLASS

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Abstract: Background: Ulotaront is a TAAR1 agonist with serotonin 5-HT1A agonist activity, distinguished from current antipsychotics by lack of D2 and 5-HT2A receptor blockade. Results of Phase 2 trials in schizophrenia support the efficacy and safety of ulotaront, which has received FDA Breakthrough Therapy designation in the treatment of schizophrenia. The WHO has assigned ulotaront the INN naming convention specifying the "-taront" stem common to the pharmacological class of TAAR1 agonists. Here we update ongoing research characterizing ulotaront as a member of the new pharmacological class of TAAR1 agonists.
Methods: Several preclinical studies were conducted to investigate the effect of ulotaront in rodent models of schizophrenia, weight gain and hyperglycemia. Also presented are new human studies, including clinical pharmacology results, analyses of negative symptom change in subjects enriched for having the Marder PANSS negative symptom (MPNS) construct, and new analyses of the safety of ulotaront relative to the adverse events expected for the dopamine D2-class effects in spontaneous reports in FAERS (FDA Adverse Event Reporting System).

Results: In a translational, PET-based mouse model of presynaptic dopamine dysfunction, treatment with ulotaront significantly reduced ketamine-induced elevation of striatal dopamine synthesis capacity. In a series of metabolic studies, ulotaront treatment in rats on high fat diet resulted in a dose-dependent reduction in body weight, food intake and liver triglycerides. Ulotaront also reversed olanzapine- and corticosterone-induced weight gain in rats and mice, respectively. In addition, acute ulotaront treatment dose-dependently reduced plasma glucose excursion in naive and diabetic mice during an oral glucose tolerance test, likely driven by TAAR1-mediated inhibition of gastric emptying. The beneficial metabolic effects may reflect peripheral TAAR1 activation and/or direct modulation of homeostatic and hedonic neurocircuits regulating energy balance. In clinical pharmacology studies ulotaront was well-absorbed with a median time to peak concentration of 2.8 hours. Ulotaront was eliminated primarily via hepatic clearance with an effective half-life of 7 hours. In vitro studies indicated ulotaront was a substrate of CYP2D6 hepatic enzyme. A clinical DDI study with co-administration of paroxetine as a CYP2D6 inhibitor increased ulotaront Cmax and AUC0-inf by approximately 30% and 70%, respectively. In clinical trials of acute schizophrenia, subjects enriched for the maximum amount of variance explained on the Marder PANSS negative symptom (MPNS) construct prior to randomization went on to achieve an endpoint MPNS factor score effect size of approximately 0.8. In clinical studies, ulotaront demonstrated markedly lower cumulative risk for the FAERS-defined dopamine D2 class-related adverse events (AEs) compared with atypical antipsychotics.

Discussion: The implications of the preclinical and clinical findings of the TAAR1 agonist ulotaront will be discussed, most notably the targeted attenuation of elevated striatal dopamine synthesis capacity characteristic of schizophrenia, the enhanced effect in treating negative symptoms in schizophrenia, the clinical pharmacology, and the unique AE profile that differs markedly from the class-specific AE profile for atypical antipsychotics.

TH47. SAFETY AND TOLERABILITY PROFILE OF ZURANOLONE FROM THE LANDSCAPE (MAJOR DEPRESSIVE DISORDER) AND NEST (POSTPARTUM DEPRESSION) CLINICAL DEVELOPMENT PROGRAMS

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Abstract: Background: Zuranolone is an investigational, oral, neuroactive steroid and GABA type A receptor positive allosteric modulator in clinical development for once-daily, 2-week treatment of major depressive disorder (MDD) and postpartum depression (PPD) in adults. Here, we summarize safety data from 4 completed placebo-controlled trials in the zuranolone clinical development programs LANDSCAPE and NEST.

Methods: The 3 completed studies in the LANDSCAPE Program (moderate/severe MDD) include MDD-201B (NCT03000530; Phase 2; zuranolone 30 mg; baseline 17-item Hamilton Depression Rating Scale [HAMD-17] total score ≥22; N = 89), MOUNTAIN (NCT03672175; Phase 3; zuranolone 20 mg or zuranolone 30 mg; baseline HAMD-17 total score ≥22; N = 581), and WATERFALL (NCT04442490; Phase 3; zuranolone 50 mg; baseline HAMD-17 total score ≥24; N = 543). The completed study in the NEST Program (severe PPD) is ROBIN (NCT02978326; Phase 3; zuranolone 30 mg; baseline HAMD-17 total score ≥26; N = 153).

Results: Treatment-emergent adverse events with incidence ≥5% in zuranolone arms (range across trials; zuranolone vs placebo) were headache (6.3%-17.8% vs 7.4%-15.9%), somnolence (5.9%-15.4% vs 2.3%-11.0%), dizziness (5.7%-13.8% vs 2.2%-5.5%), nausea (3.6%-11.1% vs 2.3%-8.2%), upper respiratory tract infection (0%-7.7% vs 0.7%-1.4%), sedation (4.4%-7.5% vs 0%-4.5%), fatigue (0%-6.8% vs 0%-2.6%), and diarrhea (0%-6.4% vs 2.7%-6.8%). No incidence of loss of consciousness, evidence of sexual dysfunction, increased incidence of suicidal ideation/behavior, or increased incidence of withdrawal symptoms after discontinuation was observed in zuranolone treatment arms in any of the trials. At Day 15, improvements in HAMD-17 individual insomnia items in zuranolone groups exceeded improvements in placebo groups. Study discontinuations (zuranolone arms) due to adverse events were low (1.3%-4.4%) across trials.

Conclusions: Zuranolone was generally well tolerated, with a safety and tolerability profile consistent across 4 completed clinical trials in adult patients with MDD/PPD.

TH48. ADJUNCTIVE USE OF TRORILUZOLE, A NOVEL GLUTAMATE MODULATOR, IN PATIENTS WITH OBSESSIVE COMPULSIVE DISORDER: IMPACT OF BASELINE DISEASE SEVERITY ON TREATMENT OUTCOMES

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Abstract: Background: Obsessive-compulsive disorder (OCD) is a prevalent psychiatric disease, affecting 2-3% of the general population. Up to 60% of patients have an inadequate response to conventional pharmacotherapy. Adjunctive neuroleptics are used off-label for more treatment resistant cases but none are currently FDA approved. Troriluzole is a third-generation glutamate modulating agent and new chemical entity that reduces glutamate, a key neurotransmitter implicated in obsessive compulsive disorder. This post hoc analysis evaluated the efficacy of troriluzole with respect to illness severity at study entry.

Methods: Patients having an inadequate response to their current standard of care (SOC) medication for the treatment of OCD were enrolled into a randomized, double-blind, placebo-controlled proof of concept study and were treated for 12 weeks with troriluzole 200 mg or placebo. Inclusion criteria included a Yale-Brown Obsessive Compulsive (Y-BOCS) score of at least 19 and patients needed to be on a stable dose of a SOC medication at study entry. The primary endpoint was the change in the Y-BOCS total score from baseline to the end of the double-blind phase of the study. Subanalysis for illness severity included only the subset of patients with baseline Y-BOCS ≥ 24.

Results: 244 patients, ages 18-65, were enrolled into the study. Troriluzole 200 mg administered once daily as adjunctive therapy resulted in a numerically greater improvement versus placebo in the change from baseline in the Y-BOCS during all efficacy assessment visits (weeks 4, 8 and 12). At week 8, the mean Y-BOCS change from baseline was -5.1 points for the troriluzole group (n = 96) versus -3.6 points for the placebo group (n=108). The treatment difference was -1.5 points (nominal p-value = 0.041). At Week 12, the mean Y-BOCS change from baseline was -5.9 points for the troriluzole group (n = 99) versus -4.9 points for the placebo group (n = 102), but the treatment difference (-1.0 point) did not reach statistical significance (p = 0.22). In post hoc analyses, the troriluzole treatment difference compared to placebo was greater both at week 8 and week 12 in subjects who had more severe OCD symptoms at baseline (Y-BOCS total score ≥ 24). At week 8, the Y-BOCS mean change from baseline in this subset was -5.7 points for the troriluzole group (n = 66) versus -3.8 for the placebo group (n = 76). The treatment difference was -1.9 points (nominal p-value = 0.051). At Week 12, the mean Y-BOCS change from baseline was -6.7 points for the troriluzole group (n = 69) versus -5.0 for the placebo group (n = 73). The treatment difference was -1.7 points (nominal p value = 0.105).

Conclusion: This proof-of-concept study in adult patients with OCD having an inadequate response to SOC treatment revealed a consistent numerical benefit of adjunctive troriluzole at all time points, however statistical significance was only seen at the Week 8 time point. Subjects with more severe illness at study entry demonstrated larger effect sizes. Phase 3 studies with adjunctive troriluzole for the treatment of OCD are currently ongoing (NCT04641143 and NCT04693351) with modifications to trial design including a larger sample size, a higher YBOCS severity score cut-off, and higher drug dose.

TH49. BRAINSONIX TECHNOLOGY OF LOW INTENSITY FOCUSED ULTRASOUND PULSE (LIFUP) FOR TARGETED TRANSCRANIAL NEUROMODULATION AND DELIVERY OF BIOLOGICAL SUBSTANCES IN THE BRAIN

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Abstract: Brainsonix Technology of Low Intensity Focused Ultrasound Pulse (LIFUP) for targeted transcranial neuromodulation and delivery of biological substances in the brain.
Transcranial Focused Ultrasound (tFUS) is one of the rapidly developing areas in brain research and clinical sciences. High Intensity Focused Ultrasound is used as a surgical intervention by heating precise areas of the brain within the skull. Approximately 20 years ago,

the founder of Brainsonix and UCLA professor Alexander Bystritsky filed the first patent proposing that Low Intensity (tFUS or LIFUP) administered as a train of impulses could alter neuronal conductivity and firing of neurons. After a series of animal research at UCLA and Brigham and Women's Hospital demonstrating that ultrasonic pulses can activate and inhibit the neurons, several other patents were filed. These patents were the grounds on which Brainsonix and the experimental device were created.

The Brainsonix Corp. device Bx Pulsar1002 is fully MRI compatible and was used in several IDE-driven human clinical trials. The investigational device has been used for brain mapping and altering pain threshold in volunteers and in several experimental clinical trials in humans including epilepsy, coma, anxiety, OCD, and Alzheimer's Disease. The main targets of the stimulation were the amygdala, temporal lobe, thalamus, ventral capsule of the ventral striatum (VCVS), and hippocampus. No significant side effects were found in any of the trials, and preliminary results have been particularly promising for the reduction of anxiety and obsessive-compulsive (OCD) symptoms. For example, in the treatment-resistant generalized anxiety disorder (GAD) open-label trial the sonication of the right amygdala was performed and caused a significant reduction (35% or more) of anxiety symptoms measured by the Beck Anxiety Inventory in 11 out of 14 patients. The preliminary trial of stimulation in VCVS in the treatment-resistant OCD, which is the usual site for deep brain stimulation, demonstrated significant improvement of OCD symptoms as measured by Yale-Brown OCD Scale (YBOCS). In this small open-label clinical trial 4 patients out of 6 demonstrated significant improvement in YBOCS scores and in 3 of them the reduction of the symptoms exceeded 35% from the baseline. The company is about to start a pivotal trial for the treatment of coma under the FDA Break-Through, Fast Track program. Also, using grants from Tiny Blue Dot Foundation and the Breakthrough Award from International Obsessive-Compulsive Disorders Foundation (IOCDF), investigators in Harvard, Baylor, and the Medical University of Southern Carolina are starting sham-controlled pilot trials in treatment-resistant OCD and GAD. Synaptec Research, Inc. holds patents on using low-intensity tFUS for biologicals and drug deliveries in specific areas of the brain across the blood-brain barrier. Brainsonix Corp. in collaboration with Synaptec Research Inc. started a series of animal experiments demonstrating the feasibility of delivering exosomes to the brain. In a collaboration with the City of Hope, Brainsonix, and Synaptic Research, the Bx Pulsar 1002 device was used to demonstrate selectively increased concentration of an I.V. infused radiotracer within a rat brain target (sized on the order of millimeters). The clinical applications are endless for a technology that can non-invasively neuromodulate deep areas of the brain and deliver small molecules to precise brain targets.

TH50. HEALTHCARE COST SAVINGS THROUGH IMPROVED BIPOLAR I DISORDER IDENTIFICATION USING THE RAPID MOOD SCREENER (RMS) IN PATIENTS WITH MAJOR DEPRESSIVE DISORDER

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Abstract: Introduction: Misdiagnosis of bipolar I disorder as major depressive disorder (MDD) leads to increased healthcare resource utilization and costs. The cost-effectiveness of

the Rapid Mood Screener (RMS), a tool to identify bipolar I disorder in patients with depressive symptoms, was assessed in patients with MDD presenting with depressive episodes.
Methods: A decision-tree model of a hypothetical cohort of 1000 patients in a US health plan was used to estimate the number of correct diagnoses and overall total healthcare costs over a 3-year timeframe for RMS-screened versus unscreened patients. Model inputs included prevalence of bipolar I disorder in patients with MDD, RMS sensitivity/specificity, and cost of misdiagnosing bipolar I disorder as MDD.

Results: The number of correct bipolar I disorder or MDD diagnoses at years 1, 2, and 3, respectively, was 977, 978, and 981 for RMS-screened patients and 806, 819, and 837 for unscreened patients. Screening with the RMS resulted in total healthcare plan cost savings of $1279/patient in year 1. Cumulative cost savings per patient for RMS screening versus no RMS screening were $2307 over 2 years, and $3011 across 3 years. Threshold analyses of model inputs suggested the RMS would remain cost-saving even in scenarios assuming lower prevalence of bipolar I disorder (10%) and reduced RMS sensitivity (≥3%).

Conclusion: The RMS is a cost-effective tool to identify bipolar I disorder in patients who would otherwise be misdiagnosed with MDD. Screening with the RMS resulted in increased cost-savings over 3 years, with model results remaining robust even with lower bipolar I disorder prevalence and reduced RMS sensitivity assumptions.

TH51. A NOVEL PREDICTION MODEL FOR THE EARLY IDENTIFICATION OF MISDIAGNOSED BIPOLAR I DISORDER AMONG PATIENTS WITH MAJOR DEPRESSIVE DISORDER

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Abstract: Introduction: Given the clinical and economic consequences of bipolar I disorder (BP-I) misdiagnosis, it is important to identify misdiagnosed patients as early as possible. This study aimed to develop a claims-based prediction algorithm to identify patients with BP-I misdiagnosed as major depressive disorder (MDD) at the time of their first MDD diagnosis.
Methods: This analysis used claims data from IBM® MarketScan® Research Databases (Commercial, Medicaid, and Medicare). Patients diagnosed with MDD and subsequently diagnosed with BP-I comprised the misdiagnosed BP-I cohort; patients with MDD and no known BP-I diagnosis comprised the MDD-only cohort. The date of first MDD diagnosis was defined as the index date for patients in both cohorts. During the 12 months preceding the index date, predictors of BP-I misdiagnosis were evaluated. LASSO logistic regression models were trained, tested, and validated in a 1:1 population that included the misdiagnosed BP-I cohort and a random sample of patients from the MDD-only cohort with ≥36 months of observation following the index date. Cross-validated performance metrics of the model included the area under the receiver operating characteristic curve (AUC) and accuracy. Odds ratios (ORs), 95% confidence intervals, and P-values were used to quantify predictors of BP-I misdiagnosis.

Results: A total of 30,560 patients in the misdiagnosed BP-I cohort and 320,464 patients in the MDD-only cohort with ≥36 months of post-index observation were included, of whom 30,560 were randomly selected to be used in model development. The prediction model was 68.2% accurate and had an AUC of 0.744, indicating a good ability to identify misdiagnosed patients.

The strongest predictor of misdiagnosis was age 18–24 years, corresponding to 2.42 times the odds of misdiagnosis relative to those ≥65 years; patients aged 25–34 years also had 86% greater odds of misdiagnosis, with an OR of 1.86. The use of atypical antipsychotics, mood stabilizers/anticonvulsants, or anxiolytics was associated with increased odds of misdiagnosis (ORs=2.34, 1.65, and 1.39, respectively); patients with a history of a mental health-related emergency room visit (OR=2.17) or drug abuse (OR=1.75) also had elevated risk. The model identified several factors that were associated with a lower risk of misdiagnosis (ie, correct diagnosis of MDD). Patients aged 55–64 years had 40% lower odds of being misdiagnosed (OR=0.60) relative to those aged ≥65 years. Patients with 1–2 antidepressant pharmacy fills had an OR of 0.85, while those with greater antidepressant use (3 or more fills) had an OR of 0.70, relative to no antidepressant use. Finally, patients with a history of non-major depressive disorder before their MDD diagnosis had lower odds of being misdiagnosed (OR=0.73). The ORs of all selected predictors were significant (P≤.001).

Conclusions: This real-world prediction model identified several important predictors of BP-I misdiagnosis at the time of first MDD diagnosis, including younger age, medication use, mental health-related emergency room visit, and history of drug abuse. Recognizing such factors in clinical practice may assist healthcare professionals in providing a timely and accurate BP-I diagnosis.

TH52. EFFECT OF LURASIDONE ON DEPRESSIVE SYMPTOMS, FUNCTION, AND QUALITY OF LIFE OUTCOMES; A POST-HOC MULTIPLE RESPONDER ANALYSIS

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Abstract: Introduction: In studies of bipolar depression, pharmacological response is often measured by improvement in depressive symptoms using specific responder criteria. In a recent Depression and Bipolar Support Alliance (DBSA) survey, patients with depression ranked improvement in function and quality of life higher than improvement in depressive symptoms. The purpose of this post-hoc analysis was to analyze response on symptom severity measures, as well as combined response to multiple measures, including symptom severity, function, and quality of life.

Methods: In a six-week, double-blind, placebo-controlled study of patients with bipolar depression randomized to lurasidone (20-60 mg/day or 80-120 mg/day) or placebo, treatment response was measured for: depression symptoms using the Montgomery-Åsberg Depression Rating Scale (MADRS), function using the Sheehan Disability Scale (SDS), and quality of life using the Quality-of-Life, Enjoyment, and Satisfaction Questionnaire–Short Form (Q-LES-Q). Patients were categorized as responders based on their level of improvement from Baseline to Week 6 on the MADRS (≥50% improvement), SDS (≥9 point improvement), and Q-LES-Q (≥20% improvement). Responder analyses were calculated for the combined lurasidone doses versus placebo using logistic regression controlling for baseline score, treatment, and geographic region (US vs Non-US). Number needed to treat (NNT) was also calculated for each comparison. In addition to individual response rates, multiple responders were calculated for MADRS+SDS, MADRS+Q-LES-Q, SDS+Q-LES-Q, and MADRS+SDS+Q-LES-Q.

Results: Significantly more patients treated with lurasidone achieved response on the MADRS compared to placebo (52% vs 30%, p<0.0001, NNT=5). Similar results were observed on the SDS (55% vs 40%, p=0.017, NNT=7) and Q-LES-Q (75% vs 57%, p=0.0002, NNT=6). Lurasidone treated patients who responded on both the MADRS and SDS demonstrated a trend toward significance compared to placebo (41% vs. 30%, p=0.054, NNT=9). The percentage of patients in the lurasidone group who responded on the MADRS and Q-LES-Q was significantly greater than placebo (52% vs. 29%, p<0.0001, NNT=5). Responders on both the functional (SDS) and quality of life (Q-LES-Q) outcomes was significantly greater for the lurasidone treatment group relative to placebo (52% vs. 32%, p=0.002, NNT=6). Finally, significantly more lurasidone treated patients showed a response on all three (MADRS+SDS+Q-LES-Q) outcome measures compared to placebo treated patients (41% vs. 26%, p=0.016, NNT=7).

Conclusions: Patients with bipolar depression treated with lurasidone demonstrated statistically significant and clinically meaningful response not only for improvement in depressive symptoms alone, but also in combination with improvement in functional and quality of life measures. Inclusion of these multi-dimensional, patient-centered outcome measures are important to patients in their journey to overall recovery.

Clinicaltrials.gov identifier: NCT00868699

TH53. DAILY AND SOCIAL FUNCTIONING IN PATIENTS WITH SCHIZOPHRENIA AFTER INITIATING TREATMENT WITH ARIPIPRAZOLE LAUROXIL

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Abstract: Background: Clinical practice guidelines endorse efforts to improve social functioning in patients with schizophrenia, but functional improvement does not necessarily follow reductions in psychotic symptomatology. Aripiprazole lauroxil (AL) is a safe and effective long-acting injectable (LAI) antipsychotic approved for the treatment of adults with schizophrenia. We analyzed patients' daily and social functioning after switching to AL treatment.

Methods: Clinically stable adults with schizophrenia and residual symptoms or intolerance following ≥3 doses of paliperidone palmitate or risperidone LAI were switched to open-label AL treatment (441, 662, or 882 mg q4weeks or 882 mg q6weeks) for 6 months (NCT02634320). Daily and social functioning were assessed on the Personal and Social Performance (PSP) scale and the Birchwood Insight Scale (BIS) both before and 6 months after AL initiation. Mean (standard deviation [SD]) change from baseline in PSP total score was recorded; P values were calculated via one-sample t-test at 6 months (completers) or at last on-treatment assessment. The proportions of patients reporting functioning issues as "not present" or "mild" on PSP subscales were also calculated. The BIS scores and change from baseline are presented overall and by reason for discontinuation.

Results: All 51 patients received ≥1 AL dose; 35 completed the study, and 45 contributed data at last assessment. Mean age was 40.6 years; most patients were male (72.5%) and Black (49.0%). Reasons for discontinuing prior LAI treatment included persistent positive symptoms (34/51; 66.7%), intolerability (9/51; 17.6%), and persistent negative symptoms (8/51; 15.7%). Baseline mean (SD) PSP total score (55.1 [10.47]) improved significantly over 6 months of

AL treatment in completers (mean [SD] change: 3.2 [7.97]; P =0.022) and in those who discontinued early (mean [SD] change: 2.9 [8.15]; P =0.021). Patients who initiated AL because of intolerability had the largest improvement in PSP total score (mean [SD] change: 5.3 [4.42] at 6 months and last assessment). The proportions of patients who rated personal and social functioning issues as "not present" or "mild" increased from baseline to 6 months across each PSP subscale: socially useful activities, 9.8% to 17.1%; personal and social relationships, 29.4% to 31.4%; disturbing and aggressive behaviors, 94.1% to 94.3%; and self-care, 64.7% to 85.7%. Mean (SD) BIS total score in the overall population at baseline was 12.0 (3.19) and showed little to no change over time (mean [SD] changes: 0.0 [3.21] at 6 months and −0.1 [3.05] at last assessment). Mean (SD) BIS score changes from baseline at 6 months were −0.3 (3.67), 0.6 (1.06), and 0.2 (3.90) among patients who initiated AL because of persistent positive symptoms, tolerability concerns, and persistent negative symptoms, respectively.

Discussion: Patients with schizophrenia who initiated AL self-reported daily and social functioning was maintained or improved over 6 months of treatment. The proportion of patients reporting issues with daily function as "not present" or "mild" on the PSP subscales increased over the course of the study. Patients reported no significant changes from baseline on the BIS. These data demonstrate that patients with schizophrenia who have persistent symptoms or tolerability issues with other LAI antipsychotics can initiate AL treatment without reductions in daily or social function.

TH54. PRAX-114, AN EXTRASYNAPTIC-PREFERRING GABA-A RECEPTOR POSITIVE ALLOSTERIC MODULATOR: A PHASE 2 TRIAL EVALUATING MULTIPLE DOSE SAFETY, TOLERABILITY, AND PRELIMINARY EFFICACY IN MAJOR DEPRESSIVE DISORDER

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Abstract: Background: Neuroactive steroid positive allosteric modulators of GABAA receptors (GABAAR PAMs) differ from benzodiazepines (BZ) by mediating both phasic and tonic inhibition through potentiation of synaptic and extrasynaptic receptors, respectively. This mechanism has demonstrated rapid efficacy in major depressive disorder (MDD), postpartum depression and essential tremor, but the therapeutic window has been limited by sedative effects related to BZ-like activity at synaptic GABAAR.

PRAX-114 is an extrasynaptic-preferring GABAAR PAM in development for treatment of MDD. We postulated this preference to be the basis for preclinical findings demonstrating >20-fold separation between antidepressant- and sedative-like effects in rodents, and the lack of dose-limiting sedation in a Phase 1 trial assessing PRAX-114 safety and tolerability in healthy participants. Here we report results from an open-label Phase 2 trial assessing safety, tolerability and preliminary efficacy in adult participants with moderate-to-severe MDD, including women with perimenopausal MDD (PMD).

Methods: The PRAX-114-202 trial comprised 3 parts. In Part A, adults with MDD received 14-days PRAX-114 (45, 60, 80 mg qPM; n=33; 7 days inpatient, 7 days outpatient). In Part B, women with PMD received 14-days PRAX-114 (60 mg qPM; n=6; outpatient). In Part C, adults with MDD received 27-days PRAX-114 (60 mg qPM; n=13; outpatient).

In Parts A and C, eligible participants were 18-65 years and had a DSM-5 diagnosis of MDD with a minimum Hamilton Depression Rating Scale (HAM-D) score of 22. In Part B, eligible women were 40 years or older, had a history of irregular menses and a minimum of 4 vasomotor symptoms (hot flashes) per day.

The key efficacy endpoint across the trial was Day 15 HAM-D change from baseline. Further efficacy endpoints included change from baseline in the Hamilton Anxiety Rating Scale (HAM-A) and the patient-reported Symptoms of Depression Questionnaire. In Part B, additional endpoints included change from baseline in the Perimenopausal Depression Questionnaire (Meno-D), and in the number and severity of vasomotor symptoms (hot flashes).

Results: Mean age was 35 years (range 19-58) in Part A, 49 years (range 43-56) in Part B, and 40.3 (range 24-54) in Part C. In Parts A and C, 55% and 30.8% of participants were male, respectively. Across all parts of the trial, mean baseline HAM-D total score was 25 (range 22-30). PRAX-114 was generally well-tolerated across the dose range tested in all parts of the trial; adverse events (AEs) were mostly mild, with no serious AEs.

PRAX-114 led to similarly marked improvement in HAM-D total scores at all doses and parts of the trial. Day 15 HAM-D least-squares mean change from baseline ranged from 11-16 points across all doses in Parts A, B, and C, with improvements in Parts A and C largely maintained 2 weeks after study drug discontinuation. Similar improvements were observed in the additional efficacy endpoints, including HAM-A.

Participants in Part B also showed marked improvements in menopausal and mood symptoms over this period, including Day 15 mean decreases from baseline of 60% in the frequency of moderate-to-severe hot flashes and 68% in Meno-D total score. Menopausal and mood symptoms trended toward baseline 2 weeks after study drug discontinuation in Part B.

Conclusion: The promising preliminary efficacy data at well-tolerated dose levels support further development of PRAX-114 as a rapid-acting antidepressant with potential to address unmet needs for patients with MDD and PMD.

TH55. GENETIC MODERATORS OF COGNITIVE AND FUNCTIONAL IMAGING PREDICTORS OF EMPLOYMENT STATUS IN PEOPLE WITH SCHIZOPHRENIA

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Abstract: Background: Current pharmacological treatments for schizophrenia fall short in addressing cognitive impairments. As cognitive impairment predicts functional outcomes including employment in this disorder, it is crucial to better understand predictors for successful employment in this population to better develop targeted treatments. Prior work has demonstrated that general measures of cognitive ability are associated with employment. However, it is unclear if this relationship is driven by specific cognitive domains. Genetic factors have also been shown to relate to cognitive ability and schizophrenia. However, there is limited information on how these domains intersect in regard to employment, as well as how neural correlates may play a role. In this study, we tested for associations of cognitive (general

and specific domains), genetic, and neurofunctional variables with future employment status (employed versus unemployed) in people with schizophrenia spectrum disorders.
Methods: After an average of 8.8 years (+/- 4.3), we recontacted 129 research participants with schizophrenia spectrum disorders (mean age 33.1 +/- 10.6 years; 41 female) who had completed neuropsychological and genetic testing, as well as a 3T fMRI during the N-Back working memory task at the National Institute of Mental Health Intramural Research Program, and we obtained information regarding long-term functional outcome. Cognitive measures from their initial visits, including 'g' (a measure of general cognition), IQ, and six cognitive subdomains (verbal memory, N-Back working memory, visual memory, processing speed, card sorting/executive function, and span working memory), were tested as predictors of patients' employment status at follow-up using logistic regressions. Polygenic scores for schizophrenia risk (PGSscz), based on summary statistics from published genome-wide association studies, were derived for a subset of patients (n=104) and the logistic regressions were repeated after including polygenic scores in the models. Finally, for the patients who participated in N-Back working memory fMRI scans (n=58), we used AFNI software to test whether neural activation of any brain region predicted future employment.

Results: At the follow-up timepoint, 43.8% of patients were actively employed. Employment at follow-up was positively associated with general intelligence (g, p=0.03), IQ (p=0.01), and verbal memory scores (p=0.03) measured at the initial visit. N-Back working memory capacity (p=0.04) and processing speed (p=0.04) effects on employment status were found to be moderated by PGSscz. Additionally, fMRI activation analyses revealed that greater activation in a network of frontal-parietal regions, including right dorsolateral prefrontal cortex (peak p=0.001, uncorrected), at the initial visit related to employment status at follow-up.

Conclusions: Given our results, employment outcomes may be ameliorated by targeting treatments toward improving broad cognitive functioning and the specific domain of verbal memory in patients with schizophrenia. How genetics may play a role in moderating cognitive influences on employment status requires further investigation. Also warranting additional investigation, fMRI activation of frontal-parietal networks may provide a biomarker that characterizes the patient population in a clinically meaningful way that could help guide treatment decisions toward interventions aimed at improving functional outcomes such as employment status.

TH56. HOW DECENTRALIZED CLINICAL TRIALS DELIVER ON DIVERSITY: CASE STUDIES

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[1]*Science 37*

Abstract: The rapid growth of decentralized and agile (hybrid) clinical trial approaches, or DCTs, is enabling greater access to clinical research for all patients, including those often excluded due to sex, race, ethnicity, age, socioeconomic status, location of residency, as well as disability and other non-demographic characteristic. The three main tenets of DCTs that are driving this more patient-centric methodology are: 1) participation from anywhere (e.g., without geographic restrictions of site locations and travel), 2) participation at any time (e.g., not bound by clinic hours), and 3) participation with ease, empowered by technology and processes (e.g., telemedicine, home visits).

Historically, only patients associated with a clinical trial site or located within a 25-mile radius (or 30-minute commute) from a site have the opportunity to participate in a study. Agile (hybrid) and fully decentralized clinical trials, however, are opening opportunities for any patient anywhere to benefit from participation in clinical research. This can have impacts on measures of diversity beyond geography, including gender and race.

This case study will review the results from a recruitment campaign for a fully decentralized phase-two treatment-resistant depression study. Recruitment was conducted simultaneously in 34 states, using primarily social media strategies supplemented by a registry containing individuals who previously expressed interest in participating in decentralized clinical trials. The campaign resulted in over 65,000 sign-ups of people who prequalified by completing a brief online questionnaire. Analysis of participant zip codes was cross-referenced with census data allowing classification as rural, suburban, urban, and metropolitan. These results, presented graphically as a heat map, show the broad US representation achieved with the recruitment methodology. Importantly, the use of a mobile nursing team allowed for any of theses "sign-ups" to participate based on eligibility. Over 36,000 potential participants were eligible to complete a pre-screening interview based on initial trial eligibility questions and of them, 3,821, were considered pre-screen eligible after completing an interview with recruitment staff. From a gender perspective, 82% of signups were female and 16% male (the remainder were either non-binary or declined to report). The ethnic breakdown was as follows: 79.6% White; 7.6% Black; 6.7% Hispanic; 1.3% Asian; 1.8% Native American; and 0.3% Pacific Islander.

Because racial and ethnic minorities make up 39% of the US population, estimated rates of clinical trial participation for this collective group ranges from 2% to 16%. For example, while nearly 14% of Americans are black, they typically make up less than 5% of trial participants. And while Latinos make up 18% of the U.S. population, they represent just 1% of clinical trial participants.

As a result of the drive towards precision medicine, more targeted drugs and gene therapies are being brought to clinical trials; this lack of diversity among participants can make it particularly challenging to get a complete picture of a drug's safety and efficacy. Ensuring people from diverse backgrounds join clinical trials is also key to advancing health equity.

This case study demonstrates the potential reach of recruitment campaigns in the context of a decentralized approach. When participation is not limited to proximity to a brick-and-mortar site, it opens up access to individuals in suburban and rural areas. Other potential barriers, such as transportation, lack of child care, and stigma, can be overcome by enabling universal participation.

TH57. A PILOT STUDY OF LOW-INTENSITY FOCUSED ULTRASOUND FOR TREATMENT-RESISTANT OBSESSIVE-COMPULSIVE DISORDER

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Abstract: Background: While obsessive-compulsive disorder (OCD) is highly prevalent, 40-60% of patients fail to remit with standard care, including behavioral therapy and selective

serotonin reuptake inhibitors (SSRIs) (Pallanti et al., 2002). Last resort interventions such as deep brain stimulation (DBS) of the caudate nucleus is invasive and associated with higher risk (Arya et al., 2019). Low-intensity focused ultrasound (LIFU) may be a non-invasive alternative to DBS. Theoretically, LIFU, may be able to disrupt altered connectivity patterns within the basal ganglia, which may be therapeutic in treatment resistant OCD (trOCD) patients (Fan et al., 2019).

Objective: This open label study aimed to assess the safety and tolerability of low-intensity focused ultrasound (LIFU) targeted at the basal ganglia in a pilot sample of individuals with trOCD.

Methods: Sixteen patients (age X = 47, STD = 13) diagnosed with trOCD and failure to remit with 3 SSRIs, antidepressants and, and/or anxiolytics were recruited from Los Angeles neurology and psychiatry clinics. All patients scored 15 or greater on the baseline Yale-Brown Obsessive Compulsive Scale (Y-BOCS). Participants continued taking any concomitant medications for the duration of the study. Structural and functional magnetic resonance imaging (MRI) data were used to navigate individual LIFU targets. The study protocol indicated eight separate ten-minute sessions of LIFU targeted at the basal ganglia. Clinical response was defined as 25% or greater reduction in the individual patient's baseline Y-BOCS score and +2 or greater on the Global Rating of Change (GRC). Data was collected from October 2020 through March 2022.

Results: The first six participants enrolled received LIFU targeted at the caudate nucleus, but only two of them completed the protocol. Due to the high drop-out rate with this target, the investigative team adjusted the LIFU target towards an adjacent structure, the ventral striatum, for the next ten participants. One of these patients was excluded due to logistical travel concerns. Of the remaining nine, six finished the eight-session protocol. One of the two that completed the caudate protocol responded and five of the six patients on the ventral striatum protocol responded. Overall, LIFU was well-tolerated in patients with trOCD without notable side effects. One subject experienced an adverse event (regression of previously indicated anxiety symptoms) just after being enrolled in the study, but the investigator and institutional review board (IRB) deemed this unrelated to the study.

Conclusion: Despite limitations, this study provides preliminary evidence supporting the safety and tolerability of LIFU targeted at the basal ganglia in trOCD. The high drop-out rate of the caudate nucleus suggests the ventral striatum may be a more effective target. Further blinded studies may be warranted to assess the use of LIFU for treating trOCD.

TH58. METHYLONE, A RAPID ACTING ENTACTOGEN WITH ROBUST ANTIDEPRESSANT-LIKE ACTIVITY IN THE FORCED SWIM TEST

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Abstract: Selective serotonin antidepressants (SRIs) represent first line pharmacological treatment for a variety of neuropsychiatric illnesses. They are slow-acting antidepressants (SAADs) with a delayed onset of action, so most patients do not show significant effects until

at least 4 weeks (and often up to 8 weeks) of continuous treatment. SRIs are also associated with impairing side-effects and, even when optimally delivered, 40% of the patients do not respond. Methylone (3,4-methylenedioxy-N-methylcathinone; also known as MDMC, bk-MDMA and M1) is a rapid-acting entactogen (RAE) that has shown significant clinical benefit in >85% of patients in an observational, naturalistic study of 28 individuals with treatment-refractory PTSD and depression. In the current study, we employ the Forced Swim Test (FST), a classic and widely used screen for antidepressants, to explore the effect of methylone. We investigate the antidepressant-like activity of methylone compared with the prototypical selective SRI (SSRI), fluoxetine, and with novel rapid-acting antidepressants such as ketamine, psilocybin, and MDMA. Results demonstrate that methylone produces a rapid, robust, dose-dependent antidepressant-like response in the FST, far greater in magnitude than any other compound tested. A single dose of methylone (15 mg/kg, IP) reduces immobility by 99% compared to controls ($p<0.001$) compared to a 54% reduction with three doses of fluoxetine (10 mg/kg, IP). At this dose, methylone also significantly increases swimming and not climbing behavior in the FST, consistent with serotonergic activity. We also confirm effects of methylone on transporter binding, uptake, and release of serotonin, norepinephrine, and dopamine. Taken together, and consistent with initial clinical findings, our results suggest that methylone may have clinical utility in the treatment of depression and other CNS disorders in which classical antidepressants are efficacious.

TH59. RISK OF MORTALITY ASSOCIATED WITH PIMAVANSERIN COMPARED WITH ATYPICAL ANTIPSYCHOTICS IN PATIENTS WITH PARKINSON'S DISEASE–RELATED PSYCHOSIS

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Abstract: Pimavanserin is the only drug approved in the United States (US) to treat hallucinations and delusions associated with Parkinson's disease psychosis (PDP); other atypical antipsychotics are sometimes used off-label in patients with PDP. In the US, all antipsychotic drugs carry a boxed warning in their approved labeling concerning an increased risk of death in older patients with dementia-related psychosis.

The objectives of this study were to compare mortality risk among patients with PDP after initiation of pimavanserin with mortality risk after initiation of comparator atypical antipsychotics and to evaluate whether mortality risk varies over time or across subgroups.

A retrospective cohort of patients aged ≥ 65 years and diagnosed with Parkinson's disease (PD) and psychosis initiating pimavanserin or a comparator antipsychotic (clozapine, quetiapine, risperidone, olanzapine, aripiprazole, brexpiprazole) were identified in 2016-2019 Medicare claims data. Differences in treatment group characteristics were balanced with 1:1 propensity score (PS) matching. Incidence of all-cause mortality between the two groups was compared with hazard ratios (HR) and 95% confidence intervals (CI) estimated with Cox proportional hazard models. Time period-specific models evaluated changes in risk over time. Analyses were repeated in subgroups, including long-term care (LTC) or skilled nursing facility (SNF) residents on the index date. A sensitivity analysis included patients without a recorded psychosis diagnosis.

We identified 2,892 pimavanserin initiators and 19,083 comparator initiators (overall 47% female, mean age = 80.9 years, LTC/SNF residents = 30%). Most patients also had dementia (79%). Overall, deaths were observed in 14.5% of the cohort. Before PS matching, pimavanserin users generally had fewer severe comorbidities and more PD medication use than comparator users. PS matching resulted in 2,891 patients in both groups, and all measured covariates were well balanced. The matched HR for mortality for pimavanserin vs. comparator was 0.78 (95% CI, 0.67-0.91), with the lowest observed time period-specific HRs in the first 180 days. In LTC/SNF residents (90% of whom had dementia), the HR was 0.78 (95% CI, 0.60-1.01). In sensitivity analyses not requiring a recorded psychosis diagnosis, the HR was 0.76 (95% CI, 0.68-0.85).

This retrospective, active-comparator, new-user study suggests a lower mortality risk among patients treated with pimavanserin compared with those treated with other atypical antipsychotic drugs. Although PS matching balanced all measured characteristics, the potential for confounding remains; however, this observed association with lower mortality was consistent across subgroups and sensitivity analyses.

TH60. ANC-501: A NOVEL V1B RECEPTOR ANTAGONIST FOR MAJOR DEPRESSIVE DISORDER

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Abstract: Depression is ranked as the leading cause of disability worldwide by the World Health Organization (WHO). Major depressive disorder (MDD) is a psychiatric disorder that is characterized by the occurrence of one or more major depressive episodes, along with an absence of any history of manic, mixed, or hypomanic episodes. In addition to the high mortality rate due to suicide, depressed patients are more likely to develop coronary artery disease and type 2 diabetes among many other related health conditions.

Even after an adequate duration of treatment, the most commonly used treatments today (e.g., SSRIs and SNRIs) only result in approximately 35% to 45% of patients achieving clinical remission. Approximately 30% of patients are resistant to a series of treatments according to the STAR*D (Sequenced Treatment Alternatives to Relieve Depression) study, there is little data-driven guidance on next steps to treatment MDD patients in the event of a first-line failure. Importantly, side effects are a major concern for patients particularly the use of antipsychotic agents as adjunctive therapies and those used to treat treatment-resistant depression (TRD). Thus, there is a clear need for new, efficacious, well-tolerated agents to both treat depression episodes and prevent recurrent episodes of depression.

Stress mediated by the hypothalamus-pituitary-adrenal (HPA) axis has been hypothesized to be a pivotal factor in the pathophysiology of depression. Specifically, both corticotropin-releasing factor and arginine vasopressin, both of which are produced in the paraventricular nucleus of the hypothalamus, are considered primary factors in the regulation of HPA axis activity. Receptor subtypes for these neuropeptides, which may be involved in the regulation of HPA axis activity, have attracted much attention as potential targets for the treatment of depression and anxiety. With chronic stress in the context of the Covid pandemic likely contributing to the dramatic increase in MDD worldwide, correcting disruption in this pathway

may be particularly important new way to treat those patients with clearly disrupted HPA axis function.

ANC-501 (formerly TS-121) is an investigational new drug with antagonistic activity of the vasopressin receptor 1b (V1b receptor), which plays a role in the modulation of stress and mood. Based on nonclinical and early clinical studies, ANC-501 appears to be a promising candidate for clinical development with a novel mode of action that may benefit MDD patients. ANC-501 is being developed as an adjunctive therapy for MDD patients who have responded inadequately to standard anti-depressants and clear disruptions in their HPA axis. A phase 2 study of ANC-501 will initiate in 2022.

TH61. A CASE STUDY OF LOW-INTENSITY FOCUSED ULTRASOUND FOR TREATMENT-RESISTANT GENERALIZED ANXIETY DISORDER AND MAJOR DEPRESSIVE DISORDER

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Abstract: Background: Traditional interventions for anxiety involve pharmacological regimens, various forms of counseling, and transcranial magnetic stimulation (TMS) which are limited by patient response rates and inability to target deeper brain structures, such as the amygdala. Low-intensity focused ultrasound (fUS) demonstrates the ability to provide safe, targeted, and non-invasive neuromodulation of deeper brain structures. An individual (Male, 59) with treatment-resistant generalized anxiety disorder (trGAD) and treatment resistant major depressive disorder (trMDD) participated in a pilot study using low-intensity fUS. Previously, the individual had sufficient trials of 8+ medications (Sertraline, Escitalopram, Bupropion HCl, Duloxetine, Venlafaxine, Aripiprazole, Olanzapine, Ketamine infusions); psychotherapy; ECT two rounds, 24 sessions; diet, exercise, and sleep interventions; acupuncture, massage therapy; and meditation.

Methods: This individual received neurological and psychiatric evaluation, completed validated symptom-specific questionnaires (Beck Anxiety Inventory; Beck Depression Inventory-II), and underwent a multimodal advanced MRI. The advanced MRI was required to show evidence of hyperactivation and/or hyper functional connectivity of the amygdala. Concurrent interventions and therapies were not considered exclusionary. The individual underwent 8 consecutive weekly 10-minute fUS sessions using the Brainsonix Pulsar 1002 device aimed at the centromedial nucleus of the right amygdala. The sonication parameters were set within FDA safety limits, with a fundamental frequency fixed at 650 kHZ, a pulse length of 0.5 ms, a pulse width of 5 ms, a focal depth of 65 mm, an ISPPA of 14.39 W/cm2 and an ISPTA of 719.73 mW/cm2. Using the structural T1 MRI, the target was determined through neuronavigation by a board-certified neurologist. Using the Osirix Pro display program, the target was localized in three-dimensional space and projected onto the scalp surface by generating an orthogonal line to fiducial landmarks on the surface (e.g., nasion, inion) on a computer display. These same measurements are then used on the patient's real head, working back from the fiducial markers to the projected target on the patient's scalp. For each session, the probe was aimed through the temporal window at the amygdalar target.

Confirmation of target accuracy was obtained by real-time 3D optical tracking using the AntNeuro Visor2™ system.

Results: The individual has historically suffered from both trGAD and trMDD (30+ years) with many tried and failed therapeutic interventions. He had previously completed two courses of navigated repeated transcranial magnetic stimulation (rTMS) for depression which exacerbated his anxiety. After completing this fUS protocol, he underwent another course of navigated rTMS for his depression and responded with nearly complete resolution of anxiety and a decrease in depression. His two-month follow up revealed virtually no remaining anxiety or depression.

Conclusion: The response pattern observed may demonstrate that fUS targeting the amygdala produces very specific symptom relief in anxiety, but not depression. A therapeutic response to treatments for comorbid conditions may have been prevented by the anxiety in this treatment resistant individual. Extremely high levels of general anxiety are often considered to be markers of non-response to antidepressants, therapy, rTMS, and ETC. These results suggest that the use of combined treatment of rTMS and fUS may be useful for other individuals suffering from similar symptoms and warrants further study.

TH62. ANGER ATTACKS AMONG CLINICAL TRIAL PARTICIPANTS WITH MAJOR DEPRESSIVE DISORDER

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Abstract: Introduction: Anger attacks are sudden and intense episodes of anger, similar to panic attacks but with the primary emotions of anger and rage rather than fear and anxiety. Anger attacks are defined by irritability, overreaction to minor annoyances, and at least one episode per month of sudden inappropriate anger and rage toward others accompanied by autonomic and/or behavioral features such as heart palpitations, shortness of breath, physically or verbally attacking others, and throwing or destroying objects. These attacks can lead to distress and conflict for individuals who experience them and can result in violent behavior. Anger attacks are estimated to affect 30-40% of individuals with major depressive disorder (MDD), yet they are rarely considered in MDD clinical trial designs. In this study we examined the prevalence of anger attacks among MDD clinical trial participants and associations between anger attacks and depressive symptoms.

Methods: Our sample includes MDD clinical trial participants recruited in 2021 who were enrolled in a site-sponsored prospective lead-in trial, the TRAIT-MDD-107 study. Eligible participants included individuals aged 18 and older who met criteria for MDD based on the Mini-International Neuropsychiatric Interview (MINI), with a Hamilton Depression Inventory (HAM-D) score of ≥ 14. TRAIT was amended in February 2021 to include the Anger Attacks Questionnaire (AAQ) at baseline and study completion. From February-December 2021, 148 individuals enrolled in TRAIT and completed the AAQ at baseline. Descriptive analyses focused on assessing the initial prevalence of anger attacks in the sample. A series of Pearson correlations were conducted to examine the relationship between anger attacks and Age, Gender, and HAMD scores at baseline.

Results: At baseline, 36% of the sample (29 female, 24 male) met criteria for anger attacks. Of those, 42% reported having 1-2 anger attacks over the past month, 38% reported 3-4 attacks over the past month, 9% reported 5-8 attacks over the past month, and 11% reported 9 or more attacks over the past month. The most commonly reported autonomic arousal symptoms and behavioral features that occurred during the attacks were feeling out of control (87%), tachycardia (81%), wanting to physically attack or yell at others (75%), and feelings of fear, panic, or anxiety (70%). 62% of participants reported physically or verbally attacking others and 40% reported throwing or destroying objects. 74% of subjects reported that the anger attacks were uncharacteristic of them, and 91% reported feeling guilt or regret about the attacks. Anger attacks were significantly correlated with scores on HAMD items 5 (terminal insomnia; $\beta=.23$, $p<.01$), 12 (psychic anxiety; $\beta=.20$, $p<.05$), and 13 (somatic anxiety; $\beta=.26$, $p<.01$). There were no significant relationships between anger attacks and Age or Gender.

Conclusion: Anger attacks are common among the MDD clinical trial population, occurring in 36% of our sample, which is consistent with prior MDD outpatient research. Similar to previous studies, depressed subjects in our sample who met criteria for anger attacks scored higher on psychic and somatic anxiety than those without anger attacks. Additionally, subjects with anger attacks scored higher on terminal insomnia. These results lend credence to the notion of anger attacks as a distinct variant of MDD symptomatology, suggesting that they should be carefully considered in future MDD trial designs.

TH63. NATURALISTIC CLINICAL EVIDENCE FOR THE USE OF METHYLONE IN THE TREATMENT OF PTSD: A CASE SERIES

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Abstract: Posttraumatic stress disorder (PTSD) is a debilitating, and often chronic, psychiatric condition with limited effective treatments and high risk for negative outcomes, including heightened suicidality. There is urgent need to identify novel rapid-acting interventions that support robust and durable clinical improvements, especially among patients who have been failed by traditionally available interventions. The rapid acting empathogen 3,4-methylenedioxy-N-methylcathinone (methylone; also known as MDMC, βk-MDMA, and M1), is a phenethylamine compound with chemical and pharmacological similarities to 3,4-methylenedioxymethamphetamine (MDMA). It has been used outside of medical settings to treat PTSD and depression with encouraging preliminary clinical outcomes. A recent observational study comparing the acute effects of methylone and MDMA in healthy participants reported that while the subjective pharmacological effects of the two drugs were categorically similar, methylone demonstrated significant clinical, physiological, and pharmacological differences, including "softer" empathogenic and psychostimulant effects that may have potential for accelerated adoption across a broader range of medical settings and clinical applications. Here we present a case series of 21 patients with a primary diagnosis of PTSD, with a range of psychiatric comorbidities, who were treated clinically with methylone in an outpatient setting. The patients were not given structured psychotherapy in conjunction

with methylone treatment, which differs from recent studies of MDMA that emphasize the importance of a manualized psychedelic-assisted psychotherapy model. Archival data was used to examine patient characteristics and clinical outcomes. Methylone appeared to be safe and well-tolerated, even among complex patients. All patients achieved at least “minimal improvement” following treatment and 81% achieved “much” or “very much” improved on the Clinician Global Impressions Scale. Durability of effect was variable, though many patients reported sustained symptom improvements. These promising findings warrant future controlled trials to further characterize the role of methylone as a monotherapy and augmentation in the pharmacotherapy of PTSD. Methylone’s short duration of action and less dramatic acute psychological and physiological effects, may make it an attractive agent for clinical use in the treatment of PTSD and may prove to be an important and urgently needed addition to the therapeutic armamentarium.