2024 ASCP ANNUAL MEETING

Innovations in Clinical Research: Broadening Clinical Trial Methods, Endpoints and Goals

ABSTRACT BOOK

MIAMI BEACH, FLORIDA **MAY 28 - 31, 2024**

Tuesday, May 28, 2024

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

Panel Sessions

*INTERVENTIONAL OPTIONS FOR TREATMENT-RESISTANT DEPRESSION (TRD): LESSONS FROM ASCERTAIN-TRD AND ELEKT-D STUDIES

Maurizio Fava, Massachusetts General Hospital

Overall Abstract: Major depressive disorder (MDD) is estimated to affect one in five adults in United States during their lifetime. As the landmark Sequenced Alternatives to Relieve Depression (STAR*D) study informed us, over a third of treatment-seeking patients with MDD do not experience adequate improvement with two or more courses of antidepressant medications, i.e., have treatment resistant depression (TRD). In fact, fewer than 1 in 6 patients with TRD attained remission in STAR*D with commonly used antidepressant medications or their combinations. Therefore, clinicians may often need to choose interventional treatments such as repetitive transcranial magnetic stimulation (rTMS), electroconvulsive therapy (ECT), or intravenous (IV) ketamine. The proposed symposium will take a deeper dive in these interventional options for TRD by showcasing results from two large pragmatic studies that were funded by the Patient Centered Outcomes Research Institute (PCORI). The ASCERTAIN-TRD study compared augmentation with either aripiprazole or rTMS to switch to another antidepressant (either venlafaxine or duloxetine) among outpatients with TRD. The ELEKT-D study enrolled both outpatients (about 90% of the sample) and inpatients (about 10% of the sample) and evaluated non-inferiority of IV ketamine to ECT. The proposed panel will include novel findings from these two clinical trials with the first presentation focusing on rapidity of symptom improvement with ketamine versus ECT in ELEKT-D. The second presentation will include primary outcomes from the ASCERTAIN-TRD study evaluating the efficacy of augmentation versus switch. The third presentation will evaluate a select set of baseline clinical features in predicting symptom improvement with ketamine versus ECT while the fourth and final presentation will evaluate symptom improvement in suicidal ideation and related symptoms in the ASCERTAIN-TRD study. Attendees of this symposium will be engaged in a lively discussion around how these neuromodulation and pharmacological interventions should be implemented in clinical practice.

Learning Objectives: 1. Summarize the use of treatment-resistant depression (TRD) specific pharmacological and neuromodulation interventions.

2. Identify potential clinical markers that can be used to inform selection between pharmacological and neuromodulation interventions.

Literary References: 1. Anand A, Mathew SJ, Sanacora G, Murrough JW, Goes FS, Altinay M, Aloysi AS, Asghar-Ali AA, Barnett BS, Chang LC, Collins KA, Costi S, Iqbal S, Jha MK, Krishnan K, Malone DA, Nikayin S, Nissen SE, Ostroff RB, Reti IM, Wilkinson ST, Wolski K, Hu B. Ketamine versus ECT for Nonpsychotic Treatment-Resistant Major Depression. N Engl J Med. 2023 Jun 22;388(25):2315-2325.

2. Fava M. The challenges of defining and managing treatment-resistant depression in research and practice. World Psychiatry. 2023 Oct;22(3):350-351.

RAPIDITY OF SYMPTOM IMPROVEMENT WITH KETAMINE VERSUS ECT IN PATIENTS WITH TREATMENT-RESISTANT DEPRESSION

Brittany Obrien, Baylor College of Medicine

Individual Abstract: Background: The primary report form the ELEKT-D trial found that rates of improvement (either response or remission) with intravenous ketamine were noninferior to electroconvulsive therapy (ECT) for non-psychotic treatment-resistant major depression (TRD). Here, we evaluated whether the time to attaining these outcomes were different between the two treatment arms.

Methods: Participants of the ELEKT-D trial (N=365) who were randomized and received either ECT (9 sessions; n=170) or ketamine (six infusions; n=195) were included. Depression severity was assessed with the Quick Inventory of Depressive Symptomatology Self-Report (QIDS-SR) and the Montgomery Asberg Depression Rating Scale. At the end-of-treatment visit, response and remission were defined as ≥50% reduction as compared to baseline and score of QIDS-SR ≤5 or MADRS ≤10, respectively. Among those who attained response or remission, time to attainment of these outcomes were compared between the two treatment groups.

Methods: As previously reported, response rate based on the QIDS-SR was 41.2% (70/170) in the ECT group and 55.4% (108/195) in the ketamine group. By the end of first-week of treatment, 33.3% (65/195) had attained response in the ketamine group as compared to 19.4% (33/170) in the ECT group. Among responders, time to attainment of response was shorter with ketamine as compared to ECT. Findings related to remission as well as those based on MADRS will be presented.

Methods: Use of ketamine (IV) may be associated with more rapid onset of improvement in symptoms as compared to ECT.

Learning Objectives: 1. Identify trajectories of symptom improvement with ketamine.
2. Evaluate the differences in rapidity of symptom improvement with ketamine versus ECT.

Literature References 1.Anand A, Mathew SJ, Sanacora G, Murrough JW, Goes FS, Altinay M, Aloysi AS, Asghar-Ali AA, Barnett BS, Chang LC, Collins KA, Costi S, Iqbal S, Jha MK, Krishnan K, Malone DA, Nikayin S, Nissen SE, Ostroff RB, Reti IM, Wilkinson ST, Wolski K, Hu B. Ketamine versus ECT for Nonpsychotic Treatment-Resistant Major Depression. N Engl J Med. 2023 Jun 22;388(25):2315-2325.
2. O'Brien B, Lee J, Kim S, Nandra GS, Pannu P, Tamman A, Amarneh D, Swann AC, Murphy N, Averill L, Jha M, Mathew SJ. Anti-Suicidal Effects of IV Ketamine in A Real-World Setting. Psychiatry Research. 2023 Nov 14:115604.

COMPARATIVE EFFECTIVENESS RESEARCH TRIAL FOR ANTIDEPRESSANT INCOMPLETE AND NON-RESPONDERS WITH TREATMENT RESISTANT DEPRESSION (ASCERTAIN-TRD): REPORT OF PRIMARY OUTCOME.

George Papakostas, Massachusetts General Hospital

Individual Abstract: Further research is needed to help improve both the standard of care and the outcome for patients with treatment-resistant depression. A particularly critical evidence gap exists with respect to whether pharmacological or non-pharmacological augmentation is superior to antidepressant switch, or vice-versa. The objective of this study was to compare the effectiveness of augmentation with aripiprazole or augmentation with repetitive transcranial

magnetic stimulation versus switching to the antidepressant venlafaxine (or duloxetine for those not eligible to receive venlafaxine) for treatment-resistant depression. In this multi-site, 8-week, randomized, open-label study, 278 subjects (196 females and 82 males, mean age 45.6 years (SD 15.3)) with treatment-resistant depression were assigned in a 1:1:1 fashion to treatment with either of these three interventions; 235 subjects completed the study. 260 randomized subjects with at least one post-baseline Montgomery-Asberg Depression Rating (MADRS) assessment were included in the analysis. Repetitive transcranial magnetic stimulation (score change (standard error (se))= -17.39 (1.3) (p=0.015) but not aripiprazole augmentation (score change (se)= -14.9 (1.1) (p=0.069) was superior to switch (score change (se)= -13.22 (1.1)) on the MADRS. Aripiprazole (mean change (se)= -37.79 (2.9) (p=0.003) but not repetitive transcranial magnetic stimulation augmentation (mean change (se)= -42.96 (3.6) (p=0.031) was superior to switch (mean change (se)= -34.45 (3.0)) on the symptoms of depression questionnaire. Repetitive transcranial magnetic stimulation augmentation was shown to be more effective than switching antidepressants in treatment-resistant depression on the study primary measure. In light of these findings, clinicians should consider repetitive transcranial magnetic stimulation augmentation early for treatment-resistant depression.

Learning Objectives: 1) By the end of this session the audience will have a better understanding of the relative effectiveness of rTMS augmentation, aripiprazole augmentation versus switching to venlafaxine/duloxetine in TRD on clinician-rated symptoms of depression. 2) By the end of this session the audience will have a better understanding of the relative effectiveness of rTMS augmentation, aripiprazole augmentation versus switching to venlafaxine/duloxetine in TRD on patient-rated symptoms of depression.

Literature References 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.

Fava M. Management of Nonresponse and Intolerance: Switching Strategies. J Clin Psychiatry. 2000;61(suppl 2):10-2.

BASELINE FEATURES THAT PREDICT IMPROVEMENT WITH KETAMINE VERSUS ELECTROCONVULSIVE THERAPY IN TRD: FINDINGS FROM THE ELEKT-D STUDY

James Murrough, Icahn School of Medicine at Mount Sinai

Individual Abstract: Background: The ELEctroconvulsive therapy (ECT) vs. Ketamine in patients with Treatment-resistant Depression (ELEKT-D) study demonstrated non-inferiority of intravenous ketamine versus ECT for non-psychotic treatment-resistant major depression (TRD). This post-hoc analysis evaluated whether select clinical and sociodemographic features predicted improvement with ketamine versus ECT.

Methods: Participants (aged 21-75 years) included those who were randomized and received either six infusions of ketamine (n=195) or nine treatments with ECT (n=170) over three weeks. The Quick Inventory of Depressive Symptomatology Self-Report (QIDS-SR16) and the Montgomery-Åsberg Depression Rating Scale (MADRS) measured depression severity. Repeated-measures mixed models (for depression levels over all acute-phase visits) and logistic regression [for response (≥50% reduction) and remission (QIDS-SR16 ≤5, MADRS ≤10) at the end-of-treatment visit] predicted improvement with ketamine versus ECT after

False Discovery Rate (FDR) adjustment. Similar models identified non-specific predictors in each group.

Methods: Participants with baseline QIDS-SR16 ≤20 and those starting treatment as outpatients reported greater reduction in QIDS-SR16 with ketamine versus ECT. Conversely, those with baseline QIDS-SR16 GREATER THAN 20 (i.e., very severe depression) and starting treatment as inpatients reported greater reduction in QIDS-SR16 earlier in course of treatment with ECT but scores were similar in both groups at the end-of-treatment visit. In the ECT group only, participants with higher scores on measures of premorbid intelligence, lower scores on memory recall, and comorbid PTSD diagnosis reported greater reduction in MADRS. Other results were not significant after FDR adjustment.

Conclusions: Intravenous ketamine may be preferred over ECT among non-psychotic outpatients with TRD who have moderately severe or severe depression.

Learning Objectives: 1. Identify baseline features that differentially predict improvement in symptom severity with ketamine versus ECT.
2. Discuss how these features can be integrated in clinical decision-making.

Literature References 1. Su L, Zhang Y, Jia Y, Sun J, Mellor D, Yuan TF, Xu Y. Predictors of Electroconvulsive Therapy Outcome in Major Depressive Disorder. Int J Neuropsychopharmacol. 2023;26:53-60.
2. Price RB, Kissel N, Baumeister A, Rohac R, Woody ML, Ballard ED, Zarate CA, Jr., Deakin W, Abdallah CG, Feder A, Charney DS, Grunebaum MF, Mann JJ, Mathew SJ, Gallagher B, McLoughlin DM, Murrough JW, Muthukumaraswamy S, McMillan R, Sumner R, Papakostas G, Fava M, Hock R, Phillips JL, Blier P, Shiroma P, Šóš P, Su TP, Chen MH, Tiger M, Lundberg J, Wilkinson ST, Wallace ML. International pooled patient-level meta-analysis of ketamine infusion for depression: In search of clinical moderators. Mol Psychiatry. 2022;27:5096-5112.

IMPROVEMENT IN SUICIDE RISK AND PROPENSITY WITH ANTIDEPRESSANT AUGMENTATION AND SWITCH APPROACHES IN ASCERTAIN-TRD

Madhukar Trivedi, UT Southwestern Medical Center

Individual Abstract: Background: Suicide-related mortality in the United States has increased by over 30% in the past decade. Un- or inadequately-treated major depressive disorder (MDD) is one of the leading causes of suicide-related mortality. Among patients with MDD, those with treatment-resistant depression (TRD) have higher rates of suicide-related mortality. Yet, how antidepressant treatments improve suicide-related outcomes among patients with TRD remains poorly understood.
Methods: Participants who were randomized to augmentation with aripiprazole, augmentation with repetitive transcranial magnetic stimulation (rTMS) or switch to venlafaxine (or duloxetine) with at least one post-baseline visit were included (N=260). The Concise Health Risk Tracking (CHRT) scale was used to measure impulsivity, suicide propensity [composite of pessimism, helplessness, perceived lack of social support, and despair], and suicidal thoughts. A mixed-effects model with repeated measures (MMRM) that included data from all patients with any post-baseline data was conducted with treatment group (augment versus switch) as the between-subjects factor, time (visits 1-7) as the within-subjects factor, and a

group by time interaction term. Separate models were used for CHRT Total Score as well as domains of impulsivity, suicide propensity and suicidal thoughts.

Methods: There was a statistically (p LESS THAN 0.05) significant improvement in total CHRT score as well as in domains of impulsivity, suicide propensity and suicidal thoughts during the 8-week course of ASCERTAIN-TRD study. However, the treatment arm did not differ in either an overall effect or in the rate of improvement during this 8-week period. Higher baseline severity was associated with higher levels of these symptoms during the course of treatment.

Methods: Patients with TRD experience significant improvement in suicidal ideation and associated symptoms with commonly used augmentation approaches for TRD. However, there was no evidence to prefer one augmentation or switch approach in this post hoc analysis of ASCERTAIN-TRD.

Learning Objectives: 1. Identify measurement approaches for suicidal ideation and related symptoms in patients with TRD.
2. Evaluate improvement in suicidal ideation and related symptoms with commonly used augmentation and monotherapy approaches for patients with TRD.

Literature References 1. Jha MK, Trivedi MH. Treatment-Resistant Depression (TRD): Management Approaches in a Rapidly Evolving Therapeutic Landscape. Psychiatr Clin North Am. 2023 Jun;46(2):xiii-xiv.
2. Mayes TL, Carmody T, Rush AJ, Nandy K, Emslie GJ, Kennard BD, Forbes K, Jha MK, Hughes JL, Heerschap JK, Trivedi MH. Predicting suicidal events: A comparison of the Concise Health Risk Tracking Self-Report (CHRT-SR) and the Columbia Suicide Severity Rating Scale (C-SSRS). Psychiatry Res. 2023 Aug;326:115306. doi: 10.1016/j.psychres.2023.115306.

*BRIDGING THE GAP BETWEEN BODY AND BRAIN – INSIGHTS FROM TRANSLATIONAL RESEARCH ON CAUSES, TREATMENTS, AND OUTCOMES

Mahavir Agarwal, Centre for Addiction and Mental Health (CAMH), Canada

Overall Abstract: Cardiometabolic comorbidities such as metabolic syndrome, type 2 diabetes, and cardiovascular disease are intrinsically 3-5 times more prevalent among patients with psychiatric illness compared to the general population. Consequently, these conditions contribute to a reduced life expectancy by 15-20 years, and also have significant implications for self-esteem, quality of life, and cognitive functioning. Obesity and other metabolic disturbances are also associated with brain alterations that further perpetuate poor functional outcomes in mental illness. Taken together, it is possible that metabolic disturbances may serve as modifiable risk factors to dually improve physical and mental/cognitive health outcomes.
This symposium, chaired by Dr. Mahavir Agarwal (University of Toronto, Canada), will present an array of translational research that seeks to disentangle the complex causes of cardiometabolic comorbidity in mental illness and the implications of treating metabolic health in relation to cognitive and physical health outcomes. Dr. Abigail Schindler (University of Washington, USA) will discuss ongoing work focused on understanding a potential role for metabolic dysfunction following trauma exposure in relation to chronic adverse mental health outcomes. She will present complementary data from both preclinical and clinical lines of

evidence to highlight how trauma exposure may result in adverse central and peripheral metabolic changes that are associated with post-traumatic stress disorder, mild traumatic brain injury, and chronic pain. Dr. Kyle Burghardt (Wayne State University, USA) will describe the role of epigenomics in skeletal muscle insulin sensitivity by surveying the skeletal muscle DNA methylome response in a fasting versus insulin-stimulated state in olanzapine-treated versus placebo-treated healthy volunteers. This work will contribute to our understanding of the molecular mechanisms that underpin antipsychotic-induced insulin resistance and could aid in the discovery of biomarkers and/or treatments aimed at reducing the metabolic consequences of antipsychotic use. Finally, Nicolette Stogios (University of Toronto, Canada), will present data from a combined analysis of 3 randomized controlled trials (Canada and Denmark) of weight loss interventions, demonstrating that reductions in BMI are associated with positive improvements in brain age. Dr. Rebecca Hendrickson (University of Washington, USA) will serve as the discussant to review the complex interplay between cognitive and metabolic health in mental illness, as well as insights for future directions that can help propel the field forward.

Collectively, this symposium will provide novel perspectives into the pathophysiological mechanisms of cardiometabolic disturbances that are highly prevalent in mental illnesses and the potential of targeting cardiometabolic comorbidity to meaningfully improve metabolic, cognitive and psychopathology outcomes in patients with mental illness.

The symposium brings together women (Drs. Schindler and Hendrickson and Ms. Stogios), trainees (Ms. Stogios), early career scientists (Drs. Schindler, and Agarwal), and clinicians (Drs. Schindler, Agarwal, Burghardt, and Hendrickson).

Learning Objectives: 1. Appreciate the bidirectional relationship between mental and physical health
2. Learn how this bidirectionality opens up a therapeutic opportunity to improve both physical and mental health

Literary References: 1. Burghardt KJ, Mando M, Seyoum B, et al. The Effect of Antipsychotic Treatment on Hormonal, Inflammatory and Metabolic Biomarkers in Healthy Volunteers; A Systematic Review and Meta-Analysis. Accepted. In Press.
2. Agarwal SM, Panda R, Costa-Dookhan K, et al. Metformin for early comorbid glucose dysregulation and schizophrenia spectrum disorders: a pilot double blind randomized study. Translational Psychiatry. 2021 Apr 14;11(1):219.

CHRONIC MENTAL AND PHYSICAL HEALTH INTERACTIONS FOLLOWING REPETITIVE TRAUMA EXPOSURE IN VETERANS AND MICE

Katharine Liang, VA Puget Sound Health Care System

Individual Abstract: The aging US population is estimated to increase from 53 million in 2018 to 88 million in 2050. Aging is associated with physical deterioration that leads to an increased risk of disease and death. Indeed, aging is the primary risk factor for most neurodegenerative diseases and has more recently been identified as a risk factor for depression, suicidality, and substance use disorder later in life. Severe distress in response to trauma is increasingly recognized as a risk factor for aging acceleration, chronic disease progression, increased morbidity, and early mortality. More recently, mild traumatic brain injury (concussion; mTBI) has also been suggested as a risk factor for aging acceleration and premature mortality. Indeed, traumatic brain injury (TBI) is a major cause of death and disability, affecting every segment of the population, with youth, elderly, and athletes being

most affected. Likewise, following a traumatic event, post-traumatic stress disorder (PTSD) is common and affects 5-10% of adults in the United States. Moreover, mTBI and battlefield PTSD have been called the “signature injuries” of military personnel serving in Iraq and Afghanistan and are major sources of morbidity among Veteran patients enrolled in the VA health care system. Preclinical research efforts using rodent models can provide much needed insight into underlying mechanisms and aid in the identification of new biomarkers and therapeutic targets. Indeed, using our well-established mouse model of repetitive mTBI (which includes comorbid stress responses and PTSD-like outcomes), we find strong evidence of adverse health consequences that are progressive in nature (metabolic dysfunction, inflammation, cognitive and behavioral difficulties, gut microbiome dysbiosis), which follow closely in line with clinical findings from Iraq/Afghanistan Veterans with history of blast polytrauma. Effective preventative and/or therapeutic approaches are critically needed and will require the identification of integrated aging related biomarkers and a deeper understanding of risk factors and associated phenotypes that accelerate aging. Here we present ongoing work focused on machine learning approaches to understand patterns and predictors of adverse trauma/physical health outcomes. Datasets presented will include results from preclinical work using a mouse model of repetitive blast polytrauma, clinical work from a well-characterized cohort of Iraq/Afghanistan Veterans, and epidemiological work using VA electronic records. Together, results underscore the ability of trauma exposure to result in adverse central and peripheral metabolic changes that are associated with posttraumatic stress disorder, mild traumatic brain injury, and chronic pain, and highlight important implications for future diagnostic and treatment development.

Learning Objectives: 1). Understand chronic health effects of blast polytrauma. 2) Describe machine learning approaches to study physical and mental health interactions following trauma exposure.

Literature References Hendrickson R.C, Schindler A.G., Pagulayan K. (2018) Untangling PTSD and TBI: Challenges and Strategies in Clinical Care and Research. Current Neurology and Neuroscience Reports. 18(12):106.

Baskin BM., Logsdon AF., Lee SJ., Foresi BD., Peskind ER., Banks WA., Cook DG., Schindler A.G. (2023) Timing matters: Sex differences in inflammatory and behavioral outcomes following repetitive blast mild traumatic brain injury. 110:222-236. doi: 10.1016/j.bbi.2023.03.003. Brain, Behavior, Immunity.

EXPLORING OMIC' PATHWAYS OF ANTIPSYCHOTIC TREATMENT IN METABOLIC TISSUES

Kyle Burghardt, Wayne State University

Individual Abstract: The purpose of the talk will be to give an overview of investigations from our group into the effects of antipsychotics on metabolic tissues, namely skeletal muscle and adipose tissue from human populations. The content and methods will include epigenomic, lipidomic and proteomic analyses from two sets of studies: 1) a cross-sectional study of schizophrenia and bipolar patients on antipsychotics and 2) a randomized controlled trial of healthy volunteers treated with olanzapine or placebo. The omic' methodologies include array technologies and mass spectrometry methods. The results of the work will detail those specific alterations in both studies described above for the omic areas with an emphasis on finding common themes and elements across omic's datasets. Findings that will be described, for example, include the differential methylation of GREATER THAN 100 sites within insulin signaling genes such as PPAR, GSK3B and AKT2, the most significant proteomic differences

and their associated pathways such as the synthesis of pyrophosphates in the cytosol and finally lipidomic differences identified in phosphatidylcholine and fatty acyl species. The importance of this work is that it is attempting to better understand the effects of antipsychotics on metabolically relevant tissues in order to better understand how antipsychotic cause metabolic side effects like diabetes, insulin resistance and metabolic syndrome.
Learning Objectives: 1) To understand the potential role of metabolic tissues in antipsychotic treatment, 2) to describe the omic' changes from antipsychotic treatment in metabolic tissues.
Literature References 1) Burghardt, Kyle J., et al. "Profiling the Skeletal Muscle Proteome in Patients on Atypical Antipsychotics and Mood Stabilizers." Brain Sciences 12.2 (2022): 259. 2) Burghardt, Kyle J., et al. "Skeletal muscle DNA methylation modifications and psychopharmacologic treatment in bipolar disorder." European Neuropsychopharmacology 29.12 (2019): 1365-1373.

THE EFFECT OF WEIGHT LOSS ON BRAIN AGE IN SCHIZOPHRENIA

Nicolette Stogios, Centre for Addiction and Mental Health, University of Toronto

Individual Abstract: Background: Individuals with schizophrenia have high rates of cardiometabolic comorbidities, including type 2 diabetes and cardiovascular disease. Owing to this, patients with schizophrenia have a 20% reduced life expectancy compared to the general population. Obese individuals often exhibit neurostructural alterations, even in the absence of other pathology. Furthermore, they tend to show higher brain age when compared to normal weight individuals. However, there is limited understanding of how metabolic disorders impact brain structure in individuals with schizophrenia, as well as how metabolic improvements following pharmacological intervention may change brain outcomes. In this study, we investigated the relationship between brain morphology, and specifically brain age, with body mass index (BMI) and other metabolic parameters in overweight or obese patients with schizophrenia with or without comorbid diabetes. We assessed these changes before and after 12-week of adjunctive pharmacological treatment targeting metabolic dysfunction. As exploratory analyses, we also looked at the association between brain age, cognition, and metabolic parameters.
Methods: This study is a secondary analysis of data collected from three distinct double-blind studies investigating adjunctive pharmacological interventions for antipsychotic-induced metabolic dysfunction. The agents studied were exenatide (Denmark), metformin (Canada) and topiramate (Canada). The sample consisted of 48 overweight or obese patients with schizophrenia across the three studies (exenatide: N=9, metformin: N=11, topiramate: N=12, placebo: N=16). Structural MRI scans, metabolic measures, cognition data, and BMI were acquired at baseline and week 12 post-intervention. A convolution neural network-based classifier was used to estimate the brain age of each participant using a high-quality T1-weighted anatomical image of the brain. Baseline and endpoint data were used to assess changes in estimated brain age scores, as well as metabolic parameters and cognitive outcomes. All pharmacological interventions were investigated in a combined group given the small sample size per medication.

Methods: Change in BMI from baseline was statistically significant in the medication ($p=0.005$) and placebo groups ($p=0.008$). Significant changes were also found in total and high-density lipoprotein (HDL)-cholesterol levels across the treatment groups. No substantial changes in psychopathological scores or cognitive data between the baseline and endpoint assessments were observed in the sample. Multiple regression analysis revealed a positive

correlation between changes in BMI and brain age for the whole sample (beta=0.263; t=1.85; p=0.05) and the medication group (beta = 0.372; t = 2.12; p=0.04), but not in the placebo group (beta = -0.106; t=-0.40; p=0.69). No significant difference in the correlation strength was observed between the medication and placebo groups (p=0.12). Furthermore, there was no significant association between changes in brain age and other metabolic parameters, including total and HDL-cholesterol. Lastly, no significant correlation was found between brain age and cognition.

Conclusions: This study demonstrates that positive improvements in brain health (as assessed by change in brain age) may be associated with weight loss and other metabolic improvements by anti-diabetic medications in patients with schizophrenia and comorbid obesity. These findings imply that large and extended weight loss, together with general improvements in cardiometabolic alterations, can prevent obesity-related abnormalities in brain health.

Learning Objectives: 1. To explore the relationship between metabolic and cognitive health as well as brain morphology in patients with schizophrenia.
2. To explore whether metabolic improvements following pharmacological interventions may relate to favourable changes in neurocognitive outcomes in patients with schizophrenia.

Literature References 1. Rajkumar AP, Horsdal HT, Wimberley T, et al. Endogenous and Antipsychotic-Related Risks for Diabetes Mellitus in Young People With Schizophrenia: A Danish Population-Based Cohort Study. Am J Psychiatry. 2017;174:686-694.
2. McWhinney S, Kolenic M, Franke K, et al. Obesity as a Risk Factor for Accelerated Brain Ageing in First-Episode Psychosis-A Longitudinal Study. Schizophr Bull. 2021 Oct 21;47(6):1772-1781.

*REVISITING MODAFINIL / ARMODAFINIL IN BIPOLAR DISORDER TARGETING COGNITION, DEPRESSION, AND SLEEP CIRCADIAN RHYTHM

Mark Frye, Mayo Clinic

Overall Abstract: Armodafinil (R-modafinil) is a wakefulness-promoting low-affinity dopamine transport inhibitor that is currently approved in the United States for the treatment of excessive sleepiness associated with shift work disorder, narcolepsy, and obstructive sleep apnea. While two of the three Phase 3 studies did not separate from placebo, which led to the discontinuation of the development program for adjunctive armodafinil in bipolar I depression, a meta-analysis reported modafinil/armodafinil to be efficacious and safe in bipolar depression. Cognitive impairment and circadian dysfunction persist in the majority of BD patients even when acute symptoms remit. The relationship between sleep quality, daytime wakefulness, and neurocognition seems intuitive with sleep deprivation resulting in lower energy and impaired cognition in animals and humans. A majority of BD patients demonstrate deficits in attention, memory, and executive functioning even when affectively-stable. Pilot controlled with modafinil shows significant changes in processing speed and verbal learning, indicating greater improvement in the modafinil group versus placebo. Results are suggestive of cognitive benefit and improved daytime sleepiness, but worse sleep quality in those patients prescribed modafinil. A fully powered clinical trial is warranted with specific attention to the characteristics of patients who are most likely to benefit from treatment with modafinil and other methodological lessons learned from this pilot. Additional research is warranted and necessary to better identify clinical predictors (e.g., atypical depressive symptoms, circadian

dysrhythmia, cognitive targets, specific combinations of therapeutic agents) that would provide optimized, individualized therapeutics for bipolar depression and or cognitive enhancement in bipolar disorder.

Learning Objectives: 1. To review the methodological limitations of developing modafinil / armodafinil for bipolar depression

2. Better understand cognitive impairment and sleep circadian rhythm in bipolar disorder and as a target for modafinil / armodafinil

Literary References: 1. Lipschitz JM, Perez-Rodriguez M, Majd M, Larsen E, Locascio J, Pike CK, Shanahan M, Burdick KE. Modafinil's effects on cognition and sleep quality in affectively-stable patients with bipolar disorder: a pilot study. Front Psychiatry. 2023 Sep 4;14:1246149. doi: 10.3389/fpsyt.2023.1246149. PMID: 37732080; PMCID: PMC10507316.

2. Nunez NA, Singh B, Romo-Nava F, Joseph B, Veldic M, Cuellar-Barboza A, Cabello Arreola A, Vande Voort JL, Croarkin P, Moore KM, Biernacka J, McElroy SL, Frye MA. Efficacy and tolerability of adjunctive modafinil/armodafinil in bipolar depression: A meta-analysis of randomized controlled trials. Bipolar Disord. 2020 Mar;22(2):109-120. doi: 10.1111/bdi.12859. Epub 2020 Jan 7. PMID: 31643130.

MODAFINIL / ARMODAFINIL IN BIPOLAR DISORDER: LESSON LEARNED, ROADMAP FORWARD

Mark Frye, Mayo Clinic

Individual Abstract: There is a compelling need for effective, well-tolerated treatments for bipolar I depression. Armodafinil (R-modafinil) is a wakefulness-promoting low-affinity dopamine transport inhibitor approved for the treatment of excessive sleepiness associated with shift work disorder and narcolepsy. While two of the three armodafinil Phase 3 studies did not separate from placebo, which led to the discontinuation of the development program, a meta-analysis reported modafinil/armodafinil to be efficacious and safe in bipolar I depression.

There are challenges in developing a non-mood stabilizing unimodal agent targeting depression where the trial design template has conventionally been designed for atypical antipsychotic mood stabilizers. All of the current FDA-approved treatments for bipolar depression were previously FDA-approved for acute mania (i.e.. bimodal mood stabilization quetiapine, cariprazine), were co-prescribed with an antimanic agent (i.e. olanzapine fluoxetine combination), or generally assumed to have antimanic properties as a class effect in bipolar disorder (i.e. lurasidone, lumataperone). The assay sensitivity (i.e., drug–placebo separation) in the armodafinil studies was potentially limited by what was identified a priori as a study design strength (i.e., potential generalizability and community translation), namely the significant heterogeneity in mood stabilizer composition.

A fully powered clinical trial is warranted with specific attention to the characteristics of patients who are most likely to benefit from treatment with armodafinil. Additional research is warranted and necessary to better identify clinical predictors (e.g., atypical depressive symptoms, circadian dysrhythmia, cognitive targets, specific combinations of therapeutic agents) that would provide optimized, individualized therapeutics for bipolar depression and or cognitive enhancement in bipolar disorder.

Learning Objectives: 1. Better understand design challenges in a non-mood stabilizer being investigated for bipolar depression

2. Appreciate subtypes of bipolar depression that may prove useful for subsequent narrower investigation

Literature References 1. Frye MA, Amchin J, Bauer M, Adler C, Yang R, Ketter TA. Randomized, placebo-controlled, adjunctive study of armodafinil for bipolar I depression: implications of novel drug design and heterogeneity of concurrent bipolar maintenance treatments. Int J Bipolar Disord. 2015 Dec;3(1):34. doi: 10.1186/s40345-015-0034-0. Epub 2015 Sep 2. PMID: 26330288; PMCID: PMC4556715.
2. Nunez NA, Singh B, Romo-Nava F, Joseph B, Veldic M, Cuellar-Barboza A, Cabello Arreola A, Vande Voort JL, Croarkin P, Moore KM, Biernacka J, McElroy SL, Frye MA. Efficacy and tolerability of adjunctive modafinil/armodafinil in bipolar depression: A meta-analysis of randomized controlled trials. Bipolar Disord. 2020 Mar;22(2):109-120. doi: 10.1111/bdi.12859. Epub 2020 Jan 7. PMID: 31643130.

A PROOF-OF-CONCEPT STUDY OF MODAFINIL FOR NEUROCOGNITIVE IMPAIRMENT IN BIPOLAR DISORDER

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

Individual Abstract: Introduction: Despite advances in the treatment of bipolar disorder (BD), most patients do not achieve complete inter-episode recovery and functional disability is common. During periods of relative remission, many patients continue to experience neurocognitive dysfunction, reduced daytime activity levels, and sleep disturbances. We conducted an 8-week, randomized, placebo-controlled pilot study to evaluate the feasibility, safety and preliminarily efficacy of the wake-promoting drug, modafinil, on neurocognitive functioning, daytime sleepiness, and sleep quality in affectively stable patients with BD.
Methods: Twelve individuals with affectively stable BD were recruited and randomized to a flexible dose of modafinil (100 to 200 mg/day) or placebo, adjunctive to a therapeutic dose of a mood stabilizer. Weekly in-person visits tracked sleep quality and daytime sleepiness as well as side effects and mood symptoms. Neurocognitive functioning was assessed at baseline, week 4, and week 8.

Methods: Preliminary evaluations of clinical efficacy showed a marginally significant interaction between treatment group and time in two cognitive domains (speed of processing and verbal learning), indicating greater improvement in the modafinil group versus placebo. Additionally, there was a marginally significant effect of treatment group on daytime sleepiness, suggesting lower daytime sleepiness in the modafinil group versus placebo. Counterintuitively, we found a significant treatment group by time interaction effect on sleep quality, suggesting greater improvement in sleep quality in the placebo group versus the modafinil group.

No serious adverse events were reported. Newly emergent side effects in the modafinil group included heart palpitations, itching, fatigue, and decreased energy. Two patients discontinued modafinil owing to side effects and one of these patients withdrew from the study. One patient discontinued placebo and was withdrawn from the study.

Discussion: Results suggest that modafinil is a relatively safe medication for affectively stable BD patients when given with adjunctive mood stabilizers. Although very preliminary, our results are suggestive of cognitive benefit and improved daytime sleepiness. Given the finding of worse sleep quality in those patients prescribed modafinil, methodological changes to drug administration should be considered in future work.

A fully powered clinical trial is warranted with specific attention to the characteristics of patients who are most likely to benefit from treatment with modafinil and other methodological lessons learned from this pilot.

Learning Objectives: Describe the potential for improving cognition with a wake-promoting agent in mood disorders; Consider the methodological challenges to modafinil treatment in mood disorders..

Literature References Russo M, Mahon K, Shanahan M, Ramjas E, Solon C, Purcell SM, Burdick KE. The relationship between sleep quality and neurocognition in bipolar disorder. Journal of Affective Disorders (2015) 187:156–162. doi: 10.1016/j.jad.2015.08.009

Lipschitz JM, Perez-Rodriguez M, Majd M, Larsen E, Locascio J, Pike CK, Shanahan M, Burdick KE. Modafinil's effects on cognition and sleep quality in affectively-stable patients with bipolar disorder: a pilot study. Front Psychiatry. 2023 Sep 4;14:1246149. doi: 10.3389/fpsyt.2023.1246149. PMID:

37732080; PMCID: PMC10507316.

HOW BEST TO UNDERSTAND SLEEP/WAKE AND CIRCADIAN FACTORS IN THE CONTEXT OF MODAFINIL TREATMENT OF BIPOLAR DISORDER

Ellen Frank, University of Pittsburgh School of Medicine

Individual Abstract: Introduction: While self-report measures and clinician assessments have their role in understanding sleep/wake and circadian factors in the context of pharmacologic treatment, they lack both the objectivity and the continuity needed for a full understanding of changes in these parameters. Sophisticated in-home and wearable assessments are associated with substantial compliance challenges that can lead to poor quality data capture. In contrast, the commercial smartphone is demonstrating its ability to achieve results that cannot be achieved with traditional assessment methods or with in home devices or wearable technology. The ubiquity and the intimacy of the smartphone make it an ideal device for the passive collection of objective data on a continuous 24/7 basis throughout the course of a pharmacologic trial. Among the potential benefits of modafinil in bipolar disorder are changes in anergia that are best evaluated with continuous, objective measurement of relevant behavioral parameters, especially in bipolar depressive states.

Methods: This presentation will describe Health Rhythm's (https://www.healthrhythms.com/) experience to date in monitoring patients to obtain information relevant to our understanding of the effects of pharmacotherapies, as it might be relevant to a fully powered study of the effects of modafinil in bipolar disorder. Given the importance of disturbances in sleep/wake and circadian factors, daytime sleep disturbances in bipolar disorder, a digital monitoring effort that is undergirded by a conceptual model that puts the body's clock at the center of our understanding of these behavioral disturbances seems particularly relevant. We will present some examples of specific other utilities of the smartphone for the improvement of our understanding of pharmacologic trial outcomes. For example, we have evolved a method for using digital data obtained during screening for predicting which patients are likely to complete a trial as a responder to the compound of interest. We have also demonstrated the ability of this kind of passive sensing to objectively characterize patients' circadian type (evening vs. morning) and to identify shifts in circadian type, changes in walking rate, and other features that may represent therapeutic targets or side effects of modafinil/R-modafinil.

Discussion: The knowledge that can be obtained from the fully powered clinical trial that is being recommended here for modafinil/R-modafinil in bipolar disorder could be substantially enhanced by the kind of continuous, objective behavioral data that can be obtained from commercial smartphone sensors. This inexpensive, non-intrusive, essentially effortless approach to measuring key parameters of bipolar disorder has multiple advantages over other potential sources of obtaining similar information including being associated with high levels of complete data collection and providing another way of monitoring the clinical status of patients.

Learning Objectives: 1. The potential of passive digital data collection for understanding the effects of pharmacotherapy
2. The specific behavioral parameters associated with functional impairment in bipolar disorder

Literature References 1. Ehlers, C.L., Frank, E. and Kupfer, D.J. Social zeitgebers and biological rhythms: A unified approach to understanding the etiology of depression. Archives of General Psychiatry, 45: 948-952, 1988
2. Mathews, M., Abdullah, S., Murnane, E.L., Voida, S., Choudhury, T. and Frank, E. Development and evaluation of a smartphone-based measure of social rhythms for bipolar disorder. Assessment. 2016.

*UNDERSTANDING DRUG SAFETY DECISIONS AS NEW THERAPIES EMERGE: THE IMPORTANCE OF PERSPECTIVE

Peter Weiden, SUNY Stony Brook

Overall Abstract: Drug safety is a cornerstone of successful drug development, from discovery to clinical development to regulatory review and finally post-approval pharmacovigilance. Over time, a rough consensus emerges for the given treatment in question. This consensus can be disrupted with the arrival of a new class of treatment(s) that brings the challenge of comparing a new set of risks and benefits that differ from those known with current therapies.
There are many historical examples of how safety narratives change after new therapies arrive. For major depression, the lower overdose risk of SSRIs was not fully appreciated until SSRIs replaced TCAs as first-line treatment. But then, SSRIs came under scrutiny because a suicide risk signal was found and led to a new warning label, which, then may have lowered appropriate use of SSRIs. For schizophrenia, there were two occasions with substantial delays in recognizing safety risks of antipsychotics: first for the 20 year delay in TD awareness after the antipsychotics first appeared in the 1960s, and later for medical risks associated with the arrival of clozapine and other atypical antipsychotics.

Panelists will discuss perspectives on emerging therapies' impact on safety and risk decisions. Joseph Goldberg will focus on clinician approaches emphasizing a shared decision-making approach. Peter Weiden will review risk decision literature on how cognitive biases that result in different decisions based on familiarity of risk influence safety decisions.. In his role as CEO of Schizophrenia and Psychosis Action Alliance, Gordon Lavigne will represent patient advocacy organization perspective on safety in context of unmet need for more effective therapies. Bernard Fischer of the FDA will offer the perspective of regulatory agencies' approach to safety evaluation of new therapies. Nina Schooler is the discussant who will summarize each perspective and put in context of past and future challenges.

The timing of this panel is relevant today given the number of emerging agents with very different safety profiles than existing options including affective disorders (e.g., zuranolone), schizophrenia (e.g., muscarinic agonists) and PTSD (e.g., psychedelics). Multiple perspectives of different stakeholders can help identify and inform important safety decisions that will happen whenever newer treatments differ from the current status quo.

Learning Objectives: 1. The panel will provide multiple perspectives on safety evaluation and decision-making when new therapies arrive that differ from those currently available, and how to better understand clinical, advocacy and regulatory approaches to new treatments.
2. Understand differences in approach to safety and risk of new and emerging therapies is based historical examples in other psychiatric therapies that were new and evolved over time and put in context with risk bias literature in complex situations with limited information and competing priorities.

Literary References: Goldberg JF, Stahl SM: Clinical Reasoning and Decision-Making in Psychiatry, Cambridge University Press, 2024; ISBN 978-1-009-18155-6
Miller AH, Raison CL. Burning down the house: reinventing drug discovery in psychiatry for the development of targeted therapies. Molecular Psychiatry. 2023;28:68-75.

BALANCING RISKS AND BENEFITS OF PSYCHOTROPIC MEDICATIONS IN CLINICAL PRACTICE

Joseph Goldberg, Icahn School of Medicine at Mount Sinai

Individual Abstract: Practitioners and clinical trialists often reconcile the risks versus benefits of a psychotropic medication in informal, narrative, or qualitative terms rather than through more structured analyses of relative efficacy and safety. In clinical trials, all-cause discontinuation (i.e., effectiveness) is sometimes viewed as a proxy for this balance. Similarly, the ratio of benefit to risk for specific adverse outcomes is sometimes usefully expressed as the likelihood-to-be-helped-or-harmed (LHH). Current approaches to such risk-benefit analyses tend not to account for patient-level factors that pragmatically affect drug choice and retention. Risk-benefit analyses may differ depending on factors such as illness severity, the availability of alternative treatment options with substantial effect sizes, “urgent” symptoms (e.g., acute suicidality), extent of treatment resistance, functional disability, the degree of disruptiveness caused by a given adverse drug effect, viability of antidote strategies for side effects, and patients’ own preferences. Patient surveys suggest that people with mood disorders tend to equally prioritize efficacy and tolerability (identifying both as shared treatment objectives). Yet, in both clinical trials and real-world practice, guesswork often ultimately drives the probability of striking an optimal balance for a given patient based on their personal preferences and unique clinical characteristics.
In this presentation, I will provide an overview of novel strategies for delineating and quantifying patient and prescriber priorities when balancing risks and benefits within shared decision-making models. We will consider the utility of side effect antidote strategies (using examples such as VMAT-2 inhibitors for tardive dyskinesia and GLP-1 agonists for iatrogenic weight gain and metabolic dysregulation). I will describe the use of analytic hierarchy processes, decision analytic matrices, best-worst scaling and Maxdiff scaling to construct personalized decision trees for patients based on individualized attributes. These strategies will take into account ways to help patients and practitioners identify points of convergence and

divergence when identifying treatment goals and priorities. Personalized decision trees also quantitatively account for patients' attitudes about medications and the viability of management strategies for potential adverse effects, particularly when considering those that range from the relatively benign (e.g., headache, nausea) to the annoying (e.g., sexual dysfunction, modest weight gain) to the medically serious (e.g., myocarditis, severe cutaneous reactions).

Learning Objectives: 1) Participants will understand how to apply and interpret principles of decision analytic theory when considering risks versus benefits of disease-relevant psychiatric medications

2) Participants will identify viable antidote strategies to improve tolerability for high-efficacy pharmacotherapies that otherwise may carry an unacceptable adverse drug effect burden

Literature References 1) Goldberg JG, Stahl SM. Clinical Reasoning and Decision Making in Psychiatry. London: Cambridge University Press, 2024

2) Weyant C, Brandeau ML, Basu S. Personalizing medical treatment decisions: integrating meta-analytic treatment comparisons with patient-specific risks and preferences. Med Decis Making 2019; 39: 998-1009

DRUG SAFETY DECISIONS ARE NOT ALWAYS RATIONAL: A KAHNEMAN PERSPECTIVE OF COGNITIVE AND EMOTIONAL BIASES

Peter Weiden, SUNY Stony Brook

Individual Abstract: If a new treatment is safer and more effective than the current ones, safety evaluation is straightforward. Of course, this is the exception not the rule. In real life, new treatments bring their own complexities and uncertainties. The efficacy and safety profile of the new treatment is less familiar relative to current treatments, and the clinical relevance of any differences is not yet fully understood. These characteristics of complexity and uncertainty are common across medicine and are amenable to risk benefit analyses ranging from clinical recommendations made in practice to regulatory decisions to public health policy. We usually make tacit assumptions of rationality in these decisions, accounting for individual values or societal norms.

The assumption of rationality has been challenged. Based on the pioneering work of Tversky and Kahneman, there is an established field of research on identifying cognitive and emotional biases that result in common and predictable errors in judgement and decision-making. By predicting when and how "irrational" decisions are made, these biases can be more easily identified and rectified ahead of time.

This presentation will review some of the key findings in the field as it applies to safety and tolerability decisions made in psychiatric practice. The presentation will use past examples from my own clinical research experience during an era when clinicians seemed to minimize severe movement disorders from antipsychotics and, years later, seemed to repeat the error with medical risks of high-risk atypical antipsychotics were downplayed and were often reluctant to use metabolically safer atypical antipsychotics due to fear of other unknown risks of QTc. These examples which in hindsight seem "irrational" are better understood using cognitive bias models. Examples in prospect theory and cognitive bias theory will be given and correlated with "irrational" decisions.

One illustration is the apparent complacency in which potentially life-threatening adverse events from using haloperidol IM in ER settings, such as malignant hyperthermia, NMS or

laryngospasm. While this was understandable prior to the availability of lower risk alternatives, continued routine use of haloperidol IM seems "irrational". It is better understood in the context of cognitive bias literature showing differential weighting of known vs unknown adverse events that lead to a biasing towards accepting higher risks from risks that are familiar compared to lower risks that are unfamiliar (e.g., "I'm ok with haloperidol because I know what happens but can't risk QTc elevation of other medications").

The presentation will conclude with a "top ten" list of cognitive biases that may influence safety assessments and decisions that may occur when newer treatments become available.

Learning Objectives: 1. The panel will show how addresing safety profiles of emerging therapies will require broad range of perspectives that account for clinician, patient and regulatory priorities.
2. The panel will address some key points of risk literature on cognitive biases that might influence decisions on safety risks for emerging treatments especially when their safety profiles are fundamentally different than those therapies currently available.

Literature References Goldberg JF, Stahl SM: Clinical Reasoning and Decision-Making in Psychiatry, Cambridge University Press, 2024; ISBN 978-1-009-18155-6
Persson E, Erlandsson A, Slovic P, Västfjäll D, Tinghög G. The prominence effect in health-care priority setting. Judgment and Decision Making. 2022;17:1379-1391.

DRUG SAFETY DECISIONS DURING TIMES OF CHANGE: A REGULATORY PERSPECTIVE

Bernard Fischer, U.S. Food and Drug Administration

Individual Abstract: The U.S. Food and Drug Administration (FDA) has multiple ways of ensuring the safety of humans exposed to new drugs during development programs. Regulators also work with pharmaceutical companies to ensure that high quality safety data is collected and submitted in support of marketing applications and as drugs are used by the public post-approval. During this talk, I will review the ways FDA approaches safety when assessing clinical trial design and during trials, including imposition of clinical holds and expedited safety reporting. I will then discuss how the safety data that is collected during drug development is assessed by review divisions when making decisions, including guidance from the International Council on Harmonisation and the FDA's benefit:risk framework. Finally, I will review the role of FDA in ensuring drug safety in a post-market setting. At each step, I will discuss whether familiarity with a medication class offers any advantages in safety monitoring versus monitoring drugs with new mechanisms of action.

Learning Objectives: • Identify standard safety precautions and data that the U.S. FDA requires prior to exposing humans to drugs and for marketing approval.
• Identify and discuss the benefit:risk framework used by the U.S. FDA when making decisions about drugs.

Literature References 1. U.S. Food and Drug Administration. E1A The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Long-term Treatment of Non-Life-Threatening Conditions (March 1995); https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e1a-extent-population-exposure-assess-clinical-safety-drugs-intended-long-term-treatment-non-life

2. U.S. Food and Drug Administration. Benefit-Risk Assessment for New Drug and Biological Products (October 2023); https://www.fda.gov/regulatory-information/search-fda-guidance-documents/benefit-risk-assessment-new-drug-and-biological-products

THE ROLE OF PATIENT VOICE IN NEW DRUG EVALUATIONS: ADVOCACY PERSPECTIVES

Gordon Lavigne, Schizophrenia and Psychosis Action Alliance

Individual Abstract: Schizophrenia and Psychosis Action Alliance (S and PAA) supports the lives and well-being of people with schizophrenia. This panel presentation provides an advocacy perspective based on our experience collaborating with the FDA to host the first schizophrenia-specific Patient-Focused Drug Development (PFDD) which occurred in late 2022. In preparation for the PFDD meeting, we surveyed individuals affected by schizophrenia on their treatment priorities, especially areas of unmet needs. The survey provided feedback on when safety decisions might complicate access to needed treatments. These were barriers to clozapine caused by problems in the current REMS program, and the need to balance safety reviews with the need to have more effective medications available.

1. REMS barriers to clozapine access: Respondents who were successfully treated with clozapine reported having great difficulties with specifically how the clozapine REMS is administered. The current REMS program is reported to be rigid and error-prone and creates ongoing anxiety and stress due to fear of running out of clozapine due to REMS errors. Based on this information, SPA and A is advocating rebooting the REMS to make it more user-friendly . We hope this will improve overall safety by reducing the chances of suddenly stopping clozapine due to a REMS glitch. Making REMS more user-friendly will also help open the door for greater acceptance of clozapine by pharmacists, clinicians and patients.

2. Supporting approval of innovative treatments. S and PAA supports innovation in developing novel treatments for schizophrenia that work differently than those available today and is encouraged by recent progress in investigational medications in the pipeline that have new mechanisms of action. Our survey shows that people with schizophrenia want more effective treatments for debilitating symptoms — ideally without any side effects or at least different from current treatments. S and PAA is concerned that a narrow focus on safety might delay approval of innovative treatments. Our experience with clozapine REMS is a reminder that approval is only a first step and factors such as product labeling matter in terms of access after a medication is approved.

These examples point to a need to consider the voice of the person and their loved ones when considering the impact of side effects of newer therapies. Often it is the person taking the medication who can provide important feedback on side effects that matter the most. Advocacy organizations need to be supportive of new therapies especially when, as with schizophrenia, current therapies fall short. Our experience with clozapine REMS shows the relevance of advocacy feedback, and we believe useful feedback to the FDA to considering unintended risks of sudden clozapine discontinuation. Advocacy organizations can partner with other key stakeholders with the shared goal of providing more effective and safer treatments to all who need them.

Learning Objectives: 1. present on the role of disease-specific advocacy organizations, with a disease focus providing greater opportunities for in-depth advocacy in key areas of unmet needs

2. discuss collaboration with the FDA in partnering on an advocacy-initiated Patient-Focused Drug Development meeting

Literature References Leung JG, Ehret M, Love RC, Cotes RO. Improving clozapine utilization will require continued advocacy, drug sponsor interest, and FDA support to address REMS issues. Expert Review of Clinical Pharmacology. 2023;16:177-179
Härmark, L., Weits, G., Meijer, R. et al. Communicating Adverse Drug Reaction Insights Through Patient Organizations: Experiences from a Pilot Study in the Netherlands. Drug Saf 43, 745–749 (2020). https://doi.org/10.1007/s40264-020-00932-5

11:00 a.m. - 12:30 p.m.

Panel Sessions

*THE FUTURE OF KETAMINE AND ESKETAMINE IN TREATMENT-RESISTANT DEPRESSION: A TRANSLATIONAL PERSPECTIVE

Gustavo Medeiros, University of Maryland School of Medicine

Overall Abstract: Ketamine and esketamine are well-established treatments for treatment-resistant depression (TRD). However, there are substantial challenges in conceptualizing how these medications exert their therapeutic effects. Most studies indicate that about 50-60% of patients with TRD respond to ketamine/esketamine and it is unknown what factors contribute to this heterogeneous response. Further, the reasons for differences in response (e.g., time to onset of action, duration of action) between ketamine and esketamine response are unresolved. In summary, the field of ketamine/esketamine is currently very dynamic and a substantial amount of research is being conducted. This panel will discuss some promising recent studies and how they may enable customized indications and new therapeutic uses of ketamine/esketamine.
Presentation 1: Dr. Medeiros' presentation titled "Personalized/precision use of ketamine and esketamine in treatment-resistant depression" will discuss the variability in response to ketamine/esketamine and the need for a personalized/precision approach. He will review three systematic reviews and meta-analyses that he first authored. First, he will examine potential clinical predictors of a better response to ketamine/esketamine. Then, he will discuss brain-based biomarkers (e.g., post-treatment increases in gamma power in frontoparietal brain regions) (1) and blood-based biomarkers (2). Finally, he will discuss that most predictors of response to ketamine/esketamine have modest effect sizes, therefore, the use of multivariate predictive models will likely be needed.

Presentation 2: Dr. Vande Voort's presentation titled "The use of ketamine and esketamine in real-world clinical practice" will discuss the implementation of ketamine and esketamine services at a tertiary academic medical center. First, she will review the structure of these clinical services. Second, she will review the literature of two systematic reviews comparing IV ketamine to intranasal esketamine. She will also review a retrospective, cohort study comparing these two treatments. Finally, she will discuss factors that are involved in the shared decision-making process with patients when selecting between ketamine and esketamine.

Presentation 3: Dr. Brown's presentation titled "Ketamine leverages synaptic plasticity mechanisms to promote sustained antidepressant actions" will focus on preclinical data and be split into two parts. First, he will discuss current evidence describing the putative antidepressant

induction mechanisms of ketamine. Specifically, Dr. Brown will talk about the several N-methyl-D-aspartate receptor (NMDAR) inhibition-dependent and independent hypotheses that have been proposed to describe ketamine's rapid antidepressant-relevant effects. In the second part of his presentation, Dr. Brown will discuss the emerging concept that targeting metaplasticity mechanisms will promote sustained antidepressant actions, which proposes that ketamine leverages NMDAR activation-dependent metaplasticity to promote sustained antidepressant effects after drug clearance.

Discussion: Dr. Iosifescu will discuss and analyze the panelists' presentations. First, he will summarize and synthesize the information presented highlighting and interpreting their key points. Feedback will be also provided to the presenters including an assessment of the strengths and limitations of the presentations. Then, Dr. Iosifescu will assess the broader context for the presentations and will discuss the current research and future directions of the ketamine/esketamine field.

Learning Objectives: 1) Become familiar with the preclinical and clinical research that is ongoing using ketamine/esketamine.
2) Understand the direction that the field of ketamine/esketamine is heading towards and potential future uses for these medications.

Literary References: 1. Medeiros GC, Matheson M, Demo I, Reid MJ, Matheson S, Twose C, Smith GS, Gould TD, Zarate CA, Barrett FS, Goes FS. Brain-based correlates of antidepressant response to ketamine: a comprehensive systematic review of neuroimaging studies. The Lancet Psychiatry. 2023 Aug 22.
2. Medeiros GC, Gould TD, Prueitt WL, Nanavati J, Grunebaum MF, Farber NB, Singh B, Selvaraj S, Machado-Vieira R, Achtyes ED, Parikh SV. Blood-based biomarkers of antidepressant response to ketamine and esketamine: A systematic review and meta-analysis. Molecular psychiatry. 2022 Sep;27(9):3658-69.

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Jennifer Vande Voort, Mayo Clinic

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Literature References 1. Medeiros GC, Matheson M, Demo I, Reid MJ, Matheson S, Twose C, Smith GS, Gould TD, Zarate CA, Barrett FS, Goes FS. Brain-based correlates of

antidepressant response to ketamine: a comprehensive systematic review of neuroimaging studies. The Lancet Psychiatry. 2023 Aug 22.
2. Medeiros GC, Gould TD, Prueitt WL, Nanavati J, Grunebaum MF, Farber NB, Singh B, Selvaraj S, Machado-Vieira R, Achtyes ED, Parikh SV. Blood-based biomarkers of antidepressant response to ketamine and esketamine: A systematic review and meta-analysis. Molecular psychiatry. 2022 Sep;27(9):3658-69.

THE FUTURE OF KETAMINE AND ESKETAMINE IN TREATMENT-RESISTANT DEPRESSION: A TRANSLATIONAL PERSPECTIVE

Kyle Brown, University of Maryland School of Medicine

Individual Abstract: Ketamine and esketamine are well-established treatments for treatment-resistant depression (TRD). However, there are substantial challenges in conceptualizing how these medications exert their therapeutic effects. Most studies indicate that about 50-60% of patients with TRD respond to ketamine/esketamine and it is unknown what factors contribute to this heterogeneous response. Further, the reasons for differences in response (e.g., time to onset of action, duration of action) between ketamine and esketamine response are unresolved. In summary, the field of ketamine/esketamine is currently very dynamic and a substantial amount of research is being conducted. This panel will discuss some promising recent studies and how they may enable customized indications and new therapeutic uses of ketamine/esketamine.

Presentation 1: Dr. Medeiros' presentation titled "Personalized/precision use of ketamine and esketamine in treatment-resistant depression" will discuss the variability in response to ketamine/esketamine and the need for a personalized/precision approach. He will review three systematic reviews and meta-analyses that he first authored. First, he will examine potential clinical predictors of a better response to ketamine/esketamine. Then, he will discuss brain-based biomarkers (e.g., post-treatment increases in gamma power in frontoparietal brain regions) (1) and blood-based biomarkers (2). Finally, he will discuss that most predictors of response to ketamine/esketamine have modest effect sizes, therefore, the use of multivariate predictive models will likely be needed.

Presentation 2: Dr. Vande Voort's presentation titled "The use of ketamine and esketamine in real-world clinical practice" will discuss the implementation of ketamine and esketamine services at a tertiary academic medical center. First, she will review the structure of these clinical services. Second, she will review the literature of two systematic reviews comparing IV ketamine to intranasal esketamine. She will also review a retrospective, cohort study comparing these two treatments. Finally, she will discuss factors that are involved in the shared decision-making process with patients when selecting between ketamine and esketamine.

Presentation 3: Dr. Brown's presentation titled "Ketamine leverages synaptic plasticity mechanisms to promote sustained antidepressant actions" will focus on preclinical data and be split into two parts. First, he will discuss current evidence describing the putative antidepressant induction mechanisms of ketamine. Specifically, Dr. Brown will talk about the several N-methyl-D-aspartate receptor (NMDAR) inhibition-dependent and independent hypotheses that have been proposed to describe ketamine's rapid antidepressant-relevant effects. In the second part of his presentation, Dr. Brown will discuss the emerging concept that targeting metaplasticity mechanisms will promote sustained antidepressant actions, which proposes that

ketamine leverages NMDAR activation-dependent metaplasticity to promote sustained antidepressant effects after drug clearance.

Discussion: Dr. Iosifescu will discuss and analyze the panelists' presentations. First, he will summarize and synthesize the information presented highlighting and interpreting their key points. Feedback will be also provided to the presenters including an assessment of the strengths and limitations of the presentations. Then, Dr. Iosifescu will assess the broader context for the presentations and will discuss the current research and future directions of the ketamine/esketamine field.

Learning Objectives: 1) Become familiar with the preclinical and clinical research that is ongoing using ketamine/esketamine.
2) Understand the direction that the field of ketamine/esketamine is heading towards and potential future uses for these medications.

Literature References 1. Medeiros GC, Matheson M, Demo I, Reid MJ, Matheson S, Twose C, Smith GS, Gould TD, Zarate CA, Barrett FS, Goes FS. Brain-based correlates of antidepressant response to ketamine: a comprehensive systematic review of neuroimaging studies. The Lancet Psychiatry. 2023 Aug 22.
2. Medeiros GC, Gould TD, Prueitt WL, Nanavati J, Grunebaum MF, Farber NB, Singh B, Selvaraj S, Machado-Vieira R, Achtyes ED, Parikh SV. Blood-based biomarkers of antidepressant response to ketamine and esketamine: A systematic review and meta-analysis. Molecular psychiatry. 2022 Sep;27(9):3658-69.

ARE WE MAKING PROGRESS WITH ANTI- SUICIDAL TREATMENTS AND BIOMARKERS FOR IMMEDIATE RISK?

Madhukar Trivedi, UT Southwestern Medical Center

Overall Abstract: Suicide and depression represent crucial public health challenges that require continual advancements in our understanding of the newest research regarding early detection, intervention, and prevention efforts. In 2022, over 15% of youth aged 12-17 reported suffering from at least one major depressive episode in the past year, and suicide was the second leading cause of death among children and young adults ages 10-24. A lack of research in these areas and inefficient interventions has only exacerbated this already-growing health epidemic. As a result, our suggested symposium will assemble a panel of investigators and researchers dedicated to mental health research that will present on a variety of initiatives and treatment interventions aimed at minimizing suicidal ideation and identifying serious risk factors in the form of biomarkers for depression and suicidality. The first presentation will discuss the various potential biomarkers for suicidality and depression as well as the progress being made on research in the field. The research will include markers from the blood, brain, and gut. The second presentation will

Learning Objectives: 1. Identify biomarkers for depression and suicide risk and how lack of research in this area has contributed to significant burden on society.
2. Recognize novel mechanisms for treatment of suicidal ideation that can serve as primary and secondary prevention efforts in reducing loss of life.

Literary References: 1. Jha, M. K., Cai, L., Minhajuddin, A., Fatt, C. C., Furman, J. L., Gadad, B. S., Mason, B. L., Greer, T. L., Hughes, J. L., Xiao, G., Emslie, G., Kennard, B., Mayes, T.,

and Trivedi, M. H. Dysfunctional adaptive immune response in adolescents and young adults with suicide behavior. Psychoneuroendocrinology. 2020;111.
2. Xiong, J., Lipsitz, O., Chen-Li, D., Rosenblat, J. D., Rodrigues, N. B., Carvalho, I., Lui, L. M. W., Gill, H., Narsi, F., Mansur, R. B., Lee, Y., and McIntyre, R. S. The acute antisuicidal effects of single-dose intravenous ketamine and intranasal esketamine in individuals with major depression and bipolar disorders: A systematic review and meta-analysis. Journal of Psychiatric Research. 2021;134, 57–68.

WHAT IS AN ANTI-SUICIDAL RESPONSE TO TREATMENT?

Elizabeth Ballard, National Institute of Mental Health

Individual Abstract: Suicide is the leading cause of psychiatric related death. There is a tremendous need for interventions that reduce the risk for suicidal behavior. However, interventions for suicide risk have lagged behind those for depression and bipolar disorder, in part because there are so few clinical trials that focus on suicidal thoughts and outcomes. This presentation will give an overview of design considerations for suicide-focused clinical trials, bringing together considerations for assessment, placebo effect and outcome selection, with the literature around ketamine as a case example. Overall, clinical trials for suicide risk can be completed, but may differ from clinical trials for mood disorders in critical ways. Implications for the field and next generation clinical trials for suicide risk will be discussed.
Learning Objectives: At the end of my presentation, the audience will be able to describe design considerations for suicide-focused clinical trials. Additionally, participants will be able to synthesize the literature around suicide focused treatments.
Literature References Bloomfield-Clagett B, Ballard ED, Greenstein DK, et al. A participant-level integrative data analysis of differential placebo response for suicidal ideation and non-suicidal depressive symptoms in clinical trials of intravenous racemic ketamine. Int J Neuropsychopharm, 2022; 25:827-838.
Ballard ED, Gilbert JR, Wusinich C, et al. New methods for assessing rapid changes in suicide risk. Frontiers in Psychiatry, 2021; 12:598434.

BIOMARKERS OF FUTURE MENTAL ILLNESS: FOCUS ON POSTPARTUM DEPRESSION

Jennifer Payne, University of Virginia

Individual Abstract: Postpartum depression (PPD) is the most common complication of childbirth and is a serious mental disorder that can result in severe morbidity for the mother and risk to the offspring. Despite PPD's high incidence and significant health impact, a simple predictive screening method for PPD risk is lacking. Epigenetic changes can mediate important interactions of our genes with the environment, including the hormonal changes associated with pregnancy. We originally investigated estrogen mediated epigenetic reprogramming events in the hippocampus and risk for PPD using a cross species translational design and identified two genetic loci, HP1BP3 and TTC9B, which were modified by estrogen exposure in a rodent model and were also prospectively predictive of PPD in antenatal blood in pregnant women with pre-existing mood disorders. Since our original finding, we have replicated our findings in six other independent samples: including pregnant women with pre-existing mood disorders, pregnant women without a previous psychiatric diagnosis and postpartum women both with and without a previous psychiatric diagnosis. Our biomarkers remain approximately

80% accurate in predicting which pregnant women are at elevated risk of developing PPD. These data add to the growing body of evidence suggesting that PPD is mediated by differential gene expression and epigenetic sensitivity to pregnancy hormones and that antenatal epigenetic variation at the genes HP1BP3 and TTC9B is predictive of PPD. Future directions include the development of a simple blood test predictive of elevated risk for postpartum depression, allowing for preventative intervention. Development of a simple blood test that is predictive of a future mental illness has the potential to move psychiatry from a reactive approach to a preventative one and to reduce stigma surrounding mental illness in general.
Learning Objectives: 1) Define the term "Reproductive Depression."
2) Describe how genes and environment interact to make epigenetic changes.

Literature References Guintivano J, Arad M, Gould TD, Payne JL, Kaminsky ZA. Antenatal prediction of postpartum depression with blood DNA methylation biomarkers. Mol Psychiatry. 2014; 19(5):633.
Payne JL, Osborne LM, Cox O, et al. DNA methylation biomarkers prospectively predict both antenatal and postpartum depression. Psychiatry Res. 2020; 285:112711.

STATEWIDE COLLABORATION TO BETTER UNDERSTAND YOUTH DEPRESSION AND SUICIDE

Holli Slater, The University of Texas Southwestern Medical Center, Department of Psychiatry

Individual Abstract: The rates of depression and suicide among youth are on the rise. In 2020, the state of Texas legislature established the Texas Child Mental Health Care Consortium to leverage health related institutions to improve mental health care for youth across the state. As part of the consortium initiatives, the Texas Youth Depression and Suicide Research Network (TX-YDSRN) was established to better understand and improve mental health services addressing depression and suicide. This presentation will give an overview of the development of the Network infrastructure and establishment of the TX-YDSRN Registry Study, along with lessons learned. A preliminary review of findings from the Registry study and next steps for the Network will also be reviewed.
Learning Objectives: 1. Learn about cutting edge approaches to experimental design for assessment of suicide and related outcomes in youth at the population level.
2. Learn about new and upcoming research on correlates of suicide across a diverse sample of youth and possible clinical implications.

Literature References Trivedi MH, Minhajuddin A, Slater H, et al. Texas Youth Depression and Suicide Research Network (TX-YDSRN) research registry and learning healthcare network: Rationale, design, and baseline characteristics. J Affect Disord. 2023;340:88-99. doi:10.1016/j.jad.2023.07.035
Kennard BD, Hughes JL, Minhajuddin A, et al. Suicidal thoughts and behaviors in youth seeking mental health treatment in Texas: Youth Depression and Suicide Network research registry. Suicide Life Threat Behav. 2023;53(5):748-763. doi:10.1111/sltb.12980

*#FINE TUNING RESPONSE IN CHILD AND ADOLESCENT PSYCHOPHARMACOLOGY RESEARCH AND PRACTICE

Paul Croarkin, Mayo Clinic

Overall Abstract: Despite considerable advances over the past decades, child and adolescent psychopharmacology research has ongoing challenges and knowledge gaps. This session focuses on efforts to understand and improve treatment response for pharmacological and neurotherapeutic agents in clinical trials. The discussions will be framed in a manner that informs clinical practice. Clinical research challenges in child and adolescent psychopharmacology includes ethical considerations, limited opportunities to execute clinical trials that consider the nuances of development, heterogenous phenotypes, and complex co-occurring conditions. Children and adolescents also have considerably variability in pharmacodynamics, pharmacokinetics, pharmacogenetics, and neurodevelopment. Current research focused on children and adolescents also has considerable deficits in diversity of samples and generalizability. Placebo response is also a considerable challenge in child and adolescent clinical trials research. Most study designs do not provide the opportunity to discern true medication or interventional effects from nonspecific effects. Current statistical methodology also does not adequately account for the considerable heterogeneity of samples, demographics, clinical features, and response trajectories. Machine learning, natural language processing, reinforcement learning and other artificial intelligence tools hold promise for refining research and clinical practice focused on children and adolescents. Most clinicians and researchers have limited understanding of the applications of artificial intelligence.
This panel includes a presentation by Dr. Jeffrey Strawn who will review recent research efforts focused on characterizing and understanding the placebo response in child and adolescent clinical trials. Dr. Jeffrey Mills will review contemporary advanced statistical methodology in a user friendly fashion to assist clinically oriented participants with the interpretation of research studies and journal articles. Dr. Arjun Athreya will provide an overview of artificial intelligence, applications in research, and its promise for advancing clinical practice focused on youth. He will use studies with wearable devices for monitoring symptoms in young children as an example. The session will conclude with a discussion by Dr. Manpreet Singh an international authority in child and adolescent psychiatry research and related clinical translations.

Learning Objectives: 1. Participants will demonstrate the ability to discuss recent advances in understanding placebo response, study design, and biostatistical considerations in child and adolescent psychopharmacology, and neurotherapeutic trials.
2. Participants will review a basic primer of artificial intelligence in the context of child and adolescent psychiatry. Participants will review recent research and clinical advances informed by artificial intelligence.

Literary References: Topol EJ. Nature Medicine. High-performance medicine: the convergence of human and artificial intelligence. 2019 Jan;25(1):44-56.DOI: 10.1038/s41591-018-0300-7
Walkup JT. Antidepressant Efficacy for Depression in Children and Adolescents: Industry- and NIMH-Funded Studies. Am J Psychiatry. 2017. May 1;174(5):430-437. DOI: 10.1176/appi.ajp.2017.16091059

UNDERSTANDING AND LEVERAGING PLACEBO RESPONSE IN PEDIATRIC ANTIDEPRESSANT TREATMENT

Jeffrey Strawn, College of Medicine, University of Cincinnati

Individual Abstract: This presentation explores placebo response in children and adolescents and examines of non-specific factors influencing placebo response as well as the temporal

course of placebo response in pediatric anxiety disorders, obsessive-compulsive disorder (OCD), and major depressive disorder. The presentation provides an in-depth analysis of placebo response patterns across anxiety and depressive disorders highlighting aspects of the design of the clinical trial that influence placebo response as well as patient and study characteristics, including the role of patient and family expectation. Drawing on data from three large NIH-funded trials investigating selective serotonin reuptake inhibitors (SSRIs) in youth with depression and anxiety disorders as well as meta-analyses of placebo response in youth, this presentation aims to illuminate the multifaceted nature of placebo response and provide valuable insights for refining clinical interventions and improving our clinical trials. Finally, the practical implications of placebo response are discussed as they relate to psychoeducation and discussions of medication efficacy with patients and families.

Learning Objectives: 1. Describe patient-specific factors that influence placebo response in pediatric trials of antidepressants.

2. Describe how design of a clinical trial contributes to placebo response in trials of antidepressants in children and adolescents.

3. Describe the time course of placebo response in children and adolescents with anxiety and depressive disorders

Literature References Mossman SA, Mills JA, Walkup JT, Strawn JR. The Impact of Failed Antidepressant Trials on Outcomes in Children and Adolescents with Anxiety and Depression: A Systematic Review and Meta-Analysis. J Child Adolesc Psychopharmacol. 2021 May;31(4):259-267.

Strawn JR, Dobson ET, Mills JA, Cornwall GJ, Sakolsky D, Birmaher B, Compton SN, Piacentini J, McCracken JT, Ginsburg GS, Kendall PC, Walkup JT, Albano AM, Rynn MA. Placebo Response in Pediatric Anxiety Disorders: Results from the Child/Adolescent Anxiety Multimodal Study. J Child Adolesc Psychopharmacol. 2017 Aug;27(6):501-508.

SEVEN MYTHS OF RANDOMIZED CONTROLLED TRIAL ANALYSIS IN CHILD & ADOLESCENT PSYCHIATRY

Jeffrey Mills, University of Cincinnati

Individual Abstract: The results from randomized controlled trials (RCTs) form the cornerstone of clinical decision-making, providing clinicians with insights into efficacious or tolerable treatment. However, the process of conducting RCTs entails substantial expenses—financially, ethically, and in terms of the invested time and effort from experts and patients. To optimize the utility of these trials and justify their high costs, fully leveraging the results of RCTs is paramount. Unfortunately, prevalent misconceptions about interpreting results and issues in the analysis and reporting of RCT results persist. This presentation explores seven myths surrounding RCTs that are particularly relevant in trials of antidepressant medications in youth and illustrates these myths with examples from recent RCTs in children and adolescents with depressive and anxiety disorders. Firstly, the belief that randomization alone rectifies bias is addressed. The efficacy and reliability of the mixed model with repeated measures (MMRM) are questioned as the second myth. The third myth challenges the notion that significance tests require correction for multiple comparisons. Additionally, the presentation dispels the fourth myth that prohibits the examination of RCT data more than once, precluding interim analyses. The requirement of demonstrating 80% or better statistical power as a prerequisite for undertaking an RCT is debunked as the fifth myth. The sixth myth questions the common perception that only results deemed "statistically significant at the 5% level" indicate an actual effect. Lastly, the presentation confronts the misconception that

anyone, regardless of statistical training, can proficiently analyze RCT results. Recognizing and dispelling these myths is crucial for clinicians to critically evaluate new evidence and advance standard methodology. A refined understanding of optimal statistical analysis methodologies for RCT results is underscored as pivotal for advancing the scientific foundation of clinical practice.

Learning Objectives: 1. Describe misconceptions related to the common statistical approaches used in randomized controlled trials of antidepressants in youth.

2. List limitations of conventional approaches to examining the change in symptoms over time in RCTs.

Literature References Aberegg SK. Post Hoc Bayesian Analyses. JAMA. 2019 Apr 23;321(16):1631-1632.

Strawn JR, Mills JA, Suresh V, Mayes T, Gentry MT, Trivedi M, Croarkin PE. The impact of age on antidepressant response: A mega-analysis of individuals with major depressive disorder. J Psychiatr Res. 2023 Mar;159:266-273. doi: 10.1016/j.jpsychires.2023.01.043.

ARTIFICIAL INTELLIGENCE AND DIGITAL PSYCHIATRY: A FRONTIER FOR PRECISION MEDICINE PARADIGM IN CHILDREN AND ADOLESCENTS

Arjun Athreya, Mayo Clinic

Individual Abstract: Background: Wearables and smartphones are ubiquitous. The increasing adoption of smartwatches is driven by awareness in monitoring one's functioning ranging from activity (i.e., steps) to sleep. The use of data from wearables as predictors of behavioral phenotypes in artificial intelligence algorithms presents a precision medicine paradigm for psychiatry – wherein onset of disruptive behavior can be predicted remotely. This presentation presents a novel paradigm of digital health approaches with wearables in monitoring pediatric behavior.

Methods: Inpatient subjects aged between 3-10 years were recruited for a study on predicting violent/disruptive behavior by using commodity smartwatches. Registered nurses phenotyped child's behavior every hour of the day during the inpatient treatment period. Machine learning algorithms were trained to predict impending disruptive behavioral states using the combination of heartrate, sleep and motor intensity data collected from the smartwatch.

Methods: Data from smartwatches predicted impending disruptive behavior in children nearly 30 minutes prior to observed disruptive behavior with accuracy of 74%. Heart rate, sleep and motor intensity measures varied significantly between calm, playful (without disruptive behavior), and 30 minutes prior to a disruptive behavior event.

Conclusion and Clinical Relevance: The development of physiological biomarkers presents a scalable means to remotely predict variations in child's behavior. When used in conjunction with behavioral therapy such as parent-child interaction therapy, alerts of impending disruptive behavior provided to parents may prompt precision parenting paradigms and alleviate the impact of behavioral outbursts. Study designs incorporating behavioral assessments to generate digital and physiologic biomarkers of a child's state may hold promise in other mental health applications including mood disorders and suicide.

Learning Objectives: 1. What is digital health in the context of child and adolescent mental health?

2. What are smartwatch based digital biomarkers in child and adolescent mental health?

3. How can machine learning and artificial intelligence predict the onset of disruptive behavior in children, in real-time?

Literature References Romanowicz, M., Croarkin, K. S., Elmaghraby, R., Skime, M., Croarkin, P. E., Vande Voort, J. L., Shekunov, J., and Athreya, A. P. (2023). Machine Learning Identifies Smartwatch-Based Physiological Biomarker for Predicting Disruptive Behavior in Children: A Feasibility Study. Journal of child and adolescent psychopharmacology, 33(9), 387–392. https://doi.org/10.1089/cap.2023.0038

Saliba, M., Drapeau, N., Skime, M., Hu, X., Accardi, C. J., Athreya, A. P., Kolacz, J., Shekunov, J., Jones, D. P., Croarkin, P. E., and Romanowicz, M. (2023). PISTACHIo (PreemptIon of diSrupTive behAvior in CHIldren): real-time monitoring of sleep and behavior of children 3-7 years old receiving parent-child interaction therapy augment with artificial intelligence - the study protocol, pilot study. Pilot and feasibility studies, 9(1), 23. https://doi.org/10.1186/s40814-023-01254-w

*NAVIGATING THE FRONTIER OF POST-TRAUMATIC STRESS DISORDER TREATMENT: EXPLORING UPDATES IN KETAMINE AND A NOVEL THERAPEUTIC CLINICAL PROGRAM OF BREXPIPRAZOLE IN COMBINATION WITH SERTRALINE

Lori Davis, Veterans Affairs Medical Center

Overall Abstract: Post-traumatic stress disorder (PTSD) is a highly prevalent neuropsychiatric disorder that may occur in people who have experienced or witnessed a traumatic event. PTSD is characterized by a range of heterogeneous symptoms. The estimated global lifetime prevalence of PTSD is 4–10%. Contrary to public perception, most PTSD cases occur in the general population rather than the military population; the most common underlying traumas include the unexpected death of a loved one, sexual violence, and interpersonal violence.

Most PTSD treatment guidelines recommend use of psychotherapies, although barriers to their effectiveness may include resource issues, concerns about recalling traumatic events, and inadequate training. Currently, the only FDA-approved pharmacotherapies for PTSD are sertraline and paroxetine. Existing pharmacotherapies have demonstrated modest and inconsistent outcomes; consequently, physicians frequently rely on off-label polypharmacy. There remains a clear unmet need for a well-tolerated pharmacotherapy with a consistent efficacy profile.

Intravenous ketamine has been explored as a potential treatment for chronic PTSD in single- and repeated-dose randomized controlled trials (RCTs). This presentation will review ketamine clinical data in severe chronic PTSD, including findings from a recently completed open-label pilot trial of trauma-focused psychotherapy added to a course of repeated ketamine infusions. In the pilot trial (n=13), patients received six ketamine infusions administered three times/week for two consecutive weeks. On Week 2, following the first four infusions, patients began a course of written exposure therapy. On the primary outcome measure, combined treatment resulted in improvement in Clinician Administered PTSD Scale for DSM-5 (CAPS-5) Total score from baseline (41.6) to 12 weeks (20.7), with Cohen's d=1.6 (95% confidence interval=1.0 – 2.2, p LESS THAN 0.001).

Brexpiprazole (oral tablet) is FDA-approved for the treatment of schizophrenia, major depressive disorder (adjunct to antidepressants), and agitation associated with dementia due to Alzheimer's disease. The brexpiprazole PTSD clinical program (total n=1,290) comprised

three RCTs of brexpiprazole + sertraline combination therapy: Trial 061 (Phase 2; flexible-dose brexpiprazole; NCT03033069), Trial 071 (Phase 3; flexible-dose brexpiprazole; NCT04124614), and Trial 072 (Phase 3; fixed-dose brexpiprazole; NCT04174170). In all trials, patients were randomized to brexpiprazole + sertraline (i.e., combination therapy), or to sertraline + placebo. Trial 061 included two additional treatment arms: brexpiprazole + placebo, and placebo only. The primary endpoint in each trial was the change in CAPS-5 Total score from randomization to Week 10. In Trials 061 and 071, brexpiprazole + sertraline combination therapy separated from sertraline + placebo on the primary endpoint (p LESS THAN 0.05). Whilst the primary endpoint was not met in Trial 072, the change observed with brexpiprazole + sertraline combination therapy was consistent with Trials 061 and 071. The totality of the results indicates that the combination of brexpiprazole + sertraline is associated with a consistent improvement in symptoms of PTSD, and is generally well tolerated.

This panel will provide attendees with background to PTSD, discuss current unmet needs from a clinical and patient perspective, and review recent clinical developments with ketamine and brexpiprazole.

Learning Objectives: 1. To gain an understanding of PTSD and current unmet needs in treatment.
2. To review and discuss data from clinical trials of intravenous ketamine in patients with PTSD, and from the PTSD clinical program of brexpiprazole in combination with sertraline.

Literary References: 1. Feder A, Costi S, Rutter SB, et al. A randomized controlled trial of repeated ketamine administration for chronic posttraumatic stress disorder. Am J Psychiatry. 2021;178(2):193–202.
2. Otsuka Pharmaceutical Co., Ltd. and H. Lundbeck A/S press release. Otsuka Pharmaceutical and Lundbeck announce topline results from two Phase 3 trials of brexpiprazole as combination therapy with sertraline for the treatment of post-traumatic stress disorder in adults. 7 September 2023.

POST-TRAUMATIC STRESS DISORDER: PATIENT PERSPECTIVES OF UNMET CARE NEEDS

Susan Gurley, anxiety and depression assoication of america (ADAA)

Individual Abstract: Post-traumatic stress disorder (PTSD) is a prevalent, disabling condition that can develop following a traumatic event. Symptoms of PTSD are wide ranging, and generally fall into four domains – intrusion/re-experiencing, avoidance, negative alterations in cognition and mood, and heightened arousal and reactivity. The disruptive nature of PTSD symptoms presents a humanistic burden; patients often experience functional impairments and reduced health-related quality of life. The avoidance symptoms of PTSD (e.g., anhedonia, detachment from others, and avoidance of trauma-related thoughts or feelings) have been associated with impairments in relationships, friendships, socializing, and parenting. Hyperarousal symptoms, such as increased anger, irritability, and aggression may also contribute to difficulties in intimate and other relationships. Work/academic performance can be impacted by multiple PTSD symptoms; avoidance symptoms and sleep disturbances (e.g., due to hyperarousal symptoms) can increase absenteeism and reduce productivity. As a result, patients with PTSD are often at risk of isolation and distress. In addition, patients with PTSD are at a higher risk of substance use disorder (prevalence of approximately 46%), suicide or suicide attempts, and higher all-cause, cardiovascular, and external-cause mortality.

Stigma surrounding PTSD (i.e., negative societal views and stereotypes), and the internalization of these views (self-stigma), adds to the burden for patients with PTSD. Greater severity of PTSD symptoms has been associated with stigma and self-stigma. Furthermore, stigmatization has been strongly associated with a higher prevalence of PTSD. Many patients also report experiencing some form of alienation or discrimination due to their disorder. Stigma, shame, and fear of discrimination are among several potential barriers to care.

Given the substantial burden of PTSD on patients and their families, consideration of patient perspectives is of critical importance. In a US-based survey of patients with PTSD, 41.8% reported an unmet need for treatment, with 16.4% of these individuals expressing that they did not want to see a professional. The use of shared decision-making is recommended by several PTSD treatment guidelines, and may enhance patient satisfaction, engagement with treatment, and treatment outcomes. Additionally, data suggest that most patients with PTSD wish to be actively involved in the decision-making process, and are willing to invest time to learn about and consider the options.

This presentation will provide a patient advocacy perspective on the humanistic burden, stigma, and patient considerations in PTSD.

Learning Objectives: 1. To discuss patient considerations in the treatment of PTSD.
2. To gain an understanding of patients' perspectives of the unmet needs in PTSD treatment.

Literature References 1. Harik J. Shared Decision-making for PTSD. PTSD Research Quarterly. 2018;29(1).
2. Rodriguez P, Holowka DW, Marx BP. Assessment of posttraumatic stress disorder-related functional impairment: a review. J Rehabil Res Dev. 2012;49(5):649–665.

POST-TRAUMATIC STRESS DISORDER: AN OVERVIEW OF CAUSES, SYMPTOMATIC CHARACTERISTICS, CLINICAL CHALLENGES, AND CLINICAL UNMET NEEDS

Thomas Neylan, University of California, San Francisco

Individual Abstract: Post-traumatic stress disorder (PTSD) is a highly prevalent neuropsychiatric disorder affecting over 13 million people in the US during a given year. The estimated global lifetime prevalence of PTSD is 4–10%. Most cases of PTSD occur in the general population rather than the military population; the most common underlying traumas include the unexpected death of a loved one, rape and other sexual relationship violence, and interpersonal violence. Some people are at a higher risk of experiencing PTSD, influenced by factors including sex, race, income, age, and concurrent conditions.
PTSD diagnosis can be complicated by stigma, a lack of awareness of the condition or its symptoms, barriers to healthcare access, and comorbid psychiatric disorders. Symptoms of PTSD typically emerge within 3 months of the traumatic incident, though can occur months or even years later. Symptoms can also vary over time, and from person to person. In addition to the humanistic burden, the economic burden of PTSD in the US is substantial; costs per individual exceed costs associated with anxiety and depressive disorders.

In the treatment of PTSD, most guidelines recommend use of psychotherapy or pharmacotherapy as first-line interventions. Evidence suggests that psychotherapy (such as cognitive behavioral therapy) is an efficacious treatment option for PTSD, which can reduce symptom severity and improve remission rates. However, the efficacy of psychotherapy

observed in clinical trials is not typically achieved in clinical practice. This is due to several barriers, including resource issues, concerns about recalling traumatic events, and inadequate training for therapists.

Despite the burden of PTSD, no new pharmacotherapies have been approved for treatment of PTSD in around 20 years. Currently, just two drugs – sertraline and paroxetine – are approved by the FDA for the treatment of PTSD. Existing pharmacotherapies have demonstrated modest efficacy and inconsistent outcomes. In addition, while existing medications have demonstrated improvements in some symptoms of PTSD, significant benefits have not been found for other symptoms (e.g., anxious and depressive symptoms).

Once diagnosed, patients often require several different lines of treatment in order to manage symptoms. US claims data indicate that 79.3% of patients have a treatment change post-diagnosis of PTSD, with 58.8% receiving ≥2 distinct PTSD-related agents within 2 years of diagnosis. In that study, the most common reason for treatment changes (51.5%) was inadequate/suboptimal management of PTSD symptoms with prior treatment. Physicians frequently rely on polypharmacy with off-label treatments, such as other selective serotonin reuptake inhibitors (SSRIs), serotonin–norepinephrine reuptake inhibitors (SNRIs), benzodiazepines, anxiolytics or sedative hypnotics, and alpha blockers. In the US, FDA-approved medications for PTSD are only prescribed in approximately 20% of veteran patients, and SSRIs or SNRIs are prescribed in just 52% of civilians. The use of off-label pharmacotherapies may contribute to an increased adverse event burden, given the lack of established efficacy and safety in PTSD clinical trials.

Treatment patterns highlight an unmet medical need to address heterogeneous symptom presentation, with a treatment regimen that provides consistent efficacy and safety.

This presentation will discuss the current unmet needs in PTSD clinical practice, and the ways in which these may be addressed.

Learning Objectives: 1. To gain an understanding of the causes, symptomatic characteristics, impact, and burden of PTSD.
2. To discuss existing treatment options and current unmet needs in PTSD treatment.

Literature References 1. Davis LL, Schein J, Cloutier M, et al. The economic burden of posttraumatic stress disorder in the United States from a societal perspective. J Clin Psychiatry. 2022;83(3):21m14116.
2. Martin A, Naunton M, Kosari S, et al. Treatment guidelines for PTSD: a systematic review. J Clin Med. 2021;10(18):4175.

CLINICAL RESEARCH ON KETAMINE FOR POST-TRAUMATIC STRESS DISORDER: UPDATE AND FUTURE DIRECTIONS

Adriana Feder, Icahn School of Medicine At Mount Sinai

Individual Abstract: Post-traumatic stress disorder (PTSD) is a chronic and disabling condition. Current evidence-based treatments have insufficient efficacy for many individuals with PTSD. This presentation will begin with a brief overview of the development of ketamine as a potential treatment for chronic PTSD, including single- and repeated-dose randomized controlled trials (RCTs). Findings from ketamine-related neuroimaging studies in PTSD will be mentioned, with implications for studying the potential role of ketamine to enhance the efficacy of trauma-focused psychotherapy. Finally, findings from a recently completed open-

label pilot clinical trial will be presented, examining the feasibility and preliminary efficacy of adding a trauma-focused psychotherapy to a course of repeated intravenous ketamine infusions for severe chronic PTSD.
N=13 patients (100% female) with severe chronic PTSD completed the pilot trial. The combined treatment lasted approximately three weeks. Patients received a total of six ketamine infusions, administered three times/week for two consecutive weeks (Weeks 1 and 2). On Week 2, after completing the first four infusions, patients began a course of written exposure therapy (WET). WET is a brief, evidence-based and highly scalable psychotherapy comprising five total sessions, which has been found to be non-inferior to gold-standard trauma-focused psychotherapies for PTSD in three published RCTs. In this pilot trial, the first two sessions of WET alternated with the last two ketamine infusions during Week 2, on different days. On Week 3, patients completed the last three WET sessions. The primary outcome was change in Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) Total score from baseline to Week 12.

The combined treatment yielded large-magnitude PTSD symptom improvement on the CAPS-5 from baseline (CAPS-5=41.6 [standard deviation=6.2]) to 12 weeks (CAPS-5=20.7 [standard deviation=14.8]), with Cohen's d=1.6 (95% confidence interval=1.0 – 2.2, p LESS THAN 0.001). Nine (69%) patients were treatment responders, and 7 (54%) no longer met DSM-5 diagnostic criteria for PTSD at 12 weeks. At their last assessment at 24 weeks (19 weeks for one patient), 8 (62%) patients maintained treatment response and no longer met DSM-5 PTSD criteria. A future RCT is needed to investigate the potential synergistic effect between ketamine and trauma-focused psychotherapy for PTSD treatment, along with neuroimaging research.

Learning Objectives: 1. To learn about the development of ketamine as a treatment for chronic PTSD.
2. To learn about new and ongoing research on ketamine for chronic PTSD, focused on combining ketamine with trauma-focused psychotherapy.

Literature References 1. Feder A, Costi S, Rutter SB, et al. A randomized controlled trial of repeated ketamine administration for chronic posttraumatic stress disorder. Am J Psychiatry. 2021;178(2):193–202.
2. Norbury A, Rutter SB, Collins AB, et al. Neuroimaging correlates and predictors of response to repeated-dose intravenous ketamine in PTSD: preliminary evidence. Neuropsychopharmacology. 2021;46(13):2266–2277.

CLINICAL PROGRAM OF BREXPIPRAZOLE IN COMBINATION WITH SERTRALINE FOR PATIENTS WITH POST-TRAUMATIC STRESS DISORDER

Saloni Behl, Otsuka (OPDC)

Individual Abstract: There is a clear unmet need for a well-tolerated pharmacotherapy, with a consistent efficacy profile, for the treatment of post-traumatic stress disorder (PTSD). Brexpiprazole is approved in the US for the treatment of schizophrenia, major depressive disorder (as adjunctive therapy to antidepressants), and agitation associated with dementia due to Alzheimer's disease, and has been investigated as a combination treatment for PTSD.
The brexpiprazole PTSD clinical program comprised three trials: Trial 061 (Phase 2; flexible-dose brexpiprazole; NCT03033069), Trial 071 (Phase 3; flexible-dose brexpiprazole; NCT04124614), and Trial 072 (Phase 3; fixed-dose brexpiprazole; NCT04174170). The three trials included male and female patients, aged 18–65 years, with a Diagnostic and Statistical

Manual of Mental Disorders, Fifth Edition (DSM-5) diagnosis of PTSD (confirmed by the Mini International Neuropsychiatric Interview), and symptoms for ≥6 months. Each trial comprised a 1-week double-blind placebo run-in phase, followed by an 11-week double-blind, randomized treatment phase. In Trial 061, patients were randomized 1:1:1:1 to brexpiprazole 1–3 mg/day + sertraline 100–200 mg/day (i.e., combination therapy), brexpiprazole 1–3 mg/day + placebo, sertraline 100–200 mg/day + placebo (active reference arm), or to placebo alone. In Trial 071, patients were randomized 1:1 to brexpiprazole 2–3 mg/day + sertraline 150 mg/day, or sertraline 150 mg/day + placebo. In Trial 072, patients were randomized 1:1:1 to brexpiprazole 2 mg/day + sertraline 150 mg/day, brexpiprazole 3 mg/day + sertraline 150 mg/day, or to sertraline 150 mg/day + placebo. The primary endpoint in each trial was the change in Clinician Administered PTSD Scale for DSM-5 (CAPS-5) Total score from baseline to Week 10. Safety assessments included treatment-emergent adverse events.

Across the three trials, a total of 1,290 patients were randomized. In Trials 061 and 071, combination therapy with brexpiprazole + sertraline separated from sertraline + placebo on the primary endpoint (p LESS THAN 0.05). Whilst the primary endpoint was not met in Trial 072, the change from baseline observed with brexpiprazole + sertraline combination therapy was consistent with observations in Trials 061 and 071.

Across the three trials, combination therapy with brexpiprazole + sertraline was generally well tolerated; the safety profile was consistent with that of sertraline + placebo, and consistent with that of brexpiprazole in other indications.

This presentation will discuss the totality of data from the clinical program of brexpiprazole in combination with sertraline for the treatment of PTSD.

Learning Objectives: 1. To understand and describe the brexpiprazole clinical program for PTSD.
2. To discuss the totality of data from the clinical program of brexpiprazole + sertraline for the treatment of PTSD.

Literature References 1. Otsuka Pharmaceutical Co., Ltd. and H. Lundbeck A/S press release. Otsuka and Lundbeck report positive Phase II data for the combination treatment of brexpiprazole and sertraline for the treatment of post-traumatic stress disorder (PTSD). 30 November 2018.
2. Otsuka Pharmaceutical Co., Ltd. and H. Lundbeck A/S press release. Otsuka Pharmaceutical and Lundbeck announce topline results from two Phase 3 trials of brexpiprazole as combination therapy with sertraline for the treatment of post-traumatic stress disorder in adults. 7 September 2023.

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

Pharmaceutical Pipeline Session

ORAL PROLONGED-RELEASE ADJUNCTIVE KETAMINE (KET01): PHASE 2 TRIAL IN TREATMENT-RESISTANT DEPRESSION AND PHASE 1 TRIAL COMPARING TOLERABILITY WITH INTRANASAL ESKETAMINE

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Hans Eriksson, HMNC Brain Health

Abstract Background: Ketamine is a rapid-acting antidepressant, and a potent inhibitor of the N-methyl-D-aspartate receptor (NMDAR). However, ketamine and its metabolites also bind to other targets. It has not been conclusively demonstrated that NMDAR inhibition is necessary for antidepressant efficacy. An intranasal formulation of the (S)-enantiomer esketamine has received regulatory approval for treatment-resistant depression (TRD) in several markets. KET01 is an oral prolonged-release formulation of racemic ketamine with a low propensity for dissociation, due to its pharmacokinetic profile. Compared to other ketamine-based medications frequently used for TRD, administration of KET01 at a similar exposure (area under the curve, AUC) leads to a later occurring and lower concentration peak of ketamine (higher Tmax, lower Cmax), and, importantly, a relatively higher concentration of the metabolites norketamine and hydroxynorketamine.

Methods: In a Phase 2 trial (KET01-02), outpatients (N=122) with TRD were randomized to receive once-daily placebo (PBO), 120 mg KET01, or 240 mg KET01, adjunctively to ongoing antidepressant treatment for 3 weeks. The first dose was administered under supervision and the remaining doses were taken at home. The primary endpoint was the mean score change from baseline (BL) in the Montgomery-Åsberg Depression Rating Scale (MADRS) on Day 21 (mixed model for repeated measures).

In a Phase 1 randomized, placebo-controlled, double-blind, double-dummy, single-center, cross-over trial (KET01-03), healthy volunteers received single antidepressant doses of 240 mg KET01 or 84 mg intranasal esketamine. Acute tolerability was assessed, and blood samples were drawn for pharmacokinetic analysis.

Dissociation was evaluated using the Clinician-Administered Dissociative States Scale (CADSS).

Methods: In KET01-02, administration of 240 mg KET01 resulted in an improvement in the MADRS score after 7 hours, and the separation from PBO reached statistical significance on Day 4 and Day 7. The improvement from BL was sustained while on treatment until Day 21, and after a 4-week follow-up.

No differences in mean CADSS scores between the treatment arms were observed at any time point. No clinically relevant changes in heart rate or blood pressure were detected. KET01 was well tolerated and treatment-emergent AEs were reported by 47.5%, 50.0%, and 62.5% in the PBO, 120 mg/day, and 240 mg/day KET01 groups, respectively. Elevations in mean plasma γ-glutamyltransferase and alanine aminotransferase concentrations were observed from week 2 for both KET01 groups and decreased during follow-up.

In KET01-03, twenty-five healthy volunteers received KET01 and intranasal esketamine. The mean maximum change in CADSS score after KET01 treatment was lower by 29.01 (SD=2.35; p LESS THAN .00000000001) than after intranasal esketamine.

Methods: The program demonstrates rapid and clinically relevant reduction of depressive symptoms in patients with TRD after treatment with 240 mg/day KET01 with only minimal signs of dissociative symptoms, suggesting a low degree of NMDAR inhibition. The findings challenge the view that NMDAR inhibition is necessary for antidepressant efficacy of ketamine-based medications. The low level of dissociative symptoms during treatment with KET01 is advantageous compared to other currently used ketamine-based depression treatments. KET01 has the potential to be developed as an antidepressant medication to be taken at home.

GLUCAGON-LIKE PEPTIDE-1 (GLP-1) RECEPTOR AGONISM AS A POTENTIAL PHARMACOTHERAPY FOR ALCOHOL USE DISORDER: CONVERGING EVIDENCE FROM RODENT AND EARLY HUMAN STUDIES

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Mehdi Farokhnia, Clinical Psychoneuroendocrinology and Neuropsychopharmacology Section, Translational Addiction Medicine Branch, NIDA and NIAAA, NIH

Abstract Consistent with the role of the glucagon-like peptide-1 (GLP-1) system in alcohol seeking and consummatory behaviors, evidence from preclinical experiments, preliminary clinical studies, and anecdotal reports suggest that GLP-1 receptor agonists (GLP-1RAs) - already approved for treating type 2 diabetes mellitus and obesity - may represent promising pharmacotherapeutic options for alcohol use disorder (AUD). Recently developed GLP-1RAs such as semaglutide are gaining significant traction as they are more potent and have longer half-lives and higher affinity for the GLP-1R, compared to the first generation of GLP-1RAs. In a series of rodent experiments, we tested the effects of semaglutide on binge-like and dependence-induced drinking in male and female mice and rats. Semaglutide dose-dependently reduced alcohol intake in both paradigms and species, with no sex differences. Electrophysiology experiments on brain slices suggested that semaglutide enhances GABA release from the central amygdala and infralimbic cortex neurons. Next, in a real-world cohort study, we examined the association between GLP-RAs receipt and change in alcohol use. We extracted data from the Veterans Aging Cohort Study (VACS) national cohort, which includes ~13.5 million veterans who ever received care in the Department of Veterans Affairs, the largest integrated healthcare system in the US. A total of 28,996 GLP-1RA initiators were propensity score matched 1:1 to two comparator groups: individuals initiating dipeptidyl peptidase 4 (DPP-4) inhibitors (active comparator) and those receiving neither GLP-1RAs or DPP-4 inhibitors (unexposed). DPP-4 inhibitors are also approved for treating type 2 diabetes mellitus and boost the endogenous GLP-1 by blocking its degradation. Changes in pre- to post-index Alcohol Use Disorder Identification Test – Consumption (AUDIT-C) scores were compared between groups, using difference-in-difference (DiD) analyses. Results showed that GLP-1RA recipients had significantly greater reductions in AUDIT-C scores over time compared with unexposed (DiD: 0.09; 95% CI: 0.03, 0.14) and DPP-4 inhibitor recipients (DiD: 0.11; 95% CI: 0.05, 0.17). Stronger DiD estimates were found among individuals with AUD or hazardous/binge drinking: 0.51 (95% CI: 0.29, 0.72) and 1.38 (95% CI: 1.07, 1.69)

for GLP-1RA vs. unexposed and 0.65 (95% CI: 0.43, 0.88) and 1.00 (95% CI: 0.68, 1.33) for GLP-1 vs. DPP-4 inhibitor comparisons. Comparing DPP-4 inhibitors recipients to unexposed showed no association with changes in AUDIT-C scores (DiD: 0.02; 95% CI: -0.02, 0.05), indicating our GLP-1RA results were not affected by residual confounding. Together, these data from rodent and human pharmacoepidemiological studies provide converging evidence in support of testing GLP-1RAs in patients with AUD. Given the known safety profile and widespread prescription of these medications, if shown to be efficacious in clinical trials, GLP-1RAs have the potential to be a successfully repurposed for AUD treatment.

POSITIVE RESULTS ACHIEVED IN A PHASE 2B, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY FOR BNC210, AN ALPHA7 NICOTINIC RECEPTOR NEGATIVE ALLOSTERIC MODULATOR, FOR THE TREATMENT OF PTSD (ATTUNE).

Spyros Papapetropoulos[1], Elisabeth Doolin[1], Michael Odontiadis[1], Dharam Paul[1], Julia Crossman[1], Mark A. Smith[1], Paul Rolan[1]*

[1]*Bionomics Ltd*

Spyros Papapetropoulos, Bionomics Ltd

Abstract Post-traumatic stress disorder (PTSD) is a serious, debilitating, and chronic condition resulting from exposure to severe trauma such as actual or threatened death, serious injury, or sexual violence. It is characterized by disabling symptoms of intrusive thoughts, nightmares and flashbacks, negative cognitions and mood, avoidance behaviors, hypervigilance, and sleep disturbance. People with PTSD continue to experience adverse effects of their exposure to trauma for years afterward. Thus, the total disease burden (disability plus premature mortality) attributable to PTSD is high. There have been no newly approved drug treatments for PTSD in the past 20 years.

BNC210 is a novel experimental alpha7 nicotinic negative allosteric modulator (NAM) in development for the treatment of psychiatric diseases. BNC210 has a novel mode of action that may be directly relevant to PTSD pathophysiology and which is differentiated from the antidepressants and other therapeutics commonly prescribed for the treatment of PTSD. BNC210 has demonstrated efficacy and evidence of biological activity in several depression preclinical models (O'Connor et al., 2024) and in completed clinical trials in Generalized Anxiety Disorder (GAD) (Wise et al., 2020) Social Anxiety Disorder (SAD), and panic attacks. It is currently also in late-stage clinical development for the acute, "as-needed" treatment of SAD.

In a Phase 2b clinical trial, ATTUNE, 900 mg BNC210 or matched placebo was administered twice daily to 209 PTSD patients (randomized 1:1) for 12 weeks. BNC210 achieved a statistically significant improvement compared to placebo on the primary endpoint of mean change from Baseline to Week 12 in the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) Total Symptom Severity scores (LS Mean difference from placebo of -4.03 and effect size of -0.40; p LESS THAN 0.05). The onset of a statistically significant effect (p LESS THAN 0.05) was observed early (at Week 4, LS Mean difference of -4.11) and was maintained throughout the study, including at Week 8 (-4.74). Importantly, BNC210 also showed statistically significant improvement (p LESS THAN 0.05) from Baseline to Week 12 on depressive symptoms (-3.19) and sleep (-2.19) as measured by the Montgomery-Åsberg Depression Rating Scale (MADRS) and Insomnia Severity Index (ISI), respectively. Trends

for improvement (p LESS THAN 0.1) were observed at Weeks 4, 8, and/or 12 in other secondary endpoint measures, including Clinical Global Impressions of Severity (CGI-S), Patient Global Impressions of Severity (PGI-S), and the Sheehan Disability Scale (SDS).

Treatment with 900 mg BNC210 twice daily had a favorable safety and tolerability profile. The most commonly reported treatment-emergent adverse events (GREATER THAN 5% of subjects) were headache, nausea, and fatigue in the BNC210 and placebo treatment groups and asymptomatic hepatic enzyme increases in the BNC210 treatment group.

In conclusion, positive results achieved in the ATTUNE Study support BNC210's potential as a safe and effective treatment for PTSD that will be further tested in future late-stage clinical trials.

AN EXPLORATORY COMPARISON OF SUBLINGUAL DEXMEDETOMIDINE WITH QUETIAPINE IN HEALTHY ELDERLY SUBJECTS

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Robert Risinger, Bioxcel Therapeutics

Abstract Background: Agitation is a severe, disruptive, and morbid complication of dementia. Commonly used agents for the treatment of this condition are antipsychotics and benzodiazepines. Though efficacy has been demonstrated for these agents, side effects remain a concern, particularly for elderly patients with greater medication and disease burden.
BioXcel Therapeutics, Inc. is developing a sublingual film of dexmedetomidine (BXCL501), a highly selective α2 adrenoceptor agonist, for acute treatment agitation in patients with Alzheimer's dementia. A study in elderly healthy volunteers evaluated the PK and safety/tolerability of potential doses for this age group.

Quetiapine, a widely prescribed therapy in elderly patients for off-label indications including dementia and with known side-effects, was included as an active comparator to explore tolerability in one part of the study.

Methods: This Phase 1, single-center, single-blind, randomized, multiple doses (40 µg or 60 µg BXCL501), sequential group study in 2 cohorts, had a total of 40 participants. The primary objective was the characterization of the BXCL501 PK in elderly subjects after single and multiple doses. An exploratory objective of Cohort 2 was the comparison of the effects of ascending doses of quetiapine with those of 60 µg of BXCL501. The PK and tolerability data from the overall study will be reported separately; this report focuses on the comparison of BXCL501 with quetiapine. The outcome measures for the comparison included the agitation calmness evaluation scale (ACES), Karolinska Sleepiness Scale (KSS) and Digit Symbol Substitution Test (DSST) at multiple time points. Cohort 2 recruited 24 participants, 12 receiving BXCL501 60 µg, 6 the matching placebo, and 6 the quetiapine tablet. Doses were administered daily for 7 days. Quetiapine tablets were given orally once daily in the morning, at the dose of 25 mg on Days 1-2, 50 mg on Days 3-4 and 100 mg on Days 5-7.

Methods: At all time points assessed, participants administered 60 µg BXCL501 showed more sleepiness as measured by KSS compared with those on placebo. Participants administered BXCL501 showed "some signs of sleepiness" (KSS scores of 6) at 2 hours on Days 1 and 2 and were "sleepy, with no effort required to keep awake" (score 7) on Day 1 at 4 hours after dosing. At all other timepoints, the participants showed a mean score ranging between 4 and 5 ("rather alert" to "neither alert nor sleepy"). Participants administered quetiapine generally had higher scores than those treated with BXCL501 and on all days at time points of 1 or more hours after dosing, showed a mean score of 6-8, denoting the sleepiness state ranging from "some signs of sleepiness" to "sleepy, some effort to keep awake". Similar observations were made when evaluating ACES scores. No meaningful differences in DSST scores were observed between the BXCL501 and quetiapine groups.

No deaths or SAEs were reported during the study and there were no study discontinuations. No severe TEAEs were reported. The most frequently reported TEAE was orthostatic hypotension: 50% with placebo, 25% in the BXCL501 60 µg group and 100% in the quetiapine group.

Methods: In this exploratory study, observations correspond to those expected for the types of medications studied: sleepiness and orthostatic hypotension. Of note, sleepiness was less pronounced with BXCL501 60 µg compared with quetiapine 25-100 mg. The limitation of the study was the small sample size; these results should thus be considered preliminary.

EFFICACY AND SAFETY OF XEN1101, A NOVEL, KV7 POTASSIUM CHANNEL OPENER IN ADULTS WITH MODERATE TO SEVERE MAJOR DEPRESSIVE DISORDER: RESULTS FROM THE PHASE 2 X-NOVA STUDY

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Joe McIntosh, Xenon

Abstract Background: Major depressive disorder (MDD) remains a significant public health concern globally, with 1 in 3 patients experiencing inadequate responses to initial antidepressant (AD) therapy. While the pathophysiology of MDD is partially elucidated, the complete spectrum of biologic pathways contributing to MDD is yet to be fully understood. Novel treatment approaches targeting distinct pathways are warranted to address this unmet need. Voltage-gated KCNQ-type potassium channels (Kv) regulate cell membrane excitability. Certain Kv7 channel openers have been shown to confer seizure reduction (Khan R et al., 2024) and have promising results in preclinical and clinical studies for depressive-like behavior in

animal models and depression in patients, respectively (Friedman AK et al., 2016; Costi S et al., 2021). XEN1101 is a novel, potent, Kv7.2/7.3-specific potassium channel opener in development for the treatment of epilepsy and MDD.

Methods: The X-NOVA trial was a multicenter, randomized, double-blind, placebo-controlled, proof-of-concept Phase 2 study conducted across 20 sites in the United States. Adults aged 18–65 years with moderate to severe MDD and anhedonia were randomized 1:1:1 to receive XEN1101 at doses of 10 mg, 20 mg, or placebo (PBO) once daily (QD) with food without titration. The primary efficacy endpoint was the change in Montgomery-Åsberg Depression Rating Scale (MADRS) score from baseline at week 6. A key secondary endpoint included changes in the Snaith-Hamilton Pleasure Scale (SHAPS) score, and exploratory endpoints included the 17-Item Hamilton Depression Rating Scale (HAM-D17) score and the Clinical Global Impression of Improvement (CGI-I) score at week 6.

Methods: Of the 168 randomized patients, 164 comprised the modified intent-to-treat population. XEN1101 demonstrated a dose-dependent reduction in MADRS scores from baseline at week 6 compared to placebo (least squares mean point reduction: 10 mg (−15.61), 20 mg (−16.94), PBO (−13.90), with the 20 mg dose showing a clinically meaningful difference (Duru G et al., 2008) of 3.04 points between PBO and XEN1101, which was not statistically significant (P=0.135). Statistically significant improvements were observed in HAM-D17 (−10.18 vs −13.26; P=0.042) and SHAPS (−5.30 vs −7.77; P=0.046), as well as at least minimally improved depressive symptoms by CGI-I (P=0.004) in the 20 mg group compared to placebo. Early onset of efficacy was noted at week 1 in the 20 mg group for MADRS change (–2.66; P=0.047). XEN1101 was generally well tolerated, with no serious adverse events reported in the treatment groups. The incidence of treatment-emergent adverse events was 52% and 66% in the 10 mg and 20 mg groups, respectively, compared to PBO (60%). XEN1101 was not associated with notable weight gain; patients did not report notable sexual dysfunction.

Methods: Despite not achieving statistical significance in its primary endpoint, XEN1101 demonstrated a clinically meaningful reduction of depression measured by the MADRS, a significant reduction in HAMD-17, an early onset of action, a significant reduction in anhedonia, and a potentially differentiated safety profile compared to other ADs. The X-NOVA results are particularly meaningful given that there was a 2 in 3 chance of receiving active treatment, which has been previously shown to increase the placebo response (Papakostos GI, et al. 2009). A Phase 3 clinical program is being planned in 2024 to continue to explore XEN1101 in MDD.

Funding: This study was funded by Xenon Pharmaceuticals Inc.

PRO-COGNITIVE PHARMACODYNAMIC EFFECTS OF ALTO-101: RESULTS FROM BRAIN AND BEHAVIORAL OUTCOMES IN A RANDOMIZED, DOUBLE-BLIND PHASE 1 STUDY

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Abstract Background: Cognitive impairment is a debilitating component of many CNS disorders, such as schizophrenia. Drugs that increase intracellular cyclic adenosine monophosphate (cAMP)/protein kinase A (PKA) signaling have shown promise as pro-cognitive therapeutics in animal models and early-stage clinical trials. ALTO-101 is a selective brain-penetrant inhibitor of phosphodiesterase-4 (PDE4), has been shown to increase cAMP levels in brain regions critical for cognition and may have potential as a novel treatment for cognitive impairment. Here we sought to identify brain/behavior-based pharmacodynamic (PD) biomarkers for ALTO-101 that could indicate the effects of the drug on cognitive processing, as well as elucidate dose-response relationships. Moreover, unlike most phase 1 studies, which are underpowered to detect PD effects (typically 4-8 participants per dose), we conducted a well-powered (N=40) cross-over design study in which each person received drug and placebo. Doing so provides greater confidence in **Conclusions** regarding the human brain mechanisms engaged by the drug.

Methods: 40 healthy adult volunteers (40-64 years old) were enrolled in a randomized, double-blind, placebo-controlled phase 1 study of ALTO-101. Each participant received a single oral dose of placebo, 0.5 mg ALTO-101, and 1.5 mg ALTO-101 in a 3-way counterbalanced crossover fashion, with a 7-day washout between each dose. During the evaluation of the acute phase of the drug effects, participants underwent neurocognitive tests and electroencephalography (EEG), including resting-state EEG (rsEEG) and event-related potentials (ERPs). Analyses focused on prespecified neurocognitive and EEG measures using mixed-effects models to evaluate the PD effects of ALTO-101 vs. placebo.

Methods: We identified multiple neurocognitive and EEG measures that differed between the ALTO-101 conditions and placebo. On the ERP outcomes, ALTO-101 led to an increase in the amplitude of the mismatch negativity potential (0.5mg: d = 0.38, p = 0.07; 1.5mg: d=0.53, p=0.02), and an increase in stimulus-driven gamma band phase locking response to auditory stimuli (0.5mg: d = 0.35, p = 0.08; 1.5mg: d=0.68, p=0.003). For rsEEG, ALTO-101 decreased relative theta power (0.5mg: d = 0.51, p = 0.02; 1.5mg: d=0.88, p=0.0003). Behaviorally, ALTO-101 demonstrated improved processing speed (0.5mg: d = 0.32, p = 0.16; 1.5mg: d=0.63, p=0.006).

Conclusions: These findings demonstrate strong PD effects of ALTO-101 in driving key brain processes important for cognition as measured by EEG, along with behavioral evidence of cognitive improvement. Since these measures index schizophrenia-related deficits in cognition and cognitive processing, these data support further development of ALTO-101 for the treatment of cognitive impairment associated with schizophrenia.

MM120 (LYSERGIDE) FOR GAD: RESULTS FROM MINDMED'S PHASE 2 TRIAL

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[1]Mind Medicine Inc, [2]Mind Medicines Inc

Paula Jacobsen, Mind Medicines Inc

Abstract Generalized Anxiety Disorder (GAD) is among the most common psychiatric disorders. Despite this, there has been little progress in the development of effective and well-tolerated therapies. GAD is a chronic disorder characterized by excessive worry and persistent general apprehensiveness, which can manifest in a wide range of psychiatric and somatic symptoms. Current treatments are often ineffective or have intolerable side effects. We evaluated the safety, tolerability, and efficacy of 4 doses of MM-120 (D-lysergic acid diethylamide D-tartrate) in patients with GAD. **Methods:** In this Phase 2b multicenter, randomized, double-blind, placebo-controlled study, adults aged 18 to 74 years with GAD and moderate to severe anxiety (Hamilton Anxiety Rating Scale [HAM-A] score ≥20) were enrolled. A total of 198 patients were randomized 1:1:1:1:1 to receive a single administration of MM-120 at a dose of 25 µg (n=39), 50 µg (n=40), 100 µg (n=40), or 200 µg (n=40) or placebo (n=39). The primary and key secondary objectives were to assess the dose-response relationship of MM-120 by evaluating the change in HAM-A total score from baseline to weeks 4 and 8, respectively. Secondary endpoints included improvements in functioning and quality of life; safety assessments were also performed. **Methods:** Both 100 µg and 200 µg doses demonstrated clinically and statistically significant efficacy. The 100 µg dose achieved the highest level of clinical activity with a statistically significant reduction of 7.6 points in HAM-A total score compared to placebo at week 4 (-21.34 MM-120 vs -13.75 placebo; P=0.0004). Moreover, clinical activity was evident as early as day 2 after treatment as measured by the Clinical Global Impressions–Severity (CGI-S) scale. At day 2, CGI-S scores improved by 1.8 points with MM-120 100 µg vs 0.7 points with placebo (P=0.0001); this improvement persisted through week 4 (P LESS THAN 0.01). At week 4, 77.5% of subjects treated with MM-120 100 µg showed a clinical response with ≥50% improvement in HAM-A vs 30.77% with placebo. Further, 50% of participants treated with 100 µg achieved remission (HAM-A ≤7) vs 17.95% with placebo. There was also a significant reduction in the Montgomery-Asberg Depression Rating Scale total score with MM-120 100 µg versus placebo (-5.73; P LESS THAN 0.05). Treatment-emergent adverse events (TEAEs) occurred in 97.5% of participants in the MM-120 100 µg group vs 56.4% in placebo. Most events were mild to moderate, occurred on dosing day, and were consistent with the expected acute effects of MM-120. The most common TEAEs (≥10% incidence) in the MM-120 100 µg group were illusion, hallucination, euphoric mood, anxiety, abnormal thinking, headache, nausea, fatigue, mydriasis, increased blood pressure, and hyperhidrosis. No deaths were reported in the study. **Methods:** These findings suggest a rapid, robust, and durable clinical response to MM-120 in patients with GAD. Mind Medicine, Inc supported this study.

A PHASE 2 RANDOMIZED PROOF-OF-CONCEPT TRIAL OF NBI-1065846 (TAK-041) IN ADULTS WITH ANHEDONIA ASSOCIATED WITH MAJOR DEPRESSIVE DISORDER: RESULTS OF THE TERPSIS STUDY

Shannon Benedetto[*1], Adrian Ionescu[1], Tingting Ge[1], Maura Furey[1], Swan Lin[1], Manish Jha[2], Andrew Krystal[3], Asim Shah[4], David Walling[5], Neel Shah[1], Sakina Rizvi[6], Sidney Kennedy[6], Antonio Laurenza[7], Venkatesha Murthy[7], Jaskaran Singh[1]*

[1]Neurocrine Biosciences, [2]University of Texas Southwestern Medical Center, [3]University of California, San Francisco, [4]Baylor College of Medicine, [5]CenExel - CNS, [6]ASR Suicide and Depression Studies Program, St. Michael's Hospital, University of Toronto, [7]Takeda Pharmaceutical Company Ltd

Shannon Benedetto, Neurocrine Biosciences

Abstract Background: Anhedonia (the inability to feel pleasure) is a symptom of several neuropsychiatric disorders, affecting up to 72% of individuals with major depressive disorder (MDD) and 80% of individuals with schizophrenia.1,2 As a core symptom of MDD, anhedonia may predict poor treatment response to antidepressants and increased suicide risk.1 Lateral habenula (LHb) hyperexcitability may contribute to the dysregulated reward circuitry underlying anhedonia in MDD.3,4 Targeting G-protein coupled receptor (GPCR) 139 (GPR139), an orphan GPCR enriched in the medial habenula5, may potentially improve anhedonia by reducing aberrant LHb activity.
NBI 1065846 (TAK-041) is an investigational GPR139 agonist that improved anhedonia, anxiety, and depression in rodent behavioural models, and increased ventral striatal activity during reward anticipation in adults with schizophrenia. Here we report efficacy and safety results from TERPSIS, a phase 2 study of NBI-1065846 in adults with MDD and anhedonia (NCT05165394).

Methods: This double-blind, proof-of-concept study was conducted in adults with MDD who were receiving or had received stable antidepressant medication for their most recent depressive episode but still had anhedonia (Snaith Hamilton Pleasure Scale ≥30 at screening and baseline [BL]). Participants were stratified by illness severity (Hamilton Depression Rating Scale [HAMD-17] scores) and allocated 1:1 to receive once-weekly placebo or NBI 1065846 at a loading dosage of 160 mg, followed by 80 mg on Weeks 2–8.

The primary endpoint was the change from BL (CFB) to Day 57 in Dimensional Anhedonia Rating Scale (DARS). Secondary endpoints were the CFB to Day 57 in Montgomery Asberg Depression Rating Scale (MADRS) in participants with a HAMD-17 score ≥19 and in Clinical Global Impression – Severity (CGI-S). Safety endpoints included treatment emergent adverse events (TEAEs) and the Columbia Suicide Severity Rating Scale (C-SSRS).

Results: Of 93 randomized participants, 88 (94.6%) completed the study treatment and 83 (89.2%) completed the study. BL demographics and characteristics were broadly similar between treatment groups. No significant improvement in DARS was observed with NBI-1065846 vs placebo at Day 57 (p = 0.8663, 1-sided), with a least-squares mean (standard error of the mean) [1 sided 90% confidence interval] difference of –3.9 (3.5) [–8.4, infinity]. MADRS and CGI S scores with NBI 1065846 were not statistically different from placebo at Day 57.

Most TEAEs were mild or moderate in severity, occurring at a slightly lower frequency with NBI 1065846 than with placebo. TEAEs occurring in ≥3 participants were headache, insomnia, COVID 19, diarrhea and fatigue. C-SSRS suicidal ideation increased from BL to post-BL in 10 participants (NBI 1065846, n=3). One participant assigned to placebo with a history (GREATER THAN 1 year before screening) of suicide attempts had a serious TEAE of suicide attempt and discontinued study treatment.

Discussion: The TERPSIS study did not meet its primary or secondary endpoints. NBI 1065846 was generally well tolerated, with fewer TEAEs observed than with placebo. Being predictive of clinical outcome in MDD, anhedonia remains an important unmet therapeutic need.

Study funded by Neurocrine Biosciences, Inc. and Takeda Pharmaceutical Company, Ltd

References

1. Am J Psychiatry 2022;179:458–69
2. Schizophr Bull 2006;32:259–73

3. Mol Psychiatry 2017;22:202–8
4. Curr Opin Neurobiol 2018;48:90–6
5. Biol Psychiatry 2017;81:296–305

CT-155: EARLY STAGE EVIDENCE IN THE DEVELOPMENT OF A PRESCRIPTION DIGITAL THERAPEUTIC TO TREAT EXPERIENTIAL NEGATIVE SYMPTOMS OF SCHIZOPHRENIA

Abhishek Pratap[*1], Cornelia Dorner-Ciossek[2], Cassandra Snipes[3], Mariya Petrova[3], Brendan D Hare[4], Thomas Mick[3], Shaheen E Lakhan[3]*

[1]Boehringer Ingelheim Pharmaceuticals, Inc., [2]Boehringer Ingelheim International GmbH, [3]Click Therapeutics, Inc., [4]Boehringer Ingelheim Pharmaceuticals, Inc. (Click Therapeutics at time of study)

Abhishek Pratap, Boehringer Ingelheim Pharmaceuticals, Inc.

Abstract Introduction: Negative symptoms are prominent in people with schizophrenia. Experiential negative symptoms (ENS) are a subdomain of negative symptoms that include avolition, asociality and anhedonia, and contribute substantially to the emotional and socioeconomic burden of schizophrenia. There are currently no FDA-approved pharmacotherapies for ENS, and access to available psychosocial therapies is limited. Prescription digital therapeutics (PDTs) are digital therapeutics (DTx) that have demonstrated rigorous evidence for efficacy and safety according to FDA regulatory controls and require a prescription for use. CT-155 is a PDT under investigation to target ENS via smartphone delivery and is co-developed and guided by patient feedback. Given widespread smartphone ownership, CT-155 could deliver scalable, evidence-based care alongside standard treatments and address access barriers to traditional therapy. Two exploratory studies were designed to evaluate the establishment and overall strength of the digital working alliance (DWA), a potentially important factor akin to the therapeutic alliance that may influence outcomes, between patients living with ENS of schizophrenia and CT-155. These studies also explored the feasibility and acceptability of treatment with CT-155 to address ENS in this population.
Methods

Two independent, single-arm, multicenter exploratory studies of abbreviated versions of CT-155 (CT-155 beta) in adults with schizophrenia and ENS on stable antipsychotics for ≥12 weeks were conducted. Treatment periods for both Study 1 and Study 2 included a 3-week orientation with lessons to build a DWA (Weeks 1–3), while Study 2 (NCT05486312) also included a subsequent abbreviated adaptive goal-setting (AGS) phase (Weeks 4–7). Engagement was assessed throughout both studies by measuring the number of lessons completed. The DWA strength between participants and CT-155 beta was measured in Study 1 and Study 2 using the mobile Agnew Relationship Measure (mARM) questionnaire. ENS were assessed at baseline in both studies and at Week 7 in Study 2 using the Clinical Assessment Interview for Negative Symptoms Motivation and Pleasure Scale (CAINS-MAP).

Results: Studies 1 and 2 enrolled 49 and 50 participants, respectively; 46 (94%) and 43 (86%) completed. Most were male (71% and 80%), non-white (57% and 70%), never attended college (63% and 64%), and had an income LESS THAN $25,000 (94% in both). Participants

completed a median of 16/21 (76.2%) lessons over the 3-week period in Study 1 and 18/21 (85.7%) lessons over the equivalent period in Study 2. Across both studies, a positive DWA was established during the orientation phase (Week 3 mean [standard deviation; SD] mARM: Study 1, 5.16 [0.77]; Study 2, 5.36 [1.06]) and was maintained after the AGS phase at Week 7 in Study 2 (mean [SD] mARM: 5.48 [0.97]). DWA was unaffected by negative symptom severity in Study 1 and Study 2. In Study 2, ENS improved after 7 weeks (mean [SD] CAINS-MAP scores: baseline, 20.2 [8.6]; Week 7, 16.8 [7.8]; p=0.004; n=43). No adverse events (AEs) were reported in Study 1; 3 non-serious, non-treatment-related AEs were reported in Study 2.

Conclusion: People living with schizophrenia engaged with beta versions of CT-155 to support their treatment during the DWA establishment and AGS phases. ENS improvement after 7 weeks suggests that this PDT under investigation could become a new scalable treatment modality for people with schizophrenia, addressing a major unmet need. These favorable results support advancing CT-155 into late-phase clinical development (CONVOKE: CT05838625/CT-155-R-001).

Funding: Boehringer Ingelheim and Click Therapeutics.

Previously presented at ECNP, Neuroscience Applied, 2023, 2(2): 103618.

TRORILUZOLE, A NOVEL GLUTAMATE MODULATING AGENT, IN DEVELOPMENT FOR OBSESSIVE-COMPULSIVE DISORDER

Azim Munivar[*1], Stephen Kaplita[1], Kimberly Gentile[1], Lia Donahue[1], Deborah Smith[1], Timothy McCormack[1], Christopher Jensen[1], Irfan Qureshi[1], Vladimir Coric[1]*

[1]Biohaven Pharmaceuticals,

Azim Munivar, Biohaven Pharmaceuticals

Abstract Introduction: Few patients with obsessive-compulsive disorder (OCD) experience a complete response to serotonergic and dopaminergic therapies, suggesting other neurochemical systems are involved in OCD pathophysiology. Preclinical, clinical, genetic, and neuroimaging studies implicate glutamatergic hyperactivity in the pathogenesis of OCD. Troriluzole, a novel glutamate modulating agent, may normalize synaptic glutamate levels by increasing expression and function of glutamate transporters and by decreasing presynaptic glutamate release. Troriluzole is designed to provide enhanced bioavailability, eliminate the need for fasting, enable once-daily dosing, reduce first pass metabolism, and minimize hepatotoxicity relative to its active metabolite, riluzole. Herein we describe the results from a Phase 2 proof of concept study and the demographic and baseline characteristics for 2 Phase 3 studies.

Methods: Adults having an inadequate response to their current standard of care medication for the treatment of OCD were enrolled into a randomized, double-blind, placebo-controlled Phase 2 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 ≥19 and patients needed to be on a stable dose of a standard of care 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. Following up on a clinical signal seen in the Phase 2 study, two identical Phase 3 randomized, double-blind, placebo-controlled trials were initiated

evaluating adjunctive troriluzole 280 mg daily in up to 700 adults for 10 weeks. Subjects have a history of OCD for ≥1 year with inadequate response to an ongoing standard of care medication, defined as a Yale-Brown Obsessive Compulsive Score (Y-BOCS) ≥ 22 at screening and baseline. The primary endpoint is change from baseline in Y-BOCS. Preliminary demographics and baseline characteristics were analyzed as of January 2024.

Results: In the Phase 2 study, 248 subjects were randomized. Troriluzole demonstrated consistent treatment benefit at all timepoints. Patients with more severe OCD symptoms at baseline demonstrated larger treatment effects. Across the two Phase 3 studies, mean (SD) age was 37.8 (13.19) years. Mean (SD) baseline Y-BOCS was 27.4 (3.56). The majority of subjects were female (65%) and white (82%); The proportion of subjects reporting 2-10, 11-20, and 21+ years of OCD history was 42%, 18%, and 17%, respectively.

Conclusion: A Phase 2 proof of concept study of troriluzole in OCD demonstrated treatment benefit, and patients with more severe OCD symptoms at baseline experienced larger treatment effects. These results informed the development of 2 ongoing Phase 3 clinical trials. These two Phase 3 clinical trials are evaluating troriluzole in a population with moderate-to-severe OCD symptoms despite standard of care therapy. These results underscore the incomplete efficacy of available therapies which are also associated with sexual dysfunction, metabolic syndrome, and extrapyramidal symptoms. If troriluzole proves to be safe and efficacious, this will be the first novel mechanism of action in OCD in over 20 years and an important breakthrough for the millions of patients suffering from this disorder.

4:15 p.m. - 6:15 p.m.

Workshops

^THE NEXT GENERATION ASCP MODEL PSYCHOPHARMACOLOGY CURRICULUM: COMBINING EDUCATIONAL TECHNOLOGY WITH CONTENT EXPERTISE TO DEVELOP AN EDUCATIONAL TOOL FOR MODERN LEARNERS

Matthew Macaluso, The University of Alabama at Birmingham

Overall Abstract: The goal of this workshop is to engage American Society of Clinical Psychopharmacology (ASCP) leaders, members, and other key stakeholders in fine-tuning the vision for the next generation model psychopharmacology curriculum. This workshop will review the history of the ASCP model curriculum, understand evidence regarding the needs of modern learners, and share a vision for the next generation model curriculum, including a pilot of the proposed curriculum in a specific topic area.

Ira Glick, MD, and colleagues first developed the American College of Neuropsychopharmacology (ACNP) Model Psychopharmacology Curriculum in the 1980's to improve the teaching of psychopharmacology nationally. The initial ACNP curriculum was an evidence based, national curriculum, targeting teachers of psychopharmacology and their students at residency programs throughout the United States. The goal of the curriculum was for knowledge gained by trainees to improve the lives of patients. By the year 2000, the model curriculum was revised and updated by a committee of the ASCP. The ASCP Model Psychopharmacology Curriculum has been available for purchase by teachers of

psychopharmacology, has been disseminated internationally to countries around the world, and produced revenues that fostered the educational mission of the ASCP.

While the ASCP curriculum was widely used throughout the 1990's and into the 2010's, follow up evaluations of the curriculum's effectiveness consistently showed that, in addition to evidence-based educational content, a psychopharmacology curriculum must use advanced technology to ensure the needs of teachers and learners are met. After eleven positively received editions of the ASCP curriculum were developed, culminating with the 11th edition in 2021, ASCP leaders agreed the curriculum would be re-formulated to meet the needs of modern learners, whose education has largely occurred in a digital space.

A committee of the ASCP, appointed by the ASCP Board, has been working to understand how modern technology can maximize educational material developed by content experts to meet the needs of end users. End users could be psychiatric residents or other post-graduate trainees learning psychopharmacology, practicing psychiatrists or other clinicians pursing continuing medical education or maintenance of certification, as well as teachers of allied health providers.

This workshop is critical to understanding if our formulation of learner needs resonates with key stakeholders and target end users. Audience attitudes, behaviors, and learning needs will be collected from focused discussion including their responses to a pilot demonstration. The pilot that will be demonstrated includes a web-based portal, recorded video presentations given by content experts, downloadable resources including presentation slides and other high yield review documents, as well as an artificial intelligence (AI) teaching assistant. While AI is new to education and not yet considered a best practice, the next generation curriculum should include a minor, exploratory, AI component to understand how AI technology can help the learners of tomorrow. Changes to the pilot will be made from end user feedback collected at this and other key professional meetings. The committee also expects to conduct formal surveys of target end users as part of the curriculum redevelopment and pilot project.

Learning Objectives: 1) Review the history of the ASCP model psychopharmacology curriculum and 2) Understand and utilize the evidence regarding the needs of modern leaners to guide the development of the next generation ASCP curriculum.

Literary References: 1. Glick ID, Zisook S. The challenge of teaching psychopharmacology in the new millennium: the role of curricula. Acad Psychiatry. 2005 May-Jun;29(2):134-40. doi: 10.1176/appi.ap.29.2.134. Erratum in: Acad Psychiatry. 2005 Jul-Aug;29(3):324. Erratum in: Acad Psychiatry. 2005Jul;29(3):324. PMID: 15937259.
2. Wulsin and Kramer: Teaching Psychopharmacology in the 21st Century, Acad Psychiatry 2001; 25:102-106.

THE NEXT GENERATION ASCP MODEL PSYCHOPHARMACOLOGY CURRICULUM: COMBINING EDUCATIONAL TECHNOLOGY WITH CONTENT EXPERTISE TO DEVELOP AN EDUCATIONAL TOOL FOR MODERN LEARNERS

Lawrence Cohen, UNT System College of Pharmacy/ Regulatory Insurance Advisors

Individual Abstract: The goal of this workshop is to engage American Society of Clinical Psychopharmacology (ASCP) leaders, members, and other key stakeholders in fine-tuning the vision for the next generation model psychopharmacology curriculum. This workshop will

review the history of the ASCP model curriculum, understand evidence regarding the needs of modern learners, and share a vision for the next generation model curriculum, including a pilot of the proposed curriculum in a specific topic area.

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psychopharmacology nationally. The initial ACNP curriculum was an evidence based, national curriculum, targeting teachers of psychopharmacology and their students at residency programs throughout the United States. The goal of the curriculum was for knowledge gained by trainees to improve the lives of patients. By the year 2000, the model curriculum was revised and updated by a committee of the ASCP. The ASCP Model Psychopharmacology Curriculum has been available for purchase by teachers of psychopharmacology, has been disseminated internationally to countries around the world, and produced revenues that fostered the educational mission of the ASCP. While the ASCP curriculum was widely used throughout the 1990's and into the 2010's, follow up evaluations of the curriculum's effectiveness consistently showed that, in addition to evidence-based educational content, a psychopharmacology curriculum must use advanced technology to ensure the needs of teachers and learners are met. After eleven positively received editions of the ASCP curriculum were developed, culminating with the 11th edition in 2021, ASCP leaders agreed the curriculum would be re-formulated to meet the needs of modern learners, whose education has largely occurred in a digital space.

Learning Objectives: 1) Review the history of the ASCP model psychopharmacology curriculum and 2) Understand and utilize the evidence regarding the needs of modern leaners to guide the development of the next generation ASCP curriculum.

Literature References 1. Glick ID, Zisook S. The challenge of teaching psychopharmacology in the new millennium: the role of curricula. Acad Psychiatry. 2005 May-Jun;29(2):134-40. doi:10.1176/appi.ap.29.2.134. Erratum in: Acad Psychiatry. 2005 Jul-Aug;29(3):324. Erratum in: Acad Psychiatry. 2005Jul;29(3):324. PMID: 15937259.

2. Wulsin and Kramer: Teaching Psychopharmacology in the 21st Century, Acad Psychiatry 2001; 25:102-106.

*GOOD NEWS/BAD NEWS: PRECISION NEUROSCIENCE AND THE CLINICAL TRIALS ECOSYSTEM

Mark Opler, WCG Inc.

Overall Abstract: The era of precision neuroscience has begun. Tools such as quantitative EEG, biomarkers, digital measures, advanced analytics, and other approaches are bringing new types of data and revealing new approaches to drug development. Proponents of these paradigms have proposed that quantitative, objective methods of diagnosis, evaluation, assessment, and treatment will bring meaningfully better results to industrial-scale clinical research. The future, they suggest, is composed of studies that are more precise, more accurate, better defined -- and potentially requiring smaller numbers of participants in order to achieve scientific, commercial, and clinical objectives. How then, does the existing industrial infrastructure need to adapt to the needs of such a future? To what extent are the current systems

maladapted for a precision neuroscience world? What might change - and what must change if this comes to pass?
This workshop will bring together participants from several related groups, including clinical and scientific leaders from pharmaceutical companies, investigators, and contract research organizations. Together, we will explore the premise that change is coming and to speak to how this change will affect stakeholders in the larger clinical trials endeavor.

The key topics to be addressed will include:

-The approach to precision neuroscience that pharmaceutical development is taking and how it will alter study designs and methods;

-The impact on CRO role, focus, and relationship to other entities;

-Investigative site perspectives on recruitment, selection, and assessment in a precision framework;

-Other vendor-partner roles as studies shift to focus on accuracy and quality.

Structured presentations will be followed by moderated discussion with audience participation encouraged and welcome.

Learning Objectives: 1. To identify the precision neuroscience methods that will impact trial design and conduct.
2. To review the potential changes that will stem from application and adoption of these methods.

Literary References: Zhang, Y., Naparstek, S., Gordon, J. et al. Machine learning-based identification of a psychotherapy-predictive electroencephalographic signature in PTSD. Nat. Mental Health 1, 284–294 (2023). https://doi.org/10.1038/s44220-023-00049-5
Hopkins, S., Ogirala A., Loebel A., Koblan K., Transformed PANSS Factors Intended to Reduce Pseudospecificity Among Symptom Domains and Enhance Understanding of Symptom Change in Antipsychotic-Treated Patients With Schizophrenia, Schizophrenia Bulletin, Volume 44, Issue 3, May 2018, Pages 593–602, https://doi.org/10.1093/schbul/sbx101

GOOD NEWS/BAD NEWS: PRECISION NEUROSCIENCE AND THE CLINICAL TRIALS ECOSYSTEM

Adam Savitz, Alto Neuroscience

Individual Abstract: The era of precision neuroscience has begun. Tools such as quantitative EEG, biomarkers, digital measures, advanced analytics, and other approaches are bringing new types of data and revealing new approaches to drug development. Proponents of these paradigms have proposed that quantitative, objective methods of diagnosis, evaluation, assessment, and treatment will bring meaningfully better results to industrial-scale clinical research. The future, they suggest, is composed of studies that are more precise, more accurate, better defined -- and potentially requiring smaller numbers of participants in order to achieve scientific, commercial, and clinical objectives. How then, does the existing industrial infrastructure need to adapt to the needs of such a future? To what extent are the current systems maladapted for a precision neuroscience world? What might change - and what must change if this comes to pass?
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-Investigative site perspectives on recruitment, selection, and assessment in a precision framework;

-Other vendor-partner roles as studies shift to focus on accuracy and quality.

Structured presentations will be followed by moderated discussion with audience participation encouraged and welcome.

Learning Objectives: Role of enrichment in psychiatry trials
Methods of obtaining biomarkers in psychiatry clinical trials.

Literature References Wu W, Zhang Y, Jiang J, et al. An electroencephalographic signature predicts antidepressant response in major depression. Nat Biotechnol. 2020 Apr;38(4):439-447.
Chin Fatt CR, Jha MK, Cooper CM, et al. Effect of Intrinsic Patterns of Functional Brain Connectivity in Moderating Antidepressant Treatment Response in Major Depression. Am J Psychiatry. 2020 Feb 1;177(2):143-154.

ENRICHMENT STRATEGIES FOR CLINICAL TRIALS IN PSYCHIATRY - SYMPTOM SCALES AND OBJECTIVE MEASURES

Seth C. Hopkins, Sumitomo Pharma America, Marlborough, MA, USA

Individual Abstract: Clinical drug development in psychiatry is challenging due to heterogeneous patient populations and the uncertainty of measuring neuropsychiatric constructs with symptom rating scales. Here we describe the development and implementation of an enrichment algorithm that identifies canonical versus anomalous symptom presentations, at the individual subject level, based on MADRS ratings obtained at screening and baseline. In addition, primary endpoints in clinical trials designed to test new medicines in psychiatric conditions are often clinician-based interviews that subjectively rate a subject's symptoms on a scale. Secondary endpoints in CNS disease often include more-objective measures like cognitive tests of neuropsychiatric functioning, however these tests are burdensome to acquire and are exploratory in nature. Here we outline how simple, face-valid measures of neuropsychiatric functioning can be quantified from patient speech during structured clinical interviews.

Learning Objectives: 1. Learn about the drug development strategy of enrichment
2. Learn about objective markers of depression obtainable during subjective rating

Literature References Loebel A, Koblan KS, Tsai J, Deng L, Fava M, Kent J, Hopkins SC.A Randomized, Double-blind, Placebo-controlled Proof-of-Concept Trial to Evaluate the Efficacy and Safety of Non-racemic Amisulpride (SEP-4199) for the Treatment of Bipolar I Depression.
J Affect Disord. 2022 Jan 1;296:549-558

Hopkins SC, Wilkinson S, Corriveau TJ, Nishikawa H, Nakamichi K, Loebel A, Koblan KS.Discovery of Nonracemic Amisulpride to Maximize Benefit/Risk of 5-HT7 and D2 Receptor Antagonism for the Treatment of Mood Disorders. Clin Pharmacol Ther. 2021 Sep;110(3):808-815

GOOD NEWS/BAD NEWS: PRECISION NEUROSCIENCE AND THE CLINICAL TRIALS ECOSYSTEM

John Carlos Diaz, GeoSera

Individual Abstract: Clinical trials have become increasingly complex in the course of the last two decade. While some of the complexity stems from innovations in design and information technology gains, it has been accompanied by tremendous increases in site and patient burden, exponential increases in cost, and elevated risks for errors in study conduct. In order to capitalize on the promise of precision neuroscience, studies must determine which technologies are "essential" and which are merely burdensome. It is vital to streamline clinical research and simplify clinical trial execution in order to improve the experience and involvement of research sites, patients, and clinical operations personnel at pharma/CROs, enabling renewed focus on the data that truly matters in drug development. From an organizational perspective, industry partners on sponsor and CRO sides need to reevaluate the utility of having a large, siloed workforce, while taking a critical look at business models which incentivize quantity over quality and lead in turn to poor clinical trial execution. Reducing complexity while improving efficiency in endpoints and objectives will focus each trial and help reverse the "more is better" paradigm that has come to dominate neuroscience clinical research execution. By collaborating and striving for elegant, simple solutions, CROs and other stakeholders can help enable a more rational approach to a precision neuroscience future.
Learning Objectives: Clinical trials should focus on answers to only a few questions and reduce the objectives and endpoints that do not help drug developers bring drugs to patients.
Reduce the new technologies and vendors to only the need to have technologies and vendors to reduce patient and site burden and drastically lower costs.

Literature References Venet D, Doffagne E, Burzykowski T, et al. A statistical approach to central monitoring of data quality in clinical trials. Clinical Trials. 2012;9(6):705-713. doi:10.1177/1740774512447898
McDermott MM, Newman AB. Remote Research and Clinical Trial Integrity During and After the Coronavirus Pandemic. JAMA. 2021;325(19):1935–1936. doi:10.1001/jama.2021.4609
Guidance for Industry Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring

More forthcoming.

GOOD NEWS/BAD NEWS: PRECISION NEUROSCIENCE AND THE CLINICAL TRIALS ECOSYSTEM

John Sonnenberg, Uptown Research Institute

Individual Abstract: The era of precision neuroscience has begun. Tools such as quantitative EEG, biomarkers, digital measures, advanced analytics, and other approaches are bringing new

types of data and revealing new approaches to drug development. Proponents of these paradigms have proposed that quantitative, objective methods of diagnosis, evaluation, assessment, and treatment will bring meaningfully better results to industrial-scale clinical research. The future, they suggest, is composed of studies that are more precise, more accurate, better defined -- and potentially requiring smaller numbers of participants in order to achieve scientific, commercial, and clinical objectives. How then, does the existing industrial infrastructure need to adapt to the needs of such a future? To what extent are the current systems maladapted for a precision neuroscience world? What might change - and what must change if this comes to pass?
This workshop will bring together participants from several related groups, including clinical and scientific leaders from pharmaceutical companies, investigators, and contract research organizations. Together, we will explore the premise that change is coming and to speak to how this change will affect stakeholders in the larger clinical trials endeavor.

The key topics to be addressed will include:

-The approach to precision neuroscience that pharmaceutical development is taking and how it will alter study designs and methods;

-The impact on CRO role, focus, and relationship to other entities;

-Investigative site perspectives on recruitment, selection, and assessment in a precision framework;

-Other vendor-partner roles as studies shift to focus on accuracy and quality.

Structured presentations will be followed by moderated discussion with audience participation encouraged and welcome.

Learning Objectives: 1. Potential positives of precision medicine
2. Potential pitfalls of precision medicine

Literature References please refer to the two references provided by Dr. Opler.

PERFORMANCE-BASED APPROACHES TO IMPROVE DATA QUALITY AND SIGNAL DETECTION

Barbara Echevarria, WCG

Individual Abstract: The trend of larger studies over time, involving more countries, more raters, and more patients has been cited as a contributing factor to reduced signal detection and elevated risk of failure, as well as to substantial associated monetary and human costs. The idea that smaller, more accurate studies are possible is no longer purely academic. Even in the absence of personalized medicine approaches or true precision neuroscience, evidence in support of this concept has recently been demonstrated in a global trial of schizophrenia (Opler et al, 2024.) Using active monitoring in near-real time, data quality indicators, including published markers of ratings fidelity (Rabinowitz et al, 2017) was employed to determine and rank site performance. Although only about one-third of the sites in the clinical trial that was analyzed could be categorized as “optimal” using study definitions, these sites produced greater drug–placebo separation on the primary endpoint and more robust effect sizes with far fewer patients than the main study. These results suggest that smaller, more accurate, and less “noisy” clinical trials are feasible, ones that put fewer patients at risk but can yield more reliable results. This method and others will be described and future directions to improved precision of measurement will be demonstrated.
Learning Objectives: 1. To describe the method and evidence in support of improved data quality in ongoing clinical trials.

2. To discuss the operational structure and implementation of these methods in trials going forward.

Literature References 1. Opler, M. S. Negash, K. Tatsumi, C. Liu, M. Komaroff, G. Capodilupo, M. Hasebe, B. Echevarria, R. Blattner, L. Citrome. Use of a novel study insight analytics (SIA) methodology to improve PANSS data quality and signal detection in a global clinical trial in schizophrenia. Schizophrenia Research, Volume 267, 2024, Pages 239-246.
2. Rabinowitz, J., Schooler, N.R., Anderson, A., Ayearst, L., Daniel, D., Davidson, M., Khan, A., Kinon, B., Menard, F., Opler, L., Opler, M., Severe, J.B., Williamson, D., Yavorsky, C., Zhao, J., ISCTM algorithms/flags to identify clinical inconsistency in the use of rating scales in CNS RCTs working group members, 2017. Consistency checks to improve measurement with the positive and negative syndrome scale (PANSS). Schizophr. Res. 190, 74–76.

DEVELOPING AND USING DATA-DRIVEN PROXIES TO ACCELERATE CNS THERAPEUTICS DEVELOPMENT.

George Garibaldi, Garibaldi Consulting GMBH

Individual Abstract: External factors involved in the successful development of CNS therapeutics are rapidly evolving. The rapidly moving scientific discoveries, patients' quest for improved therapies, research sites realities, changing regulations, and policy changes have a direct impact on the design and execution of exploratory and confirmatory clinical evidence. There is an increased and urgent need to adapt the methodology of CNS trial to the rapidly evolving environment. Moreover, development of innovative therapies that meet patients' expectations should be coupled with the development of novel clinical outcome parameters and biomarkers with the required specificity to the clinical condition and sensitivity to the therapeutic effect.
Multiple meaningful precision medicine initiatives were undertaken to move away from the classical clinical outcomes. However, continuous dialogue with regulators and policy makers is needed. Further, these initiatives have a higher chance of success if rapidly adopted across academia and the industry to ensure their scientific robustness and acceptance.

Learning Objectives: - Approaches to enhance our understanding and assessing patient expectations with novel therapies.
- Validation of novel outcomes to support the use in therapeutic studies.

Literature References - Zakrewzska et al, TNED®: Novel trigeminal neuralgia electronic pain diary - A validation study in thirty participants, EFIC European Pain Federation 2023.
- Maguire et al, A validated rating scale to accurately determine the treatment effects in childhood onset fluency disorder (Stuttering) - the MLGSSS ASCP 2023.

*^IMMUNE MECHANISMS OF MENTAL ILLNESSES: WHAT SHOULD CLINICIANS AND RESEARCHERS KNOW?

James Murrough, Icahn School of Medicine at Mount Sinai

Overall Abstract: It is now well recognized that dysregulations within immune system affect mental health and that a sizeable proportion of individuals with mental illnesses, such as major depressive disorder, have evidence for systemic inflammation. This proposed workshop will

take a deep-dive in this bidirectional relationship between immune dysregulations and mental disorders. The workshop will start with a primer on immune mechanisms and type of biospecimens that are commonly used to assay immune dysregulation, followed by a review of literature, focusing on landmark studies that showed that treatment with pro-inflammatory factors, such as interferon alpha, resulted in induction of depressive symptoms in a third of patients. Subsequently, individual presenters will focus on 1) use of inflammatory markers in guiding precision psychiatry approaches; 2) neurocircuit mechanisms that link immune dysregulation to symptoms of mental illnesses; and 3) role of early life adversity in mediating the association between immune dysregulation and mental disorders. The workshop will take a transdiagnostic approach by including findings from individuals with mood disorders and those with substance use disorders. The second half of this workshop will focus on clinical trial design. Specifically, it will focus on experimental medicine design that have used monoclonal antibodies and l-dopa where varying doses of L-DOPA over 6 weeks to patients with MDD and higher inflammation was associated with sustained increases in functional connectivity, improved motivation, and reduced anhedonia as well as overall depression symptom severity. Throughout the workshop, participants will be engaged in discussions around how these findings can be incorporated in their clinical practice and in their plans for future clinical trials.
Learning Objectives: 1. Understand the potential immune dysregulations in individuals with mental illnesses.
2. Identify approaches for integrating immune biomarker assays in clinical practice and in research studies.

Literary References: 1. Felger JC. Increased Inflammation and Treatment of Depression: From Resistance to Reuse, Repurposing, and Redesign. Adv Neurobiol. 2023;30:387-416
2. Jha MK, Trivedi MH. Personalized Antidepressant Selection and Pathway to Novel Treatments: Clinical Utility of Targeting Inflammation. Int J Mol Sci. 2018 Jan 12;19(1):233.

REPEATED LEVODOPA ADMINISTRATION IMPROVES FUNCTIONAL CONNECTIVITY IN REWARD CIRCUITY, MOTIVATION, AND ANHEDONIA IN DEPRESSED PATIENTS WITH HIGHER INFLAMMATION

Jennifer Felger, Emory University School of Medicine

Individual Abstract: A significant proportion of adults with major depressive disorder (MDD) exhibit increased inflammation, which has been associated with low functional connectivity (FC) in corticostriatal reward circuitry and symptoms of anhedonia(1). Evidence from our group and others suggests that inflammation may impact reward circuitry by decreasing the availability and release of dopamine. Accordingly, we found that FC in a classic ventral striatum (VS) to ventromedial prefrontal (vmPFC) reward circuit was increased after acute challenge with the dopamine precursor levodopa (L-DOPA) versus placebo in association with reduced anhedonia specifically in MDD patients with higher inflammation (as indexed by plasma C-reactive protein [CRP] GREATER THAN 2 mg/L)(2). To determine whether L-DOPA exerts sustained effects on FC and behavior, 18 medically stable, medication-free adult male and female MDD outpatients with CRP GREATER THAN 2 mg/L and anhedonia were randomized to receive 3 doses of L-DOPA (150, 300 and 450 mg/day/week given with carbidopa) either before or after 1 week of placebo. Patients underwent resting-state fMRI for VS-vmPFC FC (primary outcome) and behavioral assessments for motivation and anhedonia (secondary outcomes), as well as depression severity (Hamilton Depression Rating Scale) at the end of each week. All doses of L-DOPA were well-tolerated. A main effect of treatment on VS-vmPFC FC was observed ($F[1,10]=9.1$, $p=0.013$), remained significant when

controlling for order of placebo treatment (p=0.016), and revealed increased FC after L-DOPA (150 and 450 mg/day, p LESS THAN 0.05) but not placebo (p=1.00) compared to baseline. The maximum VS-vmPFC FC response to any dose of L-DOPA (treatment - baseline) was greater than that of placebo (+85 versus 15%; t=-3.5, df=13, p=0.004, p LESS THAN 0.01 controlling for treatment order, dz=0.95). Similar results were observed for motivation, anhedonia, and depression scores (all p LESS THAN 0.05 for the maximum response to L-DOPA compared to placebo, dz=0.64-0.97). While the most robust effects occurred after 150 mg L-DOPA, up to 40% of patients required higher doses for maximum response across outcomes. These results extend our prior working showing that low FC in reward circuitry may be due to decreased dopamine availability and release in depressed patients with high inflammation, and support for the use of VS-vmPFC FC as a modifiable imaging biomarker for the efficacy of pharmacological interventions targeting the effects of inflammation on the brain and behavior. They also suggest that L-DOPA can have sustained effects on FC in conjunction with reduced motivation, symptoms of anhedonia, and overall depression severity in these patients, setting the stage for future work examining the clinical benefit of dopaminergic therapies in MDD with higher CRP.

Learning Objectives: 1. To understand relationships between inflammation and depression including relevant biomarkers, brain signatures, and specific symptoms.

2. To discuss treatment implications for patients with higher inflammation including response to standard therapies and testing of potential novel therapeutics, especially dopaminergic agents.

Literature References References

1. Goldsmith DR, Bekhbat M, Mehta ND, et al. Inflammation-Related Functional and Structural Dysconnectivity as a Pathway to Psychopathology. Biol Psychiatry. 2023;93(5):405-18.

2. Bekhbat M, Li Z, Mehta ND, Treadway MT, et al. Functional connectivity in reward circuitry and symptoms of anhedonia as therapeutic targets in depression with high inflammation: evidence from a dopamine challenge study. Mol Psychiatry. 2022;27(10):4113-21.

A CLINICIAN'S PERSPECTIVE ON IMMUNE MECHANISMS OF DEPRESSION

Manish Jha, University of Texas Southwestern Medical Center

Individual Abstract: It has been well established for over two and half decades that use of pro-inflammatory markers are associated with induction of major depressive episodes. Multiple studies have also identified elevated levels of inflammatory markers in individuals with major depressive disorder (MDD), especially those with treatment-resistant depression. Among individual depressive symptoms, specific domains such as anhedonia and fatigue are preferentially associated with higher levels of pro-inflammatory markers. Improvement of depressive symptoms is associated with improvement in some inflammatory markers but not all. Furthermore, high levels of inflammatory markers such as c-reactive protein can guide the selection of serotonergic-noradrenergic medications, such as burpopion-escitalopram combination or nortriptyline, as compared to predominantly serotonergic antidepressant (such as escitalopram). This presentation of the workshop will serve as a brief primer for subsequent individual presentations of this workshop.

Learning Objectives: 1. Identify the different clinical and biological markers that can be used to evaluate patient's immune fuction.
2. Discuss the potential utility of pro-inflammatory markers in guiding antidepressant treatment selection.

Literature References 1. Jha MK, Minhajuddin A, Gadad BS, Greer T, Grannemann B, Soyombo A, Mayes TL, Rush AJ, Trivedi MH. Can C-reactive protein inform antidepressant medication selection in depressed outpatients? Findings from the CO-MED trial. Psychoneuroendocrinology. 2017 Apr;78:105-113.
2. Jha MK, Miller AH, Minhajuddin A, Trivedi MH. Association of T and non-T cell cytokines with anhedonia: Role of gender differences. Psychoneuroendocrinology. 2018 Sep;95:1-7.

NEUROIMMUNE UNDERPINNING OF CLINICAL AND SOCIAL FACTORS IN COCAINE ADDICTION

Keren Bachi, The Addiction Institute of Mount Sinai; Icahn School of Medicine at Mount Sinai

Individual Abstract: Background: Chronic cocaine use and prolonged social stress both induce peripheral and central immune activation, while concomitantly, activation of the immune system contributes to stress-induced neural/behavioral abnormalities. Immune dysregulation may provide a psychobiological link between chronic social stress, deficits in social information processing, and addiction via activation of the sympathetic stress systems and the limbic-Hypothalamic-Pituitary-Adrenal Axis.
Methods: Blood serum of 18 individuals with cocaine use disorder (iCUD) and 19 healthy controls (HC) not differing on age, gender, race, and IQ, were compared for inflammatory or immunosuppressive cytokines, chemokines and growth factors. The same cytokine panel was examined in relation to whole-brain activation while participants performed a task of simulated social interactions (Social Navigation fMRI paradigm). Immune associations were tested with non-task variables of drug use, social stress (childhood trauma), and real-life social competencies (social-adaptive traits; personality traits were standardized and averaged to form a composite score). Testing in additional participants utilizing factor analysis (to obtain a comprehensive immune signature) is ongoing.

Methods: Compared with HC, iCUD had elevated interleukin-3 [IL-3; t(36)=-4.3, p LESS THAN .001] and platelet-derived growth factor [PDGF-AA; t(36)=-2.3, p=.026], and a trend for increased Macrophage-Derived Chemokine [MDC/CCL22; t(36)=-2.0, p=.054]. At the neural level, during simulated social interaction and relative to HC, BOLD signal in iCUD was greater in the precuneus/ventral posterior cingulate cortex (Prc/vPCC; height threshold p LESS THAN .005, extent threshold k=20; X=-6, y=-53, Brodmann Area=23; z=3.5; k=454, pFWE-cor. LESS THAN .024; no activation survived correction for multiple comparisons for iCUD LESS THAN HC). Across our whole sample, Prc/vPCC activation correlated positively with RANTES, a pro-inflammatory chemokine (mediates T cells activations in acute and chronic inflammation; iCUD: r=.614, p=.007; whole sample: r=.322, p=.052). At the behavioral level, in iCUD, RANTES correlated positively with recency of cocaine use (r=.508, p=.031). Peripheral MDC (proinflammatory cytokine, implicated with post-trauma) correlated with childhood trauma sexual abuse (r=.447, p=.006), which was experienced to a greater extent in iCUDs [t(36)=-3.4, p=.003]. Proinflammatory cytokine IL-1b correlated negatively with

social-adaptive traits (r=-.523, p=.023), where the greater the immune dysregulation, the lower the social-adaptive traits in iCUD.

Conclusions: iCUD had heightened immune activation state which was associated with Prc/vPCC brain function during social processing, drug use, social stress, and real-life social competencies. These findings indicate a potential relationship between immune and social factors in cocaine addiction, providing a foundation for future causal testing. Delineating the peripheral and neural underpinnings of stress-related inflammatory signature in relation to psychosocial state in iCUD could advance the development of novel treatment to enhance efficacy and recovery.

Learning Objectives: 1. Provide an overview of the peripheral and neural underpinnings of stress-related inflammatory signature in individuals with cocaine use disorder.
2. Discuss insights gleaned from immune outcomes in relation to clinical and psychosocial state in individuals with cocaine use disorder, for the advancement of novel treatment to enhance efficacy and recovery.

Literature References 1. Bachi, K., et al. (2017). "Vascular disease in cocaine addiction." Atherosclerosis 262(Jul): 154-162.
2. Fox, H. C., et al. (2012). "Immune system inflammation in cocaine dependent individuals: implications for medications development." Hum Psychopharmacol 27(2): 156-166.

EXPERIMENTAL MEDICINE APPROACH FOR DEVELOPING IMMUNOMODULATORY DRUGS AS NOVEL TREATMENTS FOR PSYCHIATRIC DISORDERS

James Murrough, Icahn School of Medicine at Mount Sinai

Individual Abstract: Multiple lines of evidence have implicated immune system dysregulation in pathophysiology of psychiatric disorders, including major depressive disorder. Therefore, drugs targeting immune system, or immunomodulatory drugs, have the potential of serving as novel antidepressants. While an initial study of infliximab, a monoclonal antibody against tumor necrosis factor alpha, was effective in reducing depressive symptoms in individuals with MDD who have evidence for sub-threshold systemic inflammation. However, subsequent studies of infliximab in bipolar depression and of sirukumab, another monoclonal antibody that targets interleukin 6, have been negative. This presentation will focus on rationale around targeting novel potential candidates, including interleukin 17 and others, and challenges associated with implementing an experimental medicine study to evaluate its effect on reward function and on improving depressive symptoms.
Learning Objectives: 1. Identify dysfunction in brain's reward system that is associated with inflammation in depression.
2. Discuss the potential of monoclonal antibodies as novel antidepressants.

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. Boukezzi S, Costi S, Shin LM, Kim-Schulze S, Cathomas F, Collins A, Russo SJ, Morris LS, Murrough JW. Exaggerated amygdala response to threat and association with immune hyperactivity in depression. Brain Behav Immun. 2022 Aug;104:205-212.

^EARLY/MID-CAREER FUNDING WORKSHOP: BEYOND NIH: OPPORTUNITIES AND STRATEGIES FOR FOUNDATIONAL AND PHILANTHROPIC FUNDING

Elizabeth Ballard, National Institute of Mental Health

Overall Abstract: During a lengthy period of only minor NIH budget increases alongside large increases in the number of entrants to professional academic research there are greater challenges for Early/Mid-Career Researchers (E/MCRs) seeking funding than ever before. Steep competition for the gold standard NIH funding necessitates that researchers take advantage of foundation and philanthropic funding sources to further enhance their research. However, unlike federal funding there is no standardized procedure for acquiring these funds and scant few training programs to provide guidance.
The objective of this workshop is to provide E/MCRs with foundational knowledge for incorporating these alternative sources of funding to their research plans. Attendees will also hear the case for how funding generated by those with a vested interest in the field helps to provide a voice for our patients. By the end of the workshop attendees should feel confident in their ability to initiate a funding search within this previously unfamiliar landscape.

Three leaders in the field of psychopharmacologic research will present their perspectives on funding, specifically highlighting the work of the American Foundation for Suicide Prevention (AFSP), BD2: Breakthrough Discoveries for thriving with Bipolar Disorder and philanthropic funding of psychiatric research. Panelists will each give a brief presentation (20 minutes), with the second hour of the workshop reserved for active questions and answers. Participants will be able to submit their questions to their speakers for broad discussion of funding strategies for both early and mid-career researchers.

Learning Objectives: By the end of the presentation, participants will be able to describe two sources of non-NIH funding for research.
By the end of the presentation, participants will be able to synthesize how foundational and philanthropic funding differs from NIH research funding.

Literary References: Sweeney C, Schwartz LS, Toto R et al. Transition to Independence: Characteristics and Outcomes of Mentored Career Development (KL2) Scholars at Clinical and Translational Science Award Institutions. Acad Med. 2017;92(4):556-562. doi: 10.1097/ACM.0000000000001473.

Altimus CM, Baxi EG, Frye MA, et al. Supercharging collaboration for bipolar research-Breakthrough discoveries for thriving with bipolar disorder (BD2). Bipolar Disord. 2023;25(8):619-623. doi: 10.1111/bdi.13398.

EARLY/MID-CAREER FUNDING WORKSHOP: BEYOND NIH: OPPORTUNITIES AND STRATEGIES FOR FOUNDATIONAL AND PHILANTHROPIC FUNDING

Jill Harkavy-Friedman, American Foundation for Suicide Prevention

Individual Abstract: During a lengthy period of only minor NIH budget increases alongside large increases in the number of entrants to professional academic research there are greater

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EARLY/MID-CAREER FUNDING WORKSHOP: BEYOND NIH: OPPORTUNITIES AND STRATEGIES FOR FOUNDATIONAL AND PHILANTHROPIC FUNDING

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

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EARLY/MID-CAREER FUNDING WORKSHOP: BEYOND NIH: OPPORTUNITIES AND STRATEGIES FOR FOUNDATIONAL AND PHILANTHROPIC FUNDING

Mark Rapaport, University of Utah Huntsman Mental Health Institute

Individual Abstract: During a lengthy period of only minor NIH budget increases alongside large increases in the number of entrants to professional academic research there are greater challenges for Early/Mid-Career Researchers (E/MCRs) seeking funding than ever before. Steep competition for the gold standard NIH funding necessitates that researchers take advantage of foundation and philanthropic funding sources to further enhance their research. However, unlike federal funding there is no standardized procedure for acquiring these funds and scant few training programs to provide guidance.

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Wednesday, May 29, 2024

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

Regulatory Plenary

REGULATORY PLENARY: NEW TOOLS TO ENABLE TARGETED DRUG DEVELOPMENT IN PSYCHIATRY: LESSONS LEARNED AND PATH FORWARD

Tiffany Farchione, US Food and Drug Administration

Overall Abstract: Innovation in drug development requires that new methods and tools are developed to address the deeper understanding of the biology of neuropsychiatric disorders as well as the more granular definition of populations and phenomenology within diagnostic categories.

In other fields of medicine, including neurology, innovation in drug development is fueled by a growing understanding of the biology of the disorders, often at a molecular level.

In psychiatry, as new targets for drug development are being tested, there is a general expectation that specific mechanisms of actions could target a specific symptom or cluster of symptoms with common underlying biology, leading to new, more defined indications within our current diagnostic categories.

From a regulatory perspective, this could only be achievable if a symptom within a diagnostic category cold be reliably identified and measured in a given population. New methods , biomarkers and endpoints could enable this process.

There is growing interest coming from the academic research community and industry to understand the pathways necessary to utilize new methods, biomarkers and endpoints in clinical trials for drug development.

This session will provide an overview of current regulatory thinking related to the possibility to move the field of drug development to biology-based indications and the tools necessary to enable this process.

The Speakers will provide examples of the development of biomarkers for use in drug development in neurologic disorders; examples of the development of new endpoints, including digital measures, and discuss regulatory requirements and implications for the field of psychiatry.

NEW TOOLS TO ENABLE TARGETED DRUG DEVELOPMENT IN PSYCHIATRY: LESSONS LEARNED AND PATH FORWARD

Teresa Buracchio, Center for Drug Evaluation and Research, Food and Drug Administration

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Learning Objectives: Pathways for use of biomarkers to aid drug development in psychiatry. Lessons learned from use of biomarkers in neurodegenerative diseases.

Literature References FDA-NIH Biomarker Working Group, BEST (Biomarkers, EndpointS, and 1. 2024 ASCP Annual Meeting
other Tools) resource. 2016. US FDA: Silver Spring, MD, (2016).

C. Leptak, J. P. Menetski, J. A. Wagner, J. Aubrecht, L. Brady, M. Brumfield, W. W. Chin, S. Hoffmann, G. Kelloff, G. Lavezzari, What evidence do we need for biomarker qualification? Science translational medicine 9, eaal4599 (2017).

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Michelle Campbell, Center for Drug Evaluation and Research, Food and Drug Administration

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

ASCP Awards Ceremony and ASCP Lifetime Awardee Talk - Ross J. Baldessarini, M.D.

CLINICAL PSYCHOPHARMACOLOGY OF BIPOLAR DISORDER: SELECTED STUDIES

Joseph Goldberg, Icahn School of Medicine at Mount Sinai

Overall Abstract: This is an overview of selected studies carried out over the past several decades on clinical psychopharmacology with an emphasis on bipolar disorder. The work has been enabled by the contributions of more than 30 principal collaborators. Bipolar disorder (BD) is of particular interest as one of our oldest but youngest major psychiatric disorders, starting with ancient reports by Hippocrates (melancholia) and Aretaeus (mania and

melancholia in the same patients), but not included in official diagnostic systems until 1980 with DSM-III.

In a major first-episode study initiated at McLean Hospital by Mauricio Tohen in the 1980s, we found with Paola Salvatore that bipolar disorder (BD) was the most stable diagnosis over years of follow-up among the broad range of DSM and ICD psychotic and major mood disorders. We also found that younger age-at-onset was strongly associated with family history of the disorder, consistent with a biological connection. Recently with Alessandro Miola, the latency from illness-onset (typically with depression) to first episode [hypo]mania was found to be much longer (by years) with younger onset.

We also evaluated relationships between the type of first episode of BD and subsequent long-term morbidity. Depression clearly dominated overall, whereas later manialike illness was in the majority only following a [hypo]manic or psychotic first-episode, whereas depression dominated following initial depression, as expected, but also following initial states with mixed manic-depressive features and even following initial anxiety syndromes.

We collaborated with the late Athanasios Koukopoulos in Rome to compile studies of treatment response in the contrasting course-types in BD that he first described—the DMI and MDI types (depression followed soon by mania and a stable interval, or the opposite course-pattern with mania first). The DMI type proved to be much less favorable, with greater overall morbidity and disability, predominant depression, higher risk of suicide, and inferior response to mood-stabilizing treatments. We also analyzed McLean First Episode data to test Kraepelin's proposal that BD can involve progressive shortening of inter-episode periods. Instead we found that the usual long-term course was random and not progressive.

We also carried out several systematic and comprehensive reviews of treatments for acute mania, bipolar depression, and long-term prevention of recurrences in BD. With Aysegul Yildiz of Turkey we found among treatments for mania that antipsychotics appeared to be superior in efficacy to lithium or anticonvulsants. However, as most of the trials were brief, the advantage may lie mainly in rapidity of effect rather than superior efficacy. A recent comprehensive meta-analysis of long-term treatment trials for BD with Anastasiya Nestsiarovich of Belarus found that many modern antipsychotics were highly effective and somewhat superior to lithium and anticonvulsants.

We carried out a series of studies to test for effects on morbidity of the rate of discontinuing various psychotropic drugs, starting with Gianni Faedda and Leonardo Tondo of Sardinia on lithium for BD, later studies of oral and long-acting injected antipsychotics for schizophrenia with Adele Viguera, and more recent work on antidepressants for major depression with Leonardo Tondo. In all examples, rapid discontinuation (over ≤14 days) led to markedly increased early morbidity that was markedly reduced by slow dose-reduction. Notably, however, with lithium the duration of prior treatment was unrelated to risk of relapsing with discontinuation. With Dr. Viguera, we also found that risk of relapse of BD over time after discontinuing mood-stabilizers was indistinguishable in women who were pregnant or not. This lack of difference may suggest that pregnancy is risk-neutral for BD. However further study demonstrated high risk of discontinuing mood-stabilizers during pregnancy, with highest risk in the first trimester and lowest in the third, most of which was depressive or mixed, as had been observed among untreated women by Louis-Victor Marcé, as reported in his 1850s treatise on perinatal psychiatry which we evaluated with Katharina Trede. In the study of mood-stabilizer discontinuation in pregnancy with Dr. Viguera, we included an unusual group of BD women who had been clinically stable for at least a year before pregnancy without

treatment; during pregnancy, they had high risks of recurrence. This experience suggests that pregnancy may be a stressor and not neutral. With Dr. Viguera, we also found that while past history in major depressive disorder had little effect on response to treatment, the risk of relapse after discontinuing antidepressants was profoundly sensitive to prior morbidity.

The depressive phase of BD requires particular consideration. It is the most frequent initial episode type, as [hypo]mania is often delayed for several years to make differentiation from MDD difficult. Depression and dysthymia also are the most prevalent forms of long-term morbidity in BD, contributing greatly to disability and suicidal risk which is higher with BD than other psychiatric disorders. In recent years, controversy has developed about the efficacy of antidepressant treatments for bipolar depression; there also have been reports of sex-differences in response to treatments for depression. Our reviews with Gustavo Vázquez of Canada and Leonardo Tondo of Sardinia have consistently found that antidepressants were superior to placebo with both bipolar depression and unipolar major depressive disorder (MDD). In an analysis of data from Dr. Tondo's mood disorder center, we also found similarly favorable outcomes of treating depression with types 1 and 2 BD and with MDD. In a recent analysis of improvements in depression ratings in over 3,000 depressed patients we found little difference in benefits of individualized clinical treatment between BD and MDD or between women and men.

There is some risk of inducing mood-switching from depression to [hypo]mania during treatment with antidepressants. Our studies indicate that this risk is probably less than is often supposed. With Dr. Tondo we carried out a systematic review of rates of switching from depression to [hypo]mania, spontaneously or with antidepressant treatment. For BD patients, adding an antidepressant increased switch rates from about 13% to 15.5%, and the rate was not lower if a mood-stabilizer also were present. This finding indicates that new [hypo]mania with BD is little increased by antidepressant treatment (an evident ceiling effect). The relative increase in switching was much greater with MDD, rising several-fold from about 2% without, to 6% with antidepressant added. Most of such cases probably involved unrecognized BD. In over 3,000 depressed patients, we recently found that 6.67% became [hypo]manic during antidepressant treatment, and that only 1.56% became manic, indicating quite low risk. The expected protective effects of combining a mood-stabilizer with antidepressants, especially for depressed BD patients remains inadequately tested. With Dr. Tondo and others we identified a series of risk factors for mood-switching or change of diagnosis from MDD to BD. They include: family history of BD, relatively young onset of depression, ≥4 depressive episodes within 10 years, high scores for cyclothymia or hyperthymia in ratings of affective temperament, a tendency to show hypomanic features with treatment for depression, psychotic features, mixed features, severe depressions, presence of "atypical" features, substance abuse, co-occurring anxiety disorder, being suicidal (especially with attempts), and a trend to greater risk among men than women.

Surprising findings arose from a review with Alberto Forte of Switzerland of outcomes of 38 studies of long-term clinical treatment of over 6,400 mood disorder patients. Remarkably, the percentage of time unwell averaged 45% across diagnoses (BD1, BD2, MDD). With MDD, the unresolved morbidity was depressive, as expected. However, with BD, too, three-quarters of the excess morbidity also was depressive or dysthymic, with [hypo]mania accounting for less than a quarter of the total. These observations underscore the limits of modern therapeutics for mood disorders and the relative difficulty of adequate treatment of depression in MDD as well as BD.

A very important consideration related to depression in BD is the unusually high risk of suicidal behavior with this disorder. Suicide attempts and suicides are strongly associated with the depressive phase, especially with mixed features (misery plus energy). Over the years, we have developed extensive evidence that lithium has some ability to reduce risk of suicide attempts and suicides in BD patients, and possibly also with MDD. For example, in a meta-analysis of 34 studies comparing rates of suicidal behavior with vs. without lithium treatment in 3,200 subjects, we found a 4.4-fold lower risk of suicidal behavior with long-term lithium treatment. Similar observations have been made by German colleagues including Bruno Müller-Oerlinghausen. With Dr. Tondo, we also compared rates of suicidal behavior before, during, and after discontinuing lithium treatment of BD patients, finding corresponding reduction and increase of rates of suicidal acts. More recently, we pooled data from nine randomized, controlled trials in which suicidal acts were noted among adverse outcomes (not as a primary study outcome, which, other than the notable exception of the InterSePT trial of clozapine vs. olanzapine with schizophrenia, is very rare in the therapeutics of suicide prevention). The meta-analytically pooled data found a highly significant, 76.8% reduction of risk with lithium treatment, with similar results for six trials involving suicides.

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Ross Baldessarini, Harvard Medical School

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Learning Objectives: 1. To review effects and management of discontinuing psychotropic drug treatments. 2. To review evidence concerning antisuicidal effects of lithium treatment.

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

Clinical Updates in Neurotherapeutics

CLINICAL UPDATES IN NEUROTHERAPEUTICS

Carlos Blanco, National Institute on Drug Abuse

Overall Abstract: This session will feature Julia Riddle, MD to provide an update in women's mental health, Jeffrey Newcorn, MD to provide update on ADHD, and Mark H. Pollack, MD to provide update on Anxiety Disorders and PTSD.

ADHD UPDATE: CURRENT ISSUES AND EMERGING THERAPEUTICS

Jeffrey Newcorn, Icahn School of Medicine at Mount Sinai

Abstract ADHD is a multi-faceted neurodevelopmental disorder that has a strong biological basis and often persists across the lifespan. Over the last two decades, there has been an explosion in the diagnosis and treatment of ADHD, with increased interest in young (preschool) children and adults (including geriatric age adults). Although the diagnostic criteria for ADHD focus exclusively on the core symptoms of inattention and hyperactivity/impulsivity, the current conceptualization additionally highlights the importance of executive function, mood regulation, motivation and salience. Research on the neurobiological and genetic basis of ADHD is consistent with this expanded conceptualization, and offers clues regarding the relationship of ADHD to frequently comorbid psychiatric disorders. This presentation will examine new developments in the clinical phenomenology, biological basis and treatment of ADHD. It will describe new to market and near to market nonstimulant medications, as well as novel stimulant formulations, highlighting the unique characteristics of each. Finally, it will offer data-informed perspectives on treatment choice, managing treatment resistant cases, and negotiating the current stimulant shortage.

Learning Objectives: 1. Participants will appreciate current issues regarding the biological underpinnings and clinical presentation of ADHD across the lifespan. 2) Participants will learn about the unique characteristics of emerging stimulant and nonstimulant treatments for ADHD, and how to apply this information in clinical practice.

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Sonuga-Barke EJS, Becker SP, Bölte S, Castellanos FX, Franke B, Newcorn JH, Nigg JT, Rohde LA, Simonoff E. Annual Research Review: Perspectives on progress in ADHD science - from characterization to cause. J Child Psychol Psychiatry. 2023 Apr;64(4):506-532. doi: 10.1111/jcpp.13696. Epub 2022 Oct 11. PMID: 36220605; PMCID: PMC10023337.

NEUROSTEROIDS IN WOMEN'S MENTAL HEALTH CARE: PRECISION TREATMENT FOR POSTPARTUM DEPRESSION WITH BREXANOLONE AND ZURANOLONE

Julia Riddle, University of North Carolina at Chapel Hill

Abstract Postpartum Depression (PPD) is the most common complication of childbirth, impacting 15% of new mothers. Research into the role of changing hormone levels during pregnancy and childbirth has implicated neuroactive steroids as a mediator of affective illness. The recently FDA-approved neurosteroid antidepressants, brexanolone (2019) and zuranolone (2023), are the first targeted treatment for PPD. This session will focus on understanding the scientific development of and evidence for these agents.

Learning Objectives: 1. Understand the neurosteroid pathology implicated in postpartum depression.

2. Appreciate the utility and potential of neurosteroid antidepressants in reproductive mood disorders.

Literature References 1. Meltzer-Brody, S., Colquhoun, H., Riesenberg, R., Epperson, C. N., Deligiannidis, K. M., Rubinow, D. R., ... and Kanes, S. (2018). Brexanolone injection in post-

partum depression: two multicentre, double-blind, randomised, placebo-controlled, phase 3 trials. The Lancet, 392(10152), 1058-1070.
2. Deligiannidis, K. M., Meltzer-Brody, S., Gunduz-Bruce, H., Doherty, J., Jonas, J., Li, S., ... and Lasser, R. (2021). Effect of zuranolone vs placebo in postpartum depression: a randomized clinical trial. JAMA psychiatry, 78(9), 951-959.

3. Schiller, C. E., Schmidt, P. J., and Rubinow, D. R. (2014). Allopregnanolone as a mediator of affective switching in reproductive mood disorders. Psychopharmacology, 231, 3557-3567.

4. Schiller, C. E., Johnson, S. L., Abate, A. C., Schmidt, P. J., and Rubinow, D. R. (2016). Reproductive steroid regulation of mood and behavior. Comprehensive Physiology, 6(3), 1135.

UPDATE ON THE PHARMACOTHERAPY OF ANXIETY DISORDERS AND PTSD

Mark Pollack, Biopharmaceutical Consulting

Abstract For decades, the pharmacotherapy of the anxiety disorders and PTSD in clinical practice has largely centered on the use of serotonergic agents and benzodiazepines. However, there has been a recent increase in activity exploring the utility of novel classes of therapeutic agents demonstrating promise in the treatment of patients suffering with these distressing and disabling conditions. This presentation will focus on current and future directions for the pharmacotherapy of anxiety disorders and PTSD.
Learning Objectives: 1. Review current pharmacotherapies for the treatment of anxiety and PTSD
2. Discuss novel emerging potential therapeutics.

Literature References 1. Garakani A, Murrough JW, Freire RC, Thom RP, Larkin K, Buono FD, Iosifescu DV. Pharmacotherapy of Anxiety Disorders: Current and Emerging Treatment Options. Front Psychiatry. 2020 Dec 23; 11:595584. doi: 10.3389/fpsyt.2020.595584. PMID: 33424664; PMCID: PMC7786299.
2.King F and Hammond R. Psychedelics as Reemerging Treatments for AnxietyDisorders: Possibilities and Challenges in a Nascent Field. Focus 2021; 19:190–196; doi: 10.1176/appi.focus.20200047190focus.psychiatryonline.org Focus Vol. 19, No. 2, Spring 2021

3:00 p.m. - 4:30 p.m.

Individual Research Reports (IRRs): Therapeutic Pipeline for Mood Disorders

INVESTIGATIONAL COMP360 PSILOCYBIN TREATMENT FOR TREATMENT-RESISTANT DEPRESSION: ASSESSING ALTERED STATES OF CONSCIOUSNESS

Nilay Hewitt[*1], Jamie Chai-Rees[1], Megan Croal[1], Sunil Mistry[1], Joyce Tsai[1], Matt B. Young[1], Guy M. Goodwin[1]*

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Nilay Hewitt, Compass Pathfinder Ltd.

Abstract Background: The acute subjective psychedelic experience has been found to correlate with improvements in depression. The Five-Dimensional Altered States of Consciousness (5D-ASC) questionnaire is one of the most frequently used assessments of psychedelic experiences consisting of 94 participant-reported items rated on a visual analogue scale (0=no, not more than usually to 100=yes, much more than usually). Items are categorized into 5 core dimensions: Oceanic Boundlessness, Anxious Ego Dissolution, Visual Restructuralization, Reduction of Vigilance, and Auditory Alterations. An alternative way to summarise these data is on 11 subscales relating to 3 of the core dimensions: Experience of Unity, Spiritual Experience, Blissful State, and Insightfulness (relating to Oceanic Boundlessness); Disembodiment, Impaired Control and Cognition, and Anxiety (relating to Anxious Ego Dissolution); and Complex Imagery, Elementary Imagery, Audio-visual Synesthesia, and Changed Meaning of Percepts (relating to Visual Restructuralization). Both analysis schemes have been validated and demonstrate good reliability. Here, we describe the 11 subscales of the 5D ASC from the largest randomized controlled trial of psilocybin completed to date.

Methods: Participants with treatment-resistant depression (n=233) received a single 25 mg (n=79), 10 mg (n=75), or 1 mg (n=79) dose of COMP360 (Compass Pathways' proprietary, synthetic psilocybin formulation), with psychological support. The 5D-ASC was completed on the day of COMP360 administration once any acute psychedelic effects had subsided. Exploratory and post-hoc descriptive statistics and correlations were performed to examine the data by treatment group and by treatment response (response defined as a GREATER THAN 50% improvement in Montgomery-Åsberg Depression Rating Scale [MADRS] total score from Baseline at Week 3).

Methods: Across the dimensions and subscales, scores varied in a dose-dependent manner (ie scores increasing from 1 mg to 10 mg to 25 mg). The Oceanic Boundlessness and Visual Restructuralization core dimensions showed clear numerical differences between treatment responders versus non-responders in each treatment group. These differences were reflected across the eight subscales corresponding to these two dimensions. Whilst Anxious Ego Dissolution core dimension scores did not appear to be differentiated by treatment response, scores on its subscale of Disembodiment were higher in treatment responders versus non-responders. In the overall sample, nine subscale scores showed moderate negative correlations with the change from Baseline in MADRS total score at Week 3. Subscales of the Oceanic Boundlessness dimension showed the strongest correlations: Blissful State (Pearson correlation coefficients [r] r=-0.519); Spiritual Experience (r=0.494); Insightfulness (r=-0.482).

Methods: In keeping with previous literature, these results suggest that the magnitude of specific psychedelic experiences, are associated with clinical outcomes. Exploration of the 11D-ASC subscales as well as dimensions can provide further insights into aspects of the psychedelic experience that may be relevant to positive treatment outcomes. Psychedelic clinical research should continue to utilize standardized questionnaires to further characterize the quality of psychedelic experiences, including identification of potential factors that may relate to clinically meaningful experiences.

Learning Objectives: To understand the role of acute subjective psychedelic experiences in clinical outcome following psilocybin treatment.

To better understand the frequently used 5D-ASC as a measure for the assessment of acute subjective psychedelic experiences.

Literature References Goodwin GM, et al. Single-Dose Psilocybin for a Treatment-Resistant Episode of Major Depression. N Engl J Med. 2022 Nov 3;387(18):1637-1648. doi: 10.1056/NEJMoa2206443.
Goodwin GM. The psychedelic experience and treatment-resistant depression. World Psychiatry. 2023 Oct;22(3):420-422. doi: 10.1002/wps.21140.

ADJUNCTIVE TREATMENT WITH SELTOREXANT IMPROVED PATIENT-REPORTED DEPRESSIVE SYMPTOMS, INSOMNIA SYMPTOMS, AND OVERALL HEALTH IN MDD WITH INSOMNIA

Katherine B. Bevans[1], Thomas Laughren[2], Joseph M. Trombello[3], Ryan Kelly[3], Yun Zhang[4], Haiyan Xu[3], John Thipphawong[3], Sandra Ruschel[5], Yanina Flossbach[6], Carla M. Canuso[3], Andrew D. Krystal[7], Wayne C. Drevets[4], Gahan Pandina[3], Gahan Pandina[8]*

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Abstract Background: Seltorexant is a selective orexin-2 receptor antagonist being developed for the adjunctive treatment of major depressive disorder with insomnia symptoms (MDDIS). In a phase 3, double-blind (DB), randomized, placebo-controlled study in adults with MDDIS (NCT04533529), seltorexant, adjunctive to background SSRI/SNRI, met the primary efficacy endpoint, improvement of Montgomery-Åsberg Depression Rating Scale (MADRS) total score at day 43. Here we report secondary and exploratory endpoints that assessed patient-reported depressive symptoms, insomnia symptoms, and health-related quality of life (HRQoL).
Methods: Eligible participants were aged 18-74 years and had a primary DSM 5 diagnosis of MDD without psychotic features; an inadequate response to 1-2 SSRI or SNRI antidepressants; and Hamilton Depression Rating Scale total scores of ≥20 and ≥18 at first and second screening interviews. Participants received seltorexant 20 mg or placebo (randomized 1:1) once daily, on top of their underlying SSRI/SNRI, for 6 weeks. The Patient Health Questionaire-9 (PHQ-9) total score and Patient Global Impression of Change (PGI-C) were secondary and exploratory endpoints, respectively, used to assess patient-reported depressive symptoms. The Patient Global Impression of Severity (PGI-S) and the European Quality of Life Group, 5-Dimension, 5-Level EQ visual analog scale (EQ-VAS) were exploratory endpoints used to assess patient-reported insomnia symptoms and HRQoL, respectively. All analyses were conducted via mixed effects models for repeated measures (PHQ-9, PGI-C, and PGI-S) or analysis of covariance (EQ-VAS) using data from randomized participants with MDDIS who received ≥1 dose of study drug in the DB phase and had a baseline MADRS total score ≥24. A 95% CI for the least-squares (LS) mean difference that does not include 0 is suggestive of a potential treatment effect that needs to be confirmed in other studies.

Methods: The LS mean difference (95% CI) in the change in PHQ-9 total score from baseline to day 43 between the seltorexant (n=209) and placebo (n=210) groups was -2.1 (-3.30; -0.93).

The LS mean difference (95% CI) in PGI-C score at day 43 between seltorexant and placebo groups was -0.3 (-0.60, -0.09). The LS mean difference (95% CI) in change in PGI-S "difficulty falling/staying asleep" and “not feeling rested the next day” scores from baseline to day 43 between seltorexant and placebo groups were -0.4 (-0.57, -0.14) and -0.2 (-0.44, -0.04), respectively. The LS mean difference (95% CI) in the change in EQ-VAS score from baseline to day 43 between seltorexant and placebo groups was 4.8 (1.48; 8.17).

Conclusions: From the patient’s perspective, adjunctive treatment with seltorexant improved depressive symptoms, insomnia symptoms, and HRQoL, compared to placebo, in adults with MDDIS and an inadequate response to SSRI/SNRI.

Learning Objectives: 1. Describe secondary and exploratory endpoints of a phase 3 study investigating the efficacy and safety of seltorexant, adjunctive to background SSRI/SNRI antidepressant, in patients with major depressive disorder with insomnia symptoms.
2. Understand the improvements in patient-reported depressive symptoms, insomnia symptoms, and health-related quality of life observed after adjunctive treatment with seltorexant in patients with major depressive disorder with insomnia symptoms who had experienced inadequate response to SSRI/SNRI.

Literature References 1. Savitz A, Wajs E, Zhang Y, et al. Efficacy and safety of seltorexant as adjunctive therapy in major depressive disorder: a phase 2b, randomized, placebo-controlled, adaptive dose-finding study. Int J Neuropsychopharmacol. 2021;24(12):965-976.
2. Recourt K, de Boer P, Zuiker R, et al. The selective orexin-2 antagonist seltorexant (JNJ-42847922/MIN-202) shows antidepressant and sleep-promoting effects in patients with major depressive disorder. Transl Psychiatry. 2019;9(1):216.

SAFETY, TOLERABILITY, PHARMACOKINETIC, AND PHARMACODYNAMIC PROFILES OF DLX-001, A NOVEL NEUROPLASTOGEN UNDER DEVELOPMENT FOR THE TREATMENT OF MAJOR DEPRESSIVE DISORDER

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[1]Delix Therapeutics, [2]Centre for Human Drug Research

Aaron Koenig, Delix Therapeutics

Abstract Background: Psychedelic compounds have demonstrated preliminary efficacy across a range of neuropsychiatric conditions, with effects that are believed to be mediated by their rapid and enduring impact on structural neuroplasticity in key brain areas. However, the psychotomimetic and dissociative experiences produced by these compounds may limit their widespread clinical use. To discover and develop a non-hallucinogenic, non-dissociative plastogenic compound that could be used to treat neuropsychiatric conditions with high unmet need, such as MDD, we synthesized a novel isotryptamine, DLX-001, and examined its safety, tolerability, pharmacokinetic (PK), and pharmacodynamic (PD) profiles in healthy volunteers (ECTN 2023-503390-38-00).
Methods: This 3-part, randomized, double-blind, placebo-controlled study is being conducted in healthy, cytochrome P450 (CYP450) 2D6 genotyped volunteers (HVs) aged 18 to 55 years.

Part A (single ascending dose - SAD) and Part C (multiple ascending dose – MAD) investigate the safety, tolerability, PK (in plasma and CSF), and PD of single and multiple (QD for 7 days) ascending oral doses of DLX-001, while an open-label, two-way crossover Part B (food effect - FE) evaluates the effect of food on the PK of DLX-001. Safety monitoring includes clinical and laboratory assessments, ECG, and vital signs up to 30h post dose. PD assessments include psychedelic and psychotomimetic effects (Mystical Experience Questionnaire [MEQ], Clinician-Administered Dissociative States Scale [CADSS]), Bond and Lader and Bowdle Visual Analog Scales (VAS) and quantitative EEG. Non-compartmental PK analysis of plasma DLX-001 is performed up to 30h post-dose.

Results: The study is ongoing, and preliminary blinded results are presented. In the SAD (2 to 120 mg) and MAD (50 and 100 mg) cohorts completed to date, no SAEs or discontinuations due to study drug have been reported, no clinically significant changes in vital signs, laboratory, or ECG have been observed, and the most frequent AEs have been nausea, dizziness, and headache, which were self-limited and mild in intensity. Plasma PK demonstrates dose-proportionality across cohorts, limited food effect, and no accumulation over 7 days of dosing. Higher-than-expected intersubject PK variability has been observed and found to be primarily due to interindividual differences in CYP2D6 activity. The CSF to plasma exposure ratio has been consistent with those observed in preclinical species. No psychotomimetic, hallucinatory, or dissociative effects have been observed. PD effects include increases in low frequency EEG bands (delta and theta) around 1-1.5h post dose, coinciding with the Tmax of 1.5-2 hours.

Conclusion: This first-in-human study has demonstrated a clear lack of psychotomimetic, hallucinatory, or dissociative effects with DLX-001 at concentrations relevant for efficacy and producing significant central effects. Moreover, the comparable CSF drug concentration between preclinical studies and humans, and the observed increase in low frequency EEG bands, suggests that DLX-001 reaches the CNS and has central target engagement. These data support the continued clinical development of DLX-001 as a potential first-in-class neuroplastogen with the potential to address significant unmet needs within MDD and related neuropsychiatric disorders as a novel, fast-acting, outpatient oral pharmacotherapy.

Learning Objectives: Recognize the potential utility of neuroplastogens, a novel class of plasticity-promoting pharmacotherapies.
Understand the safety, tolerability, PK, and PD profiles of DLX-001, a novel neuroplastogen under development for the treatment of MDD and related disorders.

Literature References Vargas MV, Meyer R, Avanes AA, Rus M, Olson DE. Psychedelics and Other Psychoplastogens for Treating Mental Illness. Front Psychiatry. 2021 Oct 4;12:727117.
Ly C, Greb AC, Cameron LP, Wong JM, Barragan EV, Wilson PC, Burbach KF, Soltanzadeh Zarandi S, Sood A, Paddy MR, Duim WC, Dennis MY, McAllister AK, Ori-McKenney KM, Gray JA, Olson DE. Psychedelics Promote Structural and Functional Neural Plasticity. Cell Rep. 2018 Jun 12;23(11):3170-3182.

EFFECTS OF BEDTIME TNX-102 SL (SUBLINGUAL CYCLOBENZAPRINE (CBP) HCL) ON MOOD AND ANXIETY SYMPTOMS IN FIBROMYALGIA: RESULTS OF THE PHASE 3 RESILIENT TRIAL

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Seth Lederman, Tonix Pharmaceuticals

Abstract Background: Fibromyalgia (FM) is a chronic disabling condition characterized by core symptoms of widespread pain, nonrestorative sleep, fatigue, and cognitive dysfunction. FM also can include increased symptoms of depression and anxiety. RESILIENT was a confirmatory Phase 3 trial of TNX-102 SL taken daily for FM. CBP, a tricyclic, potently binds and antagonizes 5-HT2A serotonergic, α1 adrenergic, H1 histaminergic and M1 muscarinic receptors. The proposed mechanism for bedtime TNX-102 SL is that improving sleep quality in FM can lead to syndromal improvement. In addition to pain, sleep, memory and fatigue, the RESILIENT trial assessed depressive and anxiety symptoms.

Methods: Across 33 U.S. sites, the double-blind, placebo (PBO)-controlled RESILIENT study enrolled 457 patients meeting 2016 American College of Rheumatology criteria for FM; each received 2 weeks TNX-102 SL 2.8 mg, followed by 12 weeks 5.6 mg (N=231), or matching PBO (Safety N=226; ITT N=225). The primary endpoint was Week 14 change from baseline in weekly average of daily diary numeric rating scale pain scores. Secondary endpoints included the Fibromyalgia Impact Questionnaire - Revised (FIQR) - Symptoms domain, which includes depression and anxiety items. Depressive symptoms were followed with the Beck Depression Inventory-II (BDI-II). Patients on stable doses of non-excluded antidepressants were permitted to continue at baseline dosage during treatment if dosage had been stable for ≥90-days prior to baseline. A total of 59 (25.5%) patients on TNX-102 SL and 58 (25.7%) on PBO were on antidepressants or anxiolytic buspirone during treatment. Primary and continuous key secondary efficacy endpoints were analyzed by mixed model repeated measures (MMRM) with multiple imputation (MI); whereas BDI-II and individual FIQR items by MMRM without MI (no correction for multiple comparisons). Safety assessments included adverse events (AE) and Changes in Sexual Functioning Questionnaire short form (CSFQ-14).

Methods: On the primary endpoint, TNX-102 SL reduced daily pain at Week 14 (least squares (LS) mean (SE) difference vs PBO of −0.7 (0.16); P=0.00005; effect size 0.38). Statistically significant improvement was also observed in PGIC, FIQR-Symptoms, FIQR-Function, PROMIS Fatigue and PROMIS Sleep Disturbance scales. Baseline mean (SD) BDI-II total scores were 9.6 (6.32) for TNX-102 SL and 10.0 (6.72) for PBO. At Week 14, BDI-II total score for TNX-102 SL was reduced by LS mean (SE) of -3.4 (0.35) and for PBO by -2.0 (0.35), LS mean difference of -1.4 (0.49), P=0.005. The TNX-102 SL group also demonstrated greater improvement on FIQR items for depression (P LESS THAN 0.001) and anxiety (P=0.001). CSFQ-14 in females (95.4% of safety pop) demonstrated TNX-102 SL improved sexual functioning over PBO based on total score (P=0.010), and the orgasm/completion (P=0.007) and desire/frequency (P=0.010) domains. Oral hypoaesthesia was the most common AE with TNX-102 SL (23.8%) versus placebo (0.4%), and was transient, self-limited, and generally rated as mild (22.1%), occasionally moderate (1.7%), and never severe.

Conclusions: TNX-102 SL treatment improved pain, sleep quality, fatigue, depression, and anxiety symptoms. In females, sexual functioning in the TNX-102 SL group improved whereas that in the PBO group was essentially without change. Together these findings suggest the sleep disturbance in FM may be an obstacle to recovery and that pharmacotherapy that

addresses the sleep disturbance has the potential for syndromal improvement, including a reduction in depression and anxiety symptoms.

*TNX-102 SL has not been approved for any indication.

Learning Objectives: Understanding that fibromyalgia is a complex CNS disorder that is not only associated with widespread pain, but also significant sleep disturbance, fatigue, cognitive disturbance, and affective symptoms.
Learning that sleep quality is a potential therapeutic target in fibromyalgia which secondarily may lead to improvement in its broad-based syndromal symptoms including depression.

Literature References Hadlandsmyth K, Dailey DL, Rakel BA, et al. Somatic symptom presentations in women with fibromyalgia are differentially associated with elevated depression and anxiety. J Health Psychol. 2020;25(6):819-829
Moldofsky H, Scarisbrick P, England R, et al. Musculosketal symptoms and
non-REM sleep disturbance in patients with "fibrositis syndrome" and healthy
subjects. Psychosom Med. 1975;37(4):341-51.

3:00 p.m. - 4:30 p.m.

Individual Research Reports (IRRs): Neuroscience-Informed Treatment Approaches for Depression

UNRAVELING THE RELATIONSHIPS BETWEEN CHILDHOOD ADVERSITY, PSYCHOPATHOLOGY, AND THE ROSTRAL ANTERIOR CINGULATE CORTEX: A TRANSDIAGNOSTIC STUDY ACROSS DIVERSE NON-PSYCHOTIC PSYCHIATRIC DISORDERS

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Abstract Background: Childhood adversity (CA) is the leading preventable risk factor for mental illness, with CA related changes in brain structure being thought to mediate vulnerability for the development and maintenance of psychiatric disorders. While there are indications that CA affects the brain independently from psychopathology, the effects of CA have almost exclusively been studied in health and stress-related disorders, such as depression and anxiety disorders. Interestingly, the rostral anterior cingulate cortex (rACC) emerges as a region highly impacted by CA and is also implicated across diverse psychiatric disorders given its key role in emotion regulation. We set out to disentangle the relationships between CA, psychopathology, and the rACC across a diverse population consisting of healthy participants and patients with a broad range of psychiatric disorders.

Methods: We investigated 95 healthy participants and 227 patients with a stress-related and/or neurodevelopmental disorder. 3 Tesla structural T1-weighted images were acquired and subsequent automated segmentation was performed using Freesurfer. We employed a region of interest approach, focusing on the rACC. CA was measured using a childhood trauma questionnaire. For our primary analyses, we performed a multivariate analysis of covariance (MANCOVA) with the bilateral rACC thickness as dependent variables, and childhood adversity (yes/no) and psychopathology (yes/no) as fixed factors, while controlling for age, sex, and total intracranial volume. Follow-up analyses of covariance (ANCOVAs) were performed in case of significant results. Secondarily, we investigated potential associations with the childhood trauma index (a measure for trauma severity) and for broad diagnostic subgroups.

Methods: The MANCOVA showed a significant relationship of the left and right rACC thickness with CA ($F(2,314) = 3.98$, $p = 0.020$) and psychopathology ($F(2,314) = 4.43$, $p = 0.013$), but no interaction effect ($F(2,314) = 0.32$, $p = 0.728$). Follow-up ANCOVAs revealed a significant relationship between the thickness of the left rACC and CA ($F(1,315) = 7.75$, $p = 0.006$), with a relatively thinner left rACC in the participants with CA. A post-hoc partial correlation (controlling for age, sex and total intracranial volume) showed a significant correlation between the left rACC thickness and the childhood trauma index ($r = -0.121$, $p = 0.030$). In addition, there was an association between the thickness of the contralateral, right rACC and psychopathology ($F(1,315) = 4.23$, $p = 0.041$), with the patients having a thinner rACC than the controls. Further investigation of broad diagnostic subgroups revealed that the stress-related group had a thinner right rACC than the healthy controls ($p = 0.012$) and neurodevelopmental group ($p = 0.034$).

Conclusions: Our results support a key role for the rACC in relation to both CA and psychopathology. CA impacts the left rACC independently of psychopathology across our population consisting of healthy individuals and patients with diverse non-psychotic psychiatric disorders. This suggests that CA may be a crucial risk factor for the development of transdiagnostic symptom dimensions, like emotion regulation problems, across psychiatric disorders. A better understanding of the CA-related phenotype may lead to the development of neuroscience guided personalized treatments that cut across traditional diagnostic boundaries and may improve treatment outcomes.

Learning Objectives: 1. Childhood adversity impacts the left rostral anterior cingulate cortex, which is critical for emotion regulation, independently from psychopathology.
2. A better understanding of the childhood adversity related phenotype may advance the development of stratified and personalized treatments in mental health disorders.

Literature References 1. Teicher, M.H., Samson, J.A., 2013. Childhood maltreatment and psychopathology: A case for ecophenotypic variants as clinically and neurobiologically distinct subtypes. Am J Psychiatry 170, 1114-1133.
2. Teicher, M.H., Samson, J.A., Anderson, C.M., Ohashi, K., 2016. The effects of childhood maltreatment on brain structure, function and connectivity. Nat Rev Neurosci 17, 652-666.

SIMILAR AND UNIQUE IMMUNE PROTEOMIC PROFILES OF MAJOR DEPRESSIVE DISORDER AND PRIMARY DERMATOLOGICAL DISORDERS: A POTENTIAL FOR NOVEL TREATMENTS

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Mina Rizk, Icahn School of Medicine At Mount Sinai

Abstract Background: Immune dysregulation has been linked to major depressive disorder (MDD) and may contribute to treatment resistance in a subgroup of depressed patients. Depressive symptoms are common in patients with inflammatory conditions such as atopic dermatitis and psoriasis. Treatments targeting specific inflammatory markers in these disorders are commonly associated with improvement of depression, suggesting a shared underlying inflammatory process that is yet to be identified.

Methods: Blood samples collected from 108 participants (18-70 years old; 44% female) were analyzed using the proteomic Olink assay of 363 proteins consisting of four panels of general, cardiovascular, and neural inflammatory markers. The study sample included 25 individuals with MDD and no history of inflammatory conditions, 30 patients with atopic dermatitis, 21 patients with psoriasis, and 32 healthy controls (HCs). Differentially expressed proteins in blood between any comparison were defined by fold-change GREATER THAN 1.5 and false discovery rate LESS THAN 0.05. Gene set variation analyses (GSVA) were performed on previously curated datasets of immune markers.

Methods: Compared with the other 3 groups, MDD patients showed higher expression of markers related to vascular inflammation and atherosclerotic cardiovascular disease signaling (e.g., PECAM1, SELP/P-selectin, VWF, SIRT2, STAMBP) as well as pro-apoptotic pathways (e.g., CD274, CASP3, CASP8) (all ps LESS THAN 0.001). Compared with HCs, MDD and atopic dermatitis patients had higher T-helper 2 (Th2) immunomodulators such as CCL13 (p LESS THAN 0.001), whereas MDD and psoriasis patients had higher Th17 markers such as CXCL1 and KYNU (p LESS THAN 0.001, p LESS THAN 0.01, respectively). GSVA pathway analyses also showed protein enrichment of T-cell signaling pathways (e.g. Th2).

Methods: Although MDD is associated with an immune dysregulation profile that is distinct from atopic dermatitis and psoriasis, there is a striking similarity in their adaptive immune proteomics (i.e., Th2 and Th17 markers). Effective treatments targeting Th2 and Th17 markers could be promising in patients with MDD who demonstrate dysregulation of these immune pathways.

Learning Objectives: - Major Depressive Disorder has a distinct immune profile.
- Certain adaptive immune markers are dysregulated in both major depression and primary inflammatory skin disorders.

Literature References 1. Drevets, WC, et al. Immune targets for therapeutic development in depression. Nat Rev Drug Discov. 2022;21(3): 224-244.
2. Simpson, EL, et al. Efficacy and Safety of Dupilumab in Adolescents With Uncontrolled Moderate to Severe Atopic Dermatitis: A Phase 3 Randomized Clinical Trial. JAMA Dermatology. 2020156(1): 44-56.

DYSREGULATED INSULA CONNECTIVITY AND ITS ASSOCIATION WITH SUICIDE RISK

Yoojin Lee[1], Jessica Gilbert[1], Carlos Zarate[1], Elizabeth Ballard[1]*

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Abstract Suicide is a pressing health concern in the US, demanding objective markers for understanding suicidal behaviors. Research suggests a link between personality traits, such as aggression and impulsivity, and suicidal behaviors, potentially tied to reduced brain function in regions relevant to sensory regulation and decision-making, such as prefrontal cortex, precuneus, and insula. However, limited knowledge is available on the association between the impulsive aggression, suicidal behavior, and brain regions responsible for the sensory and emotional regulation, especially considering the temporal dynamics of the suicidal behavior. This study examined whether self-reported aggression and impulsivity, along with task-oriented impulsivity measure, could moderate resting-state magnetoencephalographic (MEG) power and effective connectivity.

The ongoing research initially recruited 121 participants in three groups: Individuals with recent suicidal crisis (High Risk; HR; n=14), individuals with a history of suicide attempts except for last year (Lower Risk; LR; n=41), and individuals without a history of suicidal behaviors (Control; CL; n=66). Impulsivity was assessed through two measurements: self-reported impulsivity, measured using the Barratt Impulsiveness Scale (BIS), and risk-taking impulsivity, evaluated using the Balloon Analogue Rating Task (BART). Additionally, trait-like aggression was measured using the Buss-Perry Aggression Scale (BPA). Linear mixed effects models examined differences in source-localized MEG power between groups in in the delta (2-4Hz), theta (4-8Hz), alpha (9-14Hz), beta (15-29Hz), and gamma (30-58Hz) frequencies. The study also explored the interaction between the resting-state MEG power and aggressive impulsivity measures in those ROIs. To investigate the directional connectivity between ROIs, we performed an effective connectivity analysis using dynamic causal modeling (DCM) in SPM12.

While no significant MEG power differences were found between groups, within the HR group, participants with higher self-reported aggression and impulsivity scores showed an inverse relationship between attentional BIS and BAS scores and MEG power in various bandwidths, including delta (precuneus), theta (supra marginal gyrus), alpha (angular gyrus, middle frontal, and inferior parietal gyri), beta (precuneus and inferior frontal gyrus), and gamma (postcentral gyrus), with voxel-based corrected ps LESS THAN .05. Parametric empirical Bayesian analysis revealed that compared to LR and CL groups, HR participants showed downregulated bidirectional AMPA-mediated connectivity between the precuneus (PRE) and insula (INS) and upregulated AMPA-mediated feedback from the postcentral gyrus (PCG) to the INS, posterior probability (posteriorp) GREATER THAN .95. Additionally, within the HR group, individuals with higher BIS scores exhibited downregulated AMPA feedback from PCG to INS, and those with higher BART scores displayed upregulated AMPA feedback between PCG and INS, along with downregulated AMPA feedforward connectivity from INS to PRE, when compared to LR and CL groups, posteriorps GREATER THAN .95.

The results indicate dysregulated glutamatergic connectivity in brain regions related to sensory and decision-making, which is linked to suicidal risk, particularly when considering various measures of impulsivity and the timing of suicidal behaviors. The study suggests that the glutamatergic-mediated sensory and emotion-regulation processes may serve as significant markers of suicide risk, which can be evaluated in future longitudinal studies.

Learning Objectives: 1. Attendees will have an opportunity to acknowledge and engage in discussions regarding the association between aggression, impulsivity, and the neural correlates in recent suicidal crises.
2. Attendees will gain insights into a novel electrophysiological method and its application in suicide research.

Literature References 1. Interian, A., Myers, C. E., Chesin, M. S., et al. Towards the objective assessment of suicidal states: Some neurocognitive deficits may be temporally related to suicide attempt. Psychiatry research. 2020.
2. Lalovic, A., Wang, S., Keilp, J. G., et al. A qualitative systematic review of neurocognition in suicide ideators and attempters: Implications for cognitive-based psychotherapeutic interventions. Neuroscience and biobehavioral reviews. 2022

KETAMINE OUTCOMES AND HEALTH CARE UTILIZATION: 5 YEAR EXPERIENCE FROM AN ACADEMIC KETAMINE CLINIC

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Abstract Ketamine has emerged as a valuable treatment option for patients with severe treatment-resistant mood disorders. Albeit its short-term efficacy was demonstrated in multiple controlled trials, its long-term safety and effectiveness in decreasing hospitalization and health care utilization are less well established. Moreover, dosing strategies in published samples have been heterogeneous, with some data suggesting this is a critical factor in treatment outcomes. Patients with severe, treatment-refractory disorders often are not eligible for research studies and they pursue treatment at an academic center.
We report outcome data for the 600 patients treated at the MGH ketamine clinic from October 2018 until February 2024, with over 130 currently undergoing maintenance treatment. Patients' primary diagnosis is Major Depressive Disorder (85%) (MDD) or Bipolar Disorder (15%) (BP), with patients' age ranging from 15-84 (mean age: 42.6).The majority were outpatients, referred to the clinic after experiencing four or more prior treatment failures. Exclusion criteria include current moderate to severe Substance Use Disorder (SUD) and a history of psychosis. Approximately 2/3 of patients had one or more comorbid diagnoses (PTSD, OCD, GAD and ADHD) and over 70% of patients endorsed suicidal ideation at baseline. Half of the patients had their ketamine treatments covered by insurance.

Regarding dosing strategies, the initial ketamine treatment dosage was set at 0.5mg/kg and was subsequently adjusted empirically based on efficacy and tolerability. The dose was gradually increased if tolerated by 0.15-0.2mg/kg for the first 6-8 infusions, and further adjustments were made over the following 4-8 infusions with the aim of progressively increasing the duration of the interval between maintenance treatments. We observed that the ketamine dose remained stable for most of the patients between treatments #10 and 20, with the average QIDS depression score remaining in the 10-12 range (indicating mild depression). We will discuss factors associated with the duration of intervals and dosing strategies in our sample.

The overall response rate using self-rated depression questionnaires (QIDS) was similar to other published samples in civilian and VA settings.

We analyzed the healthcare utilization in our network and compared the frequency of visits and inpatient admissions among all patients at the clinic during one calendar year before VS one year after starting ketamine IV treatment. We observed a significant (p LESS THAN 0.01) decrease in emergency room visits and inpatient admissions for any reason, with an even more significant decrease in ED visits and inpatient admission for psychiatric cause.

In our sample, overall early mood improvements were significantly maintained with repeated administration of an individually tailored dose of ketamine, which is critical for optimal efficacy and to obtain longer intervals between treatments. We did not observe any serious adverse events, nor did we observe the development of tolerance. Additionally, patients receiving IV ketamine for TRD did show a significant decrease in ED visits and inpatient admissions, a finding with important repercussion at the population management level.

Learning Objectives: Impact of ketamine treatment in reducing ED visits and admission in patients with TRD
Effective dosing strategies in long-term maintenance with ketamine

Literature References Nikolin S, Rodgers A, Schwaab A, Bahji A, Zarate C Jr, Vazquez G, Loo C. Ketamine for the treatment of major depression: a systematic review and meta-analysis. EClinicalMedicine. 2023 Aug 3;62:102127
Fava M, Freeman MP, Flynn M, Judge H, Hoeppner BB, Cusin C, Ionescu DF, Mathew SJ, Chang LC, Iosifescu DV, Murrough J, Debattista C, Schatzberg AF, Trivedi MH, Jha MK, Sanacora G, Wilkinson ST, Papakostas GI. Double-blind, placebo-controlled, dose-ranging trial of intravenous ketamine as adjunctive therapy in treatment-resistant depression (TRD). Mol Psychiatry. 2020 Jul;25(7):1592-1603.

3:00 p.m. - 4:30 p.m.

Individual Research Reports (IRRs): Innovations in Alcohol and Substance Use Disorders

PAIN RESPONSES IN ADOLESCENTS WITH DEPRESSION AND CANNABIS USE

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Abstract Introduction: Despite growing evidence for biobehavioral relationships between pain and cannabis use, there has been sparse research on pain circuitry in adolescent cannabis use. Here, we examined pain processing among adolescent cannabis users and non-users.
Methods: Our study is on-going and recruiting adolescents in the New York City metropolitan area. In this preliminary analysis, we included data from 25 subjects (age: 15.4 ± 2.5 years; 84% female). History of cannabis use was determined from clinician-based interviews, self-reported measures, and urine toxicology screens. MRI was performed on a 3T Siemens Skyra

using protocols similar to those of the Human Connectome Project (HCP) Lifespan studies, including anatomical T1w MPRAGE and T2w SPACE (0.9mm isotropic) and fMRI (2.3mm isotropic, TR=1s, 5x multiband).

Our electric pain paradigm based on a published protocol incorporated out-of-scanner and in-scanner portions. Pre-scan, an electrode was placed on the dorsal surface of the right foot, and stimulation (100Hz, 0.5ms pulses) was calibrated (0.25V steps, max 10V) to determine when shocks were first painlessly felt (innocuous threshold), became painful (pain threshold), and were as painful as could be tolerated (maximum threshold). Thresholds were confirmed and adjusted as needed in scanner. The task comprised three 5-minute runs, each with 10 trials. For each trial, the subject was first shown a cue, followed by a fixation cross, then received an electric shock. Post-shock, the subject rated pain level on a 0-10 Visual Analogue Scale. Trials were separated by jittered fixation. Preprocessing steps included motion correction, normalization to MNI space, and mild spatial smoothing (FWHM=4mm). Subject-level data were analyzed using an event-related GLM, as implemented in FSL FEAT, to model neural responses during 1) cues preceding painful vs. non-painful shocks, 2) receipt of painful vs. non-painful shocks, and 3) post-shock pain ratings. At the group level, mixed effects models with FLAME1+2 and outlier de-weighting were performed. Neural activation across phases of pain processing was compared between cannabis users (n = 8) and non-users (n = 17) as well as correlated with cannabis use frequency across the full sample. Results were controlled for multiple comparisons using cluster-based inference at Z GREATER THAN 2.58, p LESS THAN 0.05.

Methods: Adolescent cannabis users and non-users exhibited similar neural activation while viewing painful vs. non-painful cues. When experiencing painful vs. non-painful shocks, cannabis users showed stronger activation in the right frontal gyrus, frontal pole, insula, caudate, and bilateral paracingulate gyri. During pain rating, the bilateral precentral and postcentral gyri had stronger activation among CU. Heavier cannabis use correlated with activation of the right frontal gyrus during shock and the left precentral gyrus during pain rating.

Conclusions: We found that experiencing and rating pain elicited stronger neural responses in adolescent cannabis users than non-users. Though preliminary, these results align with converging evidence for cannabis-associated alterations in pain processing in youth. Recruitment for this study is ongoing, with future analyses to include a larger sample and examine the role of comorbid cannabis use and depression in pain processing.

Learning Objectives: Preliminary data suggest heightened neural pain responses among adolescent cannabis users.
More research is needed to elucidate cannabis-associated pain processing in adolescence.

Literature References Yanes, J.A., et al., Neuroimaging meta-analysis of cannabis use studies reveals convergent functional alterations in brain regions supporting cognitive control and reward processing. J Psychopharmacol, 2018. 32(3): p. 283-295.
Gogulski, H.Y. and R.M. Craft, Adolescent THC exposure: effects on pain-related, exploratory, and consummatory behaviors in adult male vs. female rats. Psychopharmacology (Berl), 2022. 239(5): p. 1563-1578.

IL17RB GENETIC VARIANTS ARE ASSOCIATED WITH ACAMPROSATE TREATMENT RESPONSE IN PATIENTS WITH ALCOHOL USE DISORDER: A MULTI-OMICS STUDY

Ming-Fen Ho[*1], Cheng Zhang[1], James Cohan[1], Mustafa Tuncturk[1], Robin Heider[1], Brandon J. Coombes[1], Joanna Biernacka[1], Irene Moon[1], Miclhelle Skime[1], Man Choi (Ada) Ho[1], Paul Croarkin[1], Tyler Oesterle[1], Victor Karpyak[1], Hu Li[1], Richard Weinshilboum[1]*

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Abstract Background and significance: Acamprosate is an FDA approved medication for the treatment of alcohol use disorder (AUD), however, only about 50% of patients will respond to acamprosate. The present study was designed to identify potential plasma markers associated with acamprosate treatment response. Specifically, we first set out to identify potential plasma markers that were associated with acamprosate treatment outcomes. Next, we applied a "proteomics-informed genome-wide association study (GWAS) research strategy, in which we performed GWAS for the concentrations of proteins associated with acamprosate treatment outcomes. We then set out to determine whether SNPs identified in the course of our proteomics-informed GWAS might be associated with acamprosate treatment outcomes. This series of studies could represent an important step toward the generation of functional hypotheses that could be tested to gain insight into the molecular mechanisms underlying acamprosate treatment response phenotypes.
Objectives: The present study was designed to identify potential plasma markers associated with acamprosate treatment response using multi-omics data.

Methods: The Mayo Clinic Center for Individualized Treatment of Alcohol Dependence study is an acamprosate clinical trial that recruited 442 patients with AUD, all of whom were treated with acamprosate for three months. The primary outcomes were 1) relapse to alcohol use and 2) relapse to heavy drinking. Relapse was defined as return to alcohol use during the three months of acamprosate treatment, and non-relapse as abstinence from alcohol (no alcohol use) during the three months of acamprosate treatment. Heavy drinking was defined as having four drinks a day for women and five drinks a day for men. Baseline plasma samples were assayed using the OLINK "Explore Inflammation" panel.

Results: We identified several proteins, including IL17RB, that appear to be associated with acamprosate treatment response. The GWAS for IL17RB concentrations identified several genome-wide significant signals, with the lowest p value of 4.8E-20 for the rs6801605 SNP on chromosome 3. The minor allele frequency (allele A) for the rs6801605 SNP was 38% in European American population. The rs6801605 SNP maps 4Kb upstream of IL17RB, and intron 1 of CHDH gene. In line with our observation, the rs6801605 SNP has been identified to be associated with the concentrations of IL17RB with a p value of 1.75E-18 in a population-based cohort of 1005 Swedish individuals. In addition, the variant genotype of this SNP is protective for alcohol relapse. Furthermore, we previously conducted GWAS meta-analysis to determine genetic contributions to AUD treatment outcomes, with a total of 1083 European ancestry AUD patients. We confirmed that the rs6801605 SNP is associated with time until relapse (p:0.01), and time until heavy relapse (p: 0.005) during 3 months of acamprosate treatment. Finally, we demonstrated that the basal level of mRNA expression of IL17RB was

inversely correlated with those of NF-κB subunits, and a significantly higher expression of NF-κB subunits was observed in AUD patients who relapsed to alcohol use. In summary, this study illustrates that IL17RB genetic variants might contribute to acamprosate treatment outcomes.

Conclusion: This series of studies demonstrates that IL17RB genetic variants might contribute to acamprosate outcomes. Our results revealed that the application of multi-omics approaches may be a feasible strategy for identifying biomarkers that could potentially aid in predicting acamprosate treatment response.

Learning Objectives: 1.The application of multi-omics in alcohol addiction research
2. Integration of multi-omics data for biomarker identification of acamprosate treatment response in alcohol use disorder patients.

Literature References 1. Ho M-F, Zhang C, Wei L, Zhang L, Moon I, Geske JR, Skime MK, Choi D-S, Biernacka JM, Oesterle TS, Frye MA, Seppala MD, Karpyak VM, Li H, Weinshilboum RM. Genetic variants associated with acamprosate treatment response in alcohol use disorder patients: A multiple omics study. British journal of pharmacology. 2022;173:16.
1. Ho MF, Zhang C, Moon I, Wei L, Coombes B, Biernacka J, Skime M, Choi DS, Frye M, Schmidt K, Gliske K, Braughton J, Ngo Q, Skillon C, Seppala M, Oesterle T, Karpyak V, Li H, Weinshilboum R. Genome-wide association study for circulating FGF21 in patients with alcohol use disorder: molecular links between the SNHG16 locus and catecholamine metabolism. Molecular Metabolism. 2022;63:101534.

EFFECTS OF ALCOHOL USE FREQUENCY AND EXOGENOUS CANNABINOIDS ON ANANDAMIDE LEVELS IN A COMMUNITY SAMPLE USING CANNABIS FOR ANXIETY

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Abstract An alcohol related disorder (ARD) can double the odds of having an anxiety disorder, but ARDs limit the efficacy of anxiety treatments. In tandem, the public is increasingly turning to cannabis for anxiety relief, which has some empirical support. Research on pharmacological manipulations to increase anandamide (AEA), an endocannabinoid affected by cannabis products, is rapidly expanding as a treatment option for anxiety. However, there is some evidence to suggest that while increasing AEA concentrations may decrease anxiety symptoms, it may also simultaneously increase risk for problematic drinking behaviors. While anxiety and AEA, and ARDs and AEA, have been examined separately, no studies to date examine these factors together in humans, nor do any studies examine how AEA levels in relation to alcohol use may be moderated by exogenous cannabinoids such as □9-tetrahydrocannabinol (THC) or cannabidiol (CBD).
Data presented here is from a longitudinal study of cannabis use, anxiety symptoms, and related biomarkers. Participants completed self-report measures on substance use and affective symptoms, and blood draws for cannabinoid and endocannabinoid levels. Using an at-home administration procedure, participants were randomly assigned to one of three chemovar conditions: THC dominant (24% THC, 1% CBD); THC+CBD (9% THC, 10% CBD); and

CBD dominant (1% THC, 23% CBD) or a sex-matched non-use condition. Using mixed effects models, we examined associations between AEA levels, cannabis chemovar groups, alcohol use frequency, and self-reported anxiety symptoms at baseline, 2 weeks, and 4 weeks.

293 participants completed the study (Age M=33.3, SD=13.6; 59.7% female sex assigned at birth). Analyses revealed a marginally significant 3-way interaction between time, condition, and alcohol frequency (F=1.92, p=0.07). Post-hoc comparisons were made at low, moderate, and high alcohol frequency levels (1 SD below, at, and above the mean). At 4 weeks, participants in the THC condition had higher AEA levels than the THC+CBD condition at low alcohol frequency (F=-2.66, p=0.04), while the THC+CBD condition had higher AEA levels than non-users at high frequency (F=2.74, p=0.03). There were also significant increases in AEA from 2 to 4 weeks for every condition at every frequency level (ps LESS THAN 0.001), while the THC+CBD condition had significant increases from baseline to 2 weeks at moderate alcohol frequency (p=0.03) and marginally so at high frequency (p=0.07). Finally, there was a significant positive association between alcohol frequency and AEA levels at week 4 for the THC+CBD group (p=0.01).

This is the first study to examine the relationships between AEA, alcohol frequency and cannabinoid exposure in humans over a period of 4 weeks. Our results suggest that alcohol frequency and varying chemovars—particularly equivalent THC and CBD formulations—uniquely impact the endocannabinoid system. Furthermore, these effects seem to become prevalent over longer time periods given that most observed changes occurred after 4 weeks. More longitudinal research is needed to understand how THC, CBD, and AEA interact in the context of anxiety and alcohol use.

Learning Objectives: 1. Consider how increasing anandamide concentrations as a treatment for anxiety may increase risk for disordered drinking behaviors
2. Explore the effects of exogenous cannabinoids on anandamide levels in the context of alcohol use and anxiety.

Literature References 1. Gimeno C, Dorado ML, Roncero C, et al. Treatment of comorbid alcohol dependence and anxiety disorder: Review of the scientific evidence and recommendations for treatment. Frontiers in Psychiatry. 2017;8(SEP):1. doi:10.3389/fpsyt.2017.00173
2. Niemela G, Terry GE. Contribution of Fatty Acid Amide Hydrolase to Alcohol Use Disorder: A Systematic Review. Cannabis and Cannabinoid Research. 2021;6(2):105-118. doi:10.1089/can.2020.0158

ALCOHOL CRAVING, CORTISOL METABOLISM AND ACAMPROSATE TREATMENT RESPONSE IN PATIENTS WITH ALCOHOL USE DISORDER

Robin Heider[*1], Cheng Zhang[2], Irene Moon[2], Brandon J. Coombes[3], Joanna Biernacka[3], Michelle Skime[4], Quyen Ngo[5], Cedric Skillon[5], Tyler Oesterle[4], Victor Karpyak[4], Hu Li[2], Richard Weinshilboum[2], Ming-Fen Ho[4]*

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Abstract Title: Alcohol Craving, Cortisol Metabolism and Acamprosate Treatment Response in Patients with Alcohol Use Disorder

Background and Objective: We previously conducted an acamprosate trial and found that baseline alcohol craving intensity is the most significant clinical variable contributing to acamprosate treatment outcomes (p: 9.36E-06). Currently, no objective biochemical measures have yet been associated with alcohol craving intensity or drug treatment response. Therefore, we designed this study to identify potential biomarkers associated with alcohol craving intensity that might contribute to acamprosate treatment outcomes. We utilized our established "pharmaco-omics informed genome-wide association study (GWAS)" approach, where we performed GWAS for plasma concentrations of candidate biomarkers associated with alcohol craving intensity. We then investigated whether any single nucleotide polymorphisms (SNPs) identified in our GWAS might also be associated with acamprosate treatment responses. This series of studies aimed to identify potential biomarkers associated with alcohol craving intensity using multi-omics data from the Mayo Clinic Acamprosate study, which is one of the largest acamprosate studies that has ever been conducted and the only existing AUD study cohort with multi-omics data.

Methods: A cohort of 442 patients with AUD were recruited through the Mayo Clinic Center for Individualized Treatment of Alcohol Dependence, all of whom received acamprosate treatment for three months. Alcohol consumption was measured using the timeline follow back (TLFB). Craving intensity was determined by use of the Penn Alcohol Craving Scale (PACS). Baseline plasma samples from participants were assayed using the OLINK "Explore Inflammation" panel. Cortisol and cortisone levels were measured using ultra-performance liquid chromatography-mass spectrometry.

Results: Clinically, we found that baseline craving intensity was strongly correlated with relapse (p: 9.36E-06). We used OLINK to identify plasma protein markers associated with both alcohol craving intensity and acamprosate response. We found that baseline plasma levels of HSD11B1, an enzyme that converts inactive cortisone to active cortisol, were associated with both craving intensity (p: 5.14E-07) and treatment outcomes (i.e. time until relapse, p: 0.02, and time until heavy relapse, p:0.01). However, this "proteomics-informed GWAS" was unable to identify gene variants associated with baseline plasma levels of HSD11B1. Given that HSD11B1 activates cortisol, we hypothesized that cortisol levels might also be associated with craving intensity. As anticipated, we found that baseline plasma cortisol levels were positively correlated with baseline craving intensity (p: 0.005). We then employed the "metabolomics-informed GWAS approach" to identify genes associated with plasma cortisol levels. We identified several genome-wide significant signals, with the lowest p value of 6.14E-09 for the rs138784599 SNP within the KHNYN gene on chromosome 14. Strikingly, this SNP was also the top signal for the GWAS for plasma cortisone concentrations (p: 4.18E-09). Even more striking, this same SNP was also associated with both treatment outcomes i.e. time until relapse (p: 0.01) and time until heavy relapse (0.01).

Methods: The present study demonstrated significant associations between 1) alcohol craving intensity and acamprosate treatment outcome, 2) alcohol craving intensity and plasma cortisol levels, as well as 3) the KHNYN genetic variant that influenced both plasma cortisol levels and acamprosate treatment outcomes.

Learning Objectives: 1. Discover research strategies utilizing a multi omics approach to enhance pharmacogenomics in the study of addiction and neuropsychiatric disorders.
2. Recognize the association between alcohol craving intensity and plasma cortisol and analyze the potential association between them and acamprosate treatment response in alcohol use disorder.

Literature References 1. Ho M-F, Zhang C, Wei L, et al. Genetic variants associated with acamprosate treatment response in alcohol use disorder patients: A multiple omics study. Br J Pharmacology. 2022; 173:16.
2. Ho M-F, Zhang C, Moon I, et al. Genome-wide association study for circulating FGF21 in patients with alcohol use disorder: molecular links between the SNHG16 locus and catecholamine metabolism. Mol Metab. 2022; 63:101534.

3:00 p.m. - 4:30 p.m.

Individual Research Reports (IRRs): Clinical Outcomes in Psychiatric Disorders

BASELINE COGNITION IS NOT ASSOCIATED WITH DEPRESSION OUTCOMES IN VORTIOXETINE FOR MAJOR DEPRESSIVE DISORDER: FINDINGS FROM PLACEBO-CONTROLLED TRIALS

Joshua Jordan[*1], Li Shen[1], Nicholas Cooper[1], Samantha Goncalves[1], Madhukar H. Trivedi[2], Alan F. Schatzberg[3], Wei Wu[1], Adam Savitz[1], Amit Etkin[1]*

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Joshua Jordan, Alto Neuroscience

Abstract Background: Major Depressive Disorder (MDD) is a common psychiatric disorder for which pharmacological standard-of-care treatments have limited efficacy, particularly among individuals with cognitive dysfunction. Cognitive dysfunction is observed in approximately 30-60% of those with MDD, where response to standard-of-care medications is reduced. Vortioxetine is an approved antidepressant that has shown evidence of pro-cognitive effects in MDD patients. It is not known if it has greater clinical efficacy in MDD patients with cognitive dysfunction, a more difficult to treat population.
Methods: This study was a reanalysis of 1,660 subjects with MDD across three eight-week, placebo-controlled trials of vortioxetine in adults aged 18-65 with moderate to severe MDD that reported superiority over placebo (NCT01422213, NCT01564862, NCT02389816). Baseline cognition was measured by the Digit Symbol Substitution Test (DSST), the primary measure used to demonstrate vortioxetine's pro-cognitive effects. Analyses examined whether baseline cognitive function was associated with differences in treatment outcomes on the Montgomery-Asberg Depression Rating Scale (MADRS) at the primary endpoint (week eight). Secondary analyses examined whether baseline cognitive performance in other domains (executive function, attention, verbal learning and memory) was associated with differences in treatment outcome.

Methods: There were 916 subjects assigned to vortioxetine and 540 to placebo across the three trials. Baseline DSST did not predict placebo-adjusted treatment effects of vortioxetine on

depressive symptoms (pooled Cohen's d = -0.01, 95% Confidence Intervals [CI] = -0.10, 0.09). There was no heterogeneity between studies (I-squared LESS THAN 0.01%). Secondary analyses of cognitive function on other cognitive measures did not reveal a significant difference in treatment outcomes (all pooled Cohen's d LESS THAN 0.04). Finally, analyses of one trial with duloxetine as an active comparator (N = 204) also revealed no significant differences in treatment outcomes across all cognitive measures (all Cohen's d LESS THAN 0.14, all P GREATER THAN 0.094).

Conclusions: These findings, taken together, suggest that vortioxetine is no more beneficial in reducing depressive symptoms for those with cognitive dysfunction despite improving aspects of cognition, with results comparable to a serotonin-norepinephrine reuptake inhibitor. Novel antidepressants that operate through a different mechanism of action that enhance synaptic plasticity or promote neurogenesis may be preferable first-line treatments for MDD with cognitive dysfunction.

Learning Objectives: 1) Participants will learn about cognitive dysfunction in major depressive disorder.
2) Participants will learn about the efficacy of vortioxetine in treating depressive symptoms among those with different levels of cognitive function.

Literature References Gualtieri CT, Morgan DW. The frequency of cognitive impairment in patients with anxiety, depression, and bipolar disorder: an unaccounted source of variance in clinical trials. J Clin Psychiatry. 2008;69(7):1122-1130. doi:10.4088/jcp.v69n0712
Groves SJ, Douglas KM, Porter RJ. A Systematic Review of Cognitive Predictors of Treatment Outcome in Major Depression. Front Psychiatry. 2018;9:382. doi:10.3389/fpsyt.2018.00382

CAN AN IMPLANTABLE DEVICE DELIVER A YEAR OF MAINTENANCE RISPERIDONE? RESULTS FROM A PHASE 1 PK/SAFETY STUDY EVALUATING 6- AND 12-MONTH VERSIONS OF THE DLP-114 DEVICE IN SCHIZOPHRENIA

Peter Weiden[*1], Leslie Citrome[2], Gregory Watkins[3], Brian Liu[3], Garrett Healy[3], Lana Ho[3], Frank Martin[3]*

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Peter Weiden, SUNY Stony Brook

Abstract Background and Purpose: Disruptions in medication continuity is a major limitation when using antipsychotics to treat patients with schizophrenia. Long-acting injectable formulations (LAIs) can help prevent such disruptions but are limited by their dosing interval. Implantable devices are an alternative technology with the potential to extend dosing intervals, with the added feature of reversibility if needed. Here we report on a Phase 1 study of DLP-114, a risperidone-containing implant device delivering up to 12 months of risperidone treatment in stable patients with schizophrenia after a single administration (NCT04418466).
Methodology: Device Description: DLP-114 is a titanium cylinder, 5mm in diameter and 4-5 cm in length, containing a propriety formulation of risperidone (RIS). The cylinder is capped at each end with a semipermeable membrane. Once implanted, RIS is passively diffused across the membrane to the surrounding tissues.

Study Overview: The study evaluates the safety, tolerability, and pharmacokinetics (PK) of 6- and 12-month versions of DLP-114 (DLP-1146M and DLP-11412M) with the 12M cylinder ~1cm longer.

Device Placement: Consenting subjects with a diagnosis of schizophrenia were stabilized on oral RIS (3mg/day for ≥ 2 weeks) and then randomized 1:1 to either 6-months, receiving 2 DLP-1146M devices, or 12-months receiving 2 DLP-11412M devices. The devices were inserted sub-dermally in the abdomen in a brief (~10min) outpatient procedure using a proprietary placement tool designed for the DLP device.

Outcomes: Safety measures included monitoring for Adverse Events (AEs), Serious AEs (SAEs), movement disorders, and device-specific AEs of interest. Safety assessments were done throughout the study including a follow-up visit after device removal. PK sampling of the risperidone active moiety (RIS+9-hydroxRIS) included baseline, daily x 7d, weekly x 3, then q2weeks until study completion at 6 or 12 months. Secondary endpoints included the Positive and Negative Syndrome Scale and the Clinical Global Impressions-Improvement scale.

Results: After device insertion, 24 of 28 subjects (86%) completed the study. Reasons for early discontinuation were: 1) lost to follow-up (n=2); signs of impending relapse (n=1); and request for early removal of DLP-114 (n=1). Device placement and removal procedures were well tolerated. There was 1 SAE (pulmonary embolism) judged to be unrelated to study drug. AEs were generally mild, and included implant site pain/soreness/tenderness, drowsiness, ecchymosis, increased appetite, insomnia, and headache. Steady-state plasma risperidone remained substantially constant for both DLP-1146M and DLP-11412M devices throughout the 6- and 12-month period, with average RIS active moiety plasma concentrations between 7-13ng/mL. All 24 study completers remained clinically stable throughout the study.

Conclusions: DLP-114 was well tolerated for up to 12 months. Only 1 subject showed signs of impending relapse. Plasma concentrations of the RIS moiety remained substantially constant throughout the 6- or 12- month implant dosing period. Overall, this study showed the potential of the DLP-114 device to offer durability benefits over and above currently available LAIs, along with potential safety benefits by being removable if needed. Future studies will explore higher plasma concentrations to allow for greater dosing flexibility.

This study was supported by the National Institute of Mental Health under Award # R44MH094036

Learning Objectives: 1. Discuss the importance of implantable device platforms as providing potential advantages over long-acting injectables, by extending intervals between doses, and having a long-acting formulation that is reversable should that be clinically needed 2. Show new data from a Phase 1 PK/safety study of an investigational device-based platform (DLP-114) designed to provide extended release of risperidone for up to 12 months after a single administration

Literature References Dankert ME, Brensinger CM, Ralph LN et al: Psychiatric health care provider attitudes towards implantable medication. Psychiatry Res. 2010;177:167-171.10.1016/j.psychres.2008.12.012

Chavda VP, Jogi G, Paiva-Santos AC et al: Biodegradable and removable implants for controlled drug delivery and release application. Expert Opinion on Drug Delivery. 2022;19:1177-1181.doi: 10.1080/17425247.2022.2110065

DESIGN OF A MOBILE MENTAL HEALTH STIGMA REDUCING INTERVENTION FOR BLACK ADULTS WITH DEPRESSION AND ANXIETY

Aderonke Bamgbose Pederson[*1], Blessing Adeleke*[1]

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Aderonke Bamgbose Pederson, Harvard Medical School/MGH

Abstract Specific purpose: Leveraging personal narratives to improve and optimize early engagement in treatment for Black patients who often delay treatment seeking due to high stigma and high mistrust of mental health services.

Content: Major depressive and anxiety disorders affect 57.3 million adults in the U.S. (ADAA; NIH, 2019; Ritchie and Roser, 2018). Stigma -- which refers to negative attitudes or beliefs about mental illness, or negative behaviors directed toward persons with mental illness (PWMI) (Corrigan et al., 2012) -- is a leading and fundamental cause of health inequities (Hatzenbuehler et al., 2013). Contact interventions, which are premised on the idea that positive and voluntary contact with PWMI can effectively reduce mental illness stigma (Cerully et al., 2018), are aimed at reducing stigma and improving health outcomes. Recent randomized controlled trials show that video-based contact has a comparable effect (to face-to-face contact) in reducing stigma (Faigin and Stein, 2008; Koike et al., 2018; Mehta et al., 2015; Thornicroft et al., 2016; Vinson et al., 2016). Interventions to reduce stigma among Black adults remain understudied (Mehta et al., 2015; Thornicroft et al., 2016), and the role of mistrust is rarely examined (Mehta et al., 2015; Thornicroft et al., 2016).

Methods: We conducted 14 key informant interview sessions (3 males and 5 females, ages 18-45). Eligibility included screening positive for moderate to severe depression or anxiety, and not being in routine mental health care (i.e. not receiving psychotherapy or pharmacologic intervention despite active symptoms of depression and/or anxiety). The interviews were transcribed, and preliminary coding was done using a grounded theory inductive analysis.

Intervention: Initial lab testing of video-based web-based app prototype has been completed. Final intervention component refinements are based on feedback from end-users (patients) and in consultation with a community advisory board.

Methods: Sample quotes from participants

EP03 (session 1)- "You never hear about people share their stories, which can be super empowering… and for people on the other end to receive it and process it. And maybe they relate to it. You know…pick up … practices that might be helpful."

EP14 (session 1) "…. I feel like… it would be good to listen to someone that looks very similar to you…there's some problems that as a Black woman we might not see eye to eye on as a from a Black man. Or you might have similar problems …that Black people go through."

EP02 (session 2) "I can connect with her because I feel like I come from a very religious family. And I related to her with the sense that people would judge and just say that you need to just pray away the mental illness … even if you need to take medication as well and prayer…."

EP08 (session 2) "…. Mental conversation in the context of a black community is still relatively new… never really men."

Findings: Key themes for the video based mobile app include importance of accessibility and affordability; optimal length of video narrative of 4-6 minutes; focus on end-users in design methods; representation of diverse experiences (e.g. based on race, ethnicity, and religiosity); and integration of the app into daily routines.

Implications: The intervention has public health impact and may be implemented in both clinical (outpatient clinics, emergency rooms) and non-clinical settings (community organizations, religious institutions) for optimization of health service engagement. This has important implications for increasing willingness to engage in psychotherapy or pharmacologic treatment.

Learning Objectives: Novel therapeutics will not reduce mental health disparities without considering how to engage patients who may have high stigma and high mistrust.
Video based personal narratives of mental illness diagnosis, treatment, relapse, and recovery have been show to reduce stigma and change short-term self report behavior.

Literature References Thornicroft, G., Mehta, N., Clement, S., Evans-Lacko, S., Doherty, M., Rose, D., Koschorke, M., Shidhaye, R., O'Reilly, C., and Henderson, C. (2016). Evidence for effective interventions to reduce mental-health-related stigma and discrimination. The Lancet, 387(10023), 1123-1132. https://doi.org/https://doi.org/10.1016/S0140-6736(15)00298-6
Vinson, E. S., Abdullah, T., and Brown, T. L. (2016). Mental Illness Stigma Intervention in African Americans: Examining Two Delivery Methods. J Nerv Ment Dis, 204(5), 400-403. https://doi.org/10.1097/nmd.0000000000000458

LOCALIZING HETEROGENOUS PATTERNS OF BRAIN ATROPHY IN SCHIZOPHRENIA TO A COMMON BRAIN NETWORK

Ahmed Makhlouf[*1], William Drew[1], Jacob Stubbs[2], Joseph Taylor[1], Donato Liloia[3], Jordan Grafman[4], David Silbersweig[1], Michael D. Fox[1], Shan Siddiqi[1]*

[1]Brigham and Women's Hospital, Harvard Medical School, [2]University of British Columbia, [3]University of Turin, Italy, [4]Northwestern University

Ahmed Makhlouf, Brigham and Women's Hospital, Harvard Medical School

Abstract: Schizophrenia presents marked heterogeneity in its neuroanatomical correlations across various neuroimaging studies, particularly regarding brain atrophy patterns. This variability impedes the development of reliable biomarkers or targeted interventions. Amidst this heterogeneity, we hypothesized that atrophy coordinates reported in published studies of patients with schizophrenia would converge to a common brain network unique to the disorder. Utilizing the human connectome as a wiring diagram, we employed coordinate network mapping —a method that identifies network-level connections between brain coordinates. Our analysis incorporated data from 113 published studies, totaling more than 11,000 individuals. Our sample included patients with schizophrenia (n=3,756), individuals at high risk for psychosis (n=1,507), and healthy controls (n=6,007). We identified a common brain network preferentially connected to atrophy coordinates in schizophrenia, which we refer to as the 'schizophrenia network.' After correcting for multiple comparisons (pFWE LESS THAN 0.05), the dorsal anterior cingulate cortex and the insula, bilaterally, emerged as peak brain regions in the network. The schizophrenia network is distinct from atrophy patterns observed in high risk individuals, normal aging (n=4,195), neurodegenerative disorders (n=3,707), and other

psychiatric conditions (n=3,432). The network also remains stable with disease progression and across various clusters of psychotic symptoms. A unique, stable, and unified schizophrenia network addresses a significant portion of the heterogeneity observed in atrophy studies. The stability of this network across disease progression underscores its potential as a trait-like characteristic, and its uniqueness suggests it could be useful for development of biomarkers and brain stimulation targets in patients with schizophrenia.

Learning Objectives: 1. Understand the concept of neuroanatomical heterogeneity in schizophrenia and how it complicates the identification of reliable biomarkers and targeted interventions for the disorder.

2. Learn about the use of coordinate network mapping- that is leveraging the human connectome to identify a common brain network associated with schizophrenia, and understand the potential implications for developing biomarkers and targets for brain stimulation therapies.

Literature References Dabiri M, Dehghani Firouzabadi F, et al. Neuroimaging in schizophrenia: A review article. Front Neurosci. 2022;16:1042814.

Yeo BT, Krienen FM, Sepulcre J, et al. The organization of the human cerebral cortex estimated by intrinsic functional connectivity. J Neurophysiol. 2011;106(3):1125-1165.

Thursday, May 30, 2024

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

Keynote Plenary

INNOVATIONS IN CLINICAL RESEARCH: BROADENING CLINICAL TRIAL METHODS, ENDPOINTS AND GOALS

Andrew Nierenberg, Massachusetts General Hospital

Overall Abstract: In this session of Innovations of Clinical Research, we will learn from Martina Pavlicova, PhD to provide a statistical perspective, Paul Kenny, PhD to speak on molecular biology and new drug development and Oleg Tcheremissine to present on the importance of understanding cellular biology.

MECHANISMS OF OPIOID REWARD AND AVERSION

Paul Kenny, Icahn School of Medicine at Mount Sinai

Abstract: Opioids that stimulate μ-opioid receptors (μORs) in the brain are highly addictive and their misuse is contributing to an unprecedented surge in drug overdose-related deaths in the United States.

In addition to their intrinsic rewarding properties, opioids can also evoke aversive reactions that protect against misuse. Cellular mechanisms that govern the interplay between opioid reward and aversion are poorly understood. We used whole-brain activity mapping to show that neurons in the dorsal peduncular nucleus (DPn), a relatively unexplored cortical territory of ventral prefrontal cortex, are highly responsive to the opioid oxycodone. Connectomic profiling revealed that DPn neurons innervate the parabrachial nucleus (PBn) and other brain regions known to regulate physiological and behavioral responses to opioids. Spatial and

single-nuclei transcriptomics resolved a unique population of cortical pyramidal neurons in the DPn that express μORs and project to the PBn. Optically stimulating these neurons or their terminals in the PBn evoked an aversive behavioral state that was reversed by oxycodone treatment. Further, disrupting μOR signaling in the DPn switched oxycodone from rewarding to aversive and exacerbated the severity of opioid withdrawal. These findings identify the DPn as a key substrate for the abuse liability of opioids.

Learning Objectives: Opioids elicit both rewarding and aversive effects that increase and decrease, respectively, risk of developing opioid use disorder.
A previously uncharacterized population of μOR-expressing pyramidal neurons spatially restricted to the DPn regulate the hedonic valence of opioids.

Literature References Ettenberg A, Pettit HO, Bloom FE, Koob GF. Heroin and cocaine intravenous self-administration in rats: mediation by separate neural systems. Psychopharmacology. 1982, 78: 204-209.
Reeves KC, et al. Mu opioid receptors on vGluT2-expressing glutamatergic neurons modulate opioid reward. Addict Biol 26. 2021, e12942.

CATALYSTS OF CHANGE: ADVANCING ALZHEIMER'S THERAPEUTICS THROUGH TARGETED INSIGHTS

Oleg Tcheremissine, Atrium Health

Abstract: Alzheimer's Disease (AD) is a progressive neurodegenerative disorder that affects millions of individuals and their families worldwide. The main pathophysiological features of AD include intraneuronal neurofibrillary tangles, formation of A β-plaques, and neurodegeneration.
The "amyloid cascade" hypothesis emerged in the 1990s after the discovery of amyloid-precursor protein (APP) and three rare genetic mutations implicated in the formation of amyloid-β proteins. The sequential cleavage of APP by betta- and gamma-secretase results in 2 primary amyloid species: Aβ-40 and Aβ-42. Aβ sub-species can penetrate the blood-brain barrier freely.

Only a few pharmacological agents, donepezil, galantamine, memantine, and rivastigmine, were approved for treating AD symptoms until 2021, but they did not target Aβ accumulation in the brain.

In recent years, a new class of therapeutics has emerged aimed at reducing amyloid β levels in the brain. These therapeutics have the potential to slow down or even block further synaptic loss, axon degeneration, and neuronal death. The successful development of these new therapeutics was primarily based on the ability to incorporate validated molecular targets to characterize biological processes objectively and quantifiably.

This presentation aims to provide an overview of the critical role of these biological targets in drug development.

Learning Objectives: 1. Overview of the amyloid cascade.
2. Recognize the importance of validated molecular target for successful drug development in Alzheimer's disorder.

Literature References 1. Hardy JA, Higgins GA. Alzheimer's Disease: the amyloid cascade hypothesis. Science.1992; 156.

2. Kumar A, Nemeroff CB, Cooper JJ, et al. Amyloid and Tau in Alzheimer's Disease: Biomarkers or Molecular targets for Therapy? Are shooting the messenger? Am J Psychiatry. 2021; 178 (11)

EMERGING INNOVATIONS IN CLINICAL TRIALS FOR PSYCHIATRY

Martina Pavlicova, Columbia University Medical Center

Abstract: The landscape of clinical trials in psychiatry is transformed with the integration of advanced technologies. This talk will outline technological innovations that are reshaping psychiatric research methodologies, including the integration of Artificial Intelligence (AI), the expansion of decentralized trial models, and the rise of wearable devices and sensors in data collection. We also delve into the concept of target trial emulation, the role of Electronic Medical Records (EMR) mining in refining patient recruitment processes, and the introduction of e-consent platforms represents a significant leap towards improving participant engagement and streamlining the consent process. This presentation aims to provide an insightful overview of how these technological advancements are facilitating more personalized, efficient, and patient-centric approaches in the realm of psychiatric clinical trials.
Learning Objectives: 1. Understand the role and impact of technological advancements and methodological innovations in Psychiatric Clinical Trials
2. Recognize the importance of innovative approaches in enhancing patient engagement and treatment personalization in psychiatry

Literature References Dwyer, D. B., Falkai, P., and Koutsouleris, N. (2018). Machine Learning Approaches for Clinical Psychology and Psychiatry. Annual review of clinical psychology, 14, 91–118. https://doi.org/10.1146/annurev-clinpsy-032816-045037
Hernán MA, Wang W, Leaf DE. Target Trial Emulation: A Framework for Causal Inference From Observational Data. JAMA. 2022;328(24):2446–2447. doi:10.1001/jama.2022.21383

10:00 a.m. - 11:30 a.m.

Update from Federal and Other Funding Agencies

UPDATE FROM FEDERAL AND OTHER FUNDING AGENCIES

Joseph Goldberg, Icahn School of Medicine at Mount Sinai

Overall Abstract: Continuing with long-standing tradition, this is the much-anticipated 2024 Update From Federal and Other Funding Agencies Plenary. Alphabet soup never tasted so good! Hear updates from NIMH, PCORI, NIDA, and the VHA.

TAILORING TREATMENTS FOR MENTAL ILLNESS

Christopher Sarampote, National Institute of Mental Health

Abstract: Effective treatments for mental illnesses exist, yet tailoring treatment for individuals is often a trial-and-error process that can lead to unacceptable delays in receiving effective treatment. NIMH is supporting research as part of its new Precision Psychiatry Initiative, a program that focuses on two parallel areas of need: biomarker development and precision

diagnostics. Research conducted as part of this effort will also focus on developing and testing quantitative, clinically relevant tools for use by clinicians in making treatment recommendations for individual patients, leading to better understanding and more effective treatments for mental illnesses. Further, this research may lay the groundwork for innovative clinical research approaches that can reach populations in need of care, such as individuals experiencing first episode psychosis.

Learning Objectives: 1. Describe the importance of advancing precision medicine research. 2. Receive an update on NIMH's precision psychiatry and clinical research approaches

Literature References Brady, L.S., Lisanby, S.H., Gordon, J.A. New directions in psychiatric drug development: promising therapeutics in the pipeline. Expert Opinion on Drug Discovery. 2023; 18(8); 835-850.

Deng, Z.-D., Luber, B., McClintock, S. M., Weiner, R. D., Husain, M. N., Lisanby, S. H. Clinical outcomes of magnetic seizure therapy vs electroconvulsive therapy for major depressive episode: A randomized clinical trial. JAMA Psychiatry. 2024;81(3):240-249.

NATIONAL INSTITUTE ON DRUG ABUSE UPDATE

Ivan Montoya, DHHS/National Institute on Drug Abuse

Abstract: The National Institute on Drug Abuse (NIDA) is one of the Institutes/Centers of the National Institutes of Health (NIH). The mission of NIDA is to advance the scientific understanding of substance use disorders (SUD) and addiction and use that knowledge to improve public health. NIDA supports or conducts research on the causes and medical and psychosocial consequences of SUDs and addiction, new approaches to prevent and treat them, new tools to reduce their harm, and disseminate the new knowledge generated by the research. Overall, NIDA works to ensure science informs drug abuse prevention and treatment efforts and reduces the public health burden of SUD and addiction. The purpose of this presentation is to provide an update about the scientific progress and activities conducted or supported by NIDA and the scientific gaps and opportunities to advance the science of SUD and addiction to have a significant public health impact.

Learning Objectives: At the end of the presentation, participants will: 1) gain knowledge about the mission of NIDA and the most recent scientific advances in the research supported or conducted by NIDA, and 2) learn about the research gaps and opportunities in the SUD and addiction field.

Literature References: Montoya ID, Volkow ND. New strategies for medications to treat substance use disorders. Pharmacol Res. 2024 Feb;200:107078. doi: 10.1016/j.phrs.2024.107078. Epub 2024 Jan 20. PMID: 38246477; PMCID: PMC10922847.

Valentino RJ, Nair SG, Volkow ND. Neuroscience in addiction research. J Neural Transm (Vienna). 2023 Nov 10. doi: 10.1007/s00702-023-02713-7. PMID: 37947883.

NIAAA UPDATE: FOCUS ON THE MEDICATIONS DEVELOPMENT PROGRAM

Daniel Falk, NIAAA/NIH

Abstract: Alcohol Use Disorder (AUD) is a prevalent and complex disorder that results in a variety of medical, psychological, social, and economic problems. More than 29.5 million

Americans are diagnosed with AUD each year, resulting in over 178,000 deaths from alcohol-related causes. Alcohol misuse costs American society more than $249 billion annually. To date, the Food and Drug Administration (FDA) has approved three medications for AUD treatment: disulfiram, acamprosate, and naltrexone, which is available in both oral and long-acting injectable formulations. In addition, several other repurposed compounds have shown efficacy for treating AUD, including nalmefene, baclofen, topiramate, gabapentin, and varenicline. The FDA approved medications are an effective and important aid in the treatment of people with AUD. Given the diverse biological processes that contribute to alcohol use disorder, new medications are needed to provide a broader spectrum of treatment options. To provide more treatment options for AUD, it is critical to identify new medications that are efficacious for reducing alcohol consumption.

This presentation will focus on the National Institute on Alcohol Abuse and Alcoholism's (NIAAA) Medications Development program, highlighting priority areas of interest and providing an overview of the AUD pharmacotherapy portfolio. Grant and contract mechanisms that may be of interest to the ASCP community will be described. These include NIAAA's IND-enabling program and Alcohol Pharmacotherapy Evaluation Program (APEP). Other priority areas of interest will be described, including precision medicine, endpoints for Phase III pharmacotherapy trials, and NIAAA-sponsored public resources related to the treatment of AUD (NIAAA Data Archive, Rethinking Drinking, NIAAA Treatment Navigator, and NIAAA Health Care Professional's Core Resource).

More information about NIAAA's Medication Development program is available at: https://www.niaaa.nih.gov/research/extramural-research/division-treatment-and-recovery-dtr

Learning Objectives: 1. To understand NIAAA's Medications Development Program, including the AUD medication pipeline, current portfolio, and programmatic priorities.
2. To understand NIAAA-sponsored public resources related to the treatment of AUD.

Literature References: 1. Litten RZ, Falk DE, Ryan ML, Fertig J, Leggio L. Five priority areas for improving medications development for alcohol use disorder and promoting their routine use in clinical practice. Alcohol Clin Exp Res. 2020 Jan;44(1):23-35. doi: 10.1111/acer.14233. Epub 2019 Dec 5. PMID: 31803968.
2. Litten RZ, Wilford BB, Falk DE, Ryan ML, Fertig JB. Potential medications for the treatment of alcohol use disorder: An evaluation of clinical efficacy and safety. Subst Abus. 2016 Apr-Jun;37(2):286-98. doi: 10.1080/08897077.2015.1133472. PMID: 26928397.

UPDATES FROM VETERANS HEALTH ADMINISTRATION OFFICE OF RESEARCH AND DEVELOPMENT

Lori Davis, Veterans Affairs Medical Center

Abstract: This presentation will cover the research portfolio and strategy for the Veterans Health Administration (VHA) research mission. The presenter will discuss recent funding opportunities that apply to psychopharmacology and mental health conditions, including a recent funding opportunity announcement for studies that focus on psychedelics for the treatment of mental health conditions.

Learning Objectives: The participant will understand the VA research funding mechanisms. The participant will be familiar with VA funding opportunities and priorities.

Literature References: Wray, C. M., Myers, U., Slightam, C., Dardashti, N., Heyworth, L., Lewinski, A., Kaboli, P., Edes, T., Trueman, K., and Zulman, D. M. (2024). Research Priorities to Expand Virtual Care Access for Patients in the Veterans Affairs Health Care

System. Journal of general internal medicine, 39(Suppl 1), 14–20. https://doi.org/10.1007/s11606-023-08463-2
McNeal, D. M., Fehling, K., Ho, P. M., Kaboli, P., Shimada, S., Saini, S. D., Youles, B., and Albright, K. (2022). Engaging Stakeholders in Identifying Access Research Priorities for the Department of Veterans Affairs. Journal of general internal medicine, 37(Suppl 1), 14–21. https://doi.org/10.1007/s11606-021-07195-5

UPDATE FROM DEFENSE HEALTH AGENCY PSYCHOLOGICAL HEALTH RESEARCH PORTFOLIO

Fuad Issa, Defense Health Agency

Abstract: Defense Health Agency (DHA) is in the process of developing nine Strategic Research Plans (SRPs) to guide research investments in their respective areas to lead the discovery of innovative medical solutions responsive to the needs of Combatant Commands, the Military Services, and the Military Health System. The DHA Deputy Assistant Director for Research and Engineering employs the SRPs to inform and describe how DoD medical capabilities will be developed over time. These SRPs will drive investment recommendations for Future Years Defense Program plans and serve as a critical tool for aligning investments with military medical health priorities. This presentation will provide an overview of the development of the Psychological Health SRP, and the two available funding mechanisms for extramural funding.
Learning Objectives: - The participant will be knowledgeable on recently approved DHA Strategic Research Plan
- The participant will be informed on the different mechanisms for extramural research funding from DHA

Literature References - Establishment of the DHA. DoD Directive, 5136.13 September 30, 2013https://www.esd.whs.mil/Portals/54/Documents/DD/issuances/dodd/513613p.pdf
- IN FOCUS, Congressional Research Service, "Defense Primer: RDT and E," updated November 10, 2022, https://crsreports.congress.gov/product/pdf/IF/IF10553

PATIENT-CENTERED COMPARATIVE EFFECTIVENESS RESEARCH

Yu-Ping Wang, Patient-Centered Outcomes Research Institute (PCORI)

Abstract Engaging patients, caregivers, clinicians, and other healthcare community members is at the core of PCORI's patient-centered approach to research funding. Our goal is to support research that will provide reliable, useful information to help people make informed healthcare decisions and improve patient care and outcomes.
Learning Objectives: Objectives:
Learn about funding opportunities patient-centered comparative clinical effectiveness research

Understand foundational expectations for patient-engagement in clinical research

Literature References PCORI's Foundational Expectations for Partnerships in Research. https://www.pcori.org/engagement/engagement-resources
Selby, Joe and Whitlock, Evelyn and Sherman, Kelly and Slutsky, Jean. (2018). The Role of Comparative Effectiveness Research. 10.1016/B978-0-12-849905-4.00019-8.

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

Panels

^MODERN CLINICAL TRIAL DESIGNS FOR HETEROGENEOUS DISORDERS: NEW APPLICATIONS OF AGGREGATED AND INDIVIDUAL N-OF-1 TRIALS IN PSYCHIATRY

Rebecca Hendrickson, VA Puget Sound Health Care System

Overall Abstract: In psychiatry, heterogeneity in both pathobiology and treatment response is the rule rather than the exception. Although the need to identify pathophysiologically similar subgroups and predictors of treatment response is widely recognized, traditional parallel-group clinical trials are poorly optimized for these goals. An alternative trial design, known as N-of-1 trials or multiple crossover block trials, involve one or more individuals who each move back and forth between treatment conditions, such as active treatment to placebo or active treatment to active treatment. These trial designs have long been used both to characterize the specific response to active treatment versus placebo or other active treatments for individuals, and, when analyzed across a cohort in an aggregated n-of-1 design, to test hypotheses about both average treatment response patterns and specific predictors or correlates of treatment response. N-of-1 designs have also been used to improve participant engagement and benefit in clinical trials, and to improve recruitment of participants who might otherwise avoid enrollment in a trial with a pure placebo group.

Recently, there have been significant advances in the statistical methods available to design, implement and interpret N-of-1 trials, improving trial efficiency and the handling of issues such as power calculations and carryover effects. Here, a panel consisting of two experts in n-of-1 statistical methods development and two psychiatric clinical trialists currently using aggregated n-of-1 clinical trial designs will describe recent methodological advances and provide examples of their application to current questions in psychopharmacologic research. Together, the presentations will provide an overview of how those interested in asking questions about the causes and predictors of variation in treatment risk and response in psychiatric research can use these types of methods to improve clinical outcomes.

Specifically, Dr. Schork will describe methods for optimizing dosing strategies, monitoring protocols and statistical inference techniques when using n-of-1 clinical trial designs to characterize response variation, while Dr. Diaz will present methods for optimally selecting the number of treatment cycles and for extracting estimates of disease severity from such designs. Dr. Hendrickson will provide an example of applying an aggregated n-of-1 trial design to test the relationships of baseline biomarkers to treatment response in a trial of prazosin for PTSD, including both methods for power calculations and analysis of such precision medicine-focused n-of-1 clinical trial designs, and the impact of these methods on trial engagement and outcomes. Dr. Davis will present an example of how an aggregated n-of-1 approach is being used in a new multi-site trial of methylphenidate for neurocognitive complaints in PTSD, including how brief repeated time point assessments are being integrated both within and across blocks. Finally, distinguished psychopharmacology researcher Dr. Rapaport will serve as discussant, helping to contextualize the presentations and their potential relationship to current key goals in our field.

Learning Objectives: 1) Participants will be able to describe the motivations for using n-of-1 clinical trial designs in psychiatry, as well as some of the challenges that come with these trial designs.
2) Participants will learn about new approaches to optimizing n-of-1 clinical trials, including strategies to select trial designs and to address common challenges such as carryover effects.

Literary References: 1. Schork NJ, Beaulieu-Jones B, Liang WS, Smalley S, Goetz LH. Exploring human biology with N-of-1 clinical trials. Cambridge Prisms: Precision Medicine Volume 1, Cambridge University Press, 2023 January 10; e12.
2. Hendrickson RC, Thomas RG, Schork NH, Raskind MA. Optimizing aggregated N-of-1 trial designs for predictive biomarker validation: Statistical methods and theoretical findings. Frontiers in Digital Health. 2020 Aug 28; Vol 2.

EXPLORING VARIATION IN TREATMENT RESPONSE USING AGGREGATED N-OF-1 CLINICAL TRIALS

Nicholas Schork, The Translational Genomics Research Institute

Individual Abstract: Most population-based clinical trials (e.g., traditional randomized controlled trials or RCTs) focus on the average response of the trial participants to an intervention, often comparing that average response to the average response of trial participants randomized to receive a placebo or comparator intervention to make broad claims about the efficacy of the intervention in the population at large. However, it is well known that individuals respond differently to interventions based their unique genetic, epigenetic, physiological, environmental exposure, and behavioral profiles. Although strategies for characterizing response variation exist that leverage data from traditional population based RCTs, they are often ad hoc and secondary to the primary aim of testing the average response. N-of-1 and aggregated N-of-1 trials can be designed to explicitly explore variation in intervention responses. In this this talk, I describe study designs and analytical methods to explore inter (and intra) individual variation in intervention responses. These designs take advantage of novel dosing strategies, monitoring protocols, and statistical inference techniques. They can also be used in a wide variety of real-world clinical settings, including complex clinical settings involving drugs used to treat neuropsychiatric conditions but appropriate phenotypic and pharmacodynamic biomarkers are needed. I show that the optimal designs to explore response variation can have opposite elements in them to optimal designs to explore average responses. Ultimately, the proposed strategies and methods are meant to not just help determine if an intervention works on average, but rather which individuals that intervention benefits and why.
Learning Objectives: 1. Appreciate the difference between average response and differential response in randomized clinical trials; 2. Understand that novel trials designs are needed to explore response variation in an era of precision medicine.
Literature References Schork NJ, Beaulieu-Jones B, Liang WS, Smalley S, Goetz LH. Exploring human biology with N-of-1 clinical trials. Camb Prism Precis Med. 2023;1:e12. doi: 10.1017/pcm.2022.15. Epub 2023 Jan 10.
PMID: 37255593.

Schork NJ.Accommodating Serial Correlation and Sequential Design Elements in Personalized Studies and Aggregated Personalized Studies. Harv Data Sci Rev. 2022;2022(SI3):10.1162/99608f92.f1eef6f4. doi: 10.1162/99608f92.f1eef6f4. Epub 2022 Sep 8. PMID: 37032736

PTSD, PUPILS, PRAZOSIN, AND PERSONALIZED MEDICINE: TESTING A PREDICTIVE BIOMARKER OF PTSD TREATMENT RESPONSE USING AN AGGREGATED N-OF-1 CLINICAL TRIAL DESIGN

Rebecca Hendrickson, VA Puget Sound Health Care System

Individual Abstract: Abstract. Despite the availability of a wide variety of effective treatments for PTSD, all show significant variability in their efficacy for individuals. Although this is presumed to relate at least in part to differences in the underlying pathophysiology of PTSD between even patients who appear clinically similar, we do not currently have validated methods for identifying these differences in underlying pathophysiology or for predicting who is likely to respond to which treatment. This leads to challenges both in matching patients with effective treatments, and in the development and validation of new treatment options, as this type of unmeasured heterogeneity in treatment response means that differences in population and recruitment patterns can significantly influence the outcome of clinical trials.

One strategy for addressing these types of challenges is to use clinical trial designs that assess not just the average response to treatment across a cohort, but which move each participant back and forth between active treatment and placebo in order to achieve a statistically meaningful estimate of the response of each individual to treatment versus placebo. Such aggregated N-of-1 trial designs allow increased insight into the role of underlying heterogeneity in determining clinical trial results, more effective hypothesis testing of the ability of baseline clinical and biologic characteristics to predict treatment response, and can also allow adaptations of the trial design to better meet the needs and goals of the clinical population of interest, improving recruitment and trial engagement.

Here, we present the application of this approach to a personalized medicine focused randomized clinical trial of prazosin for PTSD. The PREDICT trial, which is scheduled to be completed shortly before the annual meeting, begins by enrolling participants in an open-label treatment and stabilization phase that allows the enrollment of high-acuity participants for whom a traditional parallel group placebo controlled trial would rarely be appealing, then offers continuation into a blinded discontinuation phase following by two crossover blocks. The aims of the trial focus on testing the ability of baseline biomarkers of noradrenergic signaling, including pupillometry and orthostatic blood pressure measurements, to predict participants' response to prazosin versus placebo.

This presentation will focus on the motivation for the aggregated N-of-1 trial design used, the statistical methods that were developed to flexibly perform power calculations for precision medicine focused hypotheses as a function of clinical trial design including N-of-1 trial designs, statistical methods that were developed to implement the analysis of these results including the handling of carryover effects, and results of the trial in terms of participant engagement and treatment response. Preliminary results of the primary aims, relating baseline biomarkers to treatment response, will be presented as available at the time of the meeting.

Learning Objectives: 1) Participants will be able to describe the relative advantages of parallel group placebo controlled trials versus aggregated n-of-1 placebo controlled trials for testing hypotheses about baseline predictors of treatment response.
2) Participants will understand some of the pragmatic challenges and strengths of aggregated n-of-1 trials in psychiatric pharmacotherapy trials.

Literature References 1) RC Hendrickson, RG Thomas, NJ Schork, MA Raskind. Optimizing aggregated n-of-1 trial designs for predictive biomarker validation: statistical methods and theoretical findings. Frontiers in Digital Health. 2020: 2(13).
2) RC Hendrickson, MA Raskind. Noradrenergic dysregulation in the pathophysiology of PTSD. Experimental neurology. 2016: 284, p181-195.

ESTIMATING THE OPTIMAL NUMBER OF TREATMENT CYCLES FOR TREATMENT INDIVIDUALIZATION IN N-OF-1 TRIALS

Francisco Diaz, Deparment of Biostatistics and Data Science, The University of Kansas Medical Center

Individual Abstract: We present an application of certain superiority or equivalence trials that have a special cross-over design and are conducted with patient samples. Clinicians can use the information from these trials to improve treatment individualization in N-of-1 trials when improvement is possible, and investigators can determine whether individualization will be productive. The cross-over trials also allow solving the important problem of estimating the optimal number of treatment cycles in an N-of-1 trial. We follow a frequentist framework for the analysis of disease severities and treatment individual benefits based on regression models with random coefficients and measure the patient's disease severity using partial empirical Bayes (PEB). We measure the relative extent to which PEB improves the prediction error of post treatment disease severity by comparing its mean square error with that of the common treatment-without-individualization approach that prescribes only the treatment superior on average. The number of treatment cycles providing substantial relative improvement in prediction error, say 80%, is the optimal number. We illustrate with a crossover trial of hypertensive patients.
Learning Objectives: 1) To familiarize with an application of empirical Bayesian prediction to personalized medicine in the context of N-of-1 trials. 2) To learn how to calculate the optimal number of treatment cycles required to predict accurately the post-treatment severity of a chronic disease in an N-of-1 trial, in order to make appropriate decisions on treatment individualization.
Literature References Diaz FJ. Using population cross-over trials to improve the decision process regarding treatment individualization in N-of-1 trials. Stat. Med. 2021; 40: 4345-4361.
Diaz FJ. Measuring the individual benefit of a medical or behavioral treatment using generalized linear mixed-effects models. Stat. Med. 2016; 35: 4077-4092.

TREATMENT OF POST-TRAUMATIC STRESS DISORDER WITH ASSOCIATED NEUROCOGNITIVE COMPLAINTS: RATIONALE FOR A RANDOMIZED N-OF-1 TRIAL OF METHYLPHENIDATE

Lori Davis, Veterans Affairs Medical Center

Individual Abstract: Background: Subjective cognitive dysfunction is common in mood and anxiety disorders in general, and with post-traumatic stress disorder (PTSD) in particular. The use of stimulants to address cognitive symptoms that are comorbid with PTSD has increased significantly, according to VA archival clinical data. However, evidence to guide such use remains limited. While there are theoretical reasons to be concerned that stimulant medications might increase PTSD symptoms, a small pilot study by Stein and colleagues found that that low dose methylphenidate reduced both cognitive and PTSD symptoms in a small sample of individuals diagnosed with PTSD and/or a history of traumatic brain injury. Additional information clarifying both the potential risks and benefits of stimulant medications in patients with PTSD and subjective cognitive complaints, including whether there are subpopulations who may be more likely to experience benefit or adverse effects, is urgently needed to support clinical decision making.

Stimulant medications are an ideal candidate for aggregated n-of-1 clinical trial designs. They are rapidly acting, with the subjective and objectively measured benefits typically lasting for the period of pharmacologic action of the medication. At lower doses, such as those for which benefit has been observed in PTSD, they do not require titration or tapering. In addition, PTSD is a highly heterogeneous disorder, with evidence for significant variation in both underlying pathophysiology and in treatment response. It is also common for PTSD to be a chronic condition, with symptoms that are treated by a medication generally recurring when that medication is stopped.

Methods: Here, we describe the design and implementation process of a recently launched randomized placebo-controlled n-of-1 clinical trial of methylphenidate for PTSD with associated cognitive symptoms. This double-blind randomized trial is expected to enroll N=70 veterans who will each move between 4 total blocks of 4-week treatment with methylphenidate versus placebo separated by a 1-week washout. Both remote and in person assessments of PTSD symptoms and cognitive functioning are included as endpoints, to maximize the statistical advantages of repeated assessments in an n-of-1 trial design.

Methods: In this presentation, we will use this currently running clinical trial and the process by which it was planned to illustrate some of the advantages and challenges of n-of-1 clinical trial designs in real-world clinical trial settings in psychiatry. Since the trial is ongoing, no results of the current study will be presented, however, pilot study results and meta-analysis will be presented. The presentation will include a discussion of strategies that are being used to improve not just the scientific validity and efficiency of the results, but also the benefit of participation for Veterans who are participating in the trial.

Importance: An aggregated n-of-1 clinical trial design is ideal for increasing our understanding of not just the average impact of stimulants on PTSD and comorbid neurocognitive symptoms, but also baseline characteristics that may predict who is more or less likely to experience benefit or side effects from this treatment.

Learning Objectives: The participant will understand the rationale for the n-of-1 design for a randomized trial for testing a short-acting medication in the treatment of post-traumatic stress disorder with associated neurocognitive complaints.

The participant will recognize the mechanism of action and the efficacy of methylphenidate in the treatment of post-traumatic stress disorder with associated neurocognitive complaints.

Literature References Krogh HB, Storebø OJ, Faltinsen E, et al. Methodological advantages and disadvantages of parallel and crossover randomised clinical trials on methylphenidate for attention deficit hyperactivity disorder: a systematic review and meta-analyses. BMJ Open. 2019;9(3), e026478.

McAllister TW, Zafonte R, Jain S, et al. Randomized Placebo-Controlled Trial of Methylphenidate or Galantamine for Persistent Emotional and Cognitive Symptoms Associated with PTSD and/or Traumatic Brain Injury. Neuropsychopharmacology. 2016;41(5), 1191–1198.

*#EARLY RESULTS FROM THE NIMH-FUNDED EARLY PSYCHOSIS INTERVENTION NETWORK (EPINET)

John Kane, The Donald and Barbara Zucker School of Medicine at Hofstra/Northwell

Overall Abstract: Early Results From The NIMH-funded Early Psychosis Intervention Network (EPINET)
The NIMH Early Psychosis Intervention Network (EPINET) supports the systematic collection of data from over 100 clinics across the U.S. that are delivering coordinated specialty care (CSC) to individuals with first episode and early phase psychosis. The major goal of EPINET is to improve the early phase care by learning from the data that has been collected across all sites using a standardized assessment battery.

This panel will present and review early results from the EPINET program including rates of hospitalization/ER visits and the use of various pharmacologic agents.

Our initial data review indicates that 47% of patients while in CSC treatment are hospitalized or have an emergency room visit within two years. Alan Breier will present and discuss these data from a variety of perspectives.

Some factors that are related to hospitalization such as homelessness or socioeconomic status are difficult for most clinics to change. One factor that clinics can change is the medications provided. Long-acting injectable antipsychotics (LAIs) and clozapine are the most effective medications in preventing relapse and hospitalization. However, there are big differences in utilization of these medications across our EPINET hubs: the utilization of LAIs ranges from 10-36% and clozapine 3-16%. John Kane will present and discuss these data and address strategies to facilitate increased utilization of these agents when appropriate.

Delbert Robinson, utilizing data from ESPRITO (an EPINET consortium hub with clinics in 6 US states), will review patterns of psychopharmacologic treatment provided for individuals who had been in CSC treatment for 6 months or less, 7 to 12 months, 13 to 18 months and 19 to 24 months. This interim analysis is from the first 775 participants.

Susan Azrin will serve as the discussant for the panel.

Learning Objectives: To familiarize attendees with current evidenced based pharmacologic treatment for first episode and early phase schizophrenia.
To review obstacles and challenges in implementing research findings into clinical practice in the context of coordinated specialty care.

Literary References: Kane, J. M., Robinson, D. G., Schooler, N. R., Mueser, K. T., Penn, D. L., Rosenheck, R. A., ... and Heinssen, R. K. (2016). Comprehensive versus usual community care for first-episode psychosis: 2-year outcomes from the NIMH RAISE early treatment program. American Journal of Psychiatry, 173(4), 362-372.

Kane, J. M., Schooler, N. R., Marcy, P., Correll, C. U., Achtyes, E. D., Gibbons, R. D., and Robinson, D. G. (2020). Effect of long-acting injectable antipsychotics vs usual care on time to first hospitalization in early-phase schizophrenia: a randomized clinical trial. JAMA psychiatry, 77(12), 1217-1224.

LONGITUDINAL HOSPITALIZATION RATES IN EARLY PSYCHOSIS ASSOCIATED WITH COORDINATED SPECIALTY CARE: AN EPINET ASSESSMENT

Alan Breier, Indiana University School of Medicine

Individual Abstract: Background: Hospitalization is a critically important clinical endpoint as it disrupts continuity of care, creates substantial distress for participants and family members and is a major driver of health care costs. In this paper, we examined the longitudinal rates of hospitalizations in Early Psychosis (EP) participants enrolled in the Early Psychosis Intervention Network (EPINET). EPINET is a NIMH funded national network of CSC EP clinics organized into 8 multisite, centralized hubs with over 100 connected (spoke) clinics and 4,000 patients enrolled.

Methods: Each clinic utilizes a common core assessment battery (CAB) that is administered at baseline and at subsequent serial 6-month intervals up to 24 months. The CAB contains a range of validated clinical instruments and includes hospitalization incidence, episodes and days hospitalized. Two samples were used in this paper: An EPINET-wide group drawn from all 8 hubs and a subsample form one hub – the Academic-Community-EPINET comprised of 6 academic CSC clinics.

Methods: The EPINET-wide sample was comprised of 3,527 newly enrolled patients. Rates of hospitalizations/ER visits for psychiatric reasons at the 6-month serial assessment periods were as follows: 6-month 15%; 12-month 12%; 18-month 11%; and at 24-month 9% for a cumulative hospitalization rate of 47% over 2 years. The AC-EPINET subsample was comprised of a total of 572 newly enrolled EP participants. In the 6-month period prior to enrollment (baseline) 272, or 47.55% of the sample reported hospitalization for psychiatric reasons (ER visits not included).

Post-baseline rates were 13.60% at 6-months (N = 48) and 13.58% at 12-month (N = 33) and were both significantly lower than pre-baseline rates (p LESS THAN 0.001). Of those who endorsed hospitalization, the preponderance had only one episode of hospitalization at baseline (70.22%), 6 months (66.7%), and 12 months (63.64%). In terms of the number of days spent in the hospital, the central tendency remained relatively static with the median (IQR) being 11 (12) days at baseline, 9 (10) days at 6 months, and 10 (15) days at 12 months. Preliminary associations with other variables of interest suggests associations between hospitalization at baseline and DUP (rpb = -.18, p LESS THAN .001, N = 551) and marijuana use at baseline and hospitalization at baseline (rpb = .12, p LESS THAN .01, N = 424) and 6 months (rpb = .13, p LESS THAN .05, N = 270).

Conclusions: The EPINET 2-year cumulative 47% hospitalization rate is concerning. The longitudinal patterns of hospitalizations indicate relatively stable rates during CSC care with downward trending over time. In the AC-EPINET subsample, high rates of hospitalizations before EPINET enrollment may reflect the common practice of referral to EP clinics following

hospitalization. The reduced hospitalization over time suggests a salutary trend of the EPINET CSC model of care. Additional assessments of predictors of hospitalization will be presented.

Learning Objectives: To know the 2-year composite hospitalization rates for CSC patents in EPINET.
To list one baseline correlate of hospitalizations for CSC patients in EPINET.

Literature References Robinson DG et al. Predicators of hospitalization of individuals with first-episode psychosis: Data from a 2-year follow-up of the RAISE-ETP. Psychiatric Services. 2019; 70:59-577
Nossell, I, et al Results of a coordinated specialty hospital care program for early psychosis and predictors of outcomes. Psychiatric Services 2018; 69:863-870

THE UTILIZATION OF LONG-ACTING INJECTABLE ANTIPSYCHOTICS AND CLOZAPINE IN EARLY PHASE PATIENTS: DATA FROM EPINET

John Kane, The Donald and Barbara Zucker School of Medicine at Hofstra/Northwell

Individual Abstract: Background: The pharmacologic treatment of first episode schizophrenia is challenging due to client and family distress and uncertainty and - in some cases - reluctance to acknowledge the presence or seriousness of the condition. At the same time, evidence suggests that the extent to which the illness can be adequately treated and managed in the early phase has prognostic implications for future improvement and recovery. In terms of pharmacologic treatment, the key evidence-based goals are the alleviation of acute positive psychotic signs and symptoms, stabilization and prevention of subsequent relapse and hospitalization with all the associated social, vocational, emotional, familial, and societal burdens. The ultimate goal is recovery, but positive symptoms and repeated hospitalizations are a clear, immediate impediment.
Even with state-of-the-art care (coordinated specialty care/early intervention services) the mean rate of hospitalization among first episode patients over the course of 1 ½ -2 years was shown to be 32%.1 At the same time long-acting injectable (LAI) formulations and clozapine have been found to be the most effective pharmacologic strategies for significantly reducing the risk of hospitalization.2

Methods: The NIMH-funded Early Psychosis Intervention Network (EPINET) supports the systematic collection of data from over 100 clinics participating in eight "hubs" across the U.S. that are delivering coordinated specialty care (CSC) to first episode and early phase schizophrenia patients. We examined data from the first 2,150 patients enrolled in the eight EPINET hubs. Given the potential value of LAIs and clozapine we were interested in seeing the extent to which these medications are being utilized in early phase patients. This is an illness stage in which 15-20% of patients are already treatment resistant and are potential candidates for clozapine. In addition, as indicated above, even patients receiving coordinated specialty care have a high rate of hospitalization. Data from EPINET to be presented by Alan Breier in the proposed panel indicate a 47% incidence of hospitalization or ER visits over the first wo years of EPINET participation.

Methods: Examining treatment records of the first 2,150 individuals enrolled in EPINET we found the range of LAI utilization across the eight hubs to be 10%-36% and that for clozapine to be 3%-16%.

Conclusions: These results indicate considerable differences in practice patterns across a broad array of clinics delivering coordinated specialty care in the U.S. Though patient demography and characteristics can vary from clinic to clinic such heterogeneity does not account for this degree of disparity in treatment practice. We are designing implementation science strategies to address this challenge.

Learning Objectives: To present and discuss data on evidenced based pharmacologic treatment disparities across a broad range of clinics delivering coordinated specialty care to first episode and early phase schizophrenia patients.
To review and discuss potential obstacles and barriers to the implementation of evidenced based psychopharmacology.

Literature References Correll, C. U., Galling, B., Pawar, A., Krivko, A., Bonetto, C., Ruggeri, M., ... and Kane, J. M. (2018). Comparison of early intervention services vs treatment as usual for early-phase psychosis: a systematic review, meta-analysis, and meta-regression. JAMA psychiatry, 75(6), 555-565.
Tiihonen, J., Mittendorfer-Rutz, E., Majak, M., Mehtälä, J., Hoti, F., Jedenius, E., ... and Taipale, H. (2017). Real-world effectiveness of antipsychotic treatments in a nationwide cohort of 29 823 patients with schizophrenia. JAMA psychiatry, 74(7), 686-693.

MEDICATION TREATMENT DATA FROM A CONSORTIUM OF 13 CLINICS PROVIDING COORDINATED SPECIALTY CARE FOR INDIVIDUALS WITH FIRST EPISODE PSYCHOSIS

Delbert Robinson, Hofstra NS-LIJ School of Medicine

Individual Abstract: Background: The NIMH-funded EPINET project consists of 8 grants (named hubs) that support consortiums of clinics providing coordinated specialty care (CSC) for individuals with first episode psychosis. ESPRITO is a hub with clinics in 6 US states.
Methods: Each clinic within a hub assesses participants with a Core Assessment Battery (CAB) every 6 months. For examination of treatment patterns, we examined patterns of treatment provided for individuals who had been in CSC treatment for 6 months or less, 7 to 12 months, 13 to 18 months and 19 to 24 months. ESPRITO is an ongoing project. The interim presented analyses are from the first 775 participants.

Methods: 579 (75%) of participants were men. Insurance status can influence treatment provided. The percent of individuals without any insurance varied from 19.3% to 22.3% over the time periods of CSC treatment examined. Almost all individuals had at least one prescriber visit within each 6-month period; rates varied from 89.6% to 95.3%. Rates of not receiving any antipsychotic were 14.8% for being in CSC 6 months or less; rates increased in subsequent periods to 16.1% then 23.6% and 22.6%. Rates of LAI prescription by CSC treatment period were 25.5% for being in CSC 6 months or less; rates increased in subsequent periods to 36.7%, 31.9% and 30.8% respectively. Among oral antipsychotics, aripiprazole was the most commonly prescribed with the proportion of oral antipsychotic prescriptions being for aripiprazole varying between 27.6% to 32.5% during the treatment periods. Among all aripiprazole prescriptions, 76% were for a daily dosage of between 5 and 15 mg and 19.8% were for greater than 15 mg daily. The proportion of olanzapine among oral antipsychotic prescriptions decreased over time from 20.1% for CSC 6 months or less to 14.6% at CSC of 19 to 24 months. 62.3% of oral olanzapine prescriptions were for 5-15 mg daily and 33.6%

for more than 15 mg daily. Clozapine prescription rates increased over CSC treatment duration from a low of 0.4% during the first 6 months to 4.3% for CSC of 19 to 24 months. 44.8% of clozapine prescriptions were for less than 200 mg/day and 55.2% for 200-600 mg/day. At each CSC treatment duration period, between 53 to 59.7% of individuals were prescribed a class of medication other than an antipsychotic.

Conclusions: Many of the patterns of medication prescription identified in the RAISE-ETP controlled trial are similar to those found in ESPRITO. A notable difference is the increase in use of LAIs in ESPRITO. The frequency of prescriptions for medications other than antipsychotics highlights the need to consider all class of medications when evaluating first episode treatment.

Learning Objectives: At the completion of the presentation, learners will be able to discuss patterns of antipsychotic prescriptions for individuals with early phase psychotic disorders.
At the completion of the presentation, learners will be able to discuss the frequency of prescriptions for psychotropic medications other than antipsychotics given to individuals with early phase psychotic disorders.

Literature References Robinson DG, Subramaniam A, Fearis PJ, Shi R, Walsh M, Hanna LA, et al. Focused Ethnographic Examination of Barriers to Use of Long-Acting Injectable Antipsychotics. PS. 2020 Apr;71(4):337–42.
Robinson DG, Schooler NR, Correll CU, John M, Kurian BT, Marcy P, et al. Psychopharmacological Treatment in the RAISE-ETP Study: Outcomes of a Manual and Computer Decision Support System Based Intervention. Am J Psychiatry. 2018 Feb 1;175(2):169–79.

*THE USE OF PSYCHOSTIMULANTS FOR THE TREATMENT OF ADHD IN THE PRISON SETTING: BALANCING BENEFITS AND RISKS

Martin Katzman, START Clinic for Mood and Anxiety Disorders

Overall Abstract: Attention-deficit hyperactivity disorder (ADHD) is highly prevalent in the prison environment, with approximately 26% of adult inmates meeting the diagnostic criteria for ADHD. Research has indicated that incarcerated individuals with ADHD display more verbal and physical aggression, engage in more extreme behaviors, and display increased violent and non-violent infractions. These findings could be explained by impaired reward processing due to dopamine deficits and dysregulation in attention caused by low levels of norepinephrine. Although psychostimulants have been considered first-line treatment for ADHD, their use remains controversial in the prison setting, and consequently ADHD remains undertreated among inmates with ADHD.
There are unique risks and challenges associated with the use of psychostimulants in prisons. Historically, risks of diversion, substance abuse, and dependence have prohibited and/or limited the use of stimulants within this population. Moreover, side effects such as aggression/ hostility, abnormal behavior, alterations in mood, and even psychosis are all particular concerns for the prison population. Furthermore, drug interactions should also be considered as many individuals with ADHD are treated with other medications for comorbid conditions. Thus, when initiating a psychostimulant protocol in the prison, considerable caution and effort is needed to determine whether all the effort and risk-taking is worth it.

This panel will consider the concerns and risks associated with administering psychostimulants within the prison environment. The speakers will assess the role of hedonic tone in ADHD and its contribution to the development of externalizing behavior and criminality. Additionally, the speakers will discuss the biological basis of criminality and ADHD, as well as the neurobiological mechanisms of psychostimulants targeting low hedonic tone. Furthermore, this panel will provide a balance between the benefits and risks associated with prescribing psychostimulants within the prison setting. Finally, the speakers will present current research, preliminary findings, and future directions on using psychostimulants in the treatment of ADHD in the prison setting.

Learning Objectives: 1. To examine the benefits and challenges with prescribing stimulants to inmates with ADHD.
2. To highlight the neurobiological mechanism of psychostimulants and their potential use in incarcerated populations with ADHD.

Literary References: Sternat, T., and Katzman, M. A. (2016). Neurobiology of hedonic tone: the relationship between treatment-resistant depression, attention-deficit hyperactivity disorder, and substance abuse. Neuropsychiatric disease and treatment, 12, 2149–2164. https://doi.org/10.2147/NDT.S111818

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FINDING THE BALANCE WHEN TREATING ADULT PRISONERS WITH ADHD

Gunter Lorberg, Central North Correctional Centre

Individual Abstract: Tackling the burden of ADHD in correctional facilities with appropriate treatments may provide many benefits, such as reducing symptoms that contribute to issues of prison violence, relieving stress experienced by prison staff, as well as increasing inmate safety and wellbeing. Additionally, effective treatments may decrease the risk of recidivism, thus improving the wellbeing of former inmates, improving public safety, and decreasing overcrowding in prisons.

This symposium will briefly look at a focused ADHD historical timeline and an overview of recent developments in the pharmacological options approved for the treatment of ADHD to better understand shifts, trends, and future directions in treating inmates with ADHD. Furthermore, this presentation will review past published recommendations of stimulant treatment protocols for prisons in order to move forward and provide more comprehensive care for inmates with ADHD. It is important to consider whether the provision of long-acting psychostimulants in a large prison with limited resources is feasible, safe, and worth the effort.

Finally, this presentation will focus on ADHD among adults in the prison setting where prevalence rates appear to be significantly higher than in the community. Extensive literature has investigated the relationship between ADHD and criminality as those with ADHD, appear to be more likely to offend. These behavioral issues are reflected within the prison population where ADHD appears to be a predictor of institutional misconduct. Thus, the question of whether the careful introduction of long-acting psychostimulants to incarcerated adults with ADHD decrease rates of both violent and general misconducts in a Correctional Facility remains.

Learning Objectives: 1. To examine the long historical stigma related to introducing psychostimulants into the prison environment and its effects on treating inmates with ADHD. 2. To discuss the risks and benefits of treating incarcerated individuals with ADHD with long-acting psychostimulants, using emerging findings from recent literature.

Literature References Appelbaum KL. Attention deficit hyperactivity disorder in prison: A treatment protocol. Journal of the American Academy of Psychiatry and the Law Online. 2009 Mar 1;37(1):45-9.
Ginsberg Y, Hirvikoski T, Grann M, Lindefors N. Long-term functional outcome in adult prison inmates with ADHD receiving OROS-methylphenidate. European Archives of Psychiatry and Clinical Neuroscience. 2012 Dec;262:705-24.

PRELIMINARY DATA EXAMINING PSYCHOSTIMULANT THERAPY IN INCARCERATED INDIVIDUALS WITH ADHD

Martin Katzman, START Clinic for Mood and Anxiety Disorders

Individual Abstract: Research has indicated there is a significant relationship between ADHD and delinquency, demonstrating that individuals with ADHD are more likely to commit offences and be repeat offenders than those without ADHD. Appropriate treatments may be able to address symptoms of ADHD, as well as reduce misconduct behaviour, decrease the risk of recidivism, improve the wellbeing of inmates, improve public safety, and decrease overcrowding in prisons. Psychostimulant therapy is the standard treatment for ADHD; however, its use within prisons to treat incarcerated individuals with ADHD remains controversial.
This symposium will examine whether introducing psychostimulant therapy to incarcerated individuals with ADHD decreases the rates of both violent and general misconducts in correctional facilities. Preliminary data will be presented analyzing adult male inmates who were incarcerated for at least 3 weeks between 2012-2017 in a maximum-security prison in Eastern Canada. Data was collected at 18 discrete time points in 2017 from incarcerated individuals diagnosed with ADHD at this correctional facility. The findings from this investigation revealed that stimulant treatment did not significantly impact the number of general infractions; however, the rate of violent infractions remained stable with stimulants but increased without. A second set of analyses examined rates of both violent and general misconducts before and after stimulants were introduced. The results from this preliminary study indicated that pre-stimulant inmates demonstrated significantly more total, violent, and general misconducts than post-stimulant inmates.

Results from preliminary studies will be presented to demonstrate the efficacy of pharmacotherapeutic treatment of ADHD in the prison environment. The audience will have learned about the controversy surrounding treatment with controlled substances in prisoners with ADHD. Furthermore, this presentation will provide insight into the importance of improving the management, wellbeing, and mental health outcomes of inmates with ADHD in order to develop safer environments for inmates, improve overall rehabilitation, and reduce recidivism.

Learning Objectives: 1. Preliminary findings will be presented to emphasize the potential efficacy of stimulant treatment for ADHD in the prison environment.

2. The controversy of treating inmates with ADHD will be discussed while highlighting the importance of providing safe environments for staff and inmates and optimally managing the mental health of inmates with ADHD.

Literature References Young S, Cocallis K. ADHD and offending. Journal of neural transmission. 2021 Jul;128:1009-19.
Tully J. Management of ADHD in Prisoners—Evidence Gaps and Reasons for Caution. Frontiers in Psychiatry. 2022 Mar 18;13:771525.

MARKERS OF MALADAPTIVE BEHAVIOUR IN ADHD AND COMORBID PSYCHOPATHOLOGIES

Tia Sternat, START Clinic for Mood and Anxiety Disorders

Individual Abstract: Studies have continually shown a large number of misdiagnosis and undertreatment of ADHD in the psychiatric population. Approximately 34% of patients with treatment-resistant depression are shown to have undetected ADHD, similar to what is found in other mood and anxiety disorders. Moreover, behaviors of impulsivity have been shown to lead to higher rates of maladaptive behaviors, such as substance use, risky behaviors, and suicidality, which are commonly reported symptoms in patients with major depressive disorder, PTSD, and ADHD. Multiple studies have indicated that deficits in cognition, regulation of the reward system, and low hedonic tone may be some of the biological markers which explain the underlying associations between ADHD, comorbid disorders, and the maintenance of maladaptive behaviors. Understanding the underlying biological mechanisms at play and their relation to behavioral markers or symptomatology may be crucial to achieving more precise diagnosis and treatment courses for individuals with ADHD and comorbid psychopathologies, ultimately reducing maladaptive behaviors in these patients.
Using findings from large-scale databases, case studies, and real-world examples, this presentation aims to explore and examine the underlying biological and behavioral processes that may explain the presence and masking of ADHD in adult treatment-resistant psychiatric populations. Additionally, this presentation will highlight the etiology of the development of maladaptive behavior in relation to the symptomatology seen in ADHD and comorbid psychopathological disorders, while considering the mechanisms which sustain or reproduce maladaptive behaviors over time. Moreover, this presentation will seek to provide a comprehensive review of the clinical utility of assessing hedonic tone in patients presenting with comorbid psychiatric conditions. Finally, discussions of the use of neurobiological and behavioral markers will be expanded upon in relation to furthering more precise and personalized treatment plans in clinical settings.

Learning Objectives: 1. To explore underlying neurobiological and behavioral markers that may explain ADHD in treatment-resistant populations.
2. To examine the developmental course of impulsive and maladaptive behavior in relation to the prognosis and treatment outcomes of patients with ADHD and comorbid psychiatric disorders.

Literature References Willcutt EG, Nigg JT, Pennington BF, Solanto MV, Rohde LA, Tannock R, Loo SK, Carlson CL, McBurnett K, Lahey BB. Validity of DSM-IV attention deficit/hyperactivity disorder symptom dimensions and subtypes. Journal of Abnormal Psychology. 2012 Nov;121(4):991-1010.

Sherdell L, Waugh CE, Gotlib IH. Anticipatory pleasure predicts motivation for reward in major depression. Journal of Abnormal Psychology. 2012 Feb;121(1):51-60.

*PSEUDOSPECIFIC VERSUS TRANSDIAGNOSTIC SYMPTOM TARGETING IN PHARMACOTHERAPY TRIALS: AGITATION, ATTENTION, ANHEDONIA, AND MOOD INSTABILITY

Joseph Goldberg, Icahn School of Medicine at Mount Sinai

Overall Abstract: In the course of conducting randomized trials and interpreting their findings, individual symptoms sometimes garner specific attention as either stand-alone targets for treatment or epiphenomena that may improve within the broader context of treating a comprehensive psychiatric disorder. Because target symptoms within a diagnostic framework are seldom pathognomonic, it can be challenging to draw accurate inferences about symptom-specific pharmacodynamic efficacy. For example, are the antisuicide properties of clozapine or lithium generalizable to conditions beyond schizophrenia or bipolar disorder, respectively? Does the resolution of insomnia in the context of treating depression insinuate sleep-modulating properties that may be differentiable from comprehensive antidepressant efficacy? If an efficacious treatment for schizophrenia improves both negative and positive symptoms, how can one know whether improvement in one symptom domain may be contingent on improvement in the other? Clinicians, patients, and regulatory agencies often struggle, knowingly or unknowingly, with the question of treatment pseudospecificity – that is, judging whether certain pharmacodynamic properties of a given therapeutic agent may be overly narrow.

This panel will examine issues related to two linked constructs among symptom targets in clinical trials: (a) the extent to which a target symptom may be transdiagnostic (that is, manifested across numerous disorders) but responsive to different therapeutic agents depending on a broader diagnostic context (such as the putative attentional benefits of a dopamine agonist versus a procholineric versus an antidepressant within the settings and boundaries of attention deficit-hyperactivity disorder, dementia, or depression, respectively); and (b) possible pseudospecificity of therapeutic efficacy for a given target symptom within the context of treating a broader psychiatric condition (such as, treating agitation or impulsive aggression in the context of psychosis, a mood disorder, or personality disorders). For illustrative purposes we will focus on hostility and impulsive aggression (and the use of antipsychotics, alpha agonists, mood stabilizers and other agents); attention (in the setting of ADHD and mood disorders, among others); anhedonia (evident in depression, schizophrenia, and substance use disorders, among other conditions); and mood instability (across bipolar disorder, major depression, personality disorders, and substance use disorders) in connection with diagnosis-driven pharmacotherapies impacting moment-to-moment mood variability as a narrower therapeutic target). Controversies surrounding the term "pseudospecificity" itself as a valid or useful construct will be addressed, alongside practical implications for clinical trial design, clinical generalizability, and regulatory agency approval of therapeutic agents.

Learning Objectives: 1) To understand controversies regarding the concept of pseudospecificity when identifying pharmacodynamic claims about drug efficacy;
2) To understand ways in which "narrow" drug target symptoms -- notably, hostility, attention, anhedonia, or mood instability -- represent transdiagnostic phenomena or pseudospecific

features that are only responsive to treatments aimed more broadly at a distinct overarching psychiatric condition.

Literary References: McIntyre RS, Lockhaven S, Olsen CK. A randomized, double-blind, placebo-controlled study of vortioxetine on cognitive function in depressed adults. Int J Neuropsychopharmacol. 2014; 17: 1557-1567.
Guineau MG, Ikani N, Rinck M, et al. Anhedonia as a transdiagnostic symptom across psychological disorders: a network approach. Psychol Med. 2023; 53: 3908-3919.

DO ANTIPSYCHOTICS ADDRESS HOSTILITY AND AGGRESSIVE BEHAVIOR BY MANAGING PSYCHOTIC OR MANIC SYMPTOMS, OR IS THERE A SPECIFIC ANTI-HOSTILITY/ANTI-AGGRESSIVE EFFECT?

Justin Faden, Temple University

Individual Abstract: A common assumption is that the use of second-generation antipsychotics for the management of hostility and aggressive behavior in people with schizophrenia or bipolar mania is efficacious because of the agent's general antipsychotic or antimanic activity, and perhaps because of a sedative effect. The latter may be partially the case for acute "stat" or "PRN" use, but the possibility exists for a mechanism of action that is serenic in nature, as manifested over an extended period of time. Randomized controlled studies have demonstrated a specific anti-hostility and anti-aggressive effect of clozapine and olanzapine among inpatients with schizophrenia. Clozapine's anti-aggressive effect has also been reported in people with borderline personality disorder, autistic spectrum disorders, post-traumatic stress disorder, bipolar disorder and learning disability. Post hoc analyses of placebo-controlled randomized clinical trials of other second-generation antipsychotics have demonstrated effects on hostility that are at least partially independent of general antipsychotic effect in people with schizophrenia, and at least partially independent of general anti-manic effect in people with bipolar I mania, and independent of sedation. Thus, the efficacy of second-generation antipsychotics as specific anti-aggressive agents is potentially trans-diagnostic.

Learning Objectives: 1. To understand the independence of anti-hostility effect from general antipsychotic or anti-manic activity.
2. To understand the interrelationship between hostility and aggressive behavior.

Literature References 1. Frogley C, Taylor D, Dickens G, Picchioni M. A systematic review of the evidence of clozapine's anti-aggressive effects. Int J Neuropsychopharmacol. 2012;15(9):1351-71.
2. Citrome L, Volavka J. Specific anti-hostility effects of atypical antipsychotics in persons with schizophrenia: from clozapine to cariprazine. Harv Rev Psychiatry. 2021;29(1):20-34.

3. Citrome L, Landbloom R, Chang CT, Earley W. Effects of asenapine on agitation and hostility in adults with acute manic or mixed episodes associated with bipolar I disorder. Neuropsychiatr Dis Treat. 2017;13:2955-2963.

4. Citrome L, Kramer K, Nguyen HB. Effects of cariprazine on reducing symptoms of hostility and agitation in patients with manic or mixed episodes of bipolar I disorder. Poster presented at the American Society of Clinical Psychopharmacology Annual Meeting, Scottsdale, Arizona, USA, May 31–June 3, 2022.

ATTENTION AND COGNITIVE FUNCTION: IS IT SPECIFIC OR PSEUDOSPECIFIC? IMPLICATIONS FOR DRUG DISCOVERY AND DEVELOPMENT

Roger McIntyre, University of Toronto

Individual Abstract: Cognitive dysfunction is a transdiagnostic phenomenon affecting disorders across the entire lifespan. Cognitive dysfunction includes attention, learning/memory, as well as executive functions. Cognitive dysfunction is a primary detractor of quality of life mediating functional impairment, cost of illness and reduces human capital. The US Food and Drug Administration (FDA) has not approved any treatment for cognitive dysfunction in adults living with common and severe disorders, including but not limited to major depressive disorder, bipolar disorder, schizophrenia and related psychotic disorders. This presentation will speak to the transdiagnostic manifestation of cognitive dysfunction and in particular measures of attention. This presentation will discuss empirical evidence of similarities and differences in the phenomenology and neurobiology of attention in response to treatment across different mental disorders as well as review potential treatment approaches.
Learning Objectives: 1) To review cognitive dysfunction as a transdiagnostic phenomenon. 2)To introduce the disparate aspects of cognitive function in mental disorders and thoroughly to review treatment approach, implications and discovery, implications for cognitive function in psychiatry.

Literature References McIntyre RS, Lee Y. Cognition in major depressive disorder: a 'Systemically Important Functional Index' (SIFI). Curr Opin Psychiatry. 2016 Jan;29(1):48-55. doi: 10.1097/YCO.0000000000000221. PMID: 26575300.
McIntyre RS, Lophaven S, Olsen CK. A randomized, double-blind, placebo-controlled study of vortioxetine on cognitive function in depressed adults. Int J Neuropsychopharmacol. 2014 Oct;17(10):1557-67. doi: 10.1017/S1461145714000546. Epub 2014 Apr 30. PMID: 24787143; PMCID: PMC4162519.

TARGETING ANHEDONIA IN ISOLATION AND IN CONTEXT

Manpreet Singh, University of California, Davis, School of Medicine

Individual Abstract: In the course of conducting randomized trials and interpreting their findings, anhedonia has garnered specific attention as either a stand-alone target for treatment or epiphenomena that may improve within the broader context of treating a comprehensive psychiatric disorder. Because anhedonia within a diagnostic framework is seldom pathognomonic, it can be challenging to draw accurate inferences about symptom-specific pharmacodynamic efficacy. This presentation will focus on anhedonia (evident in depression, schizophrenia, and substance use disorders, among other conditions), and aim to discuss motivational processing as it manifests across different disorders (how it's similar or different in depression vs. mania vs cannabis use vs PTSD vs an eating disorder etc) and implications for initial and algorithmic sequencing of treatment to tease apart drug impact on motivation as a target symptom while controlling for treating a broader syndrome or diagnostic entity.
Learning Objectives: 1) To understand controversies regarding the concept of pseudospecificity when identifying pharmacodynamic claims about drug efficacy;

2) To understand ways in which "narrow" drug target symptoms -- notably, hostility, attention, anhedonia, or mood instability -- represent transdiagnostic phenomena or pseudospecific features that are only responsive to treatments aimed more broadly at a distinct overarching psychiatric condition.

Literature References Lucido MJ, Bekhbat M, Goldsmith DR, Treadway MT, Haroon E, Felger JC, Miller AH. Aiding and Abetting Anhedonia: Impact of Inflammation on the Brain and Pharmacological Implications. Pharmacol Rev. 2021 Jul;73(3):1084-1117. doi: 10.1124/pharmrev.120.000043. PMID: 34285088.

Wang S, Leri F, Rizvi SJ. Anhedonia as a central factor in depression: Neural mechanisms revealed from preclinical to clinical evidence. Prog Neuropsychopharmacol Biol Psychiatry. 2021 Aug 30;110:110289. doi: 10.1016/j.pnpbp.2021.110289. Epub 2021 Feb 23. PMID: 33631251.

MOOD INSTABILITY: A SYMPTOM IN SEARCH OF A DIAGNOSIS

Joseph Goldberg, Icahn School of Medicine at Mount Sinai

Individual Abstract: Mood instability is the quintessential nonpathognomonic psychiatric symptom. As an indicator of impaired emotional processing, the term is often invoked to describe a wide range of phenomena that includes moment-to-moment shifts in emotional experience to heightened “reactiveness” to emotionally provocative experiences to disproportionately intense displays of particular emotions (notably, anger or despair) to a shorthand marker for affective syndromes that arise on the scale of days to weeks (rather than seconds to minutes). It is associated with numerous psychiatric disorders including borderline personality disorder, bipolar disorder, posttraumatic stress disorder, adjustment disorders, anxiety disorders, attention deficit-hyperactivity disorder, impulse control disorders, major cognitive disorders, substance use disorders, psychotic disorders, and developmental disorders, among others. No pharmacotherapy has ever identified “mood instability” as a primary outcome target in clinical trials, although a handful of studies have operationalized a definition of mood instability (using scales that measure affective lability, or performing area-under-the-curve or other mathematical analyses on daily mood charting diaries). Little is known about the parameters that govern mood instability – such as interpersonal sensitivity and reactivity in the case of personality disorders -- or construe mood variations as the epiphenomena of a broader syndrome (such as mania) whose course follows the trajectory of other symptoms within that syndrome (such as cognitive functioning, or sleep-wake cycle function). Little also is known about whether treatments that impact core features of a broad syndrome (such as autonomic hyperarousal in PTSD, or heightened energy or impulsivity in mania) meaningfully leverage mood instability when it arises in a diagnostically-specific context. Furthermore, readers of the literature often strain to discern the relative benefits versus possible adverse impacts of antidepressants, antipsychotics, stimulants, or “mood stabilizers” on mood instability in the course of treating a specific condition such as major depressive disorder or bipolar disorder.

This presentation will provide an overview of salient considerations that arise when assessing and treating mood instability as it arises in specific contexts within and across major psychiatric disorders. We will discuss its phenomenology and emergence relative to other psychiatric symptoms, and address pharmacotherapy implications from the perspectives of both diagnosis-specific and transdiagnostic phenomenology.

Learning Objectives: 1) To understand the phenomenology of mood instability arising within the context of diverse psychiatric conditions
2) To describe the known, or potential, pharmacodynamic benefits or risks of antidepressants, antipsychotics, stimulants, and mood stabilizers on mood instability as a distinct treatment target

Literature References 1) Høegh MC, Melle I, Aiminoff Sr, et al. Affective instability across psychosis spectrum disorders. Eur Psychiatry 2020;63:e53
2) Fernandez KC, Jazaieri H, Gross JJ. Emotion regulation: a transdiagnostic perspective on a new RDoC domain. Cognit Ther Res. 2016;40(3):426–440

4:15 p.m. - 6:15 p.m.

Workshops

JUSTICE, EQUITY, DIVERSITY, AND INCLUSION IN HEALTH RESEARCH

Francisco Moreno, University of Arizona

Overall Abstract: Disparities in mental health and substance use disorders are multifactorial inclusive of social and political determinants of health, healthcare access, and quality. Importantly as well, scientific research inclusive of genomic, behavioral, and clinical trials have traditionally excluded from participation members from communities most likely to be affected by health inequities. In recent years, awareness of this important opportunity to intervene and impact outcomes, as well as the new development and adoption of guidelines from regulatory agencies such as FDA, NIH, and advocacy groups has had its impact in the clinical research industry, academic, and government funded research.
In the current panel, we will present current tangible examples from industry representatives, academic leaders, and government-based researchers on best practices to advance equity, diversity, inclusion, and justice in various forms of health research.

The panel will specifically address:A brief summary of topics covered in two previous ASCP sessions focusing on diversity in clinical trials in 2022, and 2023.

Disadvantage and underrepresentation in research.

A brief review of barriers to diverse participation in clinical trials, and strategies to address them. Specific interventions implemented in clinical trials programs across industry and academia to advance inclusive research and promote health literacy.

Utilization of tools such as the Good Pharma Score Card which ranks companies based on their bioethics, governance, and social responsibility performance which includes justice, equity, diversity, and inclusion

After the presentation, attendees will have up-to-date information regarding the common disparity populations, best practices and potential solutions to address mental health disparities.

Learning Objectives: 1.- increase their commitment to justice, equity, diversity, and inclusion as essential values; and
2.- plan individual contributions to the advancement of equity in health research.

Literary References: 1.- Ruiz-White I, Kramer L, Philips L, Wong B, Lonergan K, Moreno F. Racial and Ethnic Disparities in Physical and Mental Health Care and Clinical Trials. J Clin Psychiatry. 2023 Jun 12;84(4):23ah14887. doi: 10.4088/JCP.23ah14887. PMID: 37339364.
2.- Varma T, Mello M, Ross JS, Gross C, Miller J. Metrics, baseline scores, and a tool to improve sponsor performance on clinical trial diversity: retrospective cross sectional study. BMJ Med. 2023 Jan 4;2(1):e000395. doi: 10.1136/bmjmed-2022-000395. PMID: 36936269; PMCID: PMC9951369..

A MORE EQUITABLE FUTURE: IMPROVING REPRESENTATION IN CLINICAL RESEARCH STUDIES

Veronica Sandoval, Genentech

Individual Abstract: There are well-characterized disparities in health outcomes, particularly among patients of color and underserved communities. Given the changing demographics of the U.S. population and the growing proportion of diverse ethnic and racial populations, decisive intervention is needed or disparities will continue to exist. Learn about why representation in clinical studies matters, Genentech's efforts to improve study representation through Advancing Inclusive Research, and the importance of enhancing health literacy through education and partnering with community leaders.
Learning Objectives: 1. Why representation in clinical studies matters
2. Genentech's efforts to improve study representation through Advancing Inclusive Research
3. Enhancing health literacy through education and partnering

Literature References 1. Genomic Data Source: "Total GWAS participants diversity." GWAS Diversity Monitor. https://gwasdiversitymonitor.com/ (Accessed April 2022)
2. Clinical Trial Diversity Source: "Diversity in Clinical Trials." Clinical Research Pathways. https://clinicalresearchpathways.org/diversity/ (Accessed December 2021)
3. Physician Diversity Source: American Academy of Medical Colleges. Diversity in medicine: facts and figures 2019. www.aamc.org/data-reports/work- force/interactive-data/figure-18-percentage-all-active-physicians-race/ethnicity-2018. Accessed February 4, 2021.

PRACTICAL INTERVENTIONS TO INCREASE DIVERSITY IN TRIAL PARTICIPATION

Heather Sutton, Otsuka Pharmaceutical Development and Commercialization, Inc. (OPDC)

Individual Abstract: The presentation details the practical interventions recently and currently implemented by Otsuka to increase diversity in clinical trial participation. Processes include those related to trial design/ protocol development, site selection, site and community awareness of DE and I, and participant recruitment methods. A review of Otsuka's DE and I Goals and measurement of them are included.
Learning Objectives: Learn about processes that have been implemented within Otsuka regarding trial design and protocol development to help increase access to clinical trials by diverse participants.
Learn about processes to increase site and community awareness of DE and I that have been implemented by Otsuka to help increase recruitment of diverse participants in clinical trials.

Literature References Swartz TH, Palermo AS, Masur SK, Aberg JA. The Science and Value of Diversity: Closing the Gaps in Our Understanding of Inclusion and Diversity. J Infect Dis. 2019;220(220 Suppl 2):S33-S41.
Schwartz AL, Alsan M, Morris AA, Halpern SD. Why Diverse Clinical Trial Participation Matters. N Engl J Med. 2023;388(14):1252-1254.

DIVERSITY, EQUITY AND FAIR INCLUSION IN CLINICAL RESEARCH: METRICS FOR SUCCESS

Jennifer Miller, Yale School of Medicine

Individual Abstract: This presentation will review key methods for benchmarking adequate representation in clinical research and setting enrollment targets, along with progress meeting diversity goals over the past decade. We will conclude with a discussion on fair and equitable access to the benefits of clinical research from US and global perspectives. The results of the forthcoming Good Pharma Scorecard rankings on DEI in oncology trial enrollment may be previewed on an aggregate level.
Learning Objectives: 1. Awareness of key methods for benchmarking and conceptualizing adequate representation in clinical research
2. Familiarity with barriers and facilitators for advancing fair and equitable access to the benefits of research from US and global perspectives

Literature References Varma T, Gross CP, Miller JE. Clinical Trial Diversity—Will We Know It When We See It? JAMA Oncol. 2023;9(6):765–767. doi:10.1001/jamaoncol.2023.0143
Varma T, Mello M, Ross JS, Gross, C, Miller, JE, Metrics, baseline scores, and a tool to improve sponsor performance on clinical trial diversity: retrospective cross sectional study BMJ Medicine 2023;2:e000395. doi: 10.1136/bmjmed-2022-000395

*^BRIDGING THE RESEARCH TO PRACTICE GAPS

A. Rush, Curbstone Consultant LLC

Overall Abstract: Evidence based medicine relies heavily on randomized controlled trials, conducted for establishing efficacy of novel treatments. These data do not readily inform the care of many real-world patients who are ineligible for these trials due to suicidal risk, concurrent general medical or psychiatric conditions, treatment resistance, or chronicity, among other reasons.
Electronic health records (EHRs) contain rich information on clinical practice in a real-world setting, inclusive of conditions, clinical investigations, and assessments. However, the recording of data is inconsistent within and between healthcare providers, and translation into reliable evidence is challenging. The workshop aims to present key gaps in utilizing real-world data (RWD) — the information gap (identification, extraction, compilation of patient-level information) as well as the knowledge gap (developing evidence using these data).

This workshop will discuss and demonstrate how a large, nationally representative, multimillion patient EHR database — NeuroBlu — has been compiled across multiple healthcare providers and systems to address these gaps. It will allow attendees to use the

platform to select a patient sample using a variety of features, types of treatment, outcomes measures, observation periods, and other variables to answer clinical questions.

First, Dr. A. John Rush, MD, as chair, will present an overview of the opportunities and limitations in using RWD to enhance clinical and operational decisions. Next, Alex Vance, LMHC will present the information gap by discussing the steps taken to curate a large, reliable database that is easy to interrogate via one platform. Vance will discuss the opportunities and challenges in identifying, extracting, and compiling data across a range of EHRs and care delivery systems. He will explain the principles of Common Data Models (CDMs), confidentiality considerations, and the aspects of structured, semi-structured, and unstructured information. The presentation will discuss the use of natural language processing (NLP), which is key to curate clinically-relevant data items.

Lastly, the knowledge gap will include illustrative use cases representing the versatility of questions that researchers and clinicians encounter in their practice. This will be led by others at Holmusk: Karthik Chandran, MS Nadezda (Nadia) Lipunova, PhD, and Maxime Taquet, BM BCh PhD.

Karthik will introduce the section by highlighting how NLP labels can be used to describe a patient population with more detail than would be possible using commonly available data sources, such as health claims. To follow this, Max will present a more complex use case detailing a model using the severity status of patients to predict the likelihood of hospitalizations. Finally, Nadia will complete the section by showcasing how routinely collected data can aid the operational aspects of care delivery, primarily by prioritizing the patient assessment according to their likelihood of a crisis. To summarize, the knowledge gap will present specific use cases on what is possible to analyze using RWD and will provide an indication of similar questions that could be addressed.

Workshop will then include an interactive session in trialing research questions coming from the audience that would be fit for RWD to answer and considering limitations, benefits, and further areas of development. The presentation will end with a concluding reflection on the limitations in RWD and challenges in addressing the learning gap.

Learning Objectives: 1. Introduce key gaps in utilizing real-world data (RWD) — information and knowledge.
2. Allow attendees to utilize curated RWD in the NeuroBlu platform to develop a sample patient cohort to answer clinical questions.

Literary References: Patel R, Wee SN, Ramaswamy R, et al. NeuroBlu, an electronic health record (EHR) trusted research environment (TRE) to support mental healthcare analytics with real-world data. BMJ Open. 2022; 12:e057227.
Taquet, M, Griffiths, K, Palmer, E, et al. Early trajectory of clinical global impression as a transdiagnostic predictor of psychiatric hospitalisation: a retrospective cohort study. Lancet Psychiatry. 2023; 10: 334–41.

ADVANCING PSYCHIATRIC CARE AND TREATMENT DEVELOPMENT THROUGH FIT-FOR-PURPOSE CURATION OF EHR-DERIVED REAL-WORLD DATA

Alex Vance, Holmusk

Individual Abstract: Introduction: This presentation explores the use of electronic health records (EHRs) as a pivotal source of real-world data (RWD) for enhancing psychiatric care delivery, personalizing treatment selection, and aiding psychiatric treatment development. It details methodologies for extracting, compiling, and analyzing data from various EHR systems to fill essential information gaps in mental health services and research. The creation of a comprehensive, integrated database incorporating patient records from multiple healthcare providers and care systems is a cornerstone of this approach, providing a broad view of psychiatric treatment practices on a national scale.

Methods: Central to the data integration process is the application of Common Data Models (CDMs), ensuring data consistency and addressing confidentiality concerns. This process is vital for managing the varied nature of psychiatric data, which includes structured, semi-structured, and unstructured formats. The presentation emphasizes the challenge of inconsistent psychiatric data recording within EHRs.

A significant portion of the presentation is dedicated to the use and challenges of natural language processing (NLP) techniques. NLP is particularly valuable in extracting outcomes data crucial for measuring changes in symptomatology for psychiatric disorders. This approach is instrumental in overcoming the common issue of missing or incomplete diagnostic and outcomes information in RWD, particularly with outcomes measures and basic patient information like demographics. By parsing unstructured clinical notes, NLP enables the retrieval of nuanced patient information that is often overlooked in traditional data structures, thereby enriching the database with comprehensive and clinically relevant outcomes data. Achieving accurate NLP, however, is technically challenging. This presentation will highlight the importance of adequate clinical validation of extracted concepts and the key role that clinicians play throughout the whole cycle of NL development to ensure clinical validity.

Results: The presentation highlights the utility of this enriched EHR database in supporting a wide array of clinical and research-driven use cases. These include detailed patient population characterization, subtyping of psychiatric conditions (e. g. anhedonic depression) and the assessment of treatment effectiveness in real-world settings. The application of the database in these contexts demonstrates its versatility in advancing psychiatric treatment development and improving patient care practices.

Conclusion and discussion: In summary, the strategic employment of RWD from EHRs, facilitated by advanced data processing techniques such as NLP, represents a significant advancement in the field of psychiatric care and research. It provides novel avenues for clinical innovation, supports evidence-based treatment development, and promises to significantly enhance the quality of mental health care services.

Learning Objectives: 1. Understand the myriad processes and challenges faced in developing a harmonized, aggregated EHR-derived real-world database that reflects the reality of psychiatric care delivery and how these may be overcome by available tools and technologies. 2. Understand the value of fit-for-purpose curated EHR-derived psychiatric real-world data for application both at the point of care as well as in the development of treatments for psychiatric disorders.

Literature References Patel R, Wee SN, Ramaswamy R, et al. NeuroBlu, an electronic health record (EHR) trusted research environment (TRE) to support mental healthcare analytics with real-world data. BMJ Open. 2022;12(4):e057227. Published 2022 Apr 22. doi:10.1136/bmjopen-2021-057227

Stang, P. E., P. B. Ryan, J. A. Racoosin, J. M. Overhage, A. G. Hartzema, C. Reich, E. Welebob, T. Scarnecchia, and J. Woodcock. 2010. “Advancing the science for active surveillance: rationale and design for the Observational Medical Outcomes Partnership.” Ann. Intern. Med. 153 (9): 600–606.

A TRANSDIAGNOSTIC EARLY WARNING SCORE PREDICTING PSYCHIATRIC HOSPITALIZATION BASED ON ELECTRONIC HEALTH RECORDS DATA

Maxime Taquet, University of Oxford

Individual Abstract: Background: The use of early warning scores in physical health has greatly improved service provision and patient outcomes. The lack of such early warning scores in psychiatry means that clinical decisions and resource allocations are often left to the clinician’s intuition. Predicting psychiatric hospitalisation is particularly important since interventions exist to prevent it but are too intensive to be universally deployed. However, the development of predictive tools for relatively rare outcomes have been hampered by the lack of large-scale real-world data.

Methods: We used the NeuroBlu database with which we interacted via a web interface. We first identified two scales (Clinical Global Impression Scale - Severity (CGI-S) and Global Assessment of Functioning (GAF)) that were commonly used in clinical practice across diagnoses and widely available in NeuroBlu. We then selected patients who had a diagnosis for a range of diagnoses that can lead to hospitalisation including major depressive disorder, bipolar disorder, generalised anxiety disorder, post-traumatic stress disorder, schizophrenia or schizoaffective disorder, ADHD, or personality disorder. Among them, we selected all those who had at least 5 CGI-S and 5 GAF scores recorded over any 6 months period before any psychiatric hospitalisation. The minimum number of measurements was defined based on statistical power analysis. Clinical severity (as the average CGI-S over this 6-months period) and clinical instability (as the time-adjusted root-mean square of subsequent differences of CGI-S) were derived. Similarly functional severity and instability were calculated. We defined a score ranging from 0 to 8 by summing the tercile on each of these four metrics (+0 for lower tercile, +1 for middle tercile, and +2 for higher tercile). We tested whether this score can serve as an early warning score by assessing its ability to predict hospitalisation within the next 6 months in time-to-event analysis. Calibration and external validity were tested in a patient sample different from the one used in score development.

Results: The early warning score significantly predicted psychiatric hospitalisation. Those with a score of 8 were 10 times more likely to be hospitalised within the next 6 months than those with a score of 0, and the risk of hospitalisation increased monotonically from 0.6% (among those with a score of 0) to 6% (in those with a score of 8). The association held across diagnoses, was robust to adjustment for sociodemographic covariates, and showed good generalisability and external validity when tested in a separate healthcare organisation.

Conclusion and discussion: A transdiagnostic early warning score can reliably and robustly predict psychiatric hospitalisation. It is based on simple measurements that can easily be integrated into routine clinical care, and therefore shows great promise for clinical translation. Despite its many advantages, the use of real-world data comes with several limitations: accuracy of measurements might vary, diagnostic codes and hospitalisations might be mis-

recorded, and the mechanisms underpinning the link between instability and hospitalisation cannot be firmly established.

Learning Objectives: 1) Understand how real-world data can be used to answer a well-defined clinical research question
2) Identify advantages and limitations of large-scale real-world data in this context

Literature References Taquet M, Griffiths K, Palmer EO, Ker S, Liman C, Wee SN, Kollins SH, Patel R. Early trajectory of clinical global impression as a transdiagnostic predictor of psychiatric hospitalisation: a retrospective cohort study. The Lancet Psychiatry. 2023 May 1;10(5):334-41.
Patel R, Wee SN, Ramaswamy R, Thadani S, Tandi J, Garg R, Calvanese N, Valko M, Rush AJ, Rentería ME, Sarkar J. NeuroBlu, an electronic health record (EHR) trusted research environment (TRE) to support mental healthcare analytics with real-world data. BMJ open. 2022 Apr 1;12(4):e057227.

PREDICTION OF MAJOR DEPRESSIVE DISORDER SEVERITY AT THE TIME OF DIAGNOSIS USING MENTAL STATUS EXAMINATION

Nadezda Lipunova, Holmusk

Individual Abstract: Introduction: Psychiatric illness severity at diagnosis is an important predictor of treatment success and patient's quality of life. Severity can be assessed using various measures, ranging from disease-specific (e.g., The Positive and Negative Syndrome Scale (PANSS)) to transdiagnostic tools (e.g., Clinical Global Impression of Severity, CGI-S). Standardized clinical scores are frequently used in clinical research and clinical trials. However, they are far less common in real-world data sources such as electronic health records (EHRs) due to the time constraints associated with data recording in real-world clinical practice. Inconsistent recording of severity measures in real-world data therefore limits the generation of real-world evidence (RWE) in these large, representative patient cohorts.

The mental state examination (MSE) is a routine and structured assessment of patient psychological functioning at the point of clinical contact. Given its frequent documentation in EHRs, better understanding of how the MSE relates to standardized rating scale scores may aid better characterization of patient severity when other clinical scores are not available. The current study aimed to investigate associations between the MSE and CGI-S in patients with MDD.

Methods: The study was conducted on the NeuroBlu database, which contains de-identified individual-level electronic health record data from patients receiving mental healthcare from over 30 centers across the US. Patients with a diagnosis of MDD recorded between 1999 and 2021 were included. Extreme gradient boosting (XGBoost) was used to investigate associations between MSE features and illness severity. Here, 16 MSE features were entered as independent variables, each assigned to be either "disturbed" or "within limits". The outcome was defined as severity at the time of MDD diagnosis, categorized as mild (CGI-S LESS THAN 4) or severe (CGIS≥4) presentation. Additional variables of demographics, psychiatric comorbidity, and clinical setting (inpatient/outpatient) were included in the model. Five-fold cross validation was used for model evaluation and feature importance was assessed using SHapley Additive exPlanation (SHAP) values. F1 metric was reported for model accuracy.

Results: In total, 25,191 patients with MDD were identified, 3,459 patients with mild and 21,732 with severe MDD. The F1 score for predicting severe patients was 0.83. The model performance for predicting mild severity status at the time of diagnosis was 0.37. Overall accuracy of the model was 75%. In terms of MSE feature importance, disturbance in mood, thought content, affect, suicidal thoughts, and thought process were the most important features in predicting MDD severity.

Conclusion and discussion: MSE is a structured assessment of the patient's functioning and provides detail on cognition and behavior. While MSE is not measuring severity per se, impairment across the domains is indicative of how serious the illness manifestation is. In lieu of consistent recording of clinical scores that describe severity of mental illness, MSE provides an opportunity for retrospective data to be used in RWE studies while accounting for disease severity.

The current demonstrates that routinely recorded MSE information may be used to predict MDD illness severity to a moderate degree of accuracy. Although the performance metrics for predicting patients with severe MDD were encouraging, further refinement is required to increase discrimination between mild and severe patients with MDD. Further refinement may allow a better understanding of patients in routine care, investigate patient trajectories and response to treatment, and advance the development of measurement based care.

Learning Objectives: 1) To provide an example of real-world data use in psychiatry
2) To showcase a case of inferring information on MDD severity using routinely collected data

Literature References Voss RM, M Das J. Mental Status Examination. [Updated 2022 Sep 12]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK546682/
Huang SH, LePendu P, Iyer SV, Tai-Seale M, Carrell D, Shah NH. Toward personalizing treatment for depression: predicting diagnosis and severity. J Am Med Inform Assoc. 2014 Nov-Dec;21(6):1069-75. doi: 10.1136/amiajnl-2014-002733. Epub 2014 Jul 2. PMID: 24988898; PMCID: PMC4215055

*USE OF BIOMARKERS TO IDENTIFY TREATMENTS FOR PSYCHIATRIC PATIENTS: THE RIGHT MEDICINE FOR THE RIGHT PATIENT AT THE RIGHT TIME.

Larry Alphs, Denovo Biopharma LLC

Overall Abstract: Modern pharmacology has identified effective treatments for most psychiatric diseases. Despite these advances, currently available medications are poorly effective for many psychiatric patients and other patients do not tolerate them. Because there is no a priori way of identifying the most effective medication for a specific patient, clinicians' current practice is to prescribe treatments for patients based largely on trial and error, using medications with which they are most familiar. Emerging evidence suggests that CNS diseases like Alzheimer's disease and schizophrenia are progressive and delayed or interrupted treatment is associated with poor long-term treatment outcomes. This makes early implementation of effective treatment critically important for good long-term outcomes. These limitations in treatment understanding and clinical practice point to the value of biomarker identification and machine learning to identify precision treatments that will help get the right medicine to the right patient at the right time.

This session will provide examples of ongoing work that applies machine learning to identify phenotypic, genetic and digital biomarkers to increase the success of clinical trials. Adaptations of these learnings into the clinical setting would provide better, faster, cheaper, more successful treatment outcomes.

Learning Objectives: •This session will provide attendees a deeper understanding of the need for precision treatment for psychiatric patients and its challenges.
•This session will provide attendees with insights into multiple biomarker approaches coupled with machine learning that might be used in clinical trials and eventually clinical practice.

Literary References: Harrer S, Shah P, Antony B, Hu J, Artificial Intelligence for Clinical Trial Design, Trends in Pharmacological Sciences, 2019, DOI: https://doi.org/10.1016/j.tips.2019.05.005.
Askin S, Burkhalter D, Calado G and El Dakrouni S Artificial Intelligence Applied to clinical trials: opportunities and challenges, Health Technol (Berl). 2023; 13(2): 203–213.

MACHINE LEARNING IN MEDICAL APPLICATIONS

Moses Njuguna, Princeton University

Individual Abstract: This presentation serves as an introductory guide to machine learning within the medical domain, specifically focusing on practical applications in CNS precision medicine. It explores various regression models in the context of supervised learning, aiming to provide healthcare professionals and researchers with deeper insights into this vital area.
Supervised Learning and Outcome Measurement: Supervised learning is approached through the lens of outcome measurement (Y) and a vector of predictor measurements, crucial in solving medical prediction problems. The outcome variable Y encompasses two distinct categories:

Regression: Where Y represents quantitative values.

Classification: Where Y entails finite, unordered sets. For instance, predicting patient responses to pharmacological treatments or classifying patients based on medical scores like MADRS (Montgomery-Asberg Depression Rating Scale).Training Data and Machine **Learning Models:** Training data, comprising pairs of predictor and outcome variables, forms the foundation for machine learning models. These models enable predictions for unseen cases and identification of critical factors influencing medical outcomes.

Assessment of Prediction Quality: Emphasis will be placed on assessing prediction quality and the pursuit of an ideal prediction function, f(x). The discussion will encompass model accuracy, introducing concepts such as training error bias and test error. Moreover, it will delve into the trade-offs between model complexity, bias, and variance within medical applications, leading to the crucial Bias-Variance decomposition framework.

Parametric and Structured Models: Parametric and structured models, like linear models, will be defined and analyzed, emphasizing their utility in minimizing training error within the medical context. The presentation will contrast regularization techniques such as LASSO and ridge regression with best subset selection, highlighting the efficacy of LASSO in high-dimensional medical regression, particularly when dealing with sparse data.

Geometric Interpretations and Practical Examples: Geometric interpretations of LASSO and forward stepwise regression will be provided, supplemented by practical examples from medical research scenarios.

Keywords: Machine Learning, Supervised Learning, Medical Applications, Regression Models, Model Accuracy, Predictor Variables, LASSO, Ridge Regression, Healthcare, K-NN Algorithm, Bias-Variance Decomposition, Linear Models.

Learning Objectives: Understanding the Role of Supervised Learning in Medical Applications: Explore the fundamental concepts of supervised learning, specifically in the context of medical data analysis. This includes comprehending the distinction between regression and classification in medical prediction problems and how predictor variables contribute to outcome measurement.
Evaluating and Implementing Regression Models in Healthcare: Gain insights into regression models' application within healthcare, focusing on their utilization to predict medical outcomes. Learn about various regression techniques such as LASSO, ridge regression, and linear models, including their strengths, weaknesses, and practical implications in high-dimensional medical datasets.

Literature References 1.Gareth James, Daniela Witten, Trevor Hastie, and Robert Tibshirani (2023), An Introduction to Statistical Learning with Applications in RLinks to an external site., Second Edition, Springer
2. S. K. Mohan, M. J. Wang, A. C. Yuan, T. R. Kim, A. Vyas, Machine Learning and Data Mining in Pattern Recognition 2020

PRECISION MEASURES FOR PRECISION PSYCHIATRY: ENABLING CLINICAL DEVELOPMENT IN A NEW ERA

Gayle Wittenberg, Johnson and Johnson

Individual Abstract: Historically, clinical trials for psychiatric disorders have enrolled biologically and phenotypically heterogenous groups of patients meeting criteria for a single diagnostic category. Treatment response is measured using clinical scales capturing a broad array of potential symptoms aligned to that diagnostic category. Drug development in neuroscience typically focuses on modulating the behavior of a protein(s) in a manner that changes the operation of neural circuitry in a direction that alleviates symptoms. When patients entering into a clinical trial are biologically heterogeneous, we effectively add noise to measured endpoints by treating those who do not experience the biological dysfunction treated by that therapeutic. This reduces statistical power, and the likelihood of a significant positive outcome, even for effective compounds.
Over the last two decades, significant advances have been made in the field of neuroscience. These advances are positioned to transform the treatment of psychiatric illnesses. We are better able today than ever before to characterize a patient quantitatively based on molecular, digital, neuroimaging and real-world data.

During this session, we will describe a path forward to precision psychiatry from novel therapeutics currently positioned to address untreated patients and symptoms, to new approaches in drug discovery aimed at a data-driven rethinking of traditional diagnostic categories. We will discuss how advances in precision medicine must proceed in tandem with advances in measurement and outline a potential roadmap for discussion.

Learning Objectives: 1. Understand how advances in neuroscience will contribute to the treatment landscape in neuropsychiatry.
2. Understand why as psychiatry moves to a precision medicine paradigm we may need to rethink and evolve how we measure outcomes.

Literature References 1. Krainc, D., Martin, W. J., Casey, B., Jensen, F. E., Tishkoff, S., Potter, W. Z., and Hyman, S. E. (2023). Shifting the trajectory of therapeutic development for neurological and psychiatric disorders. Science Translational Medicine, 15(720).
2. Hampel, H., Gao, P., Cummings, J., Toschi, N., Thompson, P. M., Hu, Y., ... and Vergallo, A. (2023). The foundation and architecture of precision medicine in neurology and psychiatry. Trends in Neurosciences, 46(3), 176-198.

USING MACHINE LEARNING TO IDENTIFY BIOMARKERS FOR CLINICAL TRIAL ENRICHMENT THROUGH THE USE OF A SUB-INSIGHT LEARNING PARADIGM AND LARGE LANGUAGE MODELS

Joseph Geraci, NetraMark Holdings

Individual Abstract: Overview and Purpose: In an effort to utilize artificial intelligence (AI) to help better understand potential enrichment criteria for clinical trials, large collections of historical clinical trial data are being assembled. However, this approach can be problematic, as each trial is unique and the standards for designing them, particularly in the field of psychiatry, are constantly evolving.
We introduce a different approach – leveraging data from recent trials to enhance future ones. This shift requires AI systems capable of learning from smaller, more trial-specific datasets. Such systems use demographic and diagnostic scales currently used for patient selection as well as many other patient descriptors to identify the population of interest for study eligibility.

By focusing on current and relevant trials, AI can formulate more precise hypotheses for subsequent studies. This methodology stands in contrast to the traditional reliance on less descriptive and less relevant inputs, which may not be as applicable to current research questions and clinical practice.

Methods: The power of the machine learning (ML) methods used here come from two advances: a long-range memory mechanism that associates variables for superior explainable feature selection, and an ability for the methods to identify which patients in a trial cannot be used to make predictions. By providing a more tailored input for 'learning' about a class of patients that it cannot explain, this technology is able to provide sub-insights about patients that can be explained. In this way, the effect size of collections of variables that were hidden now become amplified and apparent. The nature of this approach allows one to use the insights derived from the explainable patient group to understand and enrich a patient population to reduce placebo response while increasing drug response. The machine generates hypotheses about the explainable patients, how they affect the endpoint being measured, and evaluates them through statistical methods. Finally, a model is constructed which predicts how well a future trial would perform. Large Language Models (LLMs) are well positioned to take these insights and generate reports using the vast medical literature that they are trained on to provide the clinicians/scientists running the trial with further insight into the recommended exclusion/inclusion criteria.

Results: Results from two trials will be described: a Phase II schizophrenia trial where successful enrichment was predicted; and a failed Phase III anxiety trial where enrichment procedures could not be identified. Finally, replication of a predictive model conducted on an external schizophrenia data set will be presented where this sub-insight process allowed for the discovery of a biomarker when standard techniques failed.

Importance of the talk: This talk addresses a critical problem in psychiatric clinical trials as it deals with two factors that drive clinical trial failures: disease heterogeneity and placebo response. Drug response is a complex and heterogeneous phenomenon which causes standard ML methods to overfit. By introducing sub-insight learning, clinical trialists can rely on accurate hypotheses that are more explainable and can be statistically evaluated before implementing as exclusion/inclusion criteria. These methods have been reviewed by psychiatric experts and validated according to standard ML methods. This approach may permit enrichment of clinical trials and avoid costly failures.

Learning Objectives: 1) To understand the progress made in machine learning methods for clinical trial enrichment
2) To review use cases for machine learning based methods for extracting exclusion/inclusion criteria for psychiatric clinical trials

Literature References Choi J, Bodenstein DF, Geraci J, Andreazza AC. Evaluation of postmortem microarray data in bipolar disorder using traditional data comparison and artificial intelligence reveals novel gene targets. J Psychiatr Res. 2021 Oct;142:328-336. doi: 10.1016/j.jpsychires.2021.08.011. Epub 2021 Aug 15. PMID: 34419753.
Smith EA, Horan WP, Demolle D, Schueler P, Fu DJ, Anderson AE, Geraci J, Butlen-Ducuing F, Link J, Khin NA, Morlock R, Alphs LD. Using Artificial Intelligence-based Methods to Address the Placebo Response in Clinical Trials. Innov Clin Neurosci. 2022 Jan-Mar;19(1-3):60-70. PMID: 35382067; PMCID: PMC8970233.

USE OF DIGITAL BIOMARKERS IN PATIENT SELECTION AND FOLLOW UP

Christopher Chatham, Hoffman La Roche Ltd.

Individual Abstract: The development of new psychiatric interventions is complicated by heterogeneity both at the level of disease etiology (e.g., the strongly polygenic basis of many psychiatric conditions) and of phenotypic presentation (e.g., the large number of possible combinations of symptoms which can yield a given diagnosis). While genomic technologies can now be efficiently scaled, such data is of limited use for the development of new medicines until the varied phenotypes associated with these disorders can also be quantitatively assessed, at an equally-large scale. Digital biomarkers offer substantial promise for addressing this gap, by leveraging wearables, smartphones, and other consumer-grade technology to support quantification of psychiatric presentation and response to treatment. Of equal importance for practical applications is the fact that digital biomarkers can also be leveraged to enable the efficient re-contact of well-characterized individuals for enrollment in trials of precision therapeutics. Here, I will share emerging work at this intersection of omics, data sharing, and digital biomarkers as a unified mechanism for scaling our understanding of psychiatric conditions and our ability to test interventions within them. As a case study, I will first focus on the utility of quantitatively assessing “the patient voice”, both literally (in terms of statistical analysis of its acoustic, semantic and interpersonal qualities) and figuratively (in terms of participatory trial design and their experience in trials). Second, I will introduce one way in

which digital biomarkers can be used to “close the loop” between patient follow-up (at the conclusion of one trial) and patient selection (at the beginning of the next), thereby opening a path towards more patient-friendly trials with quantitative outcomes in participatory research. Finally, I will conclude with proposals for how this technological nexus may ultimately interface with clinical practice, and its promise for addressing broader practical challenges posed by psychiatric heterogeneity at the point of care. Overall, the incorporation of these technologies into patient follow-up and patient selection procedures will (a) dramatically enrich the quantitative biological, phenotypic, and treatment history data available to clinicians, and (b) thereby accelerate the development and delivery of precision psychiatric interventions to the patients most likely to benefit from them.

Learning Objectives: (1) Understanding the Role of Digital Biomarkers in Psychiatric Interventions:

- Gain insight into the potential of digital biomarkers in quantitatively assessing psychiatric presentations, exploring their applications in leveraging wearables, smartphones, and consumer-grade technology.

- Explore how digital biomarkers can address the current limitations in developing psychiatric interventions by efficiently re-contacting well-characterized individuals for enrollment in precision therapeutic trials.

(2)Navigating the Intersection of Omics, Data Sharing, and Digital Biomarkers:

- Develop a comprehensive understanding of the integration of omics, data sharing, and digital biomarkers as a unified mechanism for advancing our understanding of psychiatric conditions.

- Explore case studies that illustrate the convergence of these elements and their role in scaling our ability to test interventions, with a focus on the quantification of "the patient voice" and the iterative-interventional approach to psychiatric heterogeneity

Literature References Heraty, S., Lautarescu, A., Belton, D., Boyle, A., Cirrincione, P., Doherty, M., ... and Jones, E. J. (2023). Bridge-building between communities: Imagining the future of biomedical autism research. Cell, 186(18), 3747-3752.

O’Sullivan, J., Bogaarts, G., Schoenenberger, P., Tillmann, J., Slater, D., Mesgarani, N., ... and Chatham, C. (2023). Automatic speaker diarization for natural conversation analysis in autism clinical trials. Scientific Reports, 13(1), 10270.

AN EEG-BASED, MACHINE LEARNING BIOMARKER TO IDENTIFY RESPONSIVE VS. NON-RESPONSIVE SUBJECTS IN AN MDD CLINICAL TRIAL: INITIAL VALIDATION DATA FROM THE EMBARC STUDY DATABASE

Qiang Li, Neumarker Inc.

Individual Abstract: Methodological Issue Being Addressed: Selection of machine learning approaches to explore the relationship of baseline biomarker data to trajectories of clinical change.

Introduction (Aims): The search for predictors of treatment response in syndromal psychiatric disorders has, until recently, relied on baseline clinical and demographic characteristics. However, recent advancements in incorporating quantitative biomarkers into studies have opened the door to exploratory approaches, enabling research without any firm basis for a priori hypotheses. Among these biomarkers, EEG paradigms have shown promise in subgrouping patients, either in terms of distinct biotypes or in relation to treatment response. Recognizing

the complexity of EEG data, researchers have applied machine learning approaches to publicly available datasets. These approaches have successfully identified EEG-based subgroups associated with differential responses to selective serotonin reuptake inhibitors. However, there is no universally accepted primary machine learning approach for addressing specific questions related to response prediction. Our study aimed to determine whether different machine learning methods would replicate existing relationships, generate diverse findings, or provide varying degrees of predictive accuracy. To achieve this, we utilized a proprietary approach to generate patient clusters and examined how these clusters correlated with trajectories of clinical change. Briefly, machine learning approaches were applied to generate homogeneous subgroup clusters based on EEG functional connectivity.

Methods: We conducted a post-hoc analysis using baseline scalp EEG data from the EMBARC trial, which investigated sertraline's efficacy in treating MDD. Unsupervised machine learning and clustering algorithms were applied to identify MDD subtypes based on EEG functional connectivity features. Cohen's d effect sizes and p-values were calculated for each subtype, along with HAMD-17 subscale analyses. Validation procedures, including cross-site assessments, were performed to assess the robustness of the findings.

Methods: Three distinct MDD subtypes (subtype 1, subtype 2, and subtype 3) were identified. Approximately 46% of patients belonged to subtype 1, demonstrating a significant treatment response to sertraline (Cohen's d = 1.235, p LESS THAN 0.0001). In contrast, subtype 2 patients (approximately 35% of the total population) did not respond favorably to sertraline. Surprisingly, subtype 3 (comprising around 19% of patients) exhibited a larger response to placebo than sertraline (Cohen's d = -1.447, p LESS THAN 0.0003), with specific HAMD-17 items showing notable differences. Validation analyses demonstrated the consistency of these findings. In addition, functional connectivity patterns generated by the study exhibit clear differences among the subtypes as well as the healthy control.

Conclusions: Utilizing EEG functional connectivity features and unsupervised machine learning continues to uncover patient subtypes with significantly different treatment responses. This technology has the potential to detect subpopulations that are likely to have higher responses on placebo, offering the promise of reducing trial failure rates, sample sizes, costs, and enrollment times. Ongoing research aims to validate these findings across additional MDD and CNS datasets.

Learning Objectives: Scalp EEG analysis can produce actionable biomarkers for uncovering subtypes of psychiatric patients in aiding clinical trials, treatment selection, and diagnosis. Subjects with high placebo responses can potentially be identified.

Literature References Clementz, N.A., Sweeney, J. A., Hamm, J. P., Ivleva, E. I., Ethridge, L. E., Pearlson, G.D., Keshavan, M. S., and Tamminga, C. A. (2016) Identification of Distinct Psychosis Biotypes Using Brain-Based Biomarkers. Am J Psychiatry. 173(4): 373–384.
Zhang, Y., Wu, W., Toll, R., Naparstek, S., Watts, A. M., Gordon, J., Jeong, J., Astolfi, L., Shpigel, E., Longwell, P., Sarhadi, K., El-Said, D., Li, Y., Cooper, C., Chin-Fatt, C., Arns, M., Goodkind, M., Trivedi, M. H., Marmar, C. R., Etkin, A., (2021) Identification of Psychiatric-Disorder Subtypes from Functional-Connectivity Patterns in Resting-State Electroencephalography. Nature Biomedical Engineering 5: 309–323.

MULTIMODAL PREDICTION OF ALZHEIMER'S DISEASE – OPPORTUNITIES IN NORDIC REGISTRY AND BIOBANK DATA

Ole Andreassen, University of Oslo, Ulleral Hospital

Individual Abstract: The rising number of people with dementia and the advent of new treatment alternatives demanding earlier diagnosis with higher precision is an increasing challenge to our healthcare system. A significant bottleneck is the time consuming and complex diagnostic procedures of early dementia disease. While big data and novel analytical tools, including artificial intelligence, have a tremendous impact on society, their use in the healthcare sector has been modest. We have addressed the lack of accurate prediction models and developed tools for prediction of dementia age of onset, building on multimodal data, clinical, brain MRI and genotypes, with potential for clinical stratification of treatment. Still, there is a substantial gap between research settings and validated tools used in the clinic. Based on massive samples from biobanks, registries and brain MRI data, we have developed mathematical models for the prediction of dementia age of onset with the accuracy needed for real-world health care diagnosis. Secondly, we have produced a scalable e-health solution for data integration and digital interface for decision support and communicating risk assessment. The tools have the ability to improve the diagnosis of dementia with sufficient quality for precision medicine demands, adapted to each patient's needs. We are now working to integrate the solutions in health care providers, and test the solution in in real-world health care, starting with hospitals and extending to municipalities. Here, a close collaboration between industry, academia, and healthcare providers are needed. The innovative technological solution has the potential to transform health care by paving the way for big data tools enabling precision medicine approaches, including primary healthcare/general practice. Similar solutions for stratification of treatment in mental disorders will also be presented. In conclusion, we need to clinically validate the methods and start implementing the most promising technology in clinically relevant use cases to secure implementation of precision health approached in real-world clinical settings.

Learning Objectives: How mew method combining clinical, imaging, genetics can predict dementia onset

The importance of Integration algorithms in clinical workflow, an eHR cockpit solution

Literature References Reas et al. Improved multimodal prediction of progression from MCI to Alzheimer's disease combining genetics with quantitative brain MRI and cognitive measuresAlzheimers Dement 2023 Nov;19(11):5151-5158.

Njølstad P, Andreassen OA, et al. Roadmap for a precision-medicine initiative in the Nordic region. Nat Genet 2019 Jun;51(6):924-930.

Friday, May 31, 2024

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

Panels

***EVALUATING THE EVIDENCE: IS THERE A MEANINGFUL CLINICAL DIFFERENCE BETWEEN KETAMINE AND ESKETAMINE?**

Samuel Wilkinson, Yale School of Medicine

Overall Abstract: Treatment-resistant depression (TRD) is a chronic and disabling condition and is generally defined when second-line antidepressant therapies fail to produce remission. Since 2000, an increasing number of studies have shown that low-dose racemic ketamine delivered intravenously can have powerful and rapid antidepressant effects in TRD. Yet IV ketamine is unlikely to gain FDA approval as it has no pharmaceutical sponsor and no clear path for commercialization. In 2019, the US Food and Drug Administration approved S-ketamine (the S-enantiomer of ketamine; trade name "Spravato") as a therapy for TRD in the form of a nasal spray. While some experts predicted that the availability of an FDA-approved form of ketamine would shift market pressures away from intravenous ketamine, preliminary epidemiological data suggest that intravenous ketamine has remained available for a portion of the population. Furthermore, considerable controversy exists as to whether there is a significant clinical difference between IV ketamine and intranasal esketamine, with some practitioners claiming the intravenous racemic ketamine is the "gold standard" despite a lack of evidence supporting this claim.
This workshop convenes several experts in the field to examine the state of the evidence and suggest future directions.

Dr. Roger McIntyre will present real-world effectiveness evidence comparing intravenous racemic ketamine and intranasal esketamine from two large center (Toronto, Canada, and Rome, Italy). Effectiveness, tolerability and acceptability will be discussed in what is the largest RWE effectiveness comparison of these aforementioned treatment options.

Dr. L. Alison McInnes will present comparative effectiveness data for a large sample of real-world patients diagnosed with MDD who received either esketamine or intravenous ketamine as documented in electronic health records database from a large consortium of clinics.

Dr. Gerard Sanacora will present and review data on the biological plausibility of a meaningful clinical difference between ketamine and esketamine.

Dr. Balwinder Singh will present data from the Mayo Clinic and their experience using both ketamine and esketamine in a sample of N=62 adults with a mood disorder.

Dr. Samuel Wilkinson will present data from a retrospective analysis of N=210 patients treated with either ketamine or esketamine at the Yale Interventional Psychiatric Service. He will also explore prospective opportunities and projects that can more definitively address the question as to whether a meaningful clinical difference exists between the two options.

Learning Objectives: 1. To learn the potential neurobiological differences between racemic ketamine and esketamine.
2. To learn the best clinical evidence to date with respect to racemic ketamine and esketamine as therapeutics for mood disorders, including the limitations to this evidence base.

Literary References: 1. Singh B, Kung S, Pazdernik V, Schak KM, Geske J, Schulte PJ, Frye MA, Vande Voort JL. Comparative Effectiveness of Intravenous Ketamine and Intranasal Esketamine in Clinical Practice Among Patients With Treatment-Refractory Depression: An Observational Study. J Clin Psychiatry. 2023 Feb 1;84(2).doi: 10.4088/JCP.22m14548.
2. Nikayin S, Rhee TG, Cunningham ME, de Fontnouvelle CA, Ostroff RB, Sanacora G, Wilkinson ST. Evaluation of the Trajectory of Depression Severity With Ketamine and Esketamine Treatment in a Clinical Setting. JAMA Psychiatry. 2022 Jul 1;79(7):736-738.

COMPARATIVE EFFECTIVENESS OF INTRAVENOUS RACEMIC KETAMINE AND INTRANASAL ESKETAMINE IN ADULTS WITH TREATMENT RESISTANT DEPRESSION

Roger McIntyre, University of Toronto

Individual Abstract: Treatment resistant depression (TRD) affects between 30-50% of people with major depressive disorder (MDD) depending on the definition employed. Results from short-term single- and multi-infusion studies indicate that intravenous (IV) racemic ketamine is rapidly and robustly effective with improvement reported to be not inferior to electroconvulsive therapy (ECT). Intranasal (IN) esketamine is also proven effective co-initiated with an antidepressant in TRD. In addition, when added to existing antidepressants in adults with TRD, IN esketamine has been shown to be superior to Quetiapine XR in the acute and maintenance treatment of TRD. To inform treatment decisions, controlled studies comparing IV racemic ketamine to IN esketamine are urgently needed and are currently underway. In addition, there is a need for real-world evidence (RWE) comparing these two treatment options in TRD. This presentation will present RWE effectiveness comparison from two large centers (Toronto, Canada and Rome, Italy) that have administered thousands of treatments of IV ketamine (i.e., Toronto, Canada) and IN esketamine (i.e., Rome, Italy) in adults with TRD. Effectiveness, tolerability and acceptability will be discussed in what is the largest RWE effectiveness comparison of these aforementioned treatment options.
Learning Objectives: 1) To discuss a rationale for real world evidence (RWE) comparing IV racemic ketamine to IN esketamine
2) To compare the effectiveness of IV racemic ketamine and IN esketamine in adults with TRD in two real-world international samples

Literature References McIntyre RS, Alsuwaidan M, Baune BT, Berk M, Demyttenaere K, Goldberg JF, Gorwood P, Ho R, Kasper S, Kennedy SH, Ly-Uson J, Mansur RB, McAllister-Williams RH, Murrough JW, Nemeroff CB, Nierenberg AA, Rosenblat JD, Sanacora G, Schatzberg AF, Shelton R, Stahl SM, Trivedi MH, Vieta E, Vinberg M, Williams N, Young AH, Maj M. Treatment-resistant depression: definition, prevalence, detection, management, and investigational interventions. World Psychiatry. 2023 Oct;22(3):394-412. doi: 10.1002/wps.21120. PMID: 37713549; PMCID: PMC10503923.
d'Andrea G, Pettorruso M, Rhee TG, Di Lorenzo G, McIntyre RS, Martinotti G. Exploring the potential of a bridge therapy: Synergistic approach integrating intravenous ketamine and intranasal esketamine for treatment-resistant depression. Acta Psychiatr Scand. 2023 Oct;148(4):385-387. doi: 10.1111/acps.13605. Epub 2023 Sep 8. PMID: 37688284.

EVALUATING THE EVIDENCE: IS THERE A MEANINGFUL CLINICAL DIFFERENCE BETWEEN KETAMINE AND ESKETAMINE?

Lynne McInnes, Osmind

Individual Abstract: Treatment-resistant depression (TRD) is a chronic and disabling condition and is generally defined when second-line antidepressant therapies fail to produce remission. Since 2000, an increasing number of studies have shown that low-dose racemic ketamine delivered intravenously can have powerful and rapid antidepressant effects in TRD. Yet IV ketamine is unlikely to gain FDA approval as it has no pharmaceutical sponsor and no clear path for commercialization. In 2019, the US Food and Drug Administration approved S-ketamine (the S-enantiomer of ketamine; trade name “Spravato”) as a therapy for TRD in the form of a nasal spray. While some experts predicted that the availability of an FDA-approved form of ketamine would shift market pressures away from intravenous ketamine, preliminary

epidemiological data suggest that intravenous ketamine has remained available for a portion of the population. Furthermore, considerable controversy exists as to whether there is a significant clinical difference between IV ketamine and intranasal esketamine, with some practitioners claiming the intravenous racemic ketamine is the "gold standard" despite a lack of evidence supporting this claim.
Dr. L. Alison McInnes will present comparative effectiveness data for a large sample of real-world patients diagnosed with MDD who received either esketamine or intravenous ketamine as documented in Osmind 's electronic health record (EHR)-derived de-identified database.

Objectives

1) Describe baseline demographic characteristics of patients receiving treatment with KIT versus patients receiving treatment with esketamine.

2a) Calculate the group difference in PHQ-9 scores after an initial course of treatments referred to as an induction (primary end point) and b) at treatment end

3) Calculate group differences in response rates and remission rates at the primary end point.

Learning Objectives: 1. Describe demographic characteristics of real-world patients seeking either KIT or esketamine.
2. Understand the comparative effectiveness of ketamine infusion therapy and esketamine in a very large sample of real-world patients.

Literature References Correia-Melo FS, Leal GC, Vieira F, et al.. Efficacy and safety of adjunctive therapy using esketamine or racemic ketamine for adult treatment-resistant depression: a randomized, double-blind, non-inferiority study. J Affect Disord. 2020;264:527-534. doi: 10.1016/j.jad.2019.11.086
Nikayin, S., Rhee, T. G., Cunningham, M. E., de Fontnouvelle, C. A., Ostroff, R. B., Sanacora, G., and Wilkinson, S. T. (2022). Evaluation of the Trajectory of Depression Severity With Ketamine and Esketamine Treatment in a Clinical Setting. JAMA psychiatry, 79(7), 736–738. https://doi.org/10.1001/jamapsychiatry.2022.1074

BIOLOGICAL PLAUSIBILITY AND POTENTIAL MECHANISTIC ACTIONS UNDERLYING CLINICALLY RELEVANT DIFFERENCES BETWEEN RACEMIC I.V. KETAMINE AND I.N. ESKETAMINE

Gerard Sanacora, Yale

Individual Abstract: The discovery of ketamine's unique rapid onset of antidepressant action grew out of late 20th Century evidence pointing to the potential importance of the N-methyl-D-aspartate [NMDA] receptor in the pathophysiology of depression. This led to the idea that drugs targeting the NMDA receptor could have beneficial effects in treating depression. Based on this hypothesis a small proof-of-concept clinical trial was designed to explore the potential efficacy of ketamine, a drug with known antagonist-like effects on the NMDA receptor, in treating depression. As we now know ketamine did produce a rapid and robust antidepressant action that persisted for several days following a single dose. The high replicability of the findings incited intense interest in ketamine and the NMDA receptor, assuming that the drug's effects on the NMDA receptor were critically important to its antidepressant action.
To remove the need for intravenous drug delivery, studies were undertaken to develop a formulation of the treatment as a nasal spray. The (S)-enantiomer of ketamine (esketamine) was previously shown to have higher binding potential for NMDA receptors compared to (R)-

enantiomer (arketamine). Therefore, it was believed that esketamine would have greater potency in generating antidepressant effects and require lower doses that could be administered in smaller volumes, making the intranasal delivery more feasible. Initial studies with IV esketamine appeared to support this idea of increased potency. These early data led to the development of an intranasal formulation of esketamine, designed to mimic the pharmacodynamics of IV racemic ketamine (containing equal amounts of both the (R) and (S) enantiomers), specifically with respect to its action on the NMDA receptor. After testing in a large package of rigorous clinical trials I.N. esketamine was approved by the FDA for the indication of treatment resistant depression in 2019. However, over the years other studies demonstrated that the mechanisms underlying ketamine's antidepressant action are likely more complex than first proposed. These revelations lead to questions about potentially clinically important differences that may exist between racemic ketamine (containing both (S) and (R)-ketamine molecules) and pure esketamine formulations like Spravato.

This workshop presentation will critically review several of these differences. The discussion will cover the biological plausibility of these proposed differences having clinically meaningful impacts on treatment outcome and response. The most obvious difference, the absence of (R) enantiomer, arketamine, will be discussed considering emerging data evaluating arketamine's purported unique antidepressant properties. Considering both preclinical and clinical studies provide evidence to suggest a narrow therapeutic window is associated with optimal therapeutic response to ketamine, the potentially important pharmacokinetic (PK) profiles of the different delivery methods and the effects this could have on clinically relevant drug concentrations will be examined. Lastly, we will also review potentially important differences in the non-specific effects associated with the two forms of treatment. Non-specific treatment effects, including the placebo effect, are associated with virtually all medical treatments and are especially prominent in the treatment of MDD and amplified using highly medicalized treatments such as IV drug administration. All these potential factors will be considered in the context of the findings from several small studies and meta-analyses attempting to compare the effects of racemic ketamine with esketamine in the treatment of depression.

Learning Objectives: 1. To be familiarized with the differences between I.V. racemic ketamine and I.N. esketamine that could have clinically relevant impacts.
2. To be understand the factors that need to be assessed when critically evaluating the existing data comparing I.V. racemic ketamine with I.N. esketamine.

Literature References Colloca L, Nikayin S, Sanacora G. The Intricate Interaction Between Expectations and Therapeutic Outcomes of Psychedelic Agents. JAMA Psychiatry. 2023 Sep 1;80(9):867-868. doi: 10.1001/jamapsychiatry.2023.1412.
McIntyre RS, Rosenblat JD, Nemeroff CB, Sanacora G, et al.. 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.

NAVIGATING THE KETAMINE-ESKETAMINE DILEMMA: CHOOSING THE RIGHT APPROACH FOR TREATMENT-RESISTANT DEPRESSION

Balwinder Singh, Mayo Clinic

Individual Abstract: Delving into the realm of treatment-resistant depression (TRD), the choice between ketamine and esketamine becomes a pivotal decision. In this presentation, we aim to shed light on this dilemma by offering insights derived from real-world data gathered at a tertiary center's dedicated ketamine and esketamine clinic, specifically, the Mayo Clinic in Rochester, Minnesota.

Our exploration will extend beyond the theoretical to the practical, unveiling disparities in efficacy and side-effect profiles between ketamine and esketamine for adults grappling with TRD. The presentation will unravel how these pharmacological interventions impact various depressive phenotypes, with a keen focus on significant shifts in anhedonia and suicidal ideation.

As we dissect the complexities of this decision-making process, we will delve into the nuances of choosing between intravenous (IV) ketamine and intranasal (IN) esketamine. The discussion will not only encompass the clinical considerations but will also extend to the practical challenges faced in the real world. Financial and logistical hurdles associated with the adoption of these novel treatments will be scrutinized, providing a comprehensive view of the landscape clinicians and patients must navigate when contemplating the use of ketamine or esketamine for TRD.

Join us in this exploration of the practical challenges, nuanced decision-making, and real-world implications surrounding the ketamine-esketamine dilemma in the treatment of individuals with treatment-resistant depression.

Learning Objectives: 1. To comparing the efficacy and side-effect profiles of ketamine and esketamine, exploring their impact on depressive phenotypes such as anhedonia and suicidal ideation.

2. To discuss practical considerations—such as when to choose intravenous ketamine or intranasal esketamine.

Literature References 1. Singh B, Kung S, Pazdernik V, Schak KM, Geske J, Schulte PJ, Frye MA, Vande Voort JL. Comparative Effectiveness of Intravenous Ketamine and Intranasal Esketamine in Clinical Practice Among Patients With Treatment-Refractory Depression: An Observational Study. J Clin Psychiatry. 2023 Feb 1;84(2).doi: 10.4088/JCP.22m14548.

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EVALUATING THE CLINICAL EVIDENCE: KETAMINE AND ESKETAMINE

Samuel Wilkinson, Yale School of Medicine

Individual Abstract: Background: Although intravenous racemic ketamine has rapid antidepressant properties, it is not approved for depression treatment.1 However, the US Food and Drug Administration has approved intranasal esketamine for treatment-resistant depression.

The Yale Interventional Psychiatry Service (IPS) provides both intravenous ketamine (0.5 mg/kg over 40 minutes) and intranasal esketamine (56 or 84 mg). Patients receive similar care with comparable protocols in the same physical space. We analyzed Yale IPS clinical data to evaluate these treatments in a clinical setting.

Methods: For this comparative analysis, we reviewed retrospective data for all Yale IPS patients receiving intravenous ketamine or intranasal esketamine between September 2016 and April 2021

Methods: Of 210 included patients, 129 (61.4%) received intravenous ketamine and 81 (38.6%) received intranasal esketamine. The estimated group difference in Montgomery-Åsberg Depression Rating Scale (MADRS) score by treatment end (primary outcome) was 2.15 (95% CI, −0.06 to 4.37; P = .06). Estimated group differences in Quick Inventory of Depressive Symptomatology–Self-Report (QIDS-SR) scores after full treatment course and MADRS and QIDS-SR scores after the first 6 treatments (secondary outcomes) were 1.59 (95% CI, 0.24-2.94; P = .02), 2.49 (95% CI, 0.01-4.98; P LESS THAN .05), and 1.64 (0.08-3.19; P = .04), respectively, all favoring intravenous ketamine. Other models produced similar results. There were no group differences in response rates (37.8% [95% CI, 30.0%-46.3%] vs 36.0% [95% CI, 25.9%-47.5%]) or remission (29.6% [95% CI, 22.5%-37.9%] vs 24.0% [95% CI, 15.6%-35.0%]) for ketamine vs esketamine, respectively.

Discussion: This comparative analysis evaluating the trajectory of depression severity with ketamine and esketamine yielded no significant differences between groups based on the primary outcome measure. However, secondary outcomes based on QIDS-SR scores after 8 treatments and MARDS and QIDS-SR scores comparing the first 6 treatments all favored intravenous ketamine. These findings should be interpreted with utmost caution given the study limitations.

Dr. Wilkinson will also discuss a recently approved study to definitively compare ketamine and esketamine in a clinical population using a well-powered, randomized design.

Learning Objectives: 1. To learn the potential neurobiological differences between racemic ketamine and esketamine.
2. To learn the best clinical evidence to date with respect to racemic ketamine and esketamine as therapeutics for mood disorders, including the limitations to this evidence base.

Literature References 1. Singh B, Kung S, Pazdernik V, Schak KM, Geske J, Schulte PJ, Frye MA, Vande Voort JL. Comparative Effectiveness of Intravenous Ketamine and Intranasal Esketamine in Clinical Practice Among Patients With Treatment-Refractory Depression: An Observational Study. J Clin Psychiatry. 2023 Feb 1;84(2).doi: 10.4088/JCP.22m14548.
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*PROGRESS AND NEW DEVELOPMENTS IN THE USE OF NEUROIMAGING BIOMARKERS IN PSYCHIATRIC CLINICAL TRIALS

James Murrough, Icahn School of Medicine at Mount Sinai

Overall Abstract: The current decade as witnessed an explosion of research in psychiatric neuroscience. Substantial progress has been made in basic and translational neuroscience informing our understanding of the brain and behavioral mechanisms of mental illness, including depression, psychosis, and cognitive disorders. Regarding psychiatric neuroscience studies in living humans, there has been significant advances in methodologies that allow measurement of brain function, including magnetic resonance imaging (MRI) and electroencephalographic (EEG) approaches. Despite these advances, there has been only

modest uptake of neuroimaging technologies in the development and implementation of clinical trials for psychiatric disorders, both in the realm of industry, as well as academia. In academia, there has been a significant increase in the utilization of neuroimaging approaches in clinical trials driven in part by the National Institute of Mental Health (NIMH) experimental medicine initiative, which calls for measures of target engagement in the context of clinical trials. However, it is not yet clear if the application of these technologies to clinical trials is yielding advancement in the field. The current panel will address the timely issue of the utilization of neuroimaging biomarkers in clinical research in psychiatry, and will focus on clinical trials in depression or related mood disorders. In the first talk, Dr. Murrough will provide a brief review of the current use of neuroimaging in clinical trials of depression and will present new neuroimaging and clinical data from an ongoing NIMH-funded clinical trial of a novel potassium channel positive allosteric modulator (PAM) in adult patients with depression and anhedonia. The second talk will continue the theme of an orientation to anhedonia and the reward system in the context of depression. The presence of anhedonia has been generally linked to poor response to pharmacological and psychological treatments. In this talk, Dr. Pizzagalli will summarize recent findings pointing to behavioral, MRI and positron emission tomography (PET) markers predicting response to antidepressants with dopaminergic drugs as well as behavioral activation treatment for depression. Implications for patient stratification and personalized treatments will be discussed. In the third talk, Dr. Costi will present new results of an experimental medicine study utilizing functional MRI measures of neuroplasticity in the context of a clinical trial of ketamine in adults with treatment resistant depression (TRD). Animal models suggest that ketamine affects retrieval of established memories via changes in the medial prefrontal cortex (mPFC) and presented data will inform the potential of ketamine to modulate memory consolidation and retrieval at the neurocircuit level in humans. Finally, turning to EEG, Dr. Murphy will discuss the use of electrophysiology to identify patterns that confirm target engagement in clinical trials in psychiatry. He will evaluate the utility of electrophysiology biomarkers as tools in drug discovery, and discuss how they may add in detecting clinically important effects not readily apparent by more traditional survey measures. At the conclusion of the panel, it is anticipated that the audience will have a substantially enhanced understanding of the current state of the science regarding the utilization, progress, and potential pitfalls, of neuroimaging biomarkers in psychiatric clinical trials.

Learning Objectives: 1. To understand the current utilization of neuroimaging approaches to treatment discovery in psychiatric clinical trials

2. To appreciate both the advantages as well as potential limitations of neuroimaging in the context of psychiatric clinical trials

Literary References: Costi S, Morris LS, Kirkwood KA, et al. Impact of the KCNQ2/3 Channel Opener Ezogabine on Reward Circuit Activity and Clinical Symptoms in Depression: Results From a Randomized Controlled Trial. Am J Psychiatry. 2021 May 1;178(5):437-446.
Pizzagalli DA. Toward a Better Understanding of the Mechanisms and Pathophysiology of Anhedonia: Are We Ready for Translation? Am J Psychiatry. 2022 Jul;179(7):458-469.

ROLE OF NEUROIMAGING IN DRIVING THERAPEUTIC DISCOVERY FOR MOOD DISORDERS: RECENT FINDINGS FROM KCNQ-TARGETED CLINICAL TRIALS IN DEPRESSION

James Murrough, Icahn School of Medicine at Mount Sinai

Individual Abstract: Depression is one of the largest causes of disability, and mechanistically new treatment approaches are urgently needed to address this public health problem. There is great interest in identifying neuroimaging biomarkers to advance treatment discovery efforts for mood disorders. Towards this end, clinical and translational research point towards a core neural system supporting reward processing and mood with key hubs in the ventral tegmental area (VTA), the ventral striatum (VS)/nucleus accumbens (NAc) and the ventromedial prefrontal cortex (vmPFC). In addition, basic research suggests that enhancing signaling at KCNQ (a.k.a., Kv7) type potassium channels within this reward system may represent a promising new strategy for drug discovery for depression and related conditions. The current talk will present new data from an NIMH-funded program of research designed to test the proof-of-principal that targeting KCNQ channels within the reward system in humans may be promising strategy to treat mood disorders, with an particular focus on targeting depression and anhedonia. In one study, N=45 adults with depression and prominent anhedonia underwent randomization to treatment with the KCNQ2/3 positive allosteric modulator ezogabine, or matching placebo, for 5 weeks. Herein we report new, unpublished results based on a region of interest approach focused on the VTA, as well as results based on resting-state fMRI (rs-fMRI). At baseline, higher VTA response during cue was associated with greater severity of depression (R=0.283, p=0.042). There was a drug x time interaction wherein VTA activation to cue was reduced following treatment with ezogabine but not placebo (F(1,34)=4.26, p=0.047). While preliminary, these new neuroimaging results contribute to an understanding of the neural circuit-level effects of KCNQ channel modulation in the brain in the context of depression and anhedonia.

Learning Objectives: 1. To understand the utility and potential limitations of human neuroimaging biomarkers targeting the reward system in treatment discovery for mood disorders

2. To understand the current state of evidence of the use of KCNQ-targeting compounds as potential novel antidepressants

Literature References Costi S, Morris LS, Kirkwood KA, et al. Impact of the KCNQ2/3 Channel Opener Ezogabine on Reward Circuit Activity and Clinical Symptoms in Depression: Results From a Randomized Controlled Trial. Am J Psychiatry. 2021 May 1;178(5):437-446. Costi S, Han MH, Murrough JW. The Potential of KCNQ Potassium Channel Openers as Novel Antidepressants. CNS Drugs. 2022 Mar;36(3):207-216.

REWARD-RELATED BEHAVIORAL AND NEUROIMAGING MARKERS PREDICTING TREATMENT RESPONSE IN MAJOR DEPRESSION

Peter Zhukovsky, Harvard Medical School McLean Hospital

Individual Abstract: Guiding treatment selection in major depressive disorder (MDD) remains challenging. In addition to the heterogeneity of MDD, the lack of objective markers to inform treatment selection represents a major impediment in this area. In this talk, Dr. Pizzagalli will present behavioral and neuroimaging findings implicating the brain reward system in antidepressant response. In the first study, 296 participants were randomized to receive 8 weeks of sertraline or placebo in Stage 1. Participants responding to treatment in Stage 1 continued for another 8-week course of the same intervention in Stage 2; conversely, sertraline and placebo non-responders were crossed-over in Stage 2 to bupropion and sertraline, respectively. In total, data from 241 participants were available, including 87 MDD patients who switched medication in Stage 2. 116 MDD participants treated with sertraline in Stage 1

served as an independent replication sample. To probe the functionality of the brain reward system, the probabilistic reward task and resting-state functional magnetic resonance imaging were collected at baseline. Findings indicated that greater (i.e., more normative) pretreatment reward sensitivity and higher resting-state functional connectivity between the nucleus accumbens and rostral anterior cingulate cortex predicted beneficial response to bupropion, but not sertraline. Highlighting specificity, null findings for sertraline were replicated in the Stage 1 sample. Moreover, in separate parallel analyses we found that higher depression severity and neuroticism, older age, less impairment in cognitive control and being employed were each associated with better outcomes to sertraline than placebo. Together, these data suggest that pretreatment reward sensitivity and frontostriatal connectivity may identify patients likely to benefit from bupropion following SSRI failures, whereas sertraline response can be predicted using a distinct set of variables. Based on these and related findings, we are currently performing a clinical trial in which these markers are prospectively used to assign individuals with MDD to their "intended" vs. "non-intended" treatment. Preliminary (unpublished) findings from this prospective clinical trial will be presented.

Learning Objectives: 1) Understand how behavioral and imaging markers can be used to predict treatment response

2) Evaluate the role of the brain reward system in antidepressant responses.

Literature References Ang Y-S et al. Pretreatment Reward Sensitivity and Frontostriatal Resting-State Functional Connectivity Are Associated With Response to Bupropion After Sertraline Nonresponse. Biol Psychiatry. 2020 Oct 15;88(8):657-667.

Pizzagalli DA. Toward a Better Understanding of the Mechanisms and Pathophysiology of Anhedonia: Are We Ready for Translation? Am J Psychiatry. 2022 Jul;179(7):458-469.

KETAMINE RAPID EFFECTS ON NEURAL PLASTICITY AND AFFECTIVE MEMORIES: AN EXPERIMENTAL MEDICINE MODEL USING FMRI IN TREATMENT RESISTANT DEPRESSION

Sara Costi, University of Oxford

Individual Abstract: One third of subjects with Major Depressive Disorder (MDD) fail to achieve a stable remission of symptoms following treatment with conventional antidepressants. This condition is often described as treatment resistant depression (TRD). The N-Methyl D-Aspartate (NMDA) receptor antagonist ketamine can reduce symptoms rapidly (within hours) and in a sustained fashion (up to seven days). However, the exact mechanisms underpinning ketamine antidepressant effect is still largely unknown.

Depression appears characterized by a greater tendency for recollections of general, often negatively valenced, autobiographical memories. Modulation of NMDA receptors appears to affect the decreased autobiographical memory specificity and increased negative bias in memory recall characteristic of MDD. Further, animal models of emotional memory suggests that ketamine reduces the influence of negatively biased memory on behavior choice via changes in the medial prefrontal cortex (mPFC). Conversely, the administration of conventional antidepressants appears to affect the encoding of new information, leaving former negatively biased memory unaltered. Overall, this data suggest that ketamine may reduce the negative valence associated with previously established affective memories and diminish the impact of these memories on the animal behavior.

This session will present data from a clinical trial testing whether a subanesthetic dose of ketamine compared to placebo can reduce the influence of previously encoded negative affective memories in adults with TRD using the Oxford autobiographical memory task. This task is conceptualized as two sections, including the autobiographical memories retrieval and the word sorting task. An fMRI application of the same task is also presented. Subjects enrolled in this trial completed the Oxford autobiographical memory task prior and 24-hour following drug or placebo administration. Neural response during emotional compared to non-emotional memory retrieval, assessed during fMRI scanning session within the mPFC and hippocampus, will also be discussed. This data will contribute to the understanding of the neuropsychological mechanisms underlying ketamine's antidepressant effect. It will also inform potential targets for the development of novel and rapid-acting agents for TRD.

Learning Objectives: 1. Effect of ketamine on negative valence of autobiographical memory retrieval
2. Neural response during emotional vs non-emotional memory retrieval within the mPFC and hippocampus following ketamine administration

Literature References Stuart SA, Butler P, Munafò MR, Nutt DJ, Robinson ES. (2015) Distinct Neuropsychological Mechanisms May Explain Delayed- Versus Rapid-Onset Antidepressant Efficacy Neuropsychopharmacology. 40(9):2165-74
Das RK, Gale G, Walsh K, Hennessy VE, Iskandar G, Mordecai LA, Brandner B, Kindt M, Curran HV, Kamboj SK. (2019) Ketamine can reduce harmful drinking by pharmacologically rewriting drinking memories Nat Commun. 26;10(1):5187

ELECTROPHYSIOLOGY, A COMPANION METHOD TO BOLSTER CLINICAL TRIAL EFFICACY

Nicholas Murphy, Baylor College of Medicine

Individual Abstract: The art of clinical trial design is in the rigorous approach to partialling out inappropriate factors that impede our ability to clearly observe the efficacy of a drug or device. However, it is all too often the case that trial design assumes successful pre-clinical work in animals will continue to carry over all the way to the end of the road. The resounding success of ketamine for the treatment of mood disorders has spurred on the development of alternative therapeutics that aimed to replicate the glutamatergic surge without the cognitive and dissociative effects of ketamine. The discontinuation of drugs such as AV-101 (Vistagen Therapeutics) demonstrate that translation from animal to human work is complicated and that additional biological factors often need to be implemented to achieve the same outcome.
Companion biomarkers offer the resolution to observe changes in metrics for target engagment throughout the course of the trial that can influence how the clinical outcome is evaluated. Electroencephalography (EEG) is a powerful, low cost, measure of synaptic activity that is rapidly finding a place in the clinical trial sphere. Traditional event related and spectral measures of neural circuitry can be complimented by information theoretic metrics to model not just how a candidate receptor is activated or inhibited, but also how interaction with the receptor alters the storage and transfer of information as a result. These measures provide a detailed insight into the systemic operation of pharmaceuticals that can be observed in relation to emerging clinical properties.

This session will present data from a clinical trial of ketamine dosing in late life. Subjects in this study completed the Montgomery-Asberg Depression Rating Scale (MADRS) as a measure of depression severity, which was used to evaluate changes in symptoms as a result of assignment to one of three ketamine doses or placebo. 64-channel EEG was used to measure spectral and complexity features of the resting state during pre-infusion, rapid (30 minuts to 4 hours post-infusion), and post rapid (24 hours to 7 days post-infusion) time periods relative to the infusion. While much is already understood about spectral changes post-ketamine it is less clear how this is related to signal complexity. This study demonstrates the importance of biomarker selection for understanding the timeline of biological effects following target engagement.

Learning Objectives: 1) Develop an understanding of how electrophysiological biomarkers can improve the sensitivity of clinical trial outcomes by measuring target engagement.
2) Be able to identify if the interpretation of a clinical outcome is appropriate by considering biological supporting evidence.

Literature References 1) Murphy N, Tamman AJF, Lijffijt M, Amarneh D, Iqbal S, Swann A, Averill LA, O'Brien B, Mathew SJ. Neural complexity EEG biomarkers of rapid and post-rapid ketamine effects in late-life treatment-resistant depression: a randomized control trial. Neuropsychopharmacology. 2023 Oct;48(11):1586-1593. doi: 10.1038/s41386-023-01586-4.
2) Park LT, Kadriu B, Gould TD, Zanos P, Greenstein D, Evans JW, Yuan P, Farmer CA, Oppenheimer M, George JM, Adeojo LW, Snodgrass HR, Smith MA, Henter ID, Machado-Vieira R, Mannes AJ, Zarate CA. A Randomized Trial of the N-Methyl-d-Aspartate Receptor Glycine Site Antagonist Prodrug 4-Chlorokynurenine in Treatment-Resistant Depression. Int J Neuropsychopharmacol. 2020 Jul 29;23(7):417-425. doi: 10.1093/ijnp/pyaa025. PMID: 32236521; PMCID: PMC7387765.

^ADHERENCE

Molly McVoy, Case Western University School of Medicine

Overall Abstract: Challenges with adherence and clinical care engagement among patients with psychiatric conditions leads to poor outcomes, multiple medication trials and significant morbidity (McVoy, Levin 2023). Across the lifespan and across medical and psychiatric diagnoses, adherence and engagement are particularly challenging in understudied populations including individuals with comorbidity and children and adolescents (Bain et al 2017, Klein et al 2020). Successfully addressing adherence and engagement often requires approaches that are multifaceted and include developmentally sensitive content/formats, technology-assisted models and customized, patient- centered interventions. The panel presenters draw upon recent clinical trial and systematic literature review data to present pragmatic and evidence-based strategies to improve patient adherence and engagement.
Our first presenter, Dr. Sajatovic, will present methods and findings from a recently completed NIMH-funded study designed to improve adherence in high-risk adolescents and young adults (AYA) with bipolar disorder (McVoy M et al 2022). She will address barriers and facilitators to medication adherence among AYA with bipolar disorder (Levin, J et al 2022), the assessment of adherence in people with BD across the lifespan and will provide pragmatic tips and takeaways on how clinicians might optimize psychotropic medication adherence among people with bipolar disorder across the life-span.

Our second presenter, Dr. Levin, will address supporting adherence in adults with psychiatric and medical comorbidities. She will overview medical comorbidity among people with psychiatric disorders and discuss the similarities and differences in adherence and engagement challenges in managing comorbid somatic (hypertension) and psychiatric illness (bipolar disorder (BD)). Dr. Levin and her team have piloted and are currently conducting a randomized controlled trial of a practical, technology-facilitated and patient-centered adherence intervention to improve adherence to antihypertensive medications and reduce systolic blood pressure (SBP) in poorly adherent individuals with BD and hypertension (HTN) (Levin et al 2019). Preliminary findings will be discussed and Dr. Levin will also present findings from an analysis of the literature on technology supported adherence interventions in medical and psychiatric comorbidity, (Simon E et al 2022). Practical strategies for clinicians to optimize engagement among individuals with psychiatric and medical comorbidity will be presented.

Our final presenter, Dr. McVoy, will discuss the development of a practical, customizable, patient- centered intervention for adolescents with Attention Deficit Hyperactivity Disorder (ADHD). Dr. McVoy and her team have piloted a self-management intervention, targeting adherence and engagement for transitional age youth and young adults (AYA) with ADHD (Abdallah, S et al 2023). Dr. McVoy will discuss findings from an analysis of the literature on the impact of adherence problems in adolescents and young adults with ADHD. She will also present initial data from a NIDA-funded pilot study and focus on lessons learned from stakeholder input on developing an intervention for adolescents and young adults specifically.

Learning Objectives: 1. Understand the common barriers for adherence to medication in both chronically psychiatrically and medically ill individuals across the lifespan.
2. Identify practical strategies for improving self-management and adherence in patients.

Literary References: McVoy M, Levin JB. Updated strategies for the management of poor medication adherence in patients with bipolar disorder. Expert Rev Neurother. 2023 Apr;23(4):365-376. doi: PMID: 37036814.

McVoy M, Delbello M, Levin J, Modi AC, Forthun LF, Briggs F, Appling D, Broadnax M, Conroy C, Cooley R, Eapen G, Sajatovic M. A customized adherence enhancement program for adolescents and young adults with suboptimal adherence and bipolar disorder: Trial design and methodological report. Contemp Clin Trials. 2022 Apr;115:106729. doi: 10.1016/j.cct.2022.106729. Epub 2022 Mar 9. PMID: 35278693; PMCID: PMC9022043.

Levin JB, Sajatovic M, Rahman M, Aebi ME, Tatsuoka C, Depp C, Cushman C, Johnston E, Cassidy KA, Blixen C, Eskew L, Klein PJ, Fuentes-Casiano E, Moore DJ. Outcomes of Psychoeducation and a Text Messaging Adherence Intervention Among Individuals With Hypertension and Bipolar Disorder. Psychiatr Serv. 2019 Jul 1;70(7):608-612. PMID: 30991908

IMPROVING ADHERENCE IN HIGH-RISK ADOLESCENTS AND YOUNG ADULTS (AYA) WITH BIPOLAR DISORDER

Martha Sajatovic, University Hospitals Cleveland Medical Center

Individual Abstract: The onset of bipolar disorder (BD) is common during late adolescence and early adulthood. During this developmentally vulnerable period, adolescents and young adults (AYAs) may experience relapse due to reduced caregiver oversight, higher risk-taking

behaviors and increased family conflict. While pharmacotherapy is effective for BD, poor adherence occurs in GREATER THAN 65% of AYA patients and is associated with low rates of recovery, high relapse rates and a 5.2 fold increase in suicide risk.
Poor adherence is a critical yet modifiable risk factor for poor outcomes among people with BD across the life-span. Mixed- methods research has described multiple issues and challenges among people with BD, including difficulty in coping with/ management of BD symptoms and staying on track with medications. Shared decision-making with AYA also needs to include parents/guardians and adherence promotion supports should have language that considers developmental level (e.g., teenager versus young adult) and use of visually appealing images to improve engagement. For interventions delivered via telehealth, shorter duration (30-45 minutes) may be optimal.

A recently completed 6-month prospective randomized-controlled trial (RCT) pilot tested a novel behavioral intervention adapted for AYA (CAE-AYA) vs. enhanced treatment as usual (ETAU). The 2-site RCT enrolled AYAs age 13-21 with BD, type I or II with suboptimal adherence defined as self-reporting missing ≥ 20% of prescribed evidence-based BD medications. Participants were followed for 6 months with assessments conducted at Screening, Baseline, and Weeks 8, 12 and 24. Adherence, the primary outcome, was measured via: 1) self-reported Tablets Routine Questionnaire (TRQ) in the past week and 2) electronic monitoring (SimpleMed pillbox). Participants were given SimpleMed pillboxes at screening and these data were available at baseline and follow-up time-points. Symptoms were measured with the Hamilton Depression Rating Scale (HAM-D), the Young Mania Rating Scale (YMRS), the Clinical Global Impression Scale (CGI), and the Columbia Suicide Severity Rating Scale (CSSRS).

Mean sample age (N=36) was 19.1 years (SD= 2.0); 66.7 % (N = 24) female, 25.0 % (n= 9) non-White. The majority of participants had Type I BD (86%). Mean total sample percentage of missed BD medications based on TRQ was 34.9% (SD=28.9) at screening and 30.6% (SD=33.0) at baseline. Both CAE and ETAU groups improved on TRQ from screening to baseline. Mean percentage of missed medication using SimpleMed at baseline was 42.1 (SD=37.0). At baseline, the mean HAM-D (mean=7.1, SD=4.7) and YMRS scores (mean=6.0, SD=7.3) were consistent with relatively mild BD manic and depressive symptom severity. Change from baseline to 24 weeks on past week TRQ after adjusting for age, gender, educational level, living situation, family history, race and ethnicity, showed improvement favoring CAE vs. ETAU (reduction of missed BD medication 14.9%, p= .019). There was a trend for improvement on past week SimpleMed (p=0.086) favoring CAE although interpretation is limited in this outcome domain due to substantial missing data. There were no significant treatment differences on BD symptoms.

While adherence monitoring can temporarily improve medication adherence among AYA with BD, longer-term pill monitoring appears insufficient to maintain optimal adherence. Interventions that address adherence barriers, such as CAE, may improve adherence and have potential to advance care.

Learning Objectives: 1. Participants will gain knowledge on barriers to medication adherence among adolescents and young adults (AYA) with bipolar disorder
2. Participants will identify care approaches that target barriers to AYA with bipolar disorders

Literature References 1. Sanchez M, Lytle S, Neudecker M, McVoy M. Medication Adherence in Pediatric Patients with Bipolar Disorder: A Systematic Review. J Child Adolesc Psychopharmacol. 2021 Jan 18. PMID: 33465006
2. Sajatovic M, Levin JB, Modi A, McVoy M, Forthun LF, Cooley R, Black J, Conroy C, Sarna K, Briggs FB, DelBello M. Association Between Symptom Severity and Medication Adherence in Adolescents with Bipolar Disorder Demonstrating Suboptimal Adherence. Psychopharmacology Bulletin Volume 3, Article 3, Aug 12 2023 August 12

MOVING THE NEEDLE ON MEDICATION-TAKING BEHAVIOR IN ADULTS WITH PSYCHIATRIC AND MEDICAL COMORBIDITIES

Jennifer Levin, Case Western Reserve University, School of Medicine

Individual Abstract: Despite strong evidence for antihypertensives in reducing cardiovascular risk on a population level, people with serious mental illnesses like bipolar disorder (BD) have poor outcomes due to suboptimal medication adherence and engagement. An effective adherence enhancement approach for patients with BD needs to: 1) consider the need for polypharmacy; 2) address cognitive and functional challenges such as difficulty planning and establishing stable healthcare routines, 3) address both intentional and non-intentional non-adherence, and 4) simultaneously target non-psychotropic and psychotropic medication adherence. Based on a modified version of the Attitude-Social Influence-Efficacy (ASE) model of behavioral intent, we developed an automated, customized mHealth intervention using a two-way text-messaging platform called Individualized Texting for Adherence Building – Cardiovascular (iTAB-CV) which targets physical and mental health simultaneously, primes behavioral intent with psychoeducation and motivational content, and combines cues and positive reinforcement to develop a strong and sustainable habit of medication taking behavior. In the current analysis, we examined the relationship between adherence to antihypertensive and BD medications as well as correlates with clinical symptoms in a well-characterized sample of 55 patients with BD and uncontrolled hypertension. Screening and baseline data were analyzed from an ongoing randomized controlled trial (RCT) testing iTAB-CV plus self-monitoring compared to self-monitoring alone.

Inclusion criteria were having a diagnosis of BD, being prescribed antihypertensives, and uncontrolled hypertension (systolic blood pressure/SBP ≥130mmHg). Adherence was measured for past week with 1) self-reported Tablets Routine Questionnaire for antihypertensives (TRQ-HTN) and BD (TRQ-BD) with a higher percentage reflecting worse adherence and 2) objective electronic monitoring using an eCAP© for one antihypertensive medication. Average SBP was calculated from 12 readings over one week. Symptoms of BD were measured with the Montgomery-Asberg Depression Rating Scale (MADRS) and the Brief Psychiatric Rating Scale (BPRS).

Methods: Mean age of the sample was 53.91±9.97, a majority female (61.8%), 49.1% Black and 45.5% White. Mean years of education was 14.09 ±2.83. At screen, TRQ-HTN was 35.80% ± 21.78 (N=55) while at baseline, mean TRQ-HTN was 12.94 ± 16.88%. At screen, TRQ-BD was 29.61% ±28.02 (N=55) while at baseline, TRQ-BD was 19.43% ±28.54 (N=50). At baseline, eCAP (N=43) was 39.53 ± 35.11%. There was a significant improvement in TRQ-HTN from screen to baseline (t(52) = -6.75 r = LESS THAN 0.001) and a trend for TRQ-HTN (t(49) = 1.80 p = 0.078). There was a significant correlation between TRQ-HTN and

eCAP at baseline (rs=0.307, p LESS THAN .05, N= 43) yet eCAP reported more missed days than TRQ-HTN (Mean = -25.581 t(42) = -4.903 p = LESS THAN 0.001). TRQ-BD was significantly correlated with BPRS (r = 0.313, p= 0.027, N = 50) but not with MADRS. Neither TRQ-HTN nor eCAP were correlated with SBP. SBP significantly decreased from screen to baseline (t(53) = 2.357 p = 0.022).

Our results show that adherence levels vary widely. Objective measurement identified 26% more missed medication than self-report. Self-reported BD adherence was related to global psychiatric symptoms but not depression while adherence to antihypertensives did not relate to SBP. Greater BD symptom severity may be a clinical indicator to assess for adherence problems and medication and BP monitoring alone may improve adherence and SBP.

Barriers to medication adherence will be discussed as will practical strategies to optimize engagement among those with psychiatric and medical comorbidity.

Learning Objectives: 1. Participants will gain knowledge on barriers to medication adherence among adults with psychiatric and medical comorbidities
2. Participants will learn practical strategies for increasing engagement and motivation for medication-taking behavior

Literature References 1. Levin JB, Moore DJ, Depp C, et al. Using mHealth to improve adherence and reduce blood pressure in individuals with hypertension and bipolar disorder (iTAB-CV): study protocol for a 2-stage randomized clinical trial. Trials. Jun 29 2022;23(1):539. doi:10.1186/s13063-022-06449-9
2. Levin JB, Sajatovic M, Rahman M, et al. Outcomes of Psychoeducation and a Text Messaging Adherence Intervention Among Individuals With Hypertension and Bipolar Disorder. Psychiatr Serv. Apr 2019:appips201800482. doi:10.1176/appi.ps.201800482

HOW TO HELP THE KIDS FLOURISH: A CUSTOMIZED SELF-MANAGEMENT INTERVENTION FOR ADOLESCENTS AND YOUNG ADULTS WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD)

Molly McVoy, Case Western University School of Medicine

Individual Abstract: Attention-deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterized by inattention, impulsivity and poor executive functioning. Medication for ADHD is safe, effective and positively impacts long-term outcomes. Despite this, poor medication adherence is common, particularly in adolescents and young adults (AYAs). AYAs with ADHD represent a particularly vulnerable group due to unique developmental challenges, peer influence and propensity for risk-taking behavior during this critical period. Intervening early has the potential for changing the course of the disorder.

Youth with ADHD require support from clinicians to begin planning the transition to adulthood and medication management early with practical, usable strategies. AYAs with ADHD, in particular, require specific support regarding the regulations surrounding stimulant medication, diagnosis management and interacting with the medical community. AYAs are at risk of being lost in the system as they transition from a child and parent centered system to an adult system. Our team recently completed a study to evaluate practical ways to improve the support for AYAs with ADHD.

Our team evaluated barriers and facilitators to treatment in AYAs with ADHD. AYAs with ADHD were enrolled, in addition to caregivers and treating providers. Semi-structured focus groups (n=19) were conducted to explore views regarding adherence, knowledge about ADHD, medication routines, communication, and substance use/risky behaviors. Participants in the focus groups included 8 AYAs (62.5% Female, Mage=19.4, SD=2.44), 5 caregivers and 6 healthcare providers.

5 themes emerged from the focus groups: 1) Impact of ADHD 2) Barriers to treatment adherence 3) Facilitators to treatment adherence 4) Strategies to improve AYA/provider relationship and 5) Perceptions about substance abuse. The primary barriers to ADHD treatment identified by participants were severity of ADHD symptoms, stigma, access (cost and availability of medications), and concerns regarding side effects. Facilitators to ADHD treatment adherence included having good organizational skills and/or external prompts, having knowledge about ADHD, experiencing benefits from medications, and having good support from community.

A self-management intervention was developed based on a previous AYA targeted intervention and modified for AYAs with ADHD. The intervention was developed to target AYAs with ADHD broadly. This intervention consists of 4 customized, remotely delivered 1:1 sessions regarding: psychoeducation, communication with peers, parents and clinicians, medication routines and risk taking behaviors. In addition, there is a 5th booster session with content that is customized based on the participants' needs. AYAs provided input to specifically modify the intervention and suggested limiting session length to 1 hour, allowing for and planning for breaks and "fidgeting," modifying materials to be simpler and more visually appealing and adding a more developmentally appropriate problem-solving exercise. AYAs responded positively to this intervention and noted it addressed a current gap in care. A pilot feasibility, acceptability, and preliminary efficacy study is underway.

In summary, the transition from adolescence to adulthood in individuals with ADHD is a challenging time that is also an opportunity for intervention. There is surprisingly little evidence regarding the consequences of and reasons for adherence challenges in AYAs with ADHD. Interventions that target practical skills to communicate with providers, understand and manage medication routines and problem solve are well received by AYAs with ADHD.

Learning Objectives: 1. Understand the barriers to self-management of ADHD in the transition between adolescence and adulthood.
2. Describe strategies to impact youth with ADHD as they transition from adolescence to adulthood.

Literature References Abdallah, S., Church, E., Levin, J., Chela, A., McVoy, M. Short and Long-term Outcomes of Suboptimal Medication Adherence in Adolescents with Attention-Deficit/Hyperactivity Disorder: A Systematic Literature Review; under review Nov 2023

Abdallah, S., Church, E., Chela, A., Kamimura-Nishimura, K., Levin J.B., Gray, M., Yala, J., and McVoy, M. Thematic Analysis of Focus Groups in the Development of a Customized Adherence Enhancement Treatment Intervention. 57th Annual Convention of Association for Behavioral and Cognitive Therapies. Seattle, Washington. Nov 16-19, 2023.

McVoy M, Delbello, M, Levin, J, Modi, A, Forthun, L, Briggs, F, Appling, D, Broadnax, M, Conroy, C, Cooley, R, Eapen, G, Sajatovic, M. A customized adherence enhancement program for adolescents and young adults with suboptimal adherence and bipolar disorder: Trial design and methodological report. Contemporary Clinical Trials. 2022 Mar 9. PMID: 35278693

*^INSIGHTS FOR ADVANCING TRANSLATION FROM BENCH TO CLINIC IN SUBSTANCE USE DISORDERS

Keren Bachi, The Addiction Institute of Mount Sinai; Icahn School of Medicine at Mount Sinai

Overall Abstract: The ongoing societal and public health burden of substance use disorders clearly show that the medical need for these disorders is large and is increasing. The field of substance use disorders has marked numerous advances following translation from preclinical to clinical models, including pharmacotherapeutic approaches that have been successful for the treatment of alcohol, opioids, and nicotine use disorders. Challenges yet remain, however, for optimizing translation between preclinical and clinical laboratories studies to clinical advancements. Therefore, our proposed symposium will bring together a panel of early- and mid-career investigators and senior researchers who will present cutting-edge preclinical and clinical research on novel approaches to treatment of these disorders. All presentations will incorporate elements of diversity, equity, inclusion, and belonging in clinical research.
This session centers on insights to enhance translation of research outcomes to clinical advances that are gleaned from preclinical and clinical studies, across drug classes, and subpopulations groups. The first presentation, by Dr. Venniro, will present a novel "socio-sensory" approach to investigate the mechanisms underlying volitional social reward and its protective effect on substance use disorders demonstrating the critical role of olfaction and social odors in volitional social interaction, social preference over drugs, and the social-induced buffering of drug craving. The second presentation, by Dr. Sinha, will include insights from human experimental and clinical studies to highlight stress and compulsive motivation processes in substance use disorders. Noradrenergic and neurosteroid targets that improve substance use disorders clinical outcomes will be shown to illustrate example of successful translation from animal to human studies and potential for new medications development in substance use disorders. The third presentation, by Dr. Gabbay, will highlight cross sectional and longitudinal data of cannabis use among depressed adolescents and provide insights on preventive strategies for adolescent mood and substance use disorders. Dimensional clinical data of anxiety, depression, and anhedonia severity together with resting state and task base neuroimaging data will be presented. In the fourth and final presentation, Dr. Egan will present findings from the Accelerated Development of Additive Treatment for Methamphetamine Disorder (ADAPT-2) Study. Currently, there is no FDA-approved treatment for methamphetamine use disorder. This public health crisis has led many researchers and clinicians to investigate novel interventions to mitigate methamphetamine use. Translational insights relate to **Conclusions** that combination extended-release injectable naltrexone and extended-release oral bupropion offer a possible intervention to treating methamphetamine use disorder, thus offering a potential solution to this growing problem. Together, these represent exciting new translational understandings to help bridge between research and clinic to guide development of novel treatments for substance use disorders.

Learning Objectives: 1. Recognize the burden of substance use disorders and how limited translation from research to clinic has contributed to it.
2. Identify translational insights to help bridge between research and clinic to guide development of novel treatments for substance use disorders.

Literary References: 1. Venniro, M., et al. (2020). "Improving translation of animal models of addiction and relapse by reverse translation." Nature Reviews Neuroscience 21(11): 625-643.
2. Valentino, R. J., et al. (2020). "Translating Opioid Pharmacology From Bench to Bedside, and Back." Biol Psychiatry 87(1): 4-5.

A SOCIO-SENSORY MECHANISM BUFFERING DRUG CRAVING

Marco Venniro, University of Maryland School of Medicine

Individual Abstract: Social interactions are rewarding and protective against substance use disorders, but it is unclear which specific aspect of the complex sensory social experience drives these effects. Here, we investigated the role of olfactory sensory experience on social interaction, social preference over cocaine, and cocaine craving in rats. First, we conducted bulbectomy on both male and female rats to evaluate the necessity of olfactory system experience on the acquisition and maintenance of volitional social interaction. Next, we assessed the effect of bulbectomy on rats given a choice between social interaction and cocaine. Finally, we evaluated the influence of olfactory sensory experience by training rats on volitional partner-associated odors, assessing their preference for partner odors over cocaine to achieve voluntary abstinence and assessing its effect on the incubation of cocaine craving. Bulbectomy impaired operant social interaction without affecting food and cocaine self-administration. Rats with intact olfactory systems preferred social interaction over cocaine, while rats with impaired olfactory sense showed a preference for cocaine. Providing access to a partner odor in a choice procedure led to cocaine abstinence, preventing incubation of cocaine craving, in contrast to forced abstinence or non-contingent exposure to cocaine and partner odors. Our data suggests the olfactory sensory experience is necessary and sufficient for volitional social reward. Furthermore, the active preference for partner odors over cocaine buffers drug craving. Based on these findings, translational research should explore the use of social sensory-based treatments utilizing odor-focused foundations for individuals with substance use disorders.
Learning Objectives: 1. Sensory mechanisms mediating social reward
2. The role of social odors in mitigating drug craving

Literature References Venniro M, Zhang M, Caprioli D, Hoots JK, Golden SA, Heins C, et al. Volitional social interaction prevents drug addiction in rat models. Nat Neurosci. 2018;21(11):1520-29.
Venniro M, Banks ML, Heilig M, Epstein DH, Shaham Y. Improving translation of animal models of addiction and relapse by reverse translation. Nat Rev Neurosci. 2020;21(11):625-43.

STRESS PATHOPHYSIOLOGY IN ADDICTION: BENCH TO BEDSIDE TRANSLATION TO IMPROVE SUBSTANCE USE DISORDER OUTCOMES

Rajita Sinha, Yale University School of Medicine

Individual Abstract: BACKGROUND: Stress co-occurs frequently in patients with substance use disorder (SUD) and increases risk of addiction and of poor treatment outcomes. However, multilevel stress responses in SUD samples and their effects on drug intake are not

well characterized. Also, whether drugs such as the alpha2 adrenergic agonist guanfacine (GUA) and the neurosteroid pregnenolone (PREG) may reverse such stress pathophysiology to improve drug use outcomes in patients with SUD is not known.
METHODS: Study 1 enrolled 80 individuals with and without SUD (+/-) participated in a novel stress and pain experiment with exposure to three consecutive 3-minute trials of ice cold hand/arm immersion (stress) or warm hand/arm immersion (no-stress/control) trials, presented in a randomized counterbalanced order. Study 2 enrolled women with polysubstance use disorder (PSUD, N=70) who were randomized to GUA (3mg/day) or placebo (PBO) for 10 weeks to assess cocaine, opioid, cannabis and/or alcohol use outcomes. Study 3 enrolled individuals with alcohol use disorder (AUD, N=86)) who were randomized to 300 mg/day, 500 mg/day or PBO for 8 weeks to assess drinking and related stress outcomes.

METHODS: Significant stress vs no-stress condition main effects for heart rate (HR), systolic and diastolic blood pressure (SBP/DBP), cortisol, ACTH, anxiety, pain and pain tolerance (p's LESS THAN 0.01) were observed, and condition X group interactions identified specific physiologic, endocrine, behavioral and subjective dysfunction in the SUD versus non-SUD groups (p's LESS THAN .05). In study 2, medication compliance moderated the positive GUA vs PBO response on number of abstinence days (p LESS THAN .02) and reduction in average drug craving (p LESS THAN .01). In study 3, the PREG300 mg/day vs. PBO group showed greatest improvement in reduction of any or heavy drinking days (p's LESS THAN .001) and in anxiety (p LESS THAN .0002) and alcohol craving (p LESS THAN .0001) over the 8-week period.

CONCLUSIONS: These findings indicate multi-level specific stress dysfunction in SUD groups that significantly impact drug craving and use outcomes. Noradrenergic and neurosteroid targets need further exploration in larger scale studies to assess potential benefit in reversing the stress pathophysiology in addiction to improve SUD outcomes.

Learning Objectives: 1. Articulate the key specific disruptions in stress biobehavioral responses in SUD and their association to drug use outcomes.
2. Identify at least 2 examples of novel medication targets that may rescue or reverse the stress pathophysiology in addiction and show improvements in drug use outcomes.

Literature References 1. Milivojevic V, Sullivan L, Tiber J, Fogelman N, Simpson C, Hermes G, Sinha R. Pregnenolone effects on provoked alcohol craving, anxiety, HPA axis, and autonomic arousal in individuals with alcohol use disorder. Psychopharmacology (Berl). 2023
2. Milivojevic V, Sinha R. Central and Peripheral Biomarkers of Stress Response for Addiction Risk and Relapse Vulnerability. Trends Mol Med. 2018 Feb;24(2):173-186.

CANNABIS USE AMONG ADOLESCENTS WITH DEPRESSION

Vilma Gabbay, Miller School of Medicine, University of Miami

Individual Abstract: Background: Despite the declining perceived risks of cannabis among youth, converging data suggest that adolescent cannabis use causes long-lasting alterations in reward circuitry and increased vulnerability to depression and substance use disorders. Alarmingly, epidemiological evidence indicates high rates of cannabis use among depressed adolescents to self-medicate, potentially exacerbating underlying neural alterations, leading to depression chronicity and psychiatric comorbidity. Therefore, we aimed to examine the effect

of cannabis use on clinical outcome as well as the reward neurocircuitry among youth with depression and comorbid cannabis use.
Methods: Study is ongoing and preliminary data are presented. Participants are adolescents ages 12-20 year old. All assessed with semi-structured diagnostic interviews and dimensional assessments for depression and anhedonia severity. We allowed depressive symptoms not meeting criteria of a DSM-5 depressive episode (CDRS-R GREATER THAN 30). Participants also had a neuroimaging session with resting-state and a reward fMRI task assessing reward anticipation, attainment and prediction error. Resting-state data were parcellated via the Cole-Anticevic Brain-wide Network Partition then subdivided into three reward networks based on a reward fMRI task. Weighted graph-theoretical metrics (Strength Centrality–CStr, Eigenvector Centrality–CEig, Local Efficiency–ELoc) were estimated within each network. Non-parametric group comparisons accounted for sex and familywise-error-rate (FWE).

Methods: Clinical outcome: Participants were 153 participants (Age: 15.9 ± 2.2, F: 64.1%): Cannabis naïve: 95 (Age: 15.4 ± 2.2, F: 64.2%); Cannabis use: 58 (Age: 16.8 ± 1.9, F: 63.8%). ANOVA comparing those with no and negligible cannabis use (no + low use) and substantial cannabis use (intermediate + high use) detected significant differences in anticipatory and consummatory anhedonia ($p = 0.0313$, $p = 0.0365$, respectively). There was also a significant association between cannabis use severity and anticipatory anhedonia ($r = -0.1942$; $p = 0.0251$). Neuroimaging: When adjusted for depression, adolescent cannabis users showed stronger Reward Prediction Error network ELoc in the right medial superior temporal cortex (pFWE LESS THAN 0.05). At a relaxed threshold (puncorrected LESS THAN 0.001), cannabis use implicated: a) Reward Prediction Error CStr in the left inferior parietal cortex, b) Reward Attainment CStr in the right dorsolateral prefrontal cortex and left inferior parietal cortex, and c) Reward Anticipation CEig or in the left superior medial parietal cortex.

Conclusions: Our results suggest that cannabis use can impact depression trajectory in youth, perhaps by inducing alterations across reward nodes. As our study is ongoing, future analyses will include data from additional participants.

Learning Objectives: Assess the possible clinical relationships between cannabis use and depression symptomatology among youth.
Examine the possible implications of cannabis use on brain function among adolescents with depression.

Literature References Liu, Q. et al. Neural function underlying reward expectancy and attainment in adolescents with diverse psychiatric symptoms. NeuroImage. Clinical 36, 103258, doi:10.1016/j.nicl.2022.103258 (2022).

Marmorstein, N. R. and Iacono, W. G. Explaining associations between cannabis use disorders in adolescence and later major depression: a test of the psychosocial failure model. Addictive behaviors 36, 773-776, doi:10.1016/j.addbeh.2011.02.006 (2011).

COMBINATION PHARMACOTHERAPY FOR METHAMPHETAMINE USE DISORDER (MUD): FINDINGS FROM THE ADAPT-2 TRIAL

Donald Egan, UT Southwestern

Individual Abstract: Methamphetamine is an addictive psychostimulant with high abuse potential with an increasing number of overdose deaths in the US. Despite detrimental medical and psychiatric consequences, treatments for methamphetamine use disorder (MUD) is limited. Moreover, there is no FDA-approved treatment for methamphetamine use disorder. This public health crisis has led many researchers and clinicians to investigate novel interventions to mitigate methamphetamine use. Recently, the Accelerated Development of Additive Treatment for Methamphetamine Disorder (ADAPT-2) concluded that combination extended-release injectable naltrexone and extended-release oral bupropion offered a possible intervention to treating methamphetamine use disorder, thus offering a potential solution to this growing problem .

The ADAPT-2 study was a multisite, double-blind, two-stage, placebo-controlled trial designed to evaluate the efficacy and safety of extended-release injectable naltrexone (380 mg every 3 weeks) plus oral extended-release bupropion (450 mg per day) in adults with moderate or severe methamphetamine use disorder. In stage 1 of the trial, participants were randomly assigned to receive naltrexone–bupropion or matching injectable and oral placebo for 6 weeks. Those in the placebo group who did not have a response in stage 1 underwent re-randomization in stage 2 and were assigned in a 1:1 ratio to receive naltrexone–bupropion or placebo for an additional 6 weeks. Urine samples were obtained from participants twice weekly. The primary outcome was a response, defined as at least three methamphetamine-negative urine samples out of four samples obtained at the end of stage 1 or stage 2, and the weighted average of the responses in the two stages is reported. The treatment effect was defined as the between-group difference in the overall weighted responses.

A total of 403 participants were enrolled in stage 1, and 225 in stage 2. In the first stage, 18 of 109 participants (16.5%) in the naltrexone–bupropion group and 10 of 294 (3.4%) in the placebo group had a response. In the second stage, 13 of 114 (11.4%) in the naltrexone–bupropion group and 2 of 111 (1.8%) in the placebo group had a response. The weighted average response across the two stages was 13.6% with naltrexone–bupropion and 2.5% with placebo, for an overall treatment effect of 11.1%.

Interventions for MUD are limited with relapse rates high and treatment retention rates low. A significant amount of emphasis has been placed on developing therapies that are tolerable for patients, thus increasing retention, and effective at mitigating use and cravings. The ADAPT-2 trial used combination injectable naltrexone and oral high-dose bupropion to address these concerns. The trial found significant improvement in methamphetamine use among moderate to severe users over a 12-week period. These findings offer an exciting new pharmacological intervention to target a growing health crisis.

Learning Objectives: 1. By the end of the presentation, participants will be able to describe the mechanism of actions of both bupropion and naltrexone and their implications in SUDs.
2. By the end of the presentation, participants will be able to summarize the impact of methamphetamine use disorder and recognize comorbidities and challenges of treatment.

Literature References 1. Trivedi, M. H., Walker, R., Ling, W., Dela Cruz, A., Sharma, G., Carmody, T., ... and Shoptaw, S. (2021). Bupropion and naltrexone in methamphetamine use disorder. New England Journal of Medicine, 384(2), 140-153.
2. Jones, C. M., Compton, W. M., and Mustaquim, D. (2020). Patterns and characteristics of methamphetamine use among adults—United States, 2015–2018. Morbidity and Mortality Weekly Report, 69(12), 317.

10:30 a.m. - 11:30 a.m.

Regulatory Challenges: Ask the Experts

REGULATORY CHALLENGES: ASK THE EXPERTS

Tiffany Farchione, US Food and Drug Administration

Overall Abstract: This session is intended to facilitate dialogue between expert regulators from the US Food and Drug Administration and conference participants with an interest in drug development and clinical research in psychopharmacology. There will be no pre-submitted questions, but rather regulators will take questions directly from the audience.

REGULATORY CHALLENGES: ASK THE EXPERTS

Tiffany Farchione, US Food and Drug Administration

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Learning Objectives: Participants will be able to ask questions to a panel of FDA representatives.
Participants will learn from regulators how to improve quality of clinical research .

Literature References N/A

REGULATORY CHALLENGES: ASK THE EXPERTS

Bernard Fischer, U.S. Food and Drug Administration

Abstract: This session is intended to facilitate dialogue between expert regulators from the US Food and Drug Administration and conference participants with an interest in drug development and clinical research in psychopharmacology. There will be no pre-submitted questions, but rather regulators will take questions directly from the audience.

Learning Objectives: -Participants will be able to ask questions to a panel of FDA representatives.
-Participants will learn from regulators how to improve quality of clinical research.

Literature References: N/A

REGULATORY CHALLENGES: ASK THE EXPERTS

Martine Solages, Center for Drug Evaluation and Research, Food and Drug Administration

Abstract: This session is intended to facilitate dialogue between expert regulators from the US Food and Drug Administration and conference participants with an interest in drug development and clinical research in psychopharmacology. There will be no pre-submitted questions, but rather regulators will take questions directly from the audience.

Learning Objectives: Participants will be able to ask questions to a panel of FDA representatives.
Participants will learn from regulators how to improve quality of clinical research

Literature References: N/A

Wednesday, May 29, 2024

Poster Session I with Lunch

W1. DEVELOPMENT OF A PERSONALIZED, FAST, AUTOMATED, MRI-BASED TARGETING PROCEDURE FOR LOW INTENSITY FOCUSED ULTRASOUND NEUROMODULATION

Andrea Boscutti[*1], Richard R. Bouchard[2], Benson M. Irungu[1], Khader M. Hasan[1], Jair C. Soares[1]*

[1]The University of Texas Health Science Center at Houston, [2]MD Anderson Cancer Center

Abstract Background And Rationale: Noninvasive brain stimulation of deep brain regions is currently unfeasible with techniques like transcranial magnetic and electric stimulation (TMS/TES). Low-Intensity Focused Ultrasound Stimulation (LIFU), an emerging neuromodulation technique (Dell'Italia, 2022), overcomes these limitations with:
1) Exceptional spatial resolution, significantly greater than TMS and TES (mm vs cm), allowing selective targeting of small brain regions.

2) Minimal intensity decay with depth, enabling effective stimulation of deep brain structures (depth of penetration: 2-3 cm with deep-TMS, whole-brain coverage with LIFU)

3) Focused acoustic energy that reaches deep subcortical areas without affecting intervening brain tissue.

To leverage the high spatial precision of LIFU, we developed an individualized, precise, automated, and fast targeting procedure based on subjects' MRI anatomical data and informed by acoustic simulations.

Methods: We validated our targeting pipeline using the left amygdala (LA) as the region of interest (ROI) to be targeted by the stimulation. The workflow for our targeting procedure is as follows:

1) For each subject, at the beginning of each neuromodulation session, a high-resolution (voxel size 1 mm isotropic) structural scan is acquired, with a fiducial marker (vitamin E capsule) placed on the scalp in the left temporal region.

2) Segmentation of ROI (LA) and Fiducial Marker: Localization (i.e., segmentation) of both the fiducial marker and the ROI is crucial to derive the spatial parameters (position on the scalp and tilting) for optimal ultrasound transducer positioning. For the segmentation of the ROI, we employ SynthSeg (Billot, 2023), the first convolutional neural network for segmentation of brain MRI scans of any contrast and resolution. To segment the fiducial marker, we retrained SynthSeg using an in-house procedure. Specifically, as a data augmentation strategy, we generated 10000 synthetic scans through a domain randomization strategy. Each synthetic scan featured a fiducial-like synthetic object, generated using the same domain randomization strategy and placed at random locations on the scalp surface.

3) Mesh Generation and Acoustic Simulations: Using the software FIELD-II, we compute acoustic simulations to determine beam focus location and intensity.

4) Optimization and Generation of Renderings: Through a grid search strategy, we obtain predictive renderings for optimal transducer positioning.

5) Validation through a Scout Scan: Using a low-resolution, fast MRI T1 scan, we ensure correct positioning of the transducer. To localize (i.e., segment) the transducer, we employ another fine-tuned version of Synthseg, obtained with the same training strategy described above.

Results: The procedure was validated across 26 brain scans acquired at different resolutions (1,2, 3 mm isotropic) and with various modalities (T1, T2-like, FLAIR). The quality of the segmentations was evaluated through Dice Scores, comparing predicted labels with manually annotated labels. Dice Scores ranged between 82 and 86%. The whole targeting pipeline required between 5 and 10 minutes to complete (scan time included). Two LIFU sessions targeting the left and right amygdala were performed on healthy volunteers, with no evidence of side effects.

Conclusions: Our targeting pipeline is fast, precise, individualized to patient anatomy, and informed by acoustic simulations. Although the procedure was validated using the LA as the ROI, the pipeline can be easily adapted to target other cortical or subcortical ROIs. Similarly, our segmentation networks can be retrained to localize fiducials or ultrasound transducers of varying dimensions and shapes.

W2. CORRELATES OF TREATMENT OPTIONS IN YOUTH WITH MAJOR DEPRESSIVE DISORDER: OBSERVATIONS FROM THE TEXAS YOUTH DEPRESSION AND SUICIDE RESEARCH NETWORK (TX-YDSRN)

Emine Ayvaci[*1], Karabi Nandy[1], Ryan Becker[1], Abu Minhajuddin[1], Holli Slater[1], Madhukar Trivedi[1]*

[1]*University of Texas Southwestern Medical Center*

Abstract: Objective: Treatment decisions are often a complex process, influenced by both patient-level and provider-related factors, as well as variables like access to care and treatment barriers. This study examines correlates associated with treatment options, specifically focusing on psychotherapy, pharmacotherapy, and combination treatment (concurrent use of pharmacotherapy and psychotherapy) as treatment options for youth depression.
Method: We included 646 participants (ages 8–20) with a diagnosis of major depressive disorder (MDD) from a state-wide research registry. Sociodemographic, clinical, and treatment features were compared between no treatment, pharmacotherapy only, psychotherapy only, and combination of pharmacotherapy and psychotherapy using descriptive statistics, analyses of variance (ANOVA), and chi-square. Post-hoc tests were performed for pairwise comparisons when significant omnibus tests were identified. To address multiple comparisons, Bonferroni corrections were applied.

Results: Among the 646 patients, 53% received combination treatment, 35% pharmacotherapy only, 5% psychotherapy only, and 7% no treatment. Gender and ethnicity did not differ significantly among treatment groups. Compared to those receiving pharmacotherapy alone, individuals with combination treatment had higher depression severity and higher suicidality. The no treatment group showed higher rates of social risk compared to group with combination treatment. Participants in the pharmacotherapy only group had higher rates of lower income compared to those in the combination treatment group. When treatment preferences were examined, combination treatment group had the highest rate of fitting the preferred treatment

group (58%). In pharmacotherapy only group, 40% of youth expressed a preference for combination treatment.

Conclusion: In this sample of youth with depression, psychiatric treatment options are correlated with depression severity, suicidality, presence of social risk, and income level. 40% of youth in pharmacotherapy only group expressed a preference for combination treatment. The finding that youth with pharmacotherapy only group had lower income compared to combination group may suggest a potential barrier to accessing combined treatment option.

W3. USING CLASS-EFFECT QUERIES DEFINED ON ESTABLISHED PHARMACOLOGICAL CLASSES IN CLINICAL DEVELOPMENT OF NOVEL COMPOUNDS

Solomiya Gumenyuk[*1], Ajay Ogirala[2], Steven T. Szabo[2], Kenneth Koblan[2], Seth C. Hopkins[2]*

[1]SMPA, [2]Sumitomo Pharma America

Abstract: Specific Purpose: In clinical trials, the safety of drugs is summarized by the incidence of adverse events (AE), while post-marketing reporting systems use disproportionate reporting of adverse drug reactions for signal detection. Here, we propose a method that expands on a previously published novel approach of quantifying the AE profile of an investigational new drug in clinical trials, relative to that seen postmarketing with an established pharmacological class. Here we describe the approach to classifying a compound's AE profile in clinical trials (dasotraline), relative to four related classes that are already on the market (selective serotonin reuptake inhibitor (SSRI), norepinephrine reuptake inhibitor (NRI), serotonin-norepinephrine reuptake inhibitor (SNRI), dopamine-norepinephrine reuptake inhibitor (NDRI)).

Methodology: Through Bayesian disproportionality analyses of the US Food and Drug Administration Adverse Event Reporting System (FAERS) data from Oracle Signal, we identified and ranked Preferred Terms for each of the four drug classes, selecting 3-5 drugs in each class that have the maximum market share. Adverse event rates in randomized, double-blind, placebo-controlled clinical trials of dasotraline (SEP-225289) were summarized by their class specificity among the marketed reuptake inhibitor classes. 5 studies (Drug N = 1350, Placebo N = 768) of the reuptake inhibitor dasotraline (SEP-225289) were compared with AE reports of SSRIs (N = 4.1M), SNRIs (N =2.3M), NRIs (N = 175k) and NDRIs (N =1M). Dasotraline adverse event rates were compared to adverse event rates per drug class. Adverse events reported in clinical trials and not found in the FAERS data were quantified and listed.

Results: In dasotraline pooled clinical trial data, cumulative rates for adverse events at and above a threshold of disproportional reporting (Empirical Bayes Geometric Mean (EBGM) ≥ 3 in FAERS) were 35% for NDRI, 56% for NRI, 50% for SNRI, and 25% for SSRI.

Conclusion: These results further substantiate this approach to summarize adverse events in clinical trials, where the cumulative burden of class-specific risks describes the emerging safety profile of an investigational new drug in clinical development, relative to reactions anticipated for drugs in an established pharmacological class. From the AE profile, dasotraline is closest to NRI compared to other three drug classes it is compared to. A weighted combination of % safety subjects at EBGM ≥ 3, % AEs not found in class effect query and AE with highest EBGM in the class effect query is a viable model to quantify the association of an investigational compound with established drug classes.

W4. THE BRIEF INVENTORY OF PSYCHOSOCIAL FUNCTIONING AND ZARIT BURDEN INTERVIEW ARE STRONGLY CORRELATED MEASURES FOR USE IN CARE PARTNERS OF CIVILIAN INDIVIDUALS WITH POST-TRAUMATIC STRESS DISORDER

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Abstract Background: The Zarit Burden Interview (ZBI) is a widely used, 22-item, self-report measure that assesses caregiver or care partner burden but has not been used for care partners of individuals with post-traumatic stress disorder (PTSD). The Brief Inventory of Psychosocial Functioning (B-IPF) is a 7-item self-report measure that assesses PTSD-related psychosocial functional impairment and was developed as an abridged version of the Inventory of Psychosocial Functioning (IPF) for use in settings where time is a major consideration. This research aims to evaluate the relationship between the ZBI and B-IPF and establish their use to measure burden in care partners of individuals with PTSD.

Methodology: A cohort of 250 care partners of individuals with PTSD in the United States completed a 30-minute online survey that included the 22-item ZBI and 7-item B-IPF to measure the level of care partner burden and impact on psychosocial functioning. Correlation analysis was conducted to evaluate the relationship and association between the ZBI and B-IPF based on their total scores, ZBI two-factor model, and individual items. A Shapiro-Wilks test was conducted to assess the normality of the ZBI and B-IPF survey response distributions (ZBI: $p < 0.001$, B-IPF: $p < 0.001$). As a result of the normality test, a Spearman's Rank Correlation (ρ) was performed to measure the strength of association between the two surveys. ρ scores range from -1 to 1, with values indicating a positive and negative monotonic relationship, respectively. A higher ρ value represents a higher strength of relationship between two variables.

Results: Of the care partners surveyed, the average total ZBI score was 27.10 out of 88 (SD: 12.51) with 47% of care partners experiencing "mild to moderate" levels of burden. The average total B-IPF score was 40.47 out of 100 (SD: 22.19) with 34% of care partners experiencing "moderate" impairment on their psychosocial functioning. The total scores of the B-IPF and ZBI are strongly correlated ($\rho = 0.8$) and the role strain dimension of the ZBI had the highest correlation with the friendships and socializing domain of the B-IPF ($\rho = 0.77$). The personal strain factor of the ZBI was strongly correlated with the family relationships domain of the B-IPF ($\rho = 0.68$). Additionally, the friendships and socializing domain of the B-IPF was strongly correlated with several individual items of the ZBI including lack of time for self ($\rho = 0.64$) and lack of privacy due to patient ($\rho = 0.65$).

Conclusion: Care partners of individuals with PTSD experience burden as well as impairment of their psychosocial functioning as measured by the ZBI and B-IPF, demonstrating the need for awareness of the disease burden PTSD can have on care partners. The ZBI and B-IPF are strongly correlated measures with the ZBI role strain dimension and B-IPF day-to-day activity domain having the highest correlation. In settings where employing the full 22-item ZBI is difficult, the B-IPF can be more easily administered to measure burden on care partners of

individuals with PTSD more broadly beyond its validated use for impairment on psychosocial functioning.

W5. DETERMINANTS OF BURDEN AND PSYCHOSOCIAL FUNCTIONING AMONG CARE PARTNERS OF CIVILIAN PATIENTS LIVING WITH PTSD

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Abstract Background: Post-traumatic stress disorder (PTSD) is a mental health condition triggered by either experiencing or witnessing a traumatic event. Care partners of civilian PTSD patients can be significantly impacted by their relationship with the patient, as well as time-dependent, developmental, physical, and social burdens that place them at risk of increased distress. There is limited research exploring factors that predict higher levels of burden or significant impairment in psychosocial functioning among care partners.

Methodology: A cohort of 250 care partners supporting individuals formally diagnosed with PTSD completed a 30-minute survey covering demographics, patient characteristics, and two validated scales, the Zarit Burden Interview (ZBI) (scoring range: 0-88; 4 levels of severity level), and the Brief Inventory of Psychosocial Functioning (B-IPF) (scoring range: 0-100; 5 levels of impairment). The ZBI assesses care partner burden and the B-IPF assesses PTSD-related psychosocial functional impairment. On both scales, a higher score indicates more severe impact on the respondent. Independent Simple Ordinary Least Squared Regressions were performed to assess the linear effects between individual predictor variables and ZBI and B-IPF total scores.

Results: Care partners of PTSD patients with depressive disorders exhibited an average of 21.5 B-IPF and 13.8 ZBI points higher compared to care partners of PTSD patients with no depressive disorders (B-IPF: $p < 0.001$, ZBI: $p < 0.001$). Care partners of patients with anxiety disorders had an average B-IPF and ZBI score that was 17.6 and 8.3 points higher, respectively, than care partners of patients without anxiety disorders (B-IPF: $p < 0.001$, ZBI: $p < 0.001$). Care partners that are the patient's friend exhibited an average score of 16.5 B-IPF and 4.4 ZBI points lower than that of spousal care partners (B-IPF: $p < 0.001$, ZBI: $p < 0.05$). Care partners of patients with commercial insurance had an average of 5.3 ZBI points lower than that of care partners of Medicare patients ($p < 0.05$). Female care partners, on average, had higher psychosocial impairment and burden than males (B-IPF: $\beta = 8.3$ $p < 0.01$, ZBI: $\beta = 4.6$ $p < 0.01$). Care partners that were unemployed due to care giving scored 20.1 and 12.2 B-IPF and ZBI points higher, on average, compared to employed care partners (B-IPF: $p < 0.001$, ZBI: $p < 0.001$). Care partners that live with the patient experienced higher B-IPF and ZBI scores compared to care partners that do not live with the patient (B-IPF: $\beta = 15.7$ $p < 0.001$, ZBI: $\beta = 5.2$ $p < 0.001$). Care partners of patients on pharmacotherapy and psychotherapy experience higher B-IPF and ZBI scores, compared to care partners of patients only on pharmacotherapy (B-IPF: $\beta = 11.5$ $p < 0.001$, ZBI: $\beta = 9.1$ $p < 0.001$).

Conclusion: Care partners caring for PTSD patients with comorbid mental health conditions appear to bear significant burden. Additionally, the care partner relationship, type of patient

insurance, and care partner employment status appear to all be major predictors of care partner burden and psychosocial impairment.

W6. LONGITUDINAL TRENDS IN COCAINE, METHAMPHETAMINE, AND PRESCRIPTION STIMULANT USE DISORDERS ACROSS AGE GROUPS IN THE UNITED STATES: FINDINGS FROM THE NATIONAL SURVEY ON DRUG USE AND HEALTH (NSDUH) FROM 2015-2023

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[1]*University of Texas Southwestern Medical School***Abstract Background:** Overdose deaths involving cocaine and psychostimulants such as methamphetamine have increased exponentially. Number of overdose deaths involving cocaine increased from 6,784 in 2015 to 24,486 in 2021, a 3.6-fold increase over this 5-year period. Similarly, number of overdose deaths involving cocaine increased from 5,716 in 2015 to 32,537 in 2021, an even greater 5.7-fold increase over this short period. A recent report found that during the novel coronavirus disease 19 (COVID-19) pandemic, prescription rates for C-II stimulants increased, especially among young individuals (aged 20-39 years; 30% increase from 2018 to 2022). Using publicly available data from the United States (US) Substance Abuse and Mental Health Services Administration (SAMHSA), here we sought to characterize the longitudinal trends in the use/misuse of these stimulants in US.

Methods: We used annual data report from the National Survey on Drug Use and Health (NSDUH) from years 2015-2023 providing us prevalence estimates for years 2015 through 2022. From these reports, we obtained the number in thousands and estimated percentages for prevalence of use of cocaine and methamphetamine as well as misuse of prescription stimulants for each year. These data were then sub-divided by age groups 12-17, 18-25, 18+, 26-29, 30-34, 35-39, 40-44, 45-49, 50-54, 55-59, 60-64 and 65+ years old. Due to changes in survey collection data from 2019 onward was not comparable to prior years.

Results: Using cross-sectional data from the most recent year (2022), we found a significant effect of age group in the prevalence rates. Notably, prescription stimulant misuse rates were 7.9% in 26-29 age group as compared to 1.7% in 12-17 or < 1% in those 45 or older. Highest prevalence rate for methamphetamine use were noted in 45–49-year age (1.8%) while that of cocaine was 26-29 years (5.1%). We found that trends in prevalence of the use of these stimulants over the years varied based on age group. For prescription stimulants, there was a 1.5 to 2-fold increase in prevalence from 2022 to 2022 across all age groups except for those who were 12-17 or 65+ years old. Between 2015 to 2019, there was an increasing trend in the use of methamphetamine in those who were 18 or older. However, between 2020 to 2022, prevalence rates of methamphetamine use either remained stable or declined in these age groups except 30-34, 45-49, and 60-64. The sharpest increase was noted in the age group of 60-64 where prevalence of methamphetamine use in the past year increased from 0.5% of the population to 1.8%, a sharp 3.6-fold increase over this period. Prevalence of cocaine use increased by 1.5- to 2-fold in age groups of 50-54, 55-59, and 60-64 from 2020 to 2022.

Conclusion: We found that prescription stimulant misuse and cocaine use was more common in younger adults whereas methamphetamine use rates were highest among middle-aged adults in the US. There was a marked increase in prevalence of prescription stimulant misuse between

2020 to 2022, likely reflecting the national trends in increasing rates of prescriptions for these drugs. These findings underscore the public health burden of stimulant use disorder and the need to develop more effective prevention and treatment approaches for these conditions.

W7. INTRODUCING THE TREATMENT ATTITUDE PROFILE (TAP) SCALE FOR PLACEBO RESPONSE PERSONA DISCOVERY USING ATTRACTOR AI TECHNOLOGIES: APPLICATIONS IN CLINICAL TRIAL PATIENT ENRICHMENT

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Abstract: The phenomenon of placebo response poses a significant challenge in psychiatric clinical trials, often obscuring the true effectiveness of tested interventions. Although a multitude of clinical scales are in use that try to identify problems associated with placebo response, this issue remains a major obstacle for successful CNS clinical trials.

Advancements in artificial intelligence (AI) have increased our understanding of placebo effects by identifying key variables derived from clinical scales that are predictive of placebo response. Patients with these characteristics can be excluded from trials to increase the probability of demonstrating a treatment-specific contribution to clinical effectiveness.

Central to this approach is the Attractor AI capability which permits the deconstruction of the patient population into explainable and unexplainable subpopulations. The power of this approach is based on an ability to discern variables that define the explainable subpopulations. This information provides a nuanced description of placebo responders.

Our newly developed Treatment Attitude Profile (TAP) incorporates a wide variety of factors, including the impact of symptoms, medication attitudes, adherence, sleep quality, patient relationship to physicians and appointments, as well as the number of clinical trials participants have previously entered.

The comprehensive overview of the patient attitudes provided by the TAP enhances the trialists ability to predict which patients are more likely to exhibit placebo responses. Knowledge of these variables can be used to refine patient selection and trial design. Enrichment achieved by this approach allows for more efficient trials with a higher likelihood of detecting treatment effects with smaller sample sizes, greater speed, and lower costs. As such, the TAP represents a powerful tool for researchers and clinicians to mitigate the impact of placebo response and increase the reliability of positive trial outcomes. Ultimately, this work also underscores the potential of AI for transforming clinical trials, paving the way for more effective and efficient psychiatric treatment discovery.

W8. CARIPRAZINE EFFICACY IN AFRICAN AMERICAN OR BLACK PATIENTS WITH BIPOLAR I DISORDER

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Abstract Background: African American or Black patients with bipolar I disorder (BP-I) are more likely to be misdiagnosed, leading to potential delays in appropriate treatment and

increased likelihood of experiencing more BP-I-related mood episodes. This disparity may negatively impact patient response to treatment, as patients with fewer prior BP-I mood episodes may respond better to treatment. Cariprazine, a dopamine D3-preferring D3/D2 and serotonin 5-HT1A receptor partial agonist, is approved to treat adults with manic/mixed and depressive episodes of BP-I. In this post hoc analysis, we examined response to cariprazine treatment in African American or Black patients with BP-I mania or BP-I depression.

Methods: Data from 3 randomized, double-blind, placebo-controlled trials of cariprazine in BP-I mania (NCT00488618, NCT01058096, NCT01058668) and 3 trials in BP-I depression (NCT01396447, NCT02670538, NCT02670551) were separately pooled and analyzed. For BP-I mania, mean change from baseline to week 3 in Young Mania Rating Scale (YMRS) total score was evaluated for cariprazine 3-12 mg/d versus placebo using a mixed-effects model for repeated measures; for BP-I depression, mean change from baseline to week 6 in Montgomery-Åsberg Depression Rating Scale (MADRS) total score was evaluated for cariprazine 1.5 and 3 mg/d versus placebo. The number of prior lifetime mood episodes was assessed.

Results: In the African American or Black subgroup with BP-I depression (n=299), the least squares mean difference (LSMD) vs placebo for MADRS total score change was statistically significant in favor of cariprazine 3 mg/d across all study weeks and in favor of cariprazine 1.5 mg/d from week 2 onward (week 6 LSMD [95% CI]: 1.5 mg/d = -3.51 [-6.34, -0.68]; 3 mg/d = -2.95 [-5.77, -0.12]). The mean number of prior manic and depressive episodes in the subgroup was 5.4 and 8.3, respectively. In the BP-I mania trials, 259 patients were included in the African American or Black subgroup analysis. The LSMD vs placebo in YMRS total score change was statistically significant in favor of cariprazine at day 21 only (-3.10 [-5.76, -0.44]). The mean number of prior manic and depressive episodes in the subgroup was 11.7 and 4.4, respectively. For both BP-I mania and depression, the mean number of prior episodes was higher in this subgroup than in the overall trial population.

Conclusion: Overall, cariprazine improves manic and depressive symptoms in African American or Black patients with BP-I mania and BP-I depression, respectively. The high number of prior episodes in African American or Black patients may have contributed to the more modest treatment effect seen in BP-I mania studies, similar to previous analyses that found later separation from placebo in BP-I mania patients with the highest number of prior mood episodes. Together, our findings highlight the potential impact of racial disparities in BP-I diagnosis on disease progression and outcomes. AbbVie provided support for this study.

W9. NEGATIVE SYMPTOM BURDEN PREDICTS CONVERSION TO PSYCHOSIS AMONG INDIVIDUALS AT CLINICAL HIGH RISK

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Abstract: Schizophrenia is within the top 15 causes of global disability, conferring an increased risk of premature mortality, chronic medical conditions, and an exceedingly high

economic burden. It has long been defined by positive and negative symptoms, referring to observable alterations in cognitive and motor functions that correspond to synergistic aberrations in neuronal circuitry. Although positive symptoms are reliably attenuated by antidopaminergic medications, negative symptoms have been harder to define and treat. In the decades that followed the first validated scale to measure negative symptoms, research has supported the conceptualization of five core domains: blunted affect, alogia, avolition, asociality, and anhedonia. These are among the first symptoms reported in individuals who develop schizophrenia and are important prognostic factors. They are found in nearly 80% of individuals at clinical high risk for psychosis (CHR-P), correlating with illness severity as well as both social and role functioning. Despite the importance of negative symptoms, they are not currently utilized in algorithms to predict conversion to psychosis in individuals at CHR-P. As such, there exists a critical gap in recognition and prevention of schizophrenia in symptomatic youth.

Participants from the third phase of the North American Prodrome Longitudinal Study (NAPLS3) were assessed for CHR-P via Structured Interview for Psychosis-Risk Syndromes (SIPS) at baseline, 2-, 4-, and 6-months follow up. This sample includes Healthy controls (N=96), CHR Converters (N=70), and CHR Non-Converters (N=415). Total negative symptom burden was established by adding Scale of Psychosis-Risk Symptoms (SOPS) N1-N5 ratings at each time point. Negative symptom subdomains were defined as follows, based on prior literature: Experiential = N1 + N2, Expressive = N3 + N4 + N5. Depression and positive symptom covariates were determined via the Calgary Depression Scale for Schizophrenia (CDSS) and SOPS P1-P5 ratings, respectively. Conversion to psychosis was confirmed via Structured Clinical Interview for DSM-IV (SCID-IV). Data was analyzed using SPSS software. Linear mixed-effects models for repeated measures were used to evaluate group differences over time. Cox proportional hazard regression models were used to examine the predictive associations between negative symptoms and transition to psychosis.

In NAPLS3, Converters have a higher level of negative symptoms at baseline, compared to Non-Converters and healthy controls, that is stable over the 6-month period. Non-Converters show small improvements over 6 months, but never reach levels seen in healthy controls. This pattern remains even when adjusting for attenuated positive and depressive symptoms. Baseline total negative symptom burden predicts psychosis onset, even when including other confounders in the prediction model, such as positive symptoms and depressive symptoms. This pattern holds true for Experiential and Expressive subgroups as well as individual items separately.

Our findings reinforce the importance of negative symptoms in the prediction of schizophrenia in individuals considered to be at clinical high risk. Given the need for early recognition and treatment of psychosis, the data support consideration of negative symptoms in relevant algorithms. We anticipate that our work will reinforce the importance of psychotherapeutic innovation targeting negative symptoms in schizophrenia.

W10. EXAMINING RATER TRAINING PERFORMANCE: THE RATER ONBOARDING AND QUALIFICATION PROGRAM (ROQ)

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Abstract: Introduction: Psychiatry trial rater training involves duplication of effort with raters repeating training for each study, which can be a barrier to timely study startup1. While "legacy" training exemptions can be granted, rater performance is often not considered and literature on this practice is lacking. We examined if a novel data-driven rater training approach via the Rater Onboarding and Qualification (ROQ) program may reduce site burden and maintain quality.

Methods: We examined 458 raters across 3 Major Depressive Disorder (MDD) trials using the Structured Interview Guide for the Montgomery-Asberg Depression Rating Scale (SIGMA/MADRS). Self-reported education, indication, trial, and scale experience, plus recent prior study performance, were used to categorize raters who completed training as Qualified (minimum experience met), Sponsor Override (minimum experience not met), or Exempted (given recent MADRS training completion). SIGMA didactic training was followed by an applied scoring exercise; raters who failed were remediated. Only raters who submitted MADRS data were included in performance analysis; those who accessed training multiple times and outlier durations were excluded. We explored the relationship between rater training factors (rater experience, demographics, time spent on training, MADRS scoring exercise pass/fail), and in-study rater performance from Risk-Based Data Monitoring (Rater Applied Performance Scale (RAPS) fails, number of case discussion calls, anomalous data red flags).

Results: N=256 (56%) were Qualified raters with significantly fewer red flags (M=2.84, SD=9.35) than the 44% (n=202) Sponsor Overrides (M=28.28, SD=48.87), [t(133)=4.096, p LESS THAN .001)] and had fewer (although nonsignificant) RAPS failures (M=1.22, SD=0.60) than Sponsor Overrides (M=1.60, SD=1.59). [t(36)=.889. p=.193]. N=56 (12.2%) were Legacy raters (n=16 also Overrides) with only 4 (2.6%) displaying mildly inadequate study performance (1 RAPS fail). Overall sample RAPS Fail M=1.44, SD=1.29 and red flags M=16.10, SD=40.97. Less time spent on training was associated with a higher but nonsignificant likelihood of remediation [F(3, 271)=1.71, p=.32], with most raters completing training in an average 18.04 minutes (Med=13.00, SD=14.85). Scoring exercise pass rate was 65% (n=179). After remediation, only 5.5% (n=15) were unable to be certified due to second fail. Experienced and qualified raters were more likely to pass the scoring exercise with trending significance □□□□3)=7.43, p=.059]. Number of MDD trials was the only factor significantly associated with passing the scoring exercise and training duration, after controlling for other variables [F(1,273)=3.93, p=.048). Training exercise fails were associated (approaching significance) with more rater intervention during the study to maintain rating quality, [(F2,52)=2.907, p=.064).

Conclusion: Our findings support the importance of applied skills in rater training,2 but also the judicious use of legacy training exemptions for qualified raters with recent trial performance data. The number of MDD trials and training performance data may be more reliable predictors of rater quality than unverifiable self-reported experience. Unqualified raters have more quality issues than Qualified raters, supporting a targeted approach to rater oversight and intervention, especially early in the study. Less time spent on training may be a variable added to study monitoring plans.

W11. ANTIDEPRESSANT TREATMENT AFTER ACUTE/INDUCTION PHASE OF IV KETAMINE/IN ESKETAMINE IN PATIENTS WITH TREATMENT RESISTANT DEPRESSION

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Abstract Background: The rapid antidepressant effects of intravenous (IV) ketamine and intranasal (IN) esketamine have been well studied for Treatment-Resistant Depression (TRD), with increasing use as augmentation agents. Little is known about the modifications to the antidepressant treatment after the use of IV ketamine/ IN esketamine in patients with TRD. Such information would be helpful to refine treatment strategies. We investigated changes in the pharmacotherapeutic treatments and outcomes in patients with TRD who initiated ketamine/esketamine treatment.

Methods: Using a mirror image study design, we performed a retrospective cohort study of adult patients with TRD who received IV ketamine or IN esketamine treatments and had clinical and pharmacologic data for the six months pre- and post-acute/induction phase. We identified occurrences of medication discontinuation, addition, or switch across various categories of psychotropics. A descriptive analysis was performed.

Results: We analyzed data from 67 adults (48 IV ketamine, 19 IN esketamine). Mean age was 49.3 years and 68% were female. The mean number of psychotropics at the beginning of the acute treatment phase was 3.3 (SD 1.4). 31% of patients were treated with an SSRI and 38% with an SNRI. Additionally, 32% of patients were on augmentation, with 68% on an antipsychotic and 31% on lamotrigine. After completing the acute phase, 39(58%) patients achieved response and of those, 32 (96%) underwent at least one maintenance treatment. Regarding pharmacological changes, 27 (39%) patients underwent the addition of a medication, of those, 12 (44%) an augmentation agent. In addition, 20 (30%) patients switched at least one medication, most frequently an antidepressant (95%), and of these 31% switched to a SNRI. 22% of patients discontinued at least one medication, with antidepressants, stimulants, and anxiolytics the most frequent.

Conclusion: Most patients who received an acute course of IV ketamine/IN esketamine transitioned to maintenance treatments, and more than a third had a medication added, while more than 20% had discontinuation of one agent. The most frequently switched medication class were antidepressants. Larger studies are needed to understand the patterns of medication regimen changes in patients receiving ketamine/esketamine for TRD.

W12. SAFETY AND TOLERABILITY OF BREXPIPRAZOLE IN COMBINATION WITH SERTRALINE FOR PATIENTS WITH POST-TRAUMATIC STRESS DISORDER: SUMMARY OF DATA FROM PHASE 2 AND PHASE 3 RANDOMIZED CLINICAL TRIALS

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Abstract Background: There is a need for a well-tolerated pharmacotherapy with a consistent efficacy profile for post-traumatic stress disorder (PTSD). This report summarizes safety data from three trials of brexpiprazole + sertraline combination therapy in patients with PTSD (full efficacy data will be reported elsewhere at ASCP 2024).

Methods: The three randomized, controlled, double-blind trials, conducted in the US, were Trial 061 (Phase 2; NCT03033069), Trial 071 (Phase 3; NCT04124614), and Trial 072 (Phase 3; NCT04174170). The trials enrolled male and female outpatients, aged 18–65 years, with a Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) PTSD diagnosis and symptoms for ≥6 months. Each trial included an 11-week randomized phase. In Trial 061, patients were randomized 1:1:1:1 to brexpiprazole 1–3 mg/day + sertraline 100–200 mg/day, brexpiprazole 1–3 mg/day + placebo, sertraline 100–200 mg/day + placebo, or placebo (double dummy). In Trial 071, patients were randomized 1:1 to brexpiprazole 2–3 mg/day + sertraline 150 mg/day, or sertraline 150 mg/day + placebo. In Trial 072, patients were randomized 1:1:1 to brexpiprazole 2 mg/day + sertraline 150 mg/day, brexpiprazole 3 mg/day + sertraline 150 mg/day, or sertraline 150 mg/day + placebo. In each trial, the primary endpoint was the change in Clinician Administered PTSD Scale for DSM-5 (CAPS-5) Total score from baseline to Week 10. Safety assessments included treatment-emergent adverse events (TEAEs), change in body weight, incidence of suicidality, and deaths. In the present report, safety data are presented per trial, as well as pooled (across all trials and doses) for brexpiprazole + sertraline and for sertraline + placebo, based on the safety sample (patients who received ≥1 dose of study treatment).

Results: On the primary efficacy endpoint, brexpiprazole + sertraline separated from sertraline + placebo in Trials 061 and 071, but not in Trial 072 (full efficacy data reported elsewhere). In Trial 061 (safety sample n=316), the incidence of TEAEs was 72.5% with brexpiprazole + sertraline, 70.7% with brexpiprazole + placebo, 69.6% with sertraline + placebo, and 78.0% with placebo. In Trial 071 (n=401), the incidence of TEAEs was 60.0% with brexpiprazole + sertraline, and 58.2% with sertraline + placebo. In Trial 072 (n=537), the incidence of TEAEs was 51.4% with brexpiprazole 2 mg/day + sertraline, 48.3% with brexpiprazole 3 mg/day + sertraline, and 51.2% with sertraline + placebo. Across the three studies pooled (brexpiprazole + sertraline, n=650; sertraline + placebo, n=447), the incidence of TEAEs was 55.5% with brexpiprazole + sertraline, and 56.2% with sertraline + placebo. TEAEs with incidence ≥5% in either pooled group (brexpiprazole + sertraline; sertraline + placebo) were nausea (8.0%; 11.2%), headache (5.5%; 7.6%), weight increased (5.2%; 1.3%), and diarrhea (4.8%; 6.0%). The mean change from baseline to Week 12 in body weight was +1.5 kg with brexpiprazole + sertraline, and -0.2 kg with sertraline + placebo. The pooled incidence of suicidality TEAEs was 0.6% with brexpiprazole + sertraline, and 1.1% with sertraline + placebo. Across the studies, three deaths occurred in different treatment arms (brexpiprazole 2 mg/day + sertraline, n=1; sertraline + placebo, n=1; placebo, n=1), none of which was considered related to study treatment.

Conclusion: Overall, across three randomized trials of patients with PTSD, no new safety observations were identified with brexpiprazole in combination with sertraline.

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W13. ULOTARONT IN THE TREATMENT OF SCHIZOPHRENIA: POST-HOC ANALYSES OF TWO 6-WEEK, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PHASE 3 TRIALS

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Abstract Background: Ulotaront, an investigational TAAR1 agonist with 5-HT1A agonist activity, has demonstrated efficacy in a flexible-dose (50 mg/d to 75 mg/d) Phase 2 trial [1] in acutely psychotic patients with schizophrenia (PANSS effect size [ES] 0.45). We previously reported [2] results from two Phase 3 fixed-dose studies designed to further evaluate the efficacy and safety of ulotaront (ULO) in schizophrenia, which both failed to meet their primary endpoint (DIAMOND 1 [D1], NCT04072354; and DIAMOND 2 [D2], NCT04092686). We now report results of post-hoc analyses undertaken to better understand possible contributors to the lack of ulotaront-placebo (ULO-PBO) separation in the Phase 3 studies.

Methods: Both studies were double-blind, placebo-controlled, 6-week trials evaluating the efficacy of ulotaront (50 mg/d and 75 mg/d; 75 mg/d and 100 mg/d) in adult patients with schizophrenia who were acutely psychotic (PANSS total score ≥ 80). In D1 and D2, enrollment was limited to patients with ≤ 2 or 3 prior hospitalizations for acute psychotic episodes, respectively. The primary endpoint was Baseline-to-Week-6 change in PANSS total score.

Results: Neither D1 or D2 met the primary endpoint for any ULO dose group (D1: ULO-50 mg and ULO-75 mg vs. PBO were -16.9 and -19.6 vs. -19.3; D2: ULO-75 mg and ULO-100 mg vs. PBO were -16.4 and -18.1 vs. -14.3). The previously reported flexible-dose (50-75 mg) Phase 2 trial [1] was significant for ULO-50-75-mg vs. PBO (-17.2 vs. -9.7). A review of 14 PBO-controlled NDA trials in schizophrenia conducted from 2009-2015 [3] found mean endpoint PANSS change scores of -16.9 for drug vs. -10.5 for placebo. These results suggest that the effect of ULO in the D1/D2 studies was comparable to active drug in both post 2009 NDA trials and in the previous Phase 2 ULO trial. However, the PBO response was unusually high in both D1 and D2 studies, with D1 PBO response (-19.3) the highest recorded in any pre-or-post-2009 NDA trials in schizophrenia [3]. In a pre-specified pooled D1/D2 analysis, patients enrolled prior to onset of the COVID pandemic demonstrated significant efficacy for ULO-50-100 mg vs. PBO on PANSS total score (-15.8 vs. -8.8; p=0.017; ES= -0.47). No difference was observed for ULO vs. PBO in the post-COVID sample (-17.7 vs. -17.5), potentially linked to observed regional differences in placebo response. Finally, elevated serum prolactin (PRL) at screening was a predictor of higher PBO response. For ULO vs. PBO in D1/D2 pooled, PRL≤40 ng/mL: -17.8 vs. -14.4; p=0.014; compared with PRL > 40 ng/mL: -14.1 vs. -21.7. Elevated PRL was associated with increased dose or newly initiated antipsychotic (AP) treatment proximal to study entry.

Conclusions: A large PBO effect was observed in both studies (most notable in D1) which may have masked the ability to detect a significant efficacy signal for ULO. Patients enrolled pre-COVID demonstrated notably larger effect sizes for ULO, though this finding may be due to geographic factors, as most pre-pandemic patients were recruited in the US. Initiation of a new AP or a dose increase for ongoing AP just prior to study entry appears to have contributed to a lack of drug-placebo separation. Finally, it appears that limiting enrollment to patients with ≤ 2 or 3 prior hospitalizations may have resulted in a sampling bias that favored patients who had either less illness chronicity/severity or with a history of illness that was more readily responsive to outpatient AP therapy without requiring recurrent hospitalizations.

W14. THE RISK OF POSTPARTUM HEMORRHAGE WITH SELECTIVE SEROTONIN REUPTAKE INHIBITORS OR SEROTONIN NOREPINEPHRINE REUPTAKE INHIBITORS: PRELIMINARY RESULTS FROM THE NATIONAL PREGNANCY REGISTRY FOR PSYCHIATRIC MEDICATIONS

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Abstract Purpose: Previous studies suggest an association between late pregnancy exposure to selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) and increased risk of postpartum hemorrhage (PPH). The purpose of this study was to examine the risk for PPH among women with psychiatric illness enrolled in The National Pregnancy Registry for Psychiatric Medications (NPRPM) who were either exposed versus unexposed to SSRIs/SNRIs.

Methodology: The NPRPM is a longitudinal prospective cohort study which collects maternal and neonatal outcomes based on phone interviews and medical records during pregnancy and the postpartum period from enrolled women with psychiatric illness (n=953). The sample included women with medical record data on postpartum blood loss, including n=453 unexposed to SSRIs/SNRIs during pregnancy and n=500 exposed to these medications at least during the week of delivery. PPH was defined as Estimated Blood Loss ≥500 mL after vaginal delivery or ≥1000 mL after cesarean section (C-section) within 24 hours postpartum. Univariate and multivariate logistic regression analyses were performed to determine odds ratios.

Results: The overall PPH incidence was 13.1%. SSRI/SNRI exposure was associated with an increased, but not statistically significant PPH odds compared to no exposure (unadjusted OR=1.42, 95% CI [0.97, 2.09]; adjusted OR=1.33, 95% CI [0.90, 1.97]). When stratified by delivery type, the adjusted odds of PPH following C-section increased over two-fold with SSRI/SNRI exposure (aOR=2.21, 95% CI [1.18, 4.13]). No difference in odds of PPH was found following vaginal delivery.

Importance: While underpowered for any definitive conclusions, these findings align with previous studies, suggesting late pregnancy SSRI/SNRI exposure may confer a moderately increased risk of PPH, particularly after C-section. These data highlight a need for greater clinical awareness and bleeding risk monitoring, especially among women with other known PPH risk factors.

W15. ELEVATED PLASMA ANTHRANILIC ACID-TO-INTERCELLULAR ADHESION MOLECULE 1 (AA/ICAM1) PREDICTS KETAMINE RESPONSE IN TREATMENT-RESISTANT DEPRESSION (TRD)

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Abstract Background: The rapid-acting antidepressant ketamine is a promising intervention for treatment-resistant depression (TRD), but objective markers are needed to identify the biological mechanisms for treatment response. While it is increasingly clear that immune-metabolic dysregulation is involved in the pathogenesis of TRD, few studies have characterized pre-treatment differences in plasma markers in relation to post-treatment outcomes after ketamine. Here, we present a secondary, biomarker study derived from a multisite, open clinical trial conducted in various sites of the National Network of Depression Centers and collaborative partners (BIO-K, NCT03156504; www.NNDC.org),aimed at identifying circulating biomarkers (inflammatory, kynurenine, and vascular-endothelial) implicated in ketamine response in TRD.

Methods: Our sample consisted of 74 subjects ages 18-65 years with treatment resistant unipolar or bipolar depression depression (TRD) who received 3 IV ketamine infusions over an 11-day period. By 24 hours post-infusion 3, 52% of subjects achieved clinical remission (primary outcome), defined by MADRS total score <10. The following plasma KP metabolites were measured with ultra-performance liquid chromatography at each post-infusion timepoint: tryptophan (TRP), kynurenine (KYN), kynurenic acid (KYNA), quinolinic acid (QUIN), picolinic acid (PIC), nicotinic acid (NIC), 3-hydroxykynurenine (3HK), 3-anthranilic acid (AA). Inflammatory markers were measured with ELISA, including high-sensitivity C-Reactive protein (CRP), intercellular adhesion molecule (ICAM), vascular cell adhesion molecule (VCAM), interleukin 6 (IL-6), interleukin 8 (IL-8), tumor necrosis factor alpha (TNF-α).

All biomarkers were log-transformed prior to analysis and second-generation p-values (SGPV), with a +/-5% null interval, were used to control for multiple comparisons. Robust linear regression was used to model MADRS total score at 24 hours post ketamine infusion 3 according to baseline biomarker level. Logistic ridge regression was used to estimate how well markers could predict remission status, which was assessed via the area under receiver operator characteristic curves (AUROC). All models were adjusted for sex, age, BMI, study site, and benzodiazepine use; predictive models were also adjusted for baseline MADRS scores. Sex-specific effects were assessed via relevant interactions.

Results: There was a significant negative association between baseline plasma AA and MADRS at post-infusion 3, after relevant adjustments (β = -0.45, 95% CI = [-0.83, -0.07], SGPV=0). Group comparison by remission revealed elevated baseline AA/ICAM1 ratio in remitters compared to non-remitters (1.3-fold higher, 95% CI = [1.05, 1.6], SGPV=0). Likelihood ratio tests showed baseline AA/ICAM1 and AA/KYN were both more strongly associated with MADRS at post-infusion 3 after relevant adjustments, compared to baseline AA alone. Finally, adjusted models including both baseline AA and ICAM1 were significantly more predictive of MADRS at post-infusion 3 based on a likelihood ratio test, compared to baseline AA alone (AUROC = 0.78; 95% CI = [0.66, 0.88]). The study findings were not sensitive to sex or benzodiazepine use.

Conclusion: Consistent with converging evidence of immune-metabolic dysregulation in TRD, we demonstrate that baseline elevated AA/ICAM1 ratio in plasma is a potential predictor of clinical remission by the ketamine post-infusion 3 timepoint. This constitutes preliminary

support for a biological endophenotype of ketamine response in TRD involving inflammatory and kynurenine pathways.

W16. COMPARISON OF TOLERABILITY, SAFETY, AND PHARMACOKINETICS OF ANTIDEPRESSANT DOSES OF ORAL KETAMINE PROLONGED RELEASE TABLETS (KET01) AND INTRANASAL ESKETAMINE: A RANDOMIZED, PLACEBO-CONTROLLED, DOUBLE-BLIND, CROSS-OVER TRIAL

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Abstract Objective: Ketamine and esketamine are N-methyl-D-aspartate receptor (NMDAR) inhibitors and exert rapid antidepressant effects at subanesthetic doses. Dissociative side effects and increases in heart rate and blood pressure frequently occur and are related to peak plasma levels of ketamine and mediated by NMDAR inhibition. It has been suggested that NMDAR inhibition may not be necessary for the antidepressant effect.
The objective of the trial was to compare the tolerability and safety of single antidepressant doses of KET01 (240 mg prolonged-release oral ketamine) and intranasal esketamine (84 mg) and to investigate the pharmacokinetics of ketamine and esketamine and their main metabolites.

Design: KET01-03 was a randomized, placebo-controlled, double-blind, double-dummy, single-center, cross-over trial in healthy male volunteers. Two single-dose treatment periods separated by a wash-out period of 14 to 28 days. Participants were monitored for 24 hours after each dosing. Blood samples for pharmacokinetic analysis were obtained, including at presumed peak concentrations of ketamine and esketamine.

The primary objective was to compare the maximum changes in the Clinician-Administered Dissociative States Scale (CADSS) Score from baseline within the 24 h after dosing between the two treatments. Importantly, CADSS was assessed at 40 min and 6 h 30 min after treatment, presumed to coincide with Cmax of the two formulations.

Results: 26 participants were recruited, and 25 received both KET01 and intranasal esketamine. Median age was 29 years (range 21-45).

CADSS total scores were stable for the first 24 h after KET01 treatment, with only 4 subjects (15.4%) with CADSS score >THAN 0. In contrast, intranasal esketamine induced a pronounced CADSS score increase at 40 min after treatment in most subjects, with CADSS score > 0 during the first 24 h in all 25 subjects. In the primary endpoint analysis, maximum change in CADSS score after baseline was lower after KET01 than after intranasal esketamine in both treatment periods; mean maximum change in CADSS score after KET01 treatment was lower by 29.01 (SD=2.35; $p < .00000000001$) than after intranasal esketamine.

In contrast to KET01, intranasal esketamine induced a rapid increase in heart rate and blood pressure, peaking at 40 min after administration, coinciding with the presumed Cmax for esketamine, before decreasing over several hours.

Pharmacokinetic analysis revealed a similar overall exposure to the parent molecules, with an AUC0-Tlast of 348.0 ng x h/ml for ketamine after KET01, and 369.9 ng x h/ml for esketamine

after intranasal esketamine administration. However, exposure to metabolites norketamine (NK) and hydroxynorketamine (HNK) after KET01 was 2.6 and 3.4 times higher than the exposure to (S)-NK and (S)-HNK after intranasal esketamine, respectively. Cmax was lower for KET01 than for intranasal esketamine, with 39.1 ng/ml vs 104.1 ng/ml.

Treatment-emergent adverse events (AE) were reported (all mild) by 16 subjects (61.5%) after KET01 and 25 subjects (96.2%) after intranasal esketamine dosing. No serious AE occurred.

Conclusion: An antidepressant dose of intranasal esketamine was associated with a high rate of dissociation and effects on heart rate and blood pressure, while an antidepressant dose of KET01 had a low incidence of such findings. Our results challenge the notion that NMDAR inhibition is necessary for the antidepressant efficacy of ketamine. The advantageous tolerability profile of KET01 suggests that prolonged-release oral ketamine has the potential to be developed for use without medical supervision.

W17. EFFECTS OF AXS-05 (DEXTROMETHORPHAN-BUPROPION) IN IMPROVING ANHEDONIA AND INTEREST-ACTIVITY SYMPTOMS OF MDD AND THE ASSOCIATED IMPROVEMENTS IN FUNCTIONAL IMPAIRMENT

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Abstract Introduction: Anhedonia is a core symptom of major depressive disorder (MDD) and is associated with functional impairment, reduced quality of life, suicidality, and a more chronic course of disease; it is considered among the most bothersome symptoms of MDD. Anhedonia symptoms are evaluated using the Montgomery Asberg Depression Rating Scale (MADRS) Anhedonia subscale (Items 1, 2, 6, 7, 8) and the Interest-Activity scale (MADRS Items 6, 7, 8 and Quick Inventory of Depressive Symptomatology Self Report [QIDS-SR] Items 10, 13, 14; doubled to match MADRS); this method has been utilized in trials of other antidepressants.

Current monoaminergic-targeted therapies have shown limited efficacy in treating anhedonia and residual anhedonia symptoms are associated with poorer patient outcomes. New modalities are needed that can effectively treat the broad range of depression symptoms, including anhedonia, and improve functional impairment associated with MDD.

AXS-05 (45-mg dextromethorphan/105-mg bupropion) is a novel, oral NMDA receptor antagonist and sigma-1 receptor agonist approved in the US for the treatment of MDD in adults. The NMDA receptor is part of the glutamatergic system that is thought to play a critical role in the etiology of depression; NMDA receptor modulators have shown benefits in treating MDD and improving associated functional impairment. The safety and efficacy of AXS-05 was established in 2 randomized, controlled clinical trials: GEMINI (NCT04019704) and ASCEND (NCT03595579). Pooled analyses of GEMINI and ASCEND were conducted to evaluate the effect of AXS-05 in improving anhedonia symptoms in patients with MDD and the association between changes in anhedonia symptoms and improvements in functional impairment.

Methods: GEMINI and ASCEND comprised patients (18–65 y) with MDD and MADRS total score ≥25. Efficacy outcomes included the MADRS and the QIDS-SR; GEMINI included the Sheehan Disability Scale (SDS). Anhedonia was evaluated using the MADRS Anhedonia subscale and the MADRS+QIDS-SR Interest-Activity scale. Analyses included least square mean difference (LSMD) in MADRS Anhedonia subscale and Interest-Activity Symptom scores, response (≥50% improvement), and correlations between MADRS Anhedonia subscale and SDS scores.

Results: In the pooled dataset, 199 patients each were in the AXS-05 and the control groups (GEMINI: placebo; ASCEND: bupropion). At Week 6, LSMDs for AXS-05 vs controls were -2.5 ($P < .001$) for the MADRS Anhedonia subscale and -3.0 ($P < .001$) for the Interest-Activity Symptom scores, with significant differences as early as Week 1. Response on the MADRS Anhedonia subscale was 51.3% (AXS-05) vs 36.7% (control); response on the Interest-Activity Symptom scale was 51.8% (AXS-05) vs 36.7% (control). AXS-05 treatment showed consistent benefits regardless of baseline Interest-Activity Symptom scores. There were positive correlations (0.75 correlation coefficient; $P < .001$) between improvements in MADRS Anhedonia subscale and SDS scores.

Conclusions: This post hoc analysis showed that AXS-05 significantly improved anhedonia and impaired interest-activity when compared with controls. AXS-05 exhibited comparable reductions in total MADRS scores regardless of severity of baseline interest-activity symptoms. Improvements in anhedonia symptoms were strongly correlated with improvements in functional impairment. These results suggest AXS-05 may be effective in reducing anhedonia and improving interest-activity, symptoms of MDD that can be very difficult to resolve with monoaminergic ADTs.

W18. IMPLEMENTATION AND EVALUATION OF THE PATHWAY PLATFORM IN A REAL-WORLD SETTING: A DIGITALLY ENABLED CARE PATHWAY TO IMPROVE DEPRESSION MANAGEMENT IN PRIMARY CARE

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Abstract Introduction: Measurement-based care (MBC) improves clinical outcomes through the quantitative measure of symptoms in patients with major depressive disorder (MDD) and enhances shared decision-making (SDM) between patients and their providers.1 Most patients with MDD are treated in the primary care setting, where physicians often lack sufficient time during appointments to implement MBC and SDM.2 The Pathway Platform is a digitally enabled health-technology experience linking an app interface for patients with a web-based portal for healthcare providers that can also integrate with electronic health records (EHRs). Digital tools like the Pathway Platform may help facilitate MBC and SDM by encouraging communication between patients with MDD and their primary care providers (PCPs). Through this study, we aim to implement and evaluate the use of the Pathway Platform in a primary care clinical setting to understand its application in improving depression management, patient-provider engagement, and MDD-related clinical outcomes.

Methods: In this real-world longitudinal, observational study, data from participants aged ≥18 years diagnosed with MDD and receiving a recently prescribed monotherapy antidepressant (defined as new start, medication switch, or dose change in the past 3 months) were collected 6 months retrospectively (pre-implementation) using EHRs (control cohort), and 6 months prospectively (post-implementation) using EHRs and the Pathway Platform (Pathway cohort). Primary outcome was to assess MBC by comparing 6-month utilization of 2- or 9-item Patient Health Questionnaire (PHQ); additional outcomes compared MDD remission and response, healthcare resource utilization, and patient-provider engagement between cohorts.

Results: The Pathway cohort included 89 patients (80% female) and 24 PCPs; the control cohort included 90 patients (58% female). EHR documentation of ≥2 PHQ assessments over 6 months was significantly higher among Pathway participants vs controls (55% vs 39%, P=0.03). Pathway participants were more likely to receive ≥1 medication change/switch (52%) vs controls (42%) and significantly less likely to have referrals to behavioral health (9%) vs controls (23%; $P < 0.05$). Pathway participants exhibited significant improvement in patient-provider engagement as reported by 13-item Patient Activation Measure scores at 6 months vs baseline (P=0.0004) and demonstrated greater improvements in MDD outcomes, with remission and response rates of 45% and 35% vs 29% and 29%, respectively, in the control cohort, although differences were not statistically significant.

Conclusion: The Pathway Platform improved PCP utilization of MBC, and Pathway patients demonstrated improved patient-provider engagement and MDD outcomes. This platform offers a promising approach for increasing the use of MBC and SDM and for improving treatment outcomes for patients with MDD in the primary care setting.

W19. ANTIDEPRESSANT CHANGES AND APP USAGE IMPROVE MDD OUTCOMES IN STUDY TO IMPLEMENT THE PATHWAY PLATFORM IN PRIMARY CARE: A POST HOC SUBGROUP ANALYSIS

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Abstract Background: Measurement-based care (MBC) and patient engagement allow providers to customize treatment based on recent symptoms and disease severity for people with major depressive disorder (MDD), improving clinical outcomes.1,2 Yet, these strategies are often underused.3 The digitally enabled Pathway Platform was designed to enhance patient-provider engagement and improve use of MBC in primary care.1 This post hoc subgroup analysis aimed to examine how antidepressant (AD) changes and app usage affected outcomes during the longitudinal, observational study to implement the Pathway Platform in a real-world, primary care setting.

Methods: This analysis included the Pathway cohort of all participants who were invited to use the Pathway Program. Eligibility criteria for the study included age ≥18 years, a diagnosis of MDD, and a recent AD start or switch (within past 3 months).2 Subgroups were defined by ≥1 AD change (ie, switch, dose change, add-on, or discontinuation) or no AD change. Data were collected for 6 months prospectively via electronic health records and the Pathway Platform. Outcome measures included change from baseline in 9-item Patient Health Questionnaire (PHQ-9) scores, AD changes, and proportion of days logged into app. A chi-

square test and Fisher's test were used for categorical variables, and a Wilcoxon 2-sample test was used for the continuous variables. Logistic regression analyses were performed.

Results: The Pathway cohort included 89 participants (80% female), with a median age of 35 (IQR: 28, 46) years; 40 (45%) had ≥1 AD change, and 49 (55%) had no AD change. The median number of PHQ-9 assessments completed in the app was significantly higher in the AD change group vs the no AD change group (4 [IQR: 2, 9] vs 3 [IQR: 2, 5], respectively; P=0.0339). Median changes in PHQ-9 scores from baseline to 6 months showed a significantly larger decrease (P=0.0397) in the AD change group (–5.0; 95% CI: –9.5, –0.5; P=0.0020; n=12) vs the no AD change group (–0.5; 95% CI: –2.5, 3.0; P=0.8125; n=8). Over the 6-month study, the AD change group had a significantly higher proportion of days on which participants logged into the app at least once (46% [79 days] vs 23% [39 days]; P=0.0110). Using a logistic model adjusted for baseline PHQ-9 score, age, sex, race, ethnicity, and insurance coverage, the proportion of days with a login to the app was predictive for AD change (odds ratio, 1.02; 95% CI: 1.01, 1.04; P < 0.05) within the Pathway cohort.

Conclusions: Participants who used the app more frequently had better odds of an AD change, suggesting app use may have facilitated a review and change of their AD treatment. The AD change group also had significantly greater improvement in symptom severity over 6 months vs the no AD change group. These observations provide more evidence that patient-provider engagement and MBC can lead to better outcomes.

W20. EVALUATING SAFETY AND TOLERABILITY OF SEMAGLUTIDE IN PARTICIPANTS WITH SUBSTANCE USE DISORDER

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Abstract Purpose: Preclinical findings indicate that glucagon-like peptide 1 receptor agonists (GLP-1RAs) reduce intake of various addictive drugs, including alcohol and nicotine. An increasing number of clinical reports also suggests spontaneous reductions in alcohol and nicotine intake during treatment with semaglutide (Ozempic®, Wegovy®) and other GLP-1RAs. Collectively, these preclinical and clinical/anecdotal findings suggest that GLP-1RAs should be studied as candidate treatments for substance use disorder. Little is known about the safety and tolerability profile of semaglutide in those with substance use disorder. This analysis used data from two Phase II randomized trials to provide a preliminary estimate of the safety and tolerability of semaglutide in adults with alcohol use disorder or tobacco use disorder.

Methods: Participants were non-treatment-seeking adults enrolled in one of two ongoing Phase II trials of semaglutide for alcohol use disorder (NCT05520775) or cigarette smoking (NCT05530577). Eligibility criteria included age 21-65 years and a body mass index (BMI) of 23 or higher. Participants in both trials were randomized to receive once-weekly treatment with semaglutide (Ozempic®) on a dose-escalating schedule (.25mg for 4 weeks, .50mg for 4 weeks, 1.0mg for 1 week) or placebo injections. Clinical and safety/side effect data were collected at weekly outpatient visits coinciding with medication administration. Participants also completed laboratory sessions involving alcohol administration/self-administration or cigarette lapse/smoking procedures at baseline and during-treatment. Interim side effect data were compiled for all randomized participants who had a) completed at least one week of

treatment, and b) attained a final disposition status (i.e., treatment completion or discontinuation).

Results: Data are presented in aggregate to maintain ongoing blinding (unblinded results to be presented). Among 48 participants with a final disposition status to date, 81.3% completed the full treatment sequence, whereas 18.8% discontinued (6.3% lost to follow-up, 4.2% time/logistic issues, 2.1% due to side effects, 6.3% other reason). Overall, 79.2 of participants reported at least one side effect. The most common side effects included decreased appetite (73.7%), nausea (63.2%), headache (42.1%), diarrhea (36.8%), and constipation (36.8%). Other common side effects (>10% of participants reporting) included vomiting, dizziness, and abdominal pain. No serious adverse events were recorded. One participant discontinued due to medication-attributable side effects. Adherence (proportion of scheduled doses received) was 100% among study completers and 81.3% overall. Two events of emesis were recorded during laboratory alcohol administration.

Conclusions: This preliminary analysis suggests that safety and side effect profiles of semaglutide in adults with substance use disorder are largely consistent with known side effects of this medication in other clinical populations. These results provide early indication of the safety and feasibility of semaglutide in adults with alcohol use disorder and tobacco use disorder. Limitations of this analysis include the relatively short treatment period, the limited dose range, and the aggregation of data across medication and placebo arms (to be unblinded for final presentation). Alcohol-related emesis warrants attention in future studies of GLP-1RAs in heavy drinkers. ClinicalTrials.gov identifiers: NCT05520775, NCT05530577. Supported by R21AA026931 and R21DA047663.

W21. MAINTENANCE TREATMENT WITH ESKETAMINE: INSIGHTS FROM THE 8TH LARGEST ACADEMIC MEDICAL CENTER IN THE UNITED STATES

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Abstract Background: Major Depressive Disorder is one of the most common mental disorders affecting 5% of the adult population (1). Treatment resistant depression (TRD) occurs in approximately 30% of patients with MDD (2). Intranasal esketamine is an NMDA receptor antagonist approved by the FDA for the treatment of treatment resistant depression (TRD) (3). Despite its approval and widespread use, real world data on maintenance treatment with esketamine for TRD is limited (4). We present data from the UAB intranasal esketamine clinic which was established in 2020.

Methods: The authors reviewed data from the intranasal esketamine clinic at UAB using retrospective chart review and present detailed data on patient clinical outcomes and esketamine usage, including depression severity, treatment duration, and frequency of dosing.

Results: Since its inception in 2020, our clinic has provided esketamine treatment to 200 patients, all of which were included in this review. The mean PHQ-9 score at intake and prior to receiving intranasal esketamine was 17.85. The mean number of esketamine treatments received by patients was 24.265. Frequency of esketamine dosing during the maintenance phase was as follows: an average of 16 weeks of once/week dosing, an average of 14 weeks of two times per month dosing and an average of 7 weeks of once monthly dosing frequency. While once monthly dosing is off-label, it was studied in the early, Janssen sponsored,

esketamine trials and has been used by our clinic for a variety of reasons including patient preference and the minimum needed frequency to keep patients well. Standard deviations and other descriptive statistics characterizing the patient panel, concomitant medications used, dosing frequency, dosing duration, outcomes, and adverse events will be provided in poster form as tables (all de-identified data).

Conclusion: Data from our intranasal esketamine clinic mirrors available evidence that esketamine is beneficial for treatment resistant depression. The review also indicates that an acute course of treatment (once/week or twice/week dosing) followed by maintenance treatment with twice/month or once/month dosing might be beneficial in sustaining positive effects of the treatment. There is a need for more substantial and clinically informative evidence to fine tune the algorithm for maintenance treatment with esketamine.

W22. CHILDHOOD TRAUMA AND ITS ASSOCIATION WITH DEPRESSION AND SOMATIC ANXIETY IN PATIENTS WITH MAJOR DEPRESSION PRO INFLAMMATORY PHENOTYPE: A POST HOC ANALYSIS

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Abstract Background: Prior literature has shown that more than 60% of children experience traumatic events before reaching the age of 16, with over 30% exposed to multiple such events. The repercussions of childhood trauma (CT) frequently surface in adulthood, increasing the susceptibility to depressive symptoms and anxiety disorders as well as other mental and medical conditions. This underscores the need for understanding diverse forms of CT and their correlation with depression and types of anxiety.

Methods: We conducted a post hoc analysis from our double blind randomized controlled trial that examined the impact of omega-3 doses on inflammatory biomarkers and depressive-anxiety symptoms. Sixty-one unmedicated adults (75.4% female; 50.8% White, Non-Hispanic; 45.5 ± 13.8 years) with Major Depressive Disorder and chronic inflammation (h-CRP GREATER THAN 3.0mg/l) were assessed for CT, and depressive-anxious symptoms. Study assessments included: Childhood Trauma Questionnaire (CTQ) and its subtypes Physical neglect (PN), physical abuse (PA), emotional neglect (EN), emotional abuse (EA), and sexual abuse (SA); as well as the Patient Health Questionnaire Physical Symptoms (PHQ-15), Inventory Depressive Symptomatology (IDSC-30), Clinical Global Impressions (CGI) and Hamilton Anxiety Rating Scale (HAM-A) with Somatic Anxiety and psychic anxiety subscales. Two-tailed Spearman's correlation were calculated between CT scores (overall and subtypes) and the other scales.

Results: CTQ total score was significantly associated with IDSC-30 (r=.296, p=.05), PHQ-15 (r=.544, p=.001), HAM-A total (r=.286, p=.05), Somatic Anxiety (r=.322, p=.01) but not for Psychic Anxiety (r=.171, p=.190). For CTQ subtypes, PHQ-15 was significantly associated with all CTQ subtypes; EA (r=.541, p=.001), EN (r=.350, p=.01), PN (r=.387, p=.01), PA

(r=.477, p=.001) and SA (r=.413, p=.01). Somatic Anxiety was significantly associated with EA (r=.381, p=.01), PA (r=.281, p=.05) and SA (r=.289, p=.05). Psychic Anxiety had no significant correlation with any CT subtypes.

Conclusion: Our preliminary findings revealed a significant association of childhood trauma (CT) with both depression and anxiety; however, this was driven by somatic anxiety. This underscores the importance of understanding and addressing the impact of CT on the development of depression and anxiety as a critical step in tailoring effective treatments. Further studies with larger sample sizes are required to better understand the intricacies of this depression phenotype.

W23. POSITIVE CORRELATION BETWEEN AMPA RECEPTOR DENSITY AND LOCAL AND GLOBAL FUNCTIONAL CENTRALITY: [11C]K-2 PET AND RESTING-STATE FMRI STUDY

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Abstract Background: Local Functional Connectivity Density (lFCD) and global FCD (gFCD)-lFCD (G-FCD) represent intraregional and interregional functional centrality (intra- and inter-regional FC) among all connectivities in resting-state functional magnetic resonance imaging (rsfMRI) in the whole brain, respectively. However, neurobiological mechanisms of lFCD and G-FCD remain unknown. To address these challenges, we focused on α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptors (AMPA-Rs), since AMPA-Rs have been identified as playing a major role in mediating excitatory signals in glutamate neurons. Therefore, the aim of this study was to test the hypothesis that an increase in AMPA-R density corresponds to higher intra and inter-regional FC.

Methods: [11C]K-2 (a novel PET tracer that specifically binds to AMPA-R) PET to measure AMPA-R density and rsfMRI scans were performed in 31 healthy subjects (HC). Standard Uptake Value Ratio (SUVR) was employed as a metric for AMPA-R density, with the white matter serving as the reference region. RsfMRI data were processed to extract lFCD and G-FCD values in the whole brain, in 83 Regions of Interests (ROIs) from Hammers Atlas, and in 7 networks of Yeo's Atlas regions. In one lFCD image, each voxel (a starting voxel) value represents the number of voxels in each cluster that satisfy the following two conditions: i) have significant connectivity with the starting voxel, and ii) are spatially adjacent to each other in each cluster. Conversely, in one G-FCD image, each voxel value means the number of voxels that meet i), and iii) are not spatially adjacent to each other. First of all, SUVR-lFCD correlation (l-COR) between the mean SUVR image and the mean lFCD image, and SUVR-(G-FCD) correlation (g-COR) between the mean SUVR image and the mean G-FCD image were tested in a ROI-wise manner using ROIs in Hammers atlas. Subsequently, in each ROIs or networks, the voxel-wise l-COR and g-COR were ascertained. Correlation coefficients were all tested with Spearman's rank correlation test.

Results: The whole brain ROI-wise analyses revealed that both l-COR and g-COR coefficients were significantly positive (r=0.33, p=0.0022 ; r=0.33, p=0.0025, respectively). The results of voxel-wise analyses: the mean l-COR coefficients were 0.46 in the whole brain, 0.54 in the

Default Mode Network (DMN), and 0.56 in the Visual Network (VN), 0.84 in the anterior cingulate gyrus (ACC), 0.73 in the posterior cingulate cortex (PCC), and 0.71 in the pregenual ACC (pgACC); the mean g-COR coefficients were 0.46 in the whole brain, 0.52 in DMN, 0.54 in VN, 0.84 in ACC, and 0.78 in PCC, and 0.77 in pgACC, respectively. Moreover, in all ROIs and networks, the mean voxel-wise l-COR and g-COR were positive except for in the left lateral orbitofrontal gyrus, the left substantia nigra (l-SN), the nucleus accumbens (NA), and the subcallosal area (SA) on l-COR analyses, and in l-SN, NA, and SA on g-COR analyses.

Conclusion: The present study found a positive correlation between AMPA-R density and intra- and inter-regional FC in HC in the whole brain in a ROI-wise manner, and also in a wide range of brain regions and cerebral networks in a voxel-wise manner. Voxel-wise l-COR and g-COR coefficient averages were in the highest category in ACC, PCC, and pgACC, suggesting that signal-transmissions based on AMPA-R density were among the most efficient ones in these regions in the whole brain. The fact that the voxel-wise l-COR and g-COR coefficient averages in the two main functional networks during rsfMRI imaging at rest with open eyes, DMN and VN, were the two largest of ones in all networks, might suggest that AMPA-R density was most correlated with intra- and inter-regional FC of the major brain activity networks during imaging.

W24. ASSESSING PARTICIPANT EXPERIENCE WITH KARXT TREATMENT USING IN-TRIAL QUALITATIVE INTERVIEWS: INITIAL FINDINGS FROM A LONG-TERM PHASE 3 TRIAL IN SCHIZOPHRENIA

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Abstract Background: KarXT [xanomeline and trospium] is a novel investigational muscarinic M1/M4 receptor agonist that, unlike currently available antipsychotics, does not directly block dopamine D2 receptors. In September 2023, a new drug application (NDA) for KarXT was accepted by the US Food and Drug Administration for the treatment of schizophrenia in adults. Short-term efficacy studies have been published and long-term studies are ongoing, including a 52-week safety study (NCT04820309). Since KarXT has a new mechanism of action (MOA), it is important to gather additional data on participants' experience of taking KarXT and how that experience compares to previous treatments with standard antipsychotics. We therefore conducted a qualitative sub-study consisting of in-trial interviews with a subgroup of participants in the aforementioned safety study, which aimed to characterize their experience during the trial, understand changes in symptoms, and better define meaningful treatment benefit.

Methods: The parent safety study enrolled outpatients without prior exposure to KarXT who would switch to or start open-label KarXT. Participation in the qualitative sub-study was optional. After consenting, sites notified QualityMetric, an external research group with expertise in qualitative methods, who conducted two semi-structured interviews with each participant using a secure telehealth platform after ~6- and ~26-weeks of KarXT monotherapy. An interview guide developed for this study elicited participants' views about taking KarXT, including symptom changes and differences from their most recent prior antipsychotic treatment. The interview included 2 global 10-point self-reported satisfaction ratings, 1 for KarXT and 1 for the participant's previous antipsychotic treatment. Coding and analysis of

deidentified interview transcripts were conducted independently by the QualityMetric team using NVivo software.

Results: A total of 13 (of 57) study sites enrolled a total of 70 participants who completed an initial interview (mean age 47.9 years, 75.7% male). Of those 70 participants, 47 returned for a follow-up interview. Most participants perceived an improvement in positive, negative, and cognitive symptoms of schizophrenia since initiating KarXT. Participants also reported improved health-related quality of life. On average, participants rated their satisfaction with KarXT higher (mean = 8.1 out of 10) than that of their previous antipsychotic treatment (mean = 6.1 out of 10) during the initial interviews; ratings were highly similar at follow-up.

Discussion: These preliminary data demonstrate the feasibility of conducting prospective qualitative interviews that focus on trial participant experience. Moreso, these data add a meaningful patient-centered perspective to the standard long-term safety data collected during a late Phase 3 clinical program. This is of particular importance when the MOA of the investigational treatment differs substantially from currently available treatments that are familiar to clinical practitioners. While the results are preliminary, most participants were able to differentiate between KarXT and their prior treatments, and most experienced benefit from being on a muscarinic rather than dopaminergic treatment.

W25. INCENTIVE SALIENCE OF DRUG CUES AND BRAIN REACTIVITY IN OPIOID USE DISORDER: PRELIMINARY FINDINGS FROM A PHARMACOIMAGING TRIAL OF CANNABIDIOL

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Abstract Background: We previously demonstrated the efficacy of single dose Cannabidiol (CBD) in improving drug-cue-induced craving and anxiety in heroin use disorder. Next, we set out to explore the impact of CBD on neurocircuitry of cue-induced craving and anxiety, as well as more distinct early cognitive processes in cue reactivity, i.e., incentive salience. There is a dearth of evidence on neural underpinnings of incentive salience of drug cues in humans. Hereby we present the preliminary findings from an exploratory analysis, investigating the correlation between the initial incentive salience upon exposure to drug cues, measured as attentional bias (AB) toward drugs cues, and brain activity during an extended exposure to drug cues using functional magnetic resonance imaging (fMRI).

Methods: The main study is a randomized, double-blind clinical trial (NCT04567784) comparing Epidiolex 800mg and placebo. Participants with Opioid Use Disorder were eligible if they met the following criteria: being on a stable methadone dose of 40-100mg, testing negative for alcohol, tobacco, illicit drugs, and CBD during screening. On day 1, 2h after receiving the first dose of CBD/placebo, participants went were exposed to 8 blocks of drug cues and 8 blocks of neutral cues, each for 12s, during fMRI scan. On day 3, 2h after the third dose of CBD, participants went through a modified version of the Dot Probe Task. This behavioral task consisted of 80 drug cue-neutral picture pairs and 80 neutral-neutral picture pairs, presented for 200ms. FSL software was used for first-level whole-brain analysis and subsequent second-level network-based analysis using combined region-of-interest masks from Harvard-Oxford atlases to model the six major functional networks proposed by Impaired Response Inhibition and Salience Attribution model (iRISA). The main contrast of interest was

Drug > Neutral and attentional bias scores were included as a covariate. Cluster-wise thresholds of z=3.1 and p=0.05 were considered.

Results: Eighteen participants were included in this analysis, and the study remains double-blinded as we continue the enrollment. There was a significant AB toward drug cues versus neutral cues (mean=88.6ms, CI95%=4.8 to 172.4ms, p=0.0395). Contrasting with neutral cues, drug cues were associated with hyperactivity in five clusters in the default mode network (DMN) (Zmax/cluster size= 5.2/1643, 5/564, 4.28/250, 4.82/226, 3.96/39), four clusters in the salience network (4.54/155, 4.64/113, 4.65/65, 4.07/40), three clusters in the reward network (4.33/54, 3.78/19, 3.9/16), three clusters in the habit network (4.15/24, 4.57/19, 4.04/17), two clusters in the memory network (4.12/44, 4.3/35), and one cluster in the central executive network (3.89/23). Including the attentional bias as a covariate in the model yielded four clusters in the DMN (4.28/43, 4.06/22, 3.89/19, 3.84/18), of which only one passed the p-value threshold of 0.05. No clusters were detected in other networks.

Conclusions: Our findings indicate a potential association between attentional bias as one of the earliest cognitive processes involved in visual cue processing, and hyperactivity in the DMN, over an extended course of exposure to drug cues. These findings warrant further confirmation in a larger sample size, and subgroup analysis in the two treatment arms after trial completion and unblinding. This novel finding may have implications for our understanding of the role of DMN in drug cue reactivity toward development of targeted therapeutics.

W26. FIRST DUAL NON-SULFONAMIDE OX1R AND OX2R AGONISTS AND THEIR POTENTIAL USE FOR THE TREATMENT OR PREVENTION OF NEUROLOGICAL DISEASES

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Abstract: Structurally novel classes of dihydro-benzothiazine or -quinazoline derivates for use in the prevention or treatment of neurological, psychiatric, sleep disorders and diseases were designed and evaluated in vitro using human two orexin G protein-coupled receptors (GPCRs) cell-based agonist calcium flux assay (CEREP, Eurofins Discovery) to measure agonistic activation of orexin receptors.

Orexin 1 and 2 also known as hypocretin 1 and 2 or orexin A and B are hypothalamic neuropeptides specifically produced in the lateral hypothalamic (LH) area. Acting on the two G protein-coupled receptors (GPCRs), the orexin-1 receptor (OX1R) and the orexin- 2 receptor (OX2R), they participate in a broad range of physiological functions such as sleep/wakefulness, feeding behavior, reward-seeking and stress responses.

More especially, OX1R is mainly involved in motivation and reward and the OX2R in the modulation of sleep/wake cycle and energy homeostasis, but recently it has been reported that OX1R plays an additional role in the regulation of wakefulness.

Specifically, the development of rapid eye movement (REM) sleep-related symptoms is likely to stem from the reduction of receptor functions of both OX1R and OX2R. These observations suggested that although OX2R is a primary target for developing agonists to treat narcolepsy, rescuing the function of both receptors would be ideal.

Among these series of compounds synthesized by Aexon Labs Inc. (aexonlabs.com), AEX-1, AEX-2, AEX-3, AEX-4, AEX-5, AEX-19, AEX-21, AEX-24 and AEX-41 are the most potent

OX1R and/or OX2R activators identified (PCT Application Number EP2023/088019), targeting dopamine and norepinephrine transporters, metabotropic glutamate 2, sigma-1, -2 receptors and cathepsins, these compounds indicate potential synergistic pharmacological effects on neuroinflammation and neuroimmune response implicated in various neuropsychiatric and neurodegenerative conditions, treating beyond the narcolepsy and other central hypersomnolence disorders.

Our combined results provide important information towards structurally novel classes of orexin receptor agonists distinct from current chemotypes such as sulfonamide-types developed in the treatment of narcolepsy.

W27. AID-ME: ARTIFICIAL INTELLIGENCE IN DEPRESSION – MEDICATION ENHANCEMENT: A CLUSTER RANDOMIZED, PATIENT AND RATER BLINDED, ACTIVE-CONTROLLED TRIAL OF AN AI-ENABLED CLINICAL DECISION SUPPORT SYSTEM IN ADULTS WITH MAJOR DEPRESSION

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Abstract Background: While effective pharmacological treatments exist for Major Depressive Disorder (MDD), patients often undergo a trial-and-error approach before finding effective antidepressants. There has been increasing interest in the use of Artificial Intelligence (AI)-enabled clinical decision support systems (CDSS) for the personalization of depression treatment selection and management, but there is a lack of clinical studies investigating their effectiveness.

Methods: We investigated a CDSS that combines an AI which predicts remission probabilities for individual antidepressants and a clinical algorithm based on existing guidelines for treatment management. The CDSS is web and app based and designed for rapid deployment into the clinical workflow. This was a clinician (cluster) randomized, patient-and-rater blinded and clinician-partially-blinded, active-controlled trial. Clinicians in the active group had access to the CDSS; clinicians in the active-control group received patient questionnaires; both groups received guideline training. Patients were adults with moderate or greater severity MDD who required an initiation or change in treatment, who could be managed as outpatients, and who did not have Bipolar Disorder. Other comorbidities were permitted. Both patient groups had access to the patient version of the tool to complete questionnaires. Aside from completing a specific subset of study assessments and asking active clinicians to log into the CDSS at each visit, there were no requirements placed on clinicians or patients in terms of engagement with the CDSS or adherence to the information it provided, facilitating naturalistic assessment. Patients and raters who assessed the primary study outcome were blinded to group allocation. Patient blinding was possible as they were not informed of the specific differences between groups, and because patients used the application in the same manner in both groups. Clinicians were partially blinded as they were aware of their group allocation but not of the study outcomes or expected effect sizes. Patient study length was 12 weeks, with 5 treatment visits

(baseline, 2, 4-6, 8, and 12 weeks). The primary outcome was remission (< 11 points on the Montgomery Asberg Depression Rating Scale (MADRS) at study exit).

Results: 47 clinicians and 75 patients were consented and deemed eligible to participate at 9 participating sites. An additional 15 patients were deemed ineligible during screening. All clinicians were psychiatrists or mental health nurse practitioners. Of the 75 eligible consented patients, 61 (42 active, 19 active-control) with a baseline and exit MADRS were analyzed. There were no differences in baseline mean MADRS (active= 33, SD = 7.3; control= 30, SD = 5.8; p = 0.153). On the primary outcome, there were significantly more remitters in the active (n= 12, 28.6%) than in the active-control (0%) group (p = 0.012, Fisher's exact test). While there were three serious adverse events (suicidal ideation, panic attack with suicidal ideation, suicidal gesture) in the active group, none were deemed to be causally related to the CDSS.

Conclusions: While limited by sample size and lack of primary care clinicians, these results demonstrate the first successful and safe longitudinal use of an AI-CDSS to improve outcomes in moderate and greater severity MDD. The ease of implementation of this platform suggests that it and similar devices may be able to rapidly improve outcomes.

W28. RAPID AND DURABLE RESPONSE TO A SINGLE DOSE OF MM120 (LYSERGIDE) IN GENERALIZED ANXIETY DISORDER: A DOSE-OPTIMIZATION STUDY

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Abstract: Background: Generalized Anxiety Disorder (GAD) is among the most common psychiatric disorders. Despite this, there has been little progress in the development of effective and well-tolerated therapies. GAD is a chronic disorder characterized by excessive worry and persistent general apprehensiveness, which can manifest in a wide range of psychiatric and somatic symptoms. Current treatments are often ineffective or have intolerable side effects. We evaluated the safety, tolerability, and efficacy of 4 doses of MM-120 (D-lysergic acid diethylamide D-tartrate) in patients with GAD. Methods: In this Phase 2b multicenter, randomized, double-blind, placebo-controlled study, adults aged 18 to 74 years with GAD and moderate to severe anxiety (Hamilton Anxiety Rating Scale [HAM-A] score ≥20) were enrolled. A total of 198 patients were randomized 1:1:1:1:1 to receive a single administration of MM-120 at a dose of 25 µg (n=39), 50 µg (n=40), 100 µg (n=40), or 200 µg (n=40) or placebo (n=39). The primary and key secondary objectives were to assess the dose-response relationship of MM-120 by evaluating the change in HAM-A total score from baseline to weeks 4 and 8, respectively. Secondary endpoints included improvements in functioning and quality of life; safety assessments were also performed. Results: Both 100 µg and 200 µg doses demonstrated clinically and statistically significant efficacy. The 100 µg dose achieved the highest level of clinical activity with a statistically significant reduction of 7.6 points in HAM-A total score compared to placebo at week 4 (-21.34 MM-120 vs -13.75 placebo; P=0.0004). Moreover, clinical activity was evident as early as day 2 after treatment as measured by the Clinical Global Impressions–Severity (CGI-S) scale. At day 2, CGI-S scores improved by 1.8 points with MM-120 100 µg vs 0.7 points with placebo (P=0.0001); this improvement persisted through week 4 (P LESS THAN 0.01). At week 4, 77.5% of subjects treated with MM-120 100 µg showed a clinical response with ≥50% improvement in HAM-A vs 30.77% with placebo.

Further, 50% of participants treated with 100 µg achieved remission (HAM-A ≤7) vs 17.95% with placebo. There was also a significant reduction in the Montgomery-Asberg Depression Rating Scale total score with MM-120 100 µg versus placebo (-5.73; P LESS THAN 0.05). Treatment-emergent adverse events (TEAEs) occurred in 97.5% of participants in the MM-120 100 µg group vs 56.4% in placebo. Most events were mild to moderate, occurred on dosing day, and were consistent with the expected acute effects of MM-120. The most common TEAEs (≥10% incidence) in the MM-120 100 µg group were illusion, hallucination, euphoric mood, anxiety, abnormal thinking, headache, nausea, fatigue, mydriasis, increased blood pressure, and hyperhidrosis. No deaths were reported in the study. Conclusion: These findings suggest a rapid, robust, and durable clinical response to MM-120 in patients with GAD. Mind Medicine, Inc supported this study.
Trial registration: NCT05407064 A Dose-Finding Study of MM-120 (LSD D-Tartrate) for the Treatment of Anxiety Symptoms.

W29. THE IMPACT OF CARIPRAZINE ON SHORT- AND LONG-TERM DISABILITY AMONG COMMERCIALLY-INSURED PATIENTS

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Abstract: Introduction: Atypical antipsychotics (AAs) are an important treatment consideration for several mental health (MH)-related disorders, including bipolar I disorder (BP-I), major depressive disorder (MDD), and schizophrenia spectrum disorder (SCZ). Cariprazine is a dopamine D3 preferring D3/D2 and serotonin 5-HT1A receptor partial agonist that was approved by the US Food and Drug Administration for the treatment of BP-I and SCZ and for the adjunctive treatment of MDD. Clinical studies have demonstrated that cariprazine is effective and well-tolerated across all three MH-related disorders, but real-world evidence on the indirect economic outcomes associated with cariprazine is limited. This study aimed to 1) compare all-cause and MH-related short- and long-term disability events and disability costs of patients with BP-I, MDD, or SCZ before versus after cariprazine initiation and 2) replicate analyses among patients with BP-I, MDD, or SCZ separately.
Methods: This study utilized the Merative MarketScan Commercial Database and Health and Productivity Management Database (HPM) from 01/2016-12/2021. HPM contains integrated data on disability, including short- and long-term disability claims and their associated duration and costs. Adult patients (≥18 years) with ≥2 pharmacy claims for cariprazine (first claim = index date) and ≥3 months of cariprazine use were included. Patients were required to have continuous commercial insurance coverage and HPM eligibility ≥12 months before and ≥3 months after the index date (12 months pre-index = baseline), as well as ≥1 diagnosis of BP-I, MDD (required to be using cariprazine adjunctively), or SCZ at baseline. Patients were observed until the earliest date of 1-year post-index, cariprazine discontinuation, end of insurance or HPM eligibility, or end of data availability. Outcomes included number of all-cause and MH-related short- and long-term disability claims, days (i.e., total weekdays encompassed by all disability claims), and costs, calculated as disability costs (if available) or as U.S. median daily earnings times disability days times a 60% replacement rate. Pre- and post-index rates of disability claims/days and mean costs (all reported per person per year) were compared using rate ratios (RR) and mean cost differences, respectively. Comparisons

were calculated from generalized estimating equation models, with 95% CIs generated using non-parametric bootstrap procedures. Analyses were replicated among indication-specific subgroups.

Results: The final cohort included 489 patients (BP-I = 238, MDD = 233, SCZ = 18). The mean (SD) age was 43.3 (9.8) years and 60.7% of patients were female. The average length of follow-up was 7.6 months. All-cause rates of disability events and days were 29% (RR [95% CI] = 0.71 [0.57, 0.86]; P < .001) and 28% (0.72 [0.53, 0.94]; P < .05) lower during follow-up vs. baseline, respectively, while MH-related rates of disability events and days were 40% (0.60 [0.43, 0.80]; P < .001) and 43% (0.57 [0.34, 0.84]; P < .01) lower, respectively. During follow-up, all-cause disability costs were $2,917 (95% CI = -$5,032, -$954; P < .01) lower and MH-related disability costs were $2,482 (-$4,468, -$920; P < .01) lower than baseline costs, corresponding to a 40% and a 51% decrease, respectively. Results from indication-specific subgroup analyses were similar to those of the overall cohort.

Conclusions: This retrospective observational study found that rates of disability events, days, and mean costs were significantly lower during versus before cariprazine use. These results highlight the importance of cariprazine in reducing the disability burden of employed, commercially-insured patients with BP-I, MDD, or SCZ.

W30. THE IMPACT OF ADJUNCTIVE CARIPRAZINE ON MENTAL HEALTH-RELATED QUALITY OF LIFE IN PATIENTS WITH MAJOR DEPRESSIVE DISORDER: A POOLED POST HOC ANALYSIS OF CLINICAL TRIAL DATA

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Abstract: Introduction: Patients with major depressive disorder (MDD) often experience serious deficits in health-related quality of life (QoL) as a result of impaired social, emotional, and cognitive functioning. Cariprazine is a dopamine D3-preferring D3/D2 and serotonin 5-HT1A receptor partial agonist that is approved for adjunctive treatment of MDD. QoL was evaluated in two phase 3, fixed-dose, randomized, double-blind, placebo-controlled studies in patients with MDD and inadequate response to antidepressant therapy (ADT; NCT03738215 and NCT03739203). QoL was measured by the 12-item Short Form Health Survey version 2 (SF-12v2), a validated patient-reported health-related QoL measure consisting of an aggregated mental component summary (MCS) score and physical component summary (PCS) score, and 8 domains (mental component score: vitality, social functioning, role limitations due to emotional problems, mental health; physical component score: physical functioning, role limitations due to physical problems, bodily pain, general health). Because MDD is a mental health disorder and treatment is expected to have a greater effect on mental than physical health, we conducted a pooled post hoc analysis of data from these trials focusing on cariprazine-related changes in mental health-related QoL.

Methods: Patients in the primary fixed-dose studies were randomized (1:1:1) to cariprazine + ADT (1.5 mg/d or 3.0 mg/d) or placebo + ADT; data were pooled. Least squares (LS) mean change from baseline to week 6 in the SF-12v2 mental component domains and MCS summary score were evaluated in the pooled modified intent-to-treat (mITT) population (all randomized participants with ≥1 postbaseline Montgomery–Åsberg Depression Rating Scale total score

assessment). Analyses were conducted using an ANCOVA model; P values were not adjusted for multiple comparisons. Higher SF-12v2 scores indicate better HRQoL; MCS score range is 0–100.

Results: There were 1456 patients in the pooled mITT population who had a baseline and week-6 score for ≥1 MCS domain (placebo + ADT=484; cariprazine + ADT: 1.5 mg/d=485, 3 mg/d=487). Baseline values were similar across groups for the MCS (21.9–22.2) and individual domains (vitality=33.0–33.7; social functioning=26.5–26.7; role limitations due to emotional problems=23.4–23.7; mental health=27.4–27.7). LS mean change from baseline in MCS score was significantly greater for both doses of cariprazine + ADT versus placebo + ADT (placebo=12.1; cariprazine: 1.5 mg/d=14.1, 3 mg/d=14.5 [P LESS THAN .05 both]). LS mean changes in the individual domains of the MCS were also significantly greater for cariprazine 1.5 mg/d + ADT and 3 mg/d + ADT versus placebo + ADT, respectively (P LESS THAN .05 all): vitality (8.8 and 8.7 vs 6.9), social functioning (10.3 and 10.2 vs 8.4), role limitations due to emotional problems (10.9 and 11.3 vs 9.5), and mental health (13.3 and 13.4 vs 11.7).

Conclusions: In a pooled post hoc analysis of two fixed-dose studies of adjunctive cariprazine in patients with MDD, treatment with adjunctive cariprazine versus placebo was associated with significant improvements in the SF-12v2 mental component summary score, as well as in the vitality, social functioning, role limitations due to emotional problems, and mental health MCS domains. These findings suggest that adjunctive cariprazine had a positive impact on mental health-related QoL in patients with MDD and inadequate response to ADT alone.

W31. AMNESIA IS ASSOCIATED WITH ANTIDEPRESSANT RESPONSE TO KETAMINE IN TREATMENT-RESISTANT MAJOR DEPRESSIVE EPISODES WITH SUICIDAL IDEATION: A PRELIMINARY REPORT

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Abstract Background: The nature of the relationship between the experience of acute dissociation during treatment and the subsequent antidepressant effect of ketamine remains an active area of investigation. Most published data in the field investigate this question using the Clinician-Administered Dissociative States Scale (CADSS) total score, but only less frequently are the CADSS subscales (amnesia, derealization, and depersonalization) considered. We sought to further assess the association between these different dissociative symptoms and subsequent antidepressant or antisuicidal responses to ketamine in a treatment-resistant population with chronic suicidality.

Methods: During an open-label trial, participants with major depressive disorder or bipolar disorder type II in a major depressive episode lasting at least eight weeks received a single intravenous ketamine dose (0.5mg/kg over 40 minutes). Inclusion criteria mandated a history of at least one antidepressant failure in the current episode and suicidal behavior (Beck Scale for Suicidal Ideation score ≥ 6; ClinicalTrials.gov ID: NCT04116528). Subjects were assessed with the BSSI, Montgomery–Åsberg Depression Rating Scale (MADRS), and Hamilton Depression Rating Scale (HAMD-21) before infusion and on day 3. Dissociative symptoms were measured by the CADSS before the infusion and at 40 minutes. Linear mixed models were applied for statistical analysis using R programming software 4.2.3.

Results: The study included 36 individuals, 72.2% of whom were female, and all participants received the ketamine infusion. The results showed statistically significant reductions in symptom scores on all three scales at day 3 compared to baseline. The mean MADRS score decreased from 34.7 to 21.5 ($p < 0.0001$), the mean HAMD-21 score decreased from 24.6 to 15.2 ($p < 0.0001$), and the mean BSSI score decreased from 15.14 to 7.56 ($p < 0.0001$). The mean CADSS total score at 40 minutes was 17.75 (SD ± 14.53). The CADSS total score at 40 minutes exhibited only a trend of a predictive value for clinical outcomes at day 3 on MADRS ($p=0.07$) and none at all for the HAMD-21 ($p=0.32$) and BSSI ($p=0.33$). However, when analyzing the CADSS subscales, amnesia exhibited a statistically significant predictive value for antidepressant response on MADRS ($p=0.04$) but not on HAMD-21 ($p=0.11$) and BSSI ($p=0.19$). Derealization and depersonalization did not demonstrate any predictive value for clinical outcomes. Derealization: MADRS ($p=0.13$), HAMD-21 ($p=0.44$), BSSI ($p=0.53$). Depersonalization: MADRS ($p=0.22$), HAMD-21 ($p=0.66$), BSSI ($p=0.87$).

Conclusions: Consistent with prior reports, open-label ketamine infusion was effective in reducing symptom scores on depression and suicide rating scales, and treatment-associated amnesia – but not overall dissociation – was associated with subsequent antidepressant effect. Further research is warranted to comprehensively understand the role of different dissociation features as putative behavioral biomarkers of response to ketamine therapy.

W32. ESTABLISHMENT OF A DIGITAL THERAPEUTIC ALLIANCE IN PATIENTS LIVING WITH NEGATIVE SYMPTOMS OF SCHIZOPHRENIA

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Abstract Background: There are no approved pharmacotherapies for experiential negative symptoms (ENS) of schizophrenia, and access to psychosocial interventions is limited. Prescription digital therapeutics (PDTs), which are evidence-based digital therapeutics that receive regulatory authorization and require a prescription, could deliver psychosocial interventions to people with schizophrenia. A critical success factor of in-person therapy is the effective establishment of a therapeutic alliance between patient and healthcare professional. A similar bond established between a patient and PDT (digital working alliance; DWA) may help improve treatment outcomes. Two studies determined if patients with moderate–severe ENS of schizophrenia could establish and maintain an effective DWA with beta versions of CT-155, a PDT in development for treating ENS of schizophrenia.

Methods: Two exploratory, single-arm, multicenter studies over 3 (Study 1) or 7 (Study 2; NCT05486312) weeks included adults with schizophrenia and self-reported ENS. Patients were receiving stable antipsychotic medication for ≥12 weeks and had on-demand access to CT-155 beta versions. Patient demographics were captured at screening, and negative symptoms were evaluated using the Motivation and Pleasure Scale-Self-Report (MAP-SR) at screening and the clinician-administered Clinical Assessment Interview for Negative Symptoms Motivation and Pleasure Scale (CAINS-MAP) at baseline. The overall DWA strength at Weeks 1 and 3 (Study 1) and Week 3 (Study 2) was assessed using the mobile

Agnew Relationship Measure (mARM); scores ≥5 represented a positive alliance. A post hoc analysis assessed correlations between the strength of the DWA (mARM scores) and patient age and ENS severity (MAP-SR and CAINS-MAP scores) using Spearman's correlation coefficients. mARM scores were compared across Race (Black or African American vs Other) using an F test.

Results: In Studies 1 (N=49) and 2 (N=50), patients had a median (range) age of 46 (18–64) and 53.5 (23–64) years and 71% and 80% of patients were male, respectively. The mean (standard deviation; SD) overall MAP-SR score at screening was 22.6 (6.8) in Study 1 and 14.9 (8.9) in Study 2. ENS were moderate–severe at baseline as determined by a mean (SD) overall CAINS-MAP score of 2.37 (0.76) in Study 1 and 2.28 (0.92) in Study 2. A positive DWA was established and maintained between patients and the PDT in Study 1 (mean [SD] mARM: 5.15 [0.74] at Week 1 and 5.16 [0.77] at Week 3). In Study 2, a positive DWA was observed at Week 3 (mean [SD] mARM: 5.36 [1.06]). In the post hoc analysis (Study 1: n=40, Study 2: n=45), there was no statistically significant correlation between mARM scores and either age (Study 1: r=0.31, p=0.054; Study 2: r=0.15, p=0.32), MAP-SR scores at screening (Study 2: r=0.11, p=0.48), or baseline CAINS-MAP scores (Study 1: r=-0.16, p=0.36; Study 2: r=-0.13, p=0.41). mARM scores were not significantly affected by Race (Study 1: F-test=1.193, p=0.719; Study 2: F-test=1.162, p=0.747).

Conclusions: Establishing a positive DWA may be critical for successfully treating patients with a PDT. These early findings show that patients with moderate–severe ENS of schizophrenia consistently establish a DWA with beta versions of CT-155, which overall, was unaffected by age, race, or ENS severity.

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Previously presented at SIRS 2024.

W33. DYSGLYCEMIA ASSOCIATED WITH ANTIPSYCHOTIC USE: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Abstract Background: Antipsychotics (APs) are the cornerstone of treatment for schizophrenia spectrum disorders (SSDs) and are approved for the treatment of affective disorders including bipolar disorder (BD). However, AP use is associated with severe metabolic consequences including weight gain, dyslipidemia, and dysglycemia. Although studies indicate that glucose dysfunction can occur independently of weight gain, AP-induced glycemic changes are usually considered to be a consequence of AP-induced weight gain. Therefore, the aims of this review are to: 1) specifically clarify the effect of APs on glucose

homeostasis independently of weight gain and 2) determine whether APs similarly impact glycemic control independently of drug class and treatment duration.
Methods: We searched MEDLINE, EMBASE, PsychINFO, CENTRAL, CINAHL, and Web of Science from inception to August 2023 to identify all randomized controlled trials (RCTs) that compared the effect of APs on glucose metabolism to placebo (PBO), with no restriction on psychiatric diagnosis. Glucose dysfunction was examined using a random effects meta-analysis, with subgroup analyses for study length, AP type, and age (child/adolescent vs. adult). Where possible, meta-regressions were conducted to explore the effects of weight gain, study length, and AP dose on change in glucose.
Results: Of 20954 references identified in our search, 70 RCTs in patients with SSDs (N=40 studies) and BD (N=30 studies) met our inclusion criteria. In both populations, AP use was associated with a significantly greater increase in blood glucose compared to placebo (mean difference (MD) SSD = 0.05 mmol/L [0.01, 0.09], p=0.01, I2=0%, n=8535 AP vs. n=3389 PBO; MD BD = 0.10 mmol/L [0.05, 0.15], p < 0.0001, I2=46%, n=6018 AP vs. n=4137 PBO). Sub-group analyses revealed that neither study length nor AP type altered this finding. Plasma insulin was also significantly increased by AP exposure (MD SSD = 13.97 pmol/L [6.42, 21.51], p=0.0003, I2=0%, n=3678 AP vs. n=1169 PBO; MD BD = 12.85 pmol/L [1.14, 24.56], p=0.03, I2=55%, n=2111 AP vs. n=1676 PBO), with a significant subgroup difference according to AP type in both groups (SSD: p=0.02, I2=62.1%; BD p=0.0001, I2=85.6%). There was an additional effect of study length on plasma insulin in individuals with SSDs (p=0.03, I2=79.8%). Importantly, the strength of the effect of different APs on blood glucose did not appear to follow the established hierarchy of weight gain liabilities outlined in the literature. Specifically, so-called 'weight neutral APs' such as ziprasidone and lurasidone produced comparable dysglycemia to APs traditionally associated with significant weight gain like olanzapine (SSD: p=0.45, I2=0%; BD: p=0.46, I2=0%). Subsequent meta-regression analyses found that AP-associated dysglycemia may be independent of study length and AP dose in patients with SSD (p > 0.05) and independent of study length and baseline-to-endpoint weight gain in patients with BD (p > 0.05). AP use did not appear to have a significant effect on HOMA-IR or treatment-emergent hyperglycemia (dichotomous outcome) in either patient group. DISCUSSION: Our review demonstrates that both short- and long-term exposure to APs are associated with a significant increase in dysglycemia risk as indicated by AP-induced elevations in blood glucose and insulin. Furthermore, all APs cause some degree of glucose dysregulation regardless of exposure time and established propensities for AP-induced weight gain. Further studies are required to better understand how AP use contributes to dysglycemia, including temporal changes throughout the treatment course, and how these effects could potentially be mitigated using metabolic interventions.

W34. METABOLOMIC SIGNATURES DIFFERENTIATING PSYCHOSIS SPECTRUM DISORDERS FROM HEALTHY CONTROLS AND ASSOCIATION WITH WEIGHT GAIN

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Abstract: Introduction: Psychosis spectrum disorders (PSDs) are a series of debilitating mental illnesses associated with intrinsic metabolic dysfunction, with the pathophysiological

mechanisms of both the mental and physical symptom domains being largely unknown. Antipsychotics, the main treatment of PSDs, are known to exacerbate the metabolic problems seen in patients with PSDs. One approach to help understand these mechanisms is through metabolomics which is the study of the complete set of metabolites in the body called the metabolome.

Methods: This 12-week prospective naturalistic study used untargeted metabolomic data and included 37 minimally antipsychotic-treated PSD patients and 18 non-psychiatrically ill controls comparing differences in the baseline metabolomes of patients and controls. Nineteen patients completed the study and they were grouped based on whether they gained a clinically significant amount of weight (>7%) at endpoint when compared to baseline to identify whether metabolomic signatures could predict antipsychotic-induced weight gain.

Results: The baseline comparison between patients with PSDs and controls showed two reduced metabolites in patients with PSDs: lysophosphatidylcholine (20:0), and carnitine (20:0) (FDR < 0.05). Fold change analysis at the 2.0x level showed that oleamide and serotonin were decreased in patients with PSDs. For patients who gained a clinically significant amount of weight (> 7%), we found 5 metabolites that had an increased 2.0x fold change in patients who gained > 7% weight: 3-hydroxyphenyl valeric acid, monoacylglycerol 16:0, oleamide, 2-piperidinone and bilirubin. We also found that 3 metabolites that had a decreased 2.0x fold change in patients who gained > 7% weight: L-urobin, 2-acetylpyrrolidine, and glycohyodeoxycholic acid.

Discussion: Using metabolomics to understand the pathophysiological mechanisms that underly the mental and physical symptoms of PSDs is a promising technique. Identifying early changes in metabolomic signatures may be able to help predict which patients with PSDs are prone to antipsychotic-induced weight gain and possibly clinical/functional outcomes. However, more research is needed to help identify these potential signatures.

W35. IMPACT OF LONGER DURATION OF ESKETAMINE NASAL SPRAY ON CHANGE IN DEPRESSION SYMPTOMS IN REAL-WORLD PATIENTS

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Abstract Background: Randomized controlled trials of esketamine nasal spray (ESK) for treatment resistant depression (TRD) have evaluated response rates after an induction regimen (8 treatments biweekly within 4 weeks).1 However, there is a paucity of data on real-world cumulative response rates over time beyond the induction phase for ESK.

Objectives: Our primary objective was to assess the real world clinical effectiveness of ESK based on changes from baseline in the Patient Health Questionnaire-9 (PHQ-9) scores. Our secondary objective was to assess the clinical effectiveness of ESK using other outcome measures including Beck's Depression Inventory II, Quick Inventory of Depressive Symptomatology–16, and Hamilton Rating Scale for Depression.

Methods: A retrospective longitudinal cohort analysis was conducted using Osmind's electronic health record-derived de-identified database who 1) received at least one ESK treatment, 2) were > 18 years of age at the start of treatment, 3) had a documented MDD diagnosis, and 4) had a documented depression rating scale at baseline (within 30 days prior to the first ESK treatment) and at least one depression rating scale after the start of treatment were

included. Primary analyses were conducted on a TRD ESK group who had documented prior treatment with at least two different antidepressants within two years of the start of ESK treatment. Sensitivity analyses were conducted on the All-comer ESK group, which included all patients meeting the above criteria, regardless of confirmation of at least two prior antidepressants.

Three analyses were performed for both cohorts. First, mixed effects models were used to evaluate the change in PHQ-9 score from baseline as a function of the number of treatments. Second, mixed effects logistic regressions were used to evaluate the probability that the patient was classified as a responder, defined as 50% reduction from baseline rating scale score. Third, survival analysis was used to evaluate the number of treatments to achieve initial response.

Results: Patients in both cohorts showed a consistent reduction in PHQ-9 scores that continued treatment beyond the initial maintenance phase (8-12 treatments). For the models of change in PHQ-9 score and probability of clinical response, the logarithmic model had the lowest Bayesian Information Criterion with a statistically significant effect of the number of treatments, suggesting improvement in depressive symptoms without relapse with continued ESK treatment. The median number of treatments to initial response was 12 for the TRD-ESK group and 10 for the All-comer ESK group, with response rates continuing to increase beyond those timepoints. The survival models predicted that 75% of the TRD-ESK group and 85% of the All-comer-ESK group eventually achieved initial response.

Conclusion: The results from all analyses indicate that longer duration of ESK treatment is associated with further improvements in depression symptoms. Our observation that the response rate continues to increase beyond the induction phase suggests that continuing ESK treatment yields added benefit for patients and is consistent with the findings of another real-world ESK study (Martinotti et al. 2022).

W36. N-METHYL-D-ASPARTATE RECEPTOR UNCOMPETITIVE ANTAGONISTS AND DEPRESSION, FROM PSYCHOPHARMACOLOGY AND PATHOLOGY TO PHYSIOLOGY: A UNIFYING HYPOTHESIS FOR THE EPIGENETIC CODE OF NEURAL PLASTICITY

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Abstract Background: Uncompetitive antagonists of the N-methyl-D-aspartate receptor (NMDAR) have emerged as antidepressants. NMDARs are central to neural plasticity. Incoming stimuli cause membrane potential changes in specialized receptor-cells, modulating their release of glutamate. Glutamate in the synaptic cleft activates glutamatergic receptors, including NMDARs expressed in the "hot spot", the 100-200 nm area of the membrane of second order neurons juxtaposed to presynaptic glutamate release. When in the open configuration (bound by glutamate and glycine) and free of Mg2+, NMDARs allow a subtype-specific time-controlled influx of Ca2+. The probability of Mg2+ disengagement from the NMDAR channel pore is determined α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor (AMPAR) glutamatergic-mediated depolarization. Influx of Ca2+ via NMDARs regulates the activation of enzymatic pathways in the post-synaptic density, leading to downstream events that balance stimulus-driven strengthening or weakening of synapses, also

defined as long term potentiation (LTP) and long-term depression (LTD). The activation of glutamatergic receptors is graded at resting membrane potential and massive at action potential. **Aim**: To advance the understanding of neural system physiology and pathology by integrating the discovery of the sustained antidepressant efficacy of NMDAR antagonists into the current knowledge of the central role of NMDARs in neural plasticity.

Methods: We performed a targeted literature review of the role of NMDARs and their uncompetitive antagonists in the physiology and pathology of neural plasticity and mood.

Results: Graded NMDAR Ca2+ currents at resting membrane potential regulate synaptic protein homeostasis. NMDAR uncompetitive antagonists modulate synaptic proteins and restore impaired neural plasticity in animal models. Learning induces NMDAR subunits changes. In the presence of Mg2+, uncompetitive NMDAR antagonists preferentially block activated GluN2D subtypes and these subtypes have the highest activation probability in the presence of low concentration ambient glutamate. GluN2D subtypes are activated by endogenous and exogenous NMDAR agonists and positive allosteric modulators. Uncompetitive NMDAR antagonists restore membrane expression of GluN1 subunits in an in vitro model of glutamatergic excitotoxicity.

Discussion: The primary function of the nervous system (NS) is to continuously form and modify the structure of functional circuits by preferential integration of external stimuli conducive to species-preserving prediction-based activities. Quanta of Ca2+ influx via NMDARs activate select downstream enzymatic pathways, instructing genes in control of synaptic protein homeostasis. Synaptic protein are the building blocks for the constant remodeling of the synaptic receptor framework, including AMPAR and NMDAR density and subtypes expressed at the synaptic hot spot. The constant stimulus-induced remodelling of the receptor framework at the synaptic hot spot allows integration of the flow of incoming stimuli by taking into account the molecular memory (remodelled synaptic framework) determined by prior stimuli. The molecular structure for regulating LTP and LTD is the synaptic receptor framework at the hot spot. Precisely regulated Ca2+ quanta via a continuously remodelled NMDAR framework may be the epigenetic code for neural plasticity by regulating the membrane expression of NS receptors, including NMDARs.

W37. THE ASSOCIATION BETWEEN ADHERENCE TO ESKETAMINE NASAL SPRAY THERAPY DOSING REGIMEN AND CHANGES IN DEPRESSIVE SYMPTOMS AMONG PATIENTS WITH TREATMENT-RESISTANT DEPRESSION IN THE UNITED STATES

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Abstract Background: Treatment-resistant depression (TRD) is characterized by inadequate response to ≥2 oral antidepressant therapies of adequate dose and duration during a major depressive episode (MDE). Esketamine nasal spray (ESK) was approved by the U.S. Food and Drug Administration in 2019 for the treatment of TRD in conjunction with an oral antidepressant. Reductions in depressive symptoms have been observed in patients treated with ESK (1,2). This real-world study evaluated the association between adherence to ESK dosing regimen and change in depressive symptoms among patients with TRD.

Methods: A retrospective observational cohort study of patients with TRD treated with ESK between March 2019 and June 2022 was conducted. Data were sourced from the PremiOMTM MDD Dataset (OM1, Boston, MA), a continuously updated cohort of over 440,000 patients with major depressive disorder (MDD) in the United States with linked claims and electronic medical record (EMR) data. TRD was defined as ≥1 diagnosis of MDD in the 6 months before or on the index date (first written or filled prescription for ESK) plus ≥2 unique antidepressants of adequate dose and duration any time before the index date within the same MDE (no gaps of ≥180 days between antidepressant treatments or MDD diagnoses). ESK therapy dates were identified using medical claims and review of unstructured clinical notes extracted from EMRs by expert abstractors. Patients who completed 6 or more sessions within 30 days from index date (first ESK therapy) were categorized as adherent. Depressive symptoms were assessed using available Patient Health Questionnaire-9 (PHQ-9) scores. Paired t-tests were performed between the latest PHQ-9 score after the induction phase but within the 0-3 and 3-6 months post-index and the latest PHQ-9 score available from the 6 months baseline period.

Results: There were 28 of 46 patients treated with ESK (60.9%) who were adherent and had a PHQ-9 score 0-3 months after index. The average PHQ-9 score at baseline was 18.0 for adherent ESK patients and 14.1 for non-adherent ESK patients. The average decrease in PHQ-9 scores among adherent ESK patients was 6.6 (95% CI: 3.6-9.6, $p < 0.001$, d=0.85) compared to an average decrease of 3.6 (95% CI: -0.1-7.2, p=0.057, d=0.48) among non-adherent ESK patients. There were 28 of 51 patients (54.9%) who were adherent and had a PHQ-9 score 3-6 months after index. The average PHQ-9 score at baseline was 16.7 among adherent ESK patients and 13.2 among non-adherent ESK patients. The average decrease in PHQ-9 scores among the adherent ESK patients was 7.1 (95% CI: 4.5-9.8, $p < 0.001$, d=1.05) compared to an average decrease of 4.1 (95% CI: 0.5-7.8, p=0.029, d=0.49) among non-adherent ESK patients.

Conclusions: Decreases in depressive symptoms were observed among all patients with TRD treated with ESK. The largest decreases were observed among patients who were adherent to ESK dosing regimen during the induction phase.

W38. PRELIMINARY DATA FROM THE CONNEX-X EXTENSION TRIAL EXAMINING THE LONG-TERM SAFETY OF ICLEPERTIN (BI 425809) IN PATIENTS WITH SCHIZOPHRENIA WHO COMPLETED PHASE III CONNEX TRIALS

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Abstract Background: Cognitive impairment associated with schizophrenia (CIAS) is an important unmet need as there are no effective treatments available. Iclepertin (BI 425809), a glycine transporter-1 inhibitor, has been shown to improve CIAS in Phase II trials, and Phase III trials are underway. The ongoing CONNEX-X extension study aims to collect additional safety data relating to iclepertin treatment in patients with CIAS.

Methods: CONNEX-X (NCT05211947/1346-0014) is a multinational, multicenter, open-label, single-arm extension study in patients with CIAS who completed 26 weeks of treatment (iclepertin 10 mg or placebo) in one of 3 Phase III CONNEX parent trials (NCT04846868/1346-0011, NCT04846881/1346-0012, NCT04860830/1346-0013). An estimated 1400 clinically stable outpatients will be treated (iclepertin 10 mg daily) for 1 year, irrespective of previous treatment (iclepertin/placebo). Patients are excluded if any of the following circumstances occur during the parent study and up to Visit 1 of CONNEX-X: suicidal behavior or ideation (type 5 on the Columbia-Suicide Severity Rating Scale), diagnosis with moderate/severe substance use disorder, diagnosis other than schizophrenia (according to Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition), development of any condition preventing participation, a hemoglobin level decrease (> 25% or <100g/L from baseline in parent trial) or hemoglobinopathies. The primary endpoint is the occurrence of treatment-emergent adverse events. The secondary endpoints include change from baseline (CfB) in Clinical Global Impressions-Severity (CGI-S) and CfB in hemoglobin. Further efficacy endpoints include CfB in MATRICS Consensus Cognitive Battery (MCCB) overall composite T-score, CfB in Schizophrenia Cognition Rating Scale total score and CfB in Virtual Reality Functional Capacity Assessment Tool (VRFCAT) total times.

Results: Currently, 460 patients have been enrolled and randomized from the parent trials with 0% screening failures (~80% roll-over rate, August 30, 2023). Current study status, including recruitment, screening failures and data collection experiences, are presented.

Conclusions: Patient enrollment rates from the CONNEX trials to the CONNEX-X open-label extension study remain stable at ~80%. CONNEX-X will allow the exploration of long-term safety, as well as descriptive analyses of cognitive and functional endpoints of iclepertin in the treatment of CIAS.

W39. HEALTHCARE RESOURCE UTILIZATION AND MEDICATION PATTERNS IN A REAL-WORLD DATASET OF PATIENTS WITH MAJOR DEPRESSIVE DISORDER

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Abstract Background: Pharmacogenomics (PGx)-guided treatment was associated with improved remission rates for patients with major depressive disorder (MDD) in multiple controlled trials. To evaluate potential impacts of real-world PGx testing, the current study characterized 1) prescription rates of medications with significant gene-drug interactions (GDI), 2) drug usage trends and 3) healthcare resource utilization (HRU) patterns within medication congruency groups in a dataset of patients with MDD pre- and post-PGx testing.

Methods: Combinatorial PGx test results were linked to data from the Optum Labs Data Warehouse, composed of de-identified administrative claims data for both commercially insured and Medicare Advantage enrollees. Patients were included in the study if they received PGx testing between January 1, 2015 and September 30, 2021, had an MDD diagnosis code, were age ≥18 years, and had continuous enrollment with both medical and pharmacy benefits ≥360-days prior to and ≥180-days after the PGx test result date. The PGx test report uses a

patient's genetic data to organize medications into categories: no known GDI (congruent), moderate GDI (congruent), or significant GDI (incongruent). Patients were considered as taking incongruent medications if any of their prescribed medications were incongruent. Patients were assigned to groups based on their medication congruency at 90 days pre- and post-PGx testing: no change, incongruent-to-congruent, and congruent-to-incongruent. Medication utilization patterns were also compared pre- and post-PGx testing. HRU (psychiatric hospitalizations) was compared in the 180 days pre- and post-PGx testing.

Results: A total of 20,933 patients met inclusion criteria (mean age=46 years, ~70% female), of whom 16,965 (81%) were prescribed medications in both the pre- and post-PGx testing periods. At pre- vs. post-PGx testing, 26.1% vs. 15.9% of patients, respectively, were taking medications with significant GDI. Pre- to post-PGx drug prescribing trends showed a 4.4% relative increase in antidepressant prescriptions, a small relative change in antipsychotic prescriptions (+0.6%) and an 8.4% relative decrease in benzodiazepine prescriptions. Following PGx testing, the number of patients with psychiatric hospitalizations was significantly reduced overall (39% relative decrease; $p < 0.001$), with the pattern of changes differing by congruency group; psychiatric hospitalizations were significantly reduced for those in the incongruent-to-congruent and no change in medication congruency groups (44% and 39% relative decrease, respectively; $p < 0.001$), but no significant change was observed in patients with congruent-to-incongruent medication switches.

Conclusions: MDD patients were less likely to have psychiatric-related hospitalizations after PGx testing. In addition, the 39% relative reduction in prescription of medications with significant GDI may suggest that PGx testing impacted treatment decisions. The observed decrease in benzodiazepine usage is hypothesized to be a function of prescribing more effective antidepressants post-PGx testing, resulting in improved symptom management and hence, a reduced need for benzodiazepines. These results suggest that PGx testing impacts treatment decisions and healthcare resource utilization in a real-world population.

W40. REAL-WORLD AXS-05 PATIENT CHARACTERISTICS IN MAJOR DEPRESSIVE DISORDER

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Abstract: Introduction: Major depressive disorder (MDD) is a highly prevalent and often chronic disorder associated with decreased quality of life and increased functional impairment, morbidity, and mortality. Patients with MDD are heterogenous in nature and treatment can vary based on differences in MDD presentation, patient characteristics, payer type, and physician preferences for antidepressant treatment (ADT) selection. Unfortunately, many patients do not adequately respond to initial ADTs and new options are needed to improve patient outcomes. AXS-05 (dextromethorphan-bupropion) is a novel, oral, N-methyl-D-aspartate (NMDA) receptor antagonist and sigma-1 receptor agonist recently approved (Aug 2022) by the US FDA for the treatment of MDD in adults. This is the first analysis that examines how AXS-05 is used in the real-world setting in the US.

Methods: Adult patients initiating AXS-05 in the Symphony IDV® databases (Aug 2017-Sept 2023) were identified with the first AXS-05 claim as the index date. All patients had continuous eligibility over the 12-month pre-index period and at least 1 MDD diagnosis (ICD-10-CM codes: F32.*, F33.*) over the 5-year pre-index period. Patient demographics and clinical characteristics (comorbidities and prior MDD-related medication use) were assessed during the 12-month pre-index period. AXS-05 initiation status (monotherapy vs combination therapy) was also examined.

Results: This study included 22,288 patients with MDD (mean age 45.1 years; 68.1% women) that were treated with AXS-05. All patients lived in the US, and most patients lived in the South (40.0%) and Midwest (30.8%), with 58.5% having commercial insurance, followed by Medicaid (17.9%), and Medicare (15.4%). The most common comorbidities were mental health disorders (53.5%; 47.6% had anxiety disorders), metabolic (26.4%), musculoskeletal/pain (22.6%), cardiovascular disorders (19.0%), and sleep disorders (18.4%). The last MDD-related treatment that was used prior to AXS-05 initiation comprised 22.4% SSRI (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, vilazodone, vortioxetine), 13.2% SNRI (desvenlafaxine, duloxetine, levomilnacipran, venlafaxine) and 12.8% NDRI (bupropion only) monotherapies; 294 (1.3%) patients were on esketamine. Overall, 83.7% of the patients had received treatment with SSRIs/SNRIs/NDRIs over the 12-month pre-index period; in particular, 54.9% used SSRIs, 40.4% used NDRIs, and 35.9% used SNRIs. Of note, 2.9% of patients utilized esketamine treatment. A total of 6,418 patients (28.8%) initiated AXS-05 as monotherapy vs 15,870 patients (71.2%) as an add-on; AXS-05 was most frequently combined with an SSRI alone (10.7%) or SNRI alone (6.5%). A total of 2,254 (10.1%) patients initiated AXS-05 without prior treatment in the 12-month pre-index period.

Conclusions: Using a large claims database in the US, this retrospective cohort study showed that 22,288 patients with MDD initiated AXS-05 within a year of its launch date with 10.1% of patients being treatment-naïve during the 12-month pre-index period and 28.8% initiating AXS-05 as monotherapy. Most of these patients had other mental health related comorbidities and attempted various MDD-related treatments prior to AXS-05 initiation, further emphasizing the need for alternative mechanisms of treatment.

W41. A PHASE 3, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY FOR BNC210, AN ALPHA7 NICOTINIC RECEPTOR NEGATIVE ALLOSTERIC MODULATOR, FOR THE ACUTE TREATMENT OF ANXIETY IN SOCIAL ANXIETY DISORDER (AFFIRM-1)

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Abstract: Social anxiety disorder (SAD) is one of the most common anxiety disorders. It is characterized by a persistent, intense fear of social and performance-related situations in which an individual is exposed to potential for scrutiny by others. SAD is associated with social, educational, and occupational impairment and considerable comorbidity with other psychiatric conditions, resulting in increased disability, dysfunction, and loss of productivity. SAD tends to be a chronic condition and rarely resolves without treatment.

BNC210 is a novel experimental alpha7 nicotinic negative allosteric modulator (NAM) in development for the treatment of psychiatric diseases, with a differentiated mode of action compared to current anti-anxiety therapeutics. BNC210 has demonstrated efficacy and evidence of biological activity in completed clinical trials in Generalized Anxiety Disorder (GAD) (Wise et al., 2020), panic attacks, and most recently, post-traumatic stress disorder (PTSD).

In a Phase 2 clinical trial, PREVAIL, single-dose, acute treatment with BNC210 (225 mg or 675 mg) in patients with moderate to severe SAD, the self-reported primary endpoint trended toward reduced elevation in anxiety with BNC210 compared to placebo measured as the average score during the performance phase of an anxiety-provoking public speaking challenge. Encouraging findings came from post hoc analyses, including a statistically significant reduction in overall anxiety levels measured as an area-under-the-curve analysis during the anticipation and performance phases of the challenge. These data support further evaluation of BNC210 in late-stage trials. A favorable safety profile for BNC210 was demonstrated. Further, in all studies conducted to date, there is no evidence of sedation, addiction liability (ARCI-based), cognitive or motor impairment (unlike benzodiazepines). Results of PREVAIL were first presented at the American Society of Clinical Psychopharmacology (ASCP) Annual Meeting in 2023 (Papapetropoulos et al. 2023).

The Phase 3 AFFIRM-1 study will enroll ~330 adult patients with at least moderate severity of SAD, randomized to receive a single dose of 225 mg BNC210 or placebo (1:1 ratio) 1-hour prior to a public speaking challenge. Because the 225 mg and 675 mg doses of BNC210 resulted in therapeutic responses of similar magnitude in PREVAIL, only the lower dose will be evaluated in Phase 3. As in the PREVAIL Phase 2 study, the Subjective Units of Distress Scale (SUDS, a VAS from 0-100 that measures the self-reported intensity of anxiety and/or distress) will be the primary outcome measure to capture the change from baseline to the average of the scores collected during the 5-minute performance phase of the speaking challenge. The 2-minute anticipation phase immediately prior to the performance phase will be evaluated as a secondary endpoint. Clinical and patient global impression scales (CGI and PGI) and the State-Trait Anxiety Inventory (STAI) will also be used for the secondary endpoints.

In conclusion, PREVAIL supported the potential of BNC210 as a safe and effective anxiolytic for acute "as-needed" treatment of anxiety in SAD patients, setting up an opportunity to evaluate BNC210 for this indication in Phase 3. The Phase 3 program including the study design for AFFIRM-1 (BNC210 dose, endpoints, and participant characteristics) received support from FDA during an End-of-Phase 2 meeting.

W42. INVESTIGATING VIRAL INVOLVEMENT IN SCHIZOPHRENIA

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Abstract Background: There has been no systematic approach yet to examine viral involvement in schizophrenia, an illness that affects over 24 million people worldwide, despite signs of inflammation both in the brain and periphery. Genetic studies have identified several markers in immune-related regions that are associated with schizophrenia, suggesting that immune pathways contribute to the genetic risk of developing the disorder. Postmortem brain

studies have also found elevated antiviral gene expression in multiple brain regions of people with schizophrenia (PwS). Capturing a comprehensive viral landscape and examining the difference in viral burden between PwS and non-psychiatric comparison subjects (NCs) will fundamentally advance our knowledge of the disorder, offering fresh insight into its pathogenesis and potential individualized treatment approaches.
Methods: Using new methodology to detect evidence of latent viral infections, we propose to capture viral nucleic acids from postmortem brains of PwS to identify novel potential treatment targets. We will examine fresh frozen postmortem brain samples obtained from the NIH NeuroBioBank from the prefrontal cortex, a region reported to have increased antiviral gene expression in PwS. To detect and quantify viral DNA and RNA in these samples, this project will use the ViroFind protocol developed in the Koralnik Lab at Northwestern University.**Results:** We collected 30 postmortem brain samples from PwS and NCs, along with 30 placental samples to use for optimization of the protocol, given easier accessibility and possible viral exposure as early as in utero. We expect viral presence and diversity to be increased in a subset of PwS compared to NCs, just as they may be increased in placentas with perinatal complications (intrauterine growth restriction or IUGR, and pre-eclampsia) compared to normal placentas. In a limited subset of placentas analyzed thus far (n = 8), we did not detect differences in viral burden between IUGR and normal placentas, but we were able to adapt the protocol to the manufacturer's newly designed kit, maximize nucleic acid yields, and set up quality control measures. In doing so, we discovered a likely contaminant in our initial run of the ViroFind protocol that could invalidate future results. Once the protocol is adjusted to minimize this contamination risk with the remaining placental samples, we anticipate that viral burden in the brain samples will directly correlate with levels of plasma inflammatory biomarkers, allowing for future grouping of PwS by individual inflammatory profile.

Conclusions: Being able to identify the presence of virus by correlating it with markers of inflammation in the periphery will offer an invaluable tool to aid in diagnosis, stratification, and potential treatment of PwS. This is a critical first step in developing novel treatments for schizophrenia that focus on viral infection and immune response.

W43. LITHIUM INTOXICATION FOLLOWING GASTRIC BALLOON BARIATRIC PROCEDURE: A CASE REPORT

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Abstract: Introduction: Obesity has become an epidemic in the United States, with a significant prevalence increase over the past two decades, often coexisting with psychiatric disorders. This public health crisis has prompted various medical interventions, including bariatric surgery, when lifestyle modifications prove ineffective. This case highlights the importance of understanding how non-surgical bariatric procedure alters drug pharmacokinetics, particularly in lithium, a medication with a narrow therapeutic range.
Case Summary: Mrs. L is a 69-year-old Hispanic woman diagnosed with schizoaffective disorder, who has effectively sustained stability through a decade-long course of lithium treatment. Patient is on multiple prescribed medications including antihypertensives and antacids. Mrs. L went to the emergency department with an altered mental state persisting for five days. Initially, she had distressing gastrointestinal symptoms, which rapidly progressed to

neurological effects. Remarkably stable on lithium for a decade with no recent medication changes, Mrs. L experienced severe lithium intoxication just six days after a non-surgical intragastric balloon bariatric procedure. Physical exam positive for bilateral upper extremities, tremors, dysarthria, dysmetria, ataxia. EKG, Head CT scan, Brain MRI, and EEG were unremarkable. Laboratory findings were notable for elevated serum lithium levels, electrolyte imbalance, leukocytosis, and nephrotoxicity requiring hemodialysis. The patient received immediate medical care and multidisciplinary treatment, achieving baseline clinical stability and discharge after nine days without neurological sequelae.

Discussion: The challenges concerning psychopharmacology after bariatric surgery encompass the potential for lithium toxicity due to changes in metabolism and absorption. The altered gastrointestinal anatomy of the patient after procedure can result in substantial changes in the pharmacokinetics of drug absorption. Physiological changes induced by the intragastric balloon, such as reduced stomach volume, early satiety, delayed gastric emptying, and altered gastric pH, can substantially impact the pharmacokinetics of drug absorption, potentially affecting the disintegration and dissolution of lithium tablets. Lithium is efficiently absorbed from the gastrointestinal tract, reaching peak plasma concentrations in 2 to 4 hours following oral intake.

Another identified risk factor is the concurrent use of medications that interact with lithium, such as diuretics, NSAIDs and ACEIs. For instance, ACEIs may decrease the glomerular filtration rate, impacting lithium clearance. When it comes to lithium, it's narrow therapeutic range and reliance on kidney function, even minor decreases in renal function could lead to toxicity. Lithium's renal pathway closely mimics sodium, meaning that dehydration or gastrointestinal fluid loss may result in rapid reabsorption.

Conclusion: Recognizing the potential for lithium toxicity, healthcare providers must appropriately adjust dosages. It is important to offer comprehensive patient education regarding the potential influence of bariatric surgery on lithium therapy. Obese patients considering bariatric procedures should discuss risks, benefits, diagnosis, treatment, and outcomes before interventions. We aspire for this case to contribute to the promotion of awareness and the development of guidelines for administering lithium treatment in patients undergoing bariatric procedures.

W44. THE EFFECT OF PSYCHEDELICS ON INDIVIDUALS WITH A PERSONALITY DISORDER: A PROSPECTIVE COHORT ANALYSIS

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Abstract Background: Personality disorders (PDs) are characterized by impairments in psychological functioning. Pharmacologic treatments for PDs are limited and demonstrate limited efficacy. Psychedelics may offer a unique opportunity for potential PD treatment, considering their enduring positive effects on psychological functioning and personality. However, there are limited studies examining the effects of psychedelics on individuals with PDs and there are safety concerns that commonly lead to exclusion of this population from

psychedelic research. Therefore, this study examined the effects of psychedelic use on mental health outcomes among individuals with PDs.

Methods: Data were used from two different studies. Study 1 included three prospective observational studies in which 24 individuals with PD diagnosis completed mental health measures (depressive symptoms, anxiety, suicidal ideation [SI], and well-being) before, 2 weeks (except SI) and 4 weeks after psychedelic use. Study 2 included a prospective observational study, where 55 individuals with a PD diagnosis completed mental health measures (depressive symptoms, well-being, cognitive flexibility, and emotion regulation) at before, 2-4 weeks, and 2-3 months after psychedelic use.

Results: Following psychedelic use, anxiety and depression symptoms significantly reduced post-psychedelic use in Study 1 (4 weeks: $t(14)=3.12$, $p=.008$, Hedges' $g= -.46$, and $t(13)=2.26$, $p=0.042$, Hedges' $g=-0.59$, respectively) and Study 2 (2-3 months: $t(25)=4.50$, $p=.0001$, $g= -0.89$, and $z=.29$, $p < .0001$, $r(s)=.71$ respectively). SI reduced significantly at 4 weeks ($t[16]=2.38$, $p < 0.001$, $g=0.52$; Study 1). Elevations in SI were rare (5.88%) with no elevations to high risk of suicidal behavior post-psychedelic use. All participants with high baseline risk of suicidal behavior (11.7%) were at low-risk post-psychedelic use. There were transiently significant increases in well-being at 2 weeks ($t[19]=2.30$, $p=0.033$, $g=0.38$; Study 1) and cognitive flexibility at 2-4 weeks ($t[51]=2.37$, $p=0.021$, $g=.26$; Study 2). There were sustained increases in cognitive reappraisal until 2-3 months post-psilocybin use ($t[26]=2.07$, $p=.049$, $g=.36$; Study 2).

Conclusion: For individuals with PDs, psychedelic use was associated with improvements in psychological functioning: depression, anxiety, SI, well-being, cognitive flexibility, and cognitive reappraisal. Elevations in SI were rare and not clinically significant. Further research, including larger clinical samples and controlled trials, remains necessary to evaluate the effects of psychedelic use and psychedelic therapy among individuals with diagnosed PDs.

W45. TSND-201 (METHYLONE) FOR THE TREATMENT FOR PTSD: IMPROVEMENT IN SLEEP-RELATED OUTCOMES FROM THE OPEN- LABEL PORTION OF THE IMPACT-1 STUDY

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Abstract Background: PTSD is a debilitating psychiatric illness affecting approximately 12 million adults in the US each year. Sleep disturbances with PTSD are common and typically include insomnia and nightmares. Poor sleep can worsen PTSD and result in additional health problems such as heart disease, high blood pressure, obesity, substance abuse, and stroke. Nightmares are often resistant to PTSD treatment and have been linked with a five-fold increase in suicidality; however, nightmares are often overlooked as a secondary symptom of PTSD. Existing medications (e.g., prazosin) have shown mixed results for treating nightmares, highlighting the need for new pharmacological options. Novel compounds with rapid and sustained therapeutic benefits may be clinically useful and more accessible to patients, compared to classical psychedelics. Methylone is a non-hallucinogenic, rapid-acting

neuroplastogen and the beta-ketone analog of MDMA. Both methylone and MDMA target monoamine transporters, but differences in affinity and a lack of off-target effects (vs. MDMA) produce distinctive pharmacological and subjective effects. In preclinical studies, methylone has demonstrated significant benefit in a model of PTSD as well as fast-acting, robust, and long-lasting anxiolytic and antidepressant-like activity. As such, methylone is currently being developed as a potential treatment for PTSD.

Methods: The IMPACT-1 study is a multi-center, two-part clinical trial. Part A has completed and was an open-label evaluation involving 14 participants with PTSD. Eligible participants were adults with severe PTSD (CAPS-5 ≥ 35) who had failed at least 1 prior treatment for PTSD.

Participants were treated with 4 doses of TSND-201 (methylone) given once a week for 4 weeks. Following the 4-week treatment period, participants were followed for an additional 6 weeks to evaluate the durability of the therapeutic effect. Sleep-related improvements were evaluated on the CAPS-5 (including distressing dreams [item B2; scores range 0 to 4] and sleep disturbances [item E6; scores range 0 to 4]), the Pittsburg Sleep Quality Index (PSQI; total scores range 0 to 21) and subscales, and the reduced sleep item of the Montgomery-Åsberg Depression Rating Scale (MADRS; scores range 0 to 6).

Results: On the CAPS-5 total severity score, treatment with TSND-201 resulted in rapid, robust, and durable improvements. At baseline on the CAPS-5, all participants had clinically significant Sleep Disturbances (item E6; mean score=3.3) and 79% had Distressing Dreams (item B2; mean score=2.2). After treatment with methylone, mean scores on Sleep Disturbances and Distressing Dreams decreased to 0.92 and 0.38, respectively, with absence of the symptom in 62% and 77% of participants, respectively. On the MADRS, Reduced Sleep at baseline was a mean of 4.3 points. After treatment with methylone, the mean score on Reduced Sleep was 1.08, with absence of the symptom in 62% of participants. On the PSQI, mean total scores at baseline were 13.5, indicating severe sleep disturbance. At the end of study (6 weeks after the last dose), PSQI total score improved by -4.0 points (mean score = 9.4). Similar improvements were seen on the PSQI subscales (e.g., sleep latency, disturbance, quality). Methylone was generally safe and well tolerated.

Conclusion: Treatment with TSND-201 demonstrated rapid, robust, and durable effects on both PTSD symptoms and sleep related outcomes across multiple domains. This study supports further development of TSND-201 as a treatment for PTSD. Part B of IMPACT-1; a randomized, placebo-controlled study, is currently ongoing.

W46. DETERMINING THE EXPOSURE-RESPONSE RELATIONSHIP BETWEEN ARIPIPRAZOLE ONCE-MONTHLY PLASMA CONCENTRATIONS AND TIME TO RECURRENCE OF MOOD EPISODES IN PATIENTS DIAGNOSED WITH BIPOLAR I DISORDER

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Abstract: A Phase 3 study (NCT01567527) of aripiprazole once-monthly 400 mg (AOM 400) in adult patients diagnosed with bipolar I disorder (BP-I) was conducted. The study involved 4 phases: 1) a transition onto oral aripiprazole, 2) an oral aripiprazole stabilization phase, 3) a single-blind AOM 400 stabilization phase, and 4) a randomized, double-blind placebo-controlled phase.

The purposes of these analyses were to 1) verify if the previously developed population pharmacokinetic (PK) model for AOM was able to adequately predict individual plasma concentrations for patients diagnosed with BP-I (data from Phases C and D; n=420) following administration of AOM 400, and 2) develop an exposure-response (E-R) model to characterize the relationship between predicted aripiprazole exposure and time from randomization to recurrence of any mood episode (data from Phase D; n=265).

To achieve the first objective, the previously developed population PK model was applied (all parameter values fixed to the previous values) to the data from patients diagnosed with BP-I. A quantitative predictive performance assessment was performed by calculating the percent prediction error (PE%) as a measure of accuracy of the predicted concentrations (PRED) and the absolute value of PE% (|PE%|) as a measure of bias of the PRED. A prediction-corrected visual predictive check (pcVPC) was also generated as a qualitative assessment of the model. The median PE% was -10% and the |PE%| was 35% for 1,907 plasma concentrations collected after steady-state in Phases C and D of the study. The median PE% was -2% and the |PE%| was 32% for 588 plasma concentrations collected in Phase D of the study. The results of the pcVPC indicate that the previous PK model predicted the plasma concentrations and the variability of the plasma concentrations well during Phase D of the study.

To achieve the second objective, a Cox proportional hazards model was developed to describe the E-R relationship between predicted aripiprazole exposure and time from randomization to recurrence of any mood episode. The E-R model was a Cox proportional hazards model including the effect of model-predicted aripiprazole plasma concentration 672 hours (Ctau) following the first dose of AOM 400 in Phase D of the study as a linear function. None of the tested covariates (age, sex, baseline body mass index [BMI], race, baseline Montgomery-Asberg Despresson Rating Scale [MADRS] total score, or baseline Young Mania Rating Scale [YMRS] total score) had a statistically significant effect on the risk of recurrence of any mood episode. A significant E-R relationship was established for patients diagnosed with BP-I, whereby higher aripiprazole Ctau was associated with a lower risk of recurrence of any mood episode. For patients diagnosed with BP-I and model-predicted aripiprazole Ctau ≥ 95 ng/mL, the predicted hazard for recurrence of any mood episode was decreased by 36% or 1.55-fold compared to < 95 ng/mL of aripiprazole exposure.

In summary, 1) the previous aripiprazole population PK model and parameter estimates accurately predicted the observed plasma concentrations for aripiprazole in patients diagnosed with BP-I, and 2) a significant E-R relationship was found for patients diagnosed with BP-I, whereby higher aripiprazole pre-dose plasma concentrations ≥ 95 ng/mL resulted in a 36% reduced risk of recurrence of any mood episode.

W47. CLINICAL PROFILE OF AXS-05 (DEXTROMETHORPHAN-BUPROPION) IN TREATING ALZHEIMER'S DISEASE AGITATION (ADA): RESULTS FROM THE PHASE 2/3 DEVELOPMENT PROGRAM

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Abstract: Introduction: Patients with Alzheimer's disease (AD) often experience burdensome neuropsychiatric symptoms. Agitation is common in AD (70%), occurring in both home and long-term care (LTC) facilities and is associated with substantial increases in caregiver burden and LTC placements. Brexpiprazole, an atypical antipsychotic, is the only treatment approved for ADA; however, it is associated with somnolence, weight gain, and extrapyramidal symptoms including akathisia. AXS-05 (45-mg dextromethorphan/105-mg bupropion) is a novel, oral NMDA receptor antagonist and sigma-1 receptor agonist, approved by the FDA for major depressive disorder, and is being investigated for treatment of ADA. The safety and efficacy of AXS-05 was evaluated in 2 randomized, double-blind, controlled clinical studies, as part of the AXS-05 ADA clinical development program: the Phase 2 ADVANCE-1 (NCT03226522) and the Phase 3 ACCORD (NCT04797715) studies.

Methods: ADVANCE-1 and ACCORD enrolled patients (65-90 years old) with a diagnosis of probable AD, using 2011 NIA-AA criteria. ADVANCE-1 evaluated the acute effects of AXS-05 on improving ADA. In this study, patients were randomized 1:1:1 for 5 weeks to receive either AXS-05, bupropion (105 mg), or matching placebo. The primary endpoint was change from baseline in the Cohen-Mansfield Agitation Inventory (CMAI) total score. ACCORD evaluated the effects of AXS-05 in preventing relapse of ADA using a randomized discontinuation design. It comprised an open-label period (OLP; ≤9 weeks) where all patients received AXS-05 until they showed a sustained response (≥30% improvement from baseline in the CMAI total score and improvement on the PGI-C score ≤3, both maintained for ≥4 consecutive weeks). In the double-blind period (DBP), patients were randomized 1:1 to receive either AXS-05 or placebo for up to 26 weeks in the DBP or until relapse. The primary endpoint was time to relapse.

Results: Baseline demographic and clinical characteristics were generally similar between groups in both studies. ADVANCE-1 comprised 357 patients in the modified intent-to-treat population: AXS-05 (n=152) bupropion (n=49), placebo (n=156) (mean baseline CMAI total scores=60.7, 66.1, 59.4, respectively). At Week 5, AXS-05 significantly reduced CMAI total score by 15.4 points compared with bupropion (10.0 points; $P < .001$) and placebo (11.5 points; P=.010). In ADVANCE-1, common adverse events (AEs; ≥3%) included somnolence (8.2%), dizziness (6.3%), and diarrhea (4.4%). ACCORD comprised 178 patients in the OLP (mean CMAI=70.9) and 108 patients in the DBP (AXS-05, n=53; placebo, n=55) (mean CMAI=43.7). In the DBP, AXS-05 significantly increased time-to-relapse compared with placebo (hazard ratio=0.275; P=.014); the risk of relapse was 3.6-fold lower with AXS-05 compared with placebo. AXS-05 significantly reduced relapse rates compared with placebo (7.5% vs 25.9%; $P < .05$). In ACCORD, common AEs (≥3%) included dizziness (9.6%), diarrhea (4.5%), and fall (5.1%). AXS-05 was also not associated with cognitive impairment or sedation in either study.

Conclusions: AXS-05 was associated with a substantial, rapid reduction in ADA compared with controls after 5 weeks of treatment. In longer-term treatment, AXS-05 significantly increased the time to relapse of ADA and reduced the risk of relapse. AXS-05 was generally well tolerated across studies, further supporting the continued development of AXS-05 that may be a promising treatment option for ADA.

W48. ASSESSMENT OF PATIENT-REPORTED DEPRESSION SEVERITY IN SUBPOPULATION OF ESCAPE-TRD STUDY: ESKETAMINE NASAL SPRAY VERSUS QUETIAPINE FOR TREATMENT-RESISTANT DEPRESSION

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Abstract Background: In treatment-resistant depression (TRD), commonly defined as an inadequate response to two or more consecutive antidepressant treatments in the current depressive episode, the proportion of patients achieving remission is low when they are treated with typical antidepressants (SSRI or SNRI) alone. In ESCAPE-TRD, an open-label, rater-blinded, phase 3b, randomized, active-controlled 32-week trial, patients were assigned, in a 1:1 ratio, to receive flexible doses of esketamine nasal spray (NS) or extended-release (XR) quetiapine, both in combination with an SSRI or SNRI. While the clinician-rated Montgomery–Asberg Depression Rating Scale (MADRS) score at week 8 was the primary endpoint of ESCAPE-TRD, the patient-rated Patient Health Questionnaire-9 (PHQ-9) score was a secondary endpoint that provides a complementary view of patients' experience of their disease and treatment outcomes.

Methods: This subgroup analysis of the ESCAPE-TRD population included adults who received treatment according to U.S. prescribing information and focused on PHQ-9 ratings. Remission was defined as a PHQ-9 score of less than 5, at week 8 (scores range from 0 to 27, with higher scores indicating more severe depression). Other measures include response, defined as a 50% improvement in PHQ-9 score from baseline or a PHQ-9 score of less than 5, at week 8, response/remission at week 32, times to first remission, time to first response, time to confirmed remission, time to confirmed response, and mean change in PHQ-9 score from baseline to week 32. Patients discontinuing study treatment without having reached response/remission were assumed to never achieve response/remission for all analyses except for mean change in PHQ-9 score from baseline (imputed last observation carried forward).

Results: Among 636 patients in this subgroup analysis 316 patients were assigned to the esketamine group and 320 to the quetiapine group. A significantly higher proportion of patients in the esketamine group than in the quetiapine group achieved remission at week 8 (61/316 patients [19.3%] vs. 39/320 patients [12.2%]; RD [95% CI]: 7.1% [1.5%, 12.8%]; p=0.0134) and response at week 8 (156/316 patients [49.4%] vs. 105/320 patients [32.8%]; RD [95% CI]:16.6% [9.0%, 24.1%]; $p < 0.0001$). At 32 weeks, more patients in the esketamine group achieved remission and response compared to the quetiapine group (remission: 110/316 patients [34.8%] vs. 58/320 patients [18.1%], RD [95% CI]: 16.7% [9.9%, 23.4%]; $p < 0.0001$; response: 186/316 patients [58.9%] vs. 129/320 patients [40.3%], RD [95% CI]:18.5% [10.9%, 26.2%]; $p < 0.0001$). Patients in the esketamine group were more likely to achieve first remission (HR: 1.9; $p < 0.0001$), first response (HR: 1.7; $p < 0.0001$), confirmed remission (HR: 1.7; $p < 0.0001$), and confirmed response (HR: 1.7; $p < 0.0001$). The mean change in PHQ-9 score from baseline to 32 weeks (-10.2 vs. -8.0) favored esketamine NS ($p < 0.001$) (difference of LS means [95% CI]: -1.9 [-2.9, -1.0]; $p < 0.001$).

Conclusion: Using the patient-reported PHQ-9 data, esketamine NS significantly increased the proportion of patients achieving remission and response at 8 and 32 weeks, and shortened

time to remission and response vs. quetiapine XR in the subgroup. The findings were consistent with the overall study population. (Funded by Janssen EMEA; ESCAPE-TRD ClinicalTrials.gov number, NCT04338321)

W49. LUMATEPERONE IN THE TREATMENT OF PATIENTS WITH MAJOR DEPRESSIVE DISORDER AND BIPOLAR DISORDER WITH ANXIOUS DISTRESS AND MIXED FEATURES

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Abstract Background: Anxious distress and mixed features are DSM-5 episode specifiers for major depressive episodes (MDE) associated with major depressive disorder (MDD) and bipolar disorder. Patients with depressive episodes with the specifiers have more severe symptoms, more comorbidities, increased suicide risk, and poorer treatment response than patients without the specifiers.

Lumateperone is an FDA-approved antipsychotic indicated to treat schizophrenia and depressive episodes associated with bipolar I or bipolar II disorder. In a randomized, double-blind, placebo-controlled trial (Study 403; NCT04285515) lumateperone 42mg was efficacious over placebo with a favorable safety profile in patients with MDD or bipolar depression (BPD) with mixed features. This post hoc analysis of Study 403 investigated efficacy of lumateperone 42mg in patients with MDD or BPD with mixed features and anxious distress.

Methods: Eligible adults (18-75 years) met DSM-5 criteria for an MDE with mixed features and had MDD, bipolar I, or bipolar II disorder, with Montgomery-Åsberg Depression Rating Scale (MADRS) Total score ≥24 and Clinical Global Impression Scale-Severity (CGI-S) score ≥4. Patients were stratified by MDD or bipolar disorder diagnosis and randomized 1:1 to 6-weeks lumateperone 42mg or placebo. This analysis evaluated patients with mixed features and DSM-5 anxious distress in the overall population (combined MDD/BPD) and separately in MDD and BPD individual populations. Assessments included change from baseline in MADRS Total score, CGI-S score, and MADRS inner tension item score.

Results: Of 383 patients in the combined MDD/BPD modified intent to treat (mITT) population with mixed features, 244 (63.7% of mITT; placebo, 121; lumateperone, 123) had anxious distress. Anxious distress was common in patients with MDD (73.9% of MDD mITT; placebo, 69; lumateperone, 67) and BPD (54.3% of BPD mITT; placebo, 52; lumateperone, 56).

Compared with placebo, lumateperone significantly improved change from baseline for MADRS Total score at Day 43 in all 3 populations with anxious distress: combined MDD/BPD population (least squares mean difference vs placebo [LSMD], −6.1; 95% CI −8.52 to −3.71; effect size [ES], −0.67; $P < .0001$), MDD individual population (LSMD, −6.8; 95% CI −9.82 to −3.77; ES, −0.79; $P < .0001$), and BPD individual population (LSMD, −5.5; 95% CI −9.34 to −1.62; ES, −0.59; $P < .01$). In all 3 populations, significantly greater ($P < .05$) reductions in change from baseline of MADRS Total score occurred by Day 15 and persisted throughout the study in lumateperone-treated patients.

Similarly, lumateperone significantly improved change from baseline for CGI-S score at Day 43 vs placebo for patients with anxious distress in the combined MDD/BPD population

(LSMD, −0.5; 95% CI −0.78 to −0.26; ES, −0.54; P < .0001), MDD individual population (LSMD, −0.6; 95% CI −0.98 to −0.30; ES, −0.66; P < .001), and BPD individual population (LSMD, −0.4; 95% CI −0.82 to −0.05; ES, −0.48; P < .05). Lumateperone also significantly improved change from baseline for the inner tension MADRS single-item score at Day 43 compared with placebo for all 3 populations (P < .05).

Conclusion: Lumateperone 42mg demonstrated efficacy in improving symptoms of major depression with mixed features and anxious distress, including global disease severity and inner tension, in patients with MDD or bipolar disorder.

W50. DOSING TO EFFECT WITH SUBCUTANEOUS AND SUBLINGUAL BUPRENORPHINE FOR OPIOID USE DISORDER

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Abstract: Introduction: CAM2038 is a subcutaneous (SC) buprenorphine (BPN) depot shown to be efficacious in the treatment of OUD. Compared to sublingual (SL) BPN, CAM2038 has been associated with superior reduction of illicit opioid use, and non-inferior likelihood of being a treatment responder. A range of doses are available for CAM2038 and SL BPN, allowing for flexible dosing to address individual treatment needs. Further research is needed to understand the association of BPN dose with treatment outcomes. The aim of this post-hoc analysis was to assess whether dose of CAM2038 and SL BPN was associated with treatment outcomes.

Methods: This was a post-hoc analysis of a phase 3, 24-week, randomized, double-blind, double-dummy, active-controlled, multicenter trial. Adults with moderate-to-severe OUD were randomized to receive CAM2038 and daily SL placebo (PBO) or SC PBO injections and daily SL BPN/naloxone (NX). CAM2038 or PBO injections were given weekly for 12 weeks then monthly for 12 weeks.

Doses were individualized per clinical judgement based on practice guidelines. The effect of each dose given was evaluated at the end of that dosing interval by examining four outcomes: 1) urine drug screen (UDS); 2) Clinical Opiate Withdrawal Scale (COWS); 3) Subjective Opiate Withdrawal Scale (SOWS); 4) need- and desire-to-use opioid visual analog scale (VAS, 0–100). UDS results (mean percentage of opioid negative urine samples; missing samples imputed as positive) and mean COWS, SOWS and VAS scores were calculated for weeks 5–24. Associations between dose and outcomes were assessed by descriptive statistics.

Results: No association of dose with percentage of negative UDS was identified for either weekly CAM2038 (16 mg, n=9: 76.4%; 24 mg, n=99: 47.0%; 32 mg, n=74: 53.4%), monthly CAM2038 (64 mg, n=9: 55.6%; 96 mg, n=75: 52.0%; 128 mg, n=63: 57.9%; 160 mg, n=7: 57.1%), or SL BPN (8 mg, n=4: 87.5%; 16 mg, n=83: 34.9%; 24 mg, n=161: 36.6%; 32 mg, n=84: 39.9%). No clinically significant differences were observed in mean COWS scores across different doses for weekly CAM2038 (16 mg, n=9: 2.0; 24 mg, n=100: 2.1; 32 mg, n=76: 3.0), monthly CAM2038 (64 mg, n=11: 0.5; 96 mg, n=77: 2.0; 128 mg, n=63: 2.7; 160 mg, n=9: 3.9), or SL BPN (8 mg, n=4: 0.4; 16 mg, n=85: 2.1; 24 mg, n=168: 2.5; 32 mg, n=85:

3.1). These scores were reduced from a mean of 12 at baseline for CAM2038 and SL BPN/NX. The previous n values reported for COWS scores apply for all subsequent outcomes. Increasing dose was not associated with any clinically significant differences in mean SOWS scores for weekly CAM2038 (16 mg: 4.3; 24 mg: 5.0; 32 mg: 8.3), monthly CAM2038 (64 mg: 1.3; 96 mg: 4.7; 128 mg: 7.3; 160 mg: 10.2), or SL BPN (8 mg: 0.1; 16 mg: 5.1; 24 mg: 6.0; 32 mg: 7.0). These scores were reduced from a mean of 32 and 31 at baseline for CAM2038 and SL BPN/NX, respectively. Mean need-to-use opioid VAS scores did not show any clinically significant differences across different doses for weekly CAM2038 (16 mg: 2.9; 24 mg: 12.2; 32 mg: 16.7), monthly CAM2038 (64 mg: 3.8; 96 mg: 8.9; 128 mg: 16.1; 160 mg: 36.0), or SL BPN (8 mg: 1.7; 16 mg: 12.7; 24 mg: 14.4; 32 mg: 20.0). There were also no clinically significant differences observed in mean desire-to-use opioid VAS scores with increasing dose for weekly CAM2038 (16 mg: 4.9; 16 mg: 15.5; 24 mg: 19.8), monthly CAM2038 (64 mg: 2.8; 96 mg: 10.3; 128 mg: 19.0; 160 mg: 32.7) or SL BPN (8 mg: 1.7; 16 mg: 13.1; 24 mg: 16.1; 32 mg: 22.2).

Conclusion: Although higher rates of negative UDS were observed with CAM2038 than SL BPN, efficacy was observed across all doses of CAM2038 and SL BPN. No apparent association of dose with outcomes (negative UDS, withdrawal, and craving) was identified after titrating dose to effect. Our findings support individualization of OUD treatment to clinical effect.

W51. FUNCTIONAL REMISSION AFTER A SINGLE ADMINISTRATION OF COMP360 PSILOCYBIN TREATMENT FOR TREATMENT-RESISTANT DEPRESSION

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Abstract Background and Objective: Treatment-resistant depression (TRD) is associated with poorer long-term outcomes than non-resistant depression, including poorer functioning. Functioning has been identified as an outcome of importance to patients with depression, but improvements often lag behind symptomatic change. Here, we assess the proportion of TRD patients reaching functional remission following a single administration of COMP360 (Compass Pathways' proprietary pharmaceutical-grade synthetic investigational psilocybin formulation), delivered with psychological support. We descriptively characterize this group according to change in depressive symptoms and improvements in quality of life.

Methods: TRD participants were randomized to a single administration of COMP360 25mg (n=79), 10mg (n=75) or 1mg (n=79) monotherapy with psychological support and followed up over 12 weeks. Change in depression severity was assessed with the Montgomery-Åsberg Depression Rating Scale (MADRS) and functioning was assessed using the Sheehan Disability Scale (SDS). Quality of life was assessed via the EQ-5D-3L which consists of 2 parts, generating a utility score and a visual analogue scale (EQ-VAS) score. The present analyses include post-hoc EQ-VAS scores only. Functional remission was defined as a score of ≤2 on each of the work/school, social life, and family life/home responsibilities items on the SDS. SDS items are scored from 0 to 10.

Results: The proportion of functional remitters was higher in the 25mg group than in the 10mg and 1mg groups at week 3 (n=18 [31.0%], n=5 [9.3%] and n=5 [10.0%] and at week 12 (n=19

[30.2%], n=10 [17.5%], and n=9 [18.4%]). For the 25mg group, 88.9% of week 3 functional remitters met criteria for MADRS remission (score ≤10) at the same timepoint, as did 89.5% of week 12 functional remitters. 78.9% of functional remitters at week 12 in the 25mg group also met criteria for sustained response according to the MADRS (≥50% reduction in total score at all assessments from week 3 to week 12). The mean (standard deviation [SD]) EQ-VAS score at week 12 was 78.7 (15.48) for week 12 functional remitters in the 25mg group, representing a mean (SD) change from baseline of 19.0 (17.10) points.

Conclusions: The number of patients meeting functional remission criteria following a single administration of COMP360 treatment was greatest for the 25mg group, with a similar proportion meeting criteria at week 3 as at week 12. The majority of functional remitters in the 25mg group also met MADRS remission and sustained response criteria and improvements in perceived health related quality of life were reported. These are promising findings, particularly given the treatment resistant nature of this population and single administration study design. The potential for relatively rapid functional, as well as depressive, symptom remission following COMP360 treatment for TRD will be further explored in future studies.

W52. CHARACTERIZING THE SAFETY PROFILE OF KARXT RELATIVE TO ANTICIPATED D2-DOPAMINE-BASED ANTIPSYCHOTIC MEDICATIONS IN FAERS

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Abstract Background: KarXT is a novel investigational antipsychotic treatment that pairs xanomeline and trospium chloride. In the acute efficacy trials within our EMERGENT program, EMERGENT-1, 2 and 3 (randomized, double-blind, placebo-controlled, 5-week inpatient trials in patients with schizophrenia experiencing acute psychosis) showed KarXT significantly reduced PANSS scores compared to placebo in schizophrenia. However, unlike approved antipsychotic drugs, KarXT is an M1 /M4 preferring central muscarinic receptor agonist and likely has a different side-effect profile compared to traditional D2-receptor antagonists. Here we use a previously published methodology from the literature to compare KarXT clinical trial data to real-world pharmacovigilance data from established antipsychotics already on the market.

Methods: Adverse event (AE) data from EMERGENT-1 (NCT03697252), EMERGENT-2 (NCT04659161), and EMERGENT-3 (NCT04738123) were pooled across participants assigned to KarXT (N=340) or placebo (N=343). First, to identify the most prominent side-effects associated with KarXT, we calculated risk-difference scores for treatment emergent AEs by FDA Medical query (FMQ) and preferred term (PT) occurring in ≥2% of participants in the KarXT group. Second, to compare AE data for KarXT to the dopamine D2-based class of drugs, we used previously published data that assessed the disproportionality (using Empirical Bayes Geometric Mean; EBGM) of PTs derived from post-marketing safety-surveillance data in the FDA Adverse Event Reporting System (FAERS) database. To compare KarXT to placebo, we plotted the cumulative distribution of participants whose PT EBGM values were equal to or less than the disproportionality of each PT from the D2 class (where EBGM≥3.0).

Results: Risk difference scores identified prominent AEs for which KarXT was greater than placebo, including nausea, constipation, dyspepsia, and vomiting (all risk-difference scores >

10%). In examination of the cumulative distributions of AEs compared to the FAERS database, KarXT participants (12.6%) had fewer D2-Dopamine class-specific AEs (with EBGM values of three-fold or greater) compared to the placebo group (16.3%).

Conclusion: In 5-week placebo-controlled trials, KarXT showed a side-effect profile that is consistent with pro-cholinergic AEs including nausea and dyspepsia. These side-effects are distinguished from common anti-cholinergic AEs observed in post-marketing safety-surveillance data from D2 antagonists in the FAERS database. Of note, the placebo group showed more similarities with D2-antagonists compared to KarXT, though no direct comparison between KarXT and established antipsychotics has been conducted. These preliminary findings may indicate that KarXT characterizes a new class of antipsychotics.

W53. LONG-TERM FOLLOW-UP OF IMPLEMENTATION OF PSYCHOTROPIC MEDICATION UTILIZATION PARAMETERS FOR CHILDREN AND ADOLESCENTS IN TEXAS FOSTER CARE

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Abstract Background: Increased attention has focused on the appropriate use of psychotropic medication in children. Youth in foster care are a vulnerable population that are often fraught with emotional distress and mental disorders. Improved use of psychotropic medications in this population is needed.

Methods: Subsequent to legislative action in 2003, the Texas Department of Family and Protective Services (DFPS) appointed a taskforce to develop psychotropic utilization parameters for foster children. The first edition was published and disseminated in early 2005, with succeeding editions in 2007, 2010, 2013, 2016, 2019, with review and revision planned for 2024. The parameters were developed by an interprofessional taskforce with external peer review. While an evidence-based approach was used, expert consensus was used to fill in missing gaps of evidence. Using the Texas Medicaid prescription database, utilization was monitored on a quarterly basis. The parameters were initially disseminated by DFPS, and in 2008 a single mental health managed care organization (Superior Healthplan) implemented a system to utilize these parameters as a component of prospective quality of care assessment and clinician feedback.

Results: The dispensing of at least one psychotropic prescription decreased from 37.7% in FY 2004 to 23.2% in FY 2021. The use psychotropic medication for > 60 days in foster children decreased from 31.4% of children in FY 2004 to 17.9% in FY 2021. Within class polypharmacy decreased from 6.2% in FY 2004 to 2.9% in FY 2021. The percent of children receiving >5 psychotropic medications decreased from 2.2% in FY 2004 to 0.8% in FY 2021, and the percent receiving > 4 medications decreased from 6.3% in FY 2004 to 2.9% in FY 2021. The percent of children < 4 years of age receiving psychotropics > 60 days decreased from 4.2% in FY 2004 to 1.5% in FY 2021.

CHANGE in PARAMETERS: In 2013, the parameters were revised to include a decrease to 4 concomitant psychotropics for review of multidrug polypharmacy, the adoption of metabolic monitoring parameters, and enhanced dosing information. Major revisions in the medication tables were made in 2023.

Conclusion: The implementation of state-wide psychotropic medication utilization parameters for foster children was associated with a sustained decrease in psychotropic prescriptions and a decrease in polypharmacy. Prospective review and prescriber feedback improved utilization over dissemination and education alone.

W54. PREVALENCE OF MILD TO MODERATE MENTAL ILLNESS, CORRELATES OF TREATMENT PATTERNS, AND PERCEIVED UNMET NEED AMONG U.S. ADULTS: RESULTS FROM THE NATIONAL SURVEY ON DRUG USE AND HEALTH, 2021

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Abstract Background: Mental health issues continue to affect millions despite the availability of evidence-based treatment. The COVID-19 pandemic caused a shift in the delivery of care to more virtual settings. Since the advent of the pandemic, several researchers have published work focused on the appropriateness and effectiveness of virtual delivery of mental health services, including for those with mental health concerns accompanied by more severe forms of impairment. The prevalence of mild to moderate mental illness (MMMI) and its treatment landscape, including the perceived unmet need for mental health services, however, have not been reported in the peer-reviewed literature to date.

Methods: Analyses of the 2021 National Survey on Drug Use and Health (NSDUH) conducted in households and non-institutional group settings either in-person or virtually across the US allowed for the estimation of the prevalence and correlates of MMMI as well as of the overall and virtual treatment landscape, perceived unmet need, and barriers to care. Chi-square statistics and logistic regression models were used to study bivariate and adjusted associations, respectively, between sociodemographic correlates and each indicator, with p LESS THAN 0.05 considered statistically significant.

Results: Nearly 44 million (17.2%) US adults are estimated to have past-year MMMI, with treatment receipt reported by 41.3%. Over 62% of those with MMMI who received mental health treatment did so virtually, 74.1% reported having been prescribed a mental health-related medication, and 45.8% received non-virtual outpatient mental health treatment. About one in five of those with MMMI who did not receive past-year treatment perceived an unmet need for it, with not being able to afford it (40.1%), not knowing where to go for services (31.1%), thinking they could handle the issues without mental health treatment (27.1%), and not having time to get treatment (20.4%) as the most frequently cited barriers. Significant associations between MMMI, the receipt of treatment, and/or having a perceived unmet need for care were found for sex, race/ethnicity, education level, sexual orientation, and insurance status.

Conclusion: This study is among the first of its kind to report nationally representative estimates and correlates of MMMI among US adults. About one in six US adults were categorized as having past-year MMMI, with less than half reporting past-year mental health treatment. Perceived unmet need for care and barriers to receiving care demonstrate the need for improved access to low-cost, easily accessible, on-demand mental health services to better serve adults with MMMI. Sociodemographic disparities continue to exist, suggesting that continued efforts to decrease these inequities are needed.

W55. ASSOCIATION BETWEEN SYMPTOM SEVERITY AND MEDICATION ADHERENCE IN ADULTS WITH BIPOLAR DISORDER REPORTING ADHERENCE CHALLENGES

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Abstract: Introduction: Medication non-adherence is common among individuals with bipolar disorder (BD) and associated with relapse and suicide. Assessing medication adherence in BD remains a challenge and complicates adherence promotion. This analysis from an ongoing U.S. National Institute of Mental Health-funded randomized controlled trial (RCT) examined the relationship between BD symptoms, functional status and adherence in 69 poorly adherent adults with BD.

Method: Study inclusion criteria included being ≥ 18 years old, with BD Type 1 or 2 for at least 2 years, with current or past difficulties with medication adherence based on self-report, and actively symptomatic as measured by Brief Psychiatric Rating Scale (BPRS) ≥ 36 or the Young Mania Rating Scale (YMRS) > 8 or Montgomery Asberg Depression Rating Scale (MADRS) > 8. Adherence was measured in 2 ways: 1) the self-reported Tablets Routine Questionnaire (TRQ) and 2) electronic pill container monitoring (eCap pillbox). BD symptoms and functioning were measured with the MADRS, YMRS, and the Global Assessment of Functioning (GAF). Screening and baseline data were examined.

Results: Mean age was 42.3 (SD 13.0) years, with 72.5% (n=50) female and 43.5 % (n= 30) non-white. The majority (n=58; 84.1%) had Type 1 BD. Mean baseline scores on MADRS, YMRS and GAF were 21.7 (SD 10.1), 8.9 (SD 5.2) and 60.3 (SD 10.4), respectively, indicating moderate levels of depression, minimal manic symptoms and moderate difficulty in social or occupational functioning. At screening, the mean percentage of missed BD medications in the prior week measured using TRQ was 40.6% (SD 32.6) and 30.3% (SD 30.4) at baseline. At baseline, the mean percentage of missed medication in the prior week measured using eCap was 42.2% (SD 35.9) in those with available eCap data (n=41). Adherence assessed via TRQ and eCap were significantly correlated ($r=0.68$, $p < 0.001$). In the full sample, worse adherence based on TRQ was significantly associated with higher MADRS scores ($p < 0.05$) and lower GAF scores ($p < 0.05$). In the sub-set with eCap data, there were similar trending associations for MADRS ($p=0.14$) and GAF ($p=0.17$).

Conclusion: In adults with BD who acknowledge medication adherence difficulties, monitoring increased self-reported adherence by approximately 10%. Electronic pill-monitoring found individuals were approximately 12% less adherent compared to self-report. While worse symptoms and lower functional status could help to identify sub-optimal adherence, reliance on either patient self-report or symptom presentation may give an incomplete picture of medication-taking behaviors among adults with BD.

W56. LAYPERSON/PLAIN LANGUAGE SUMMARIES: GLOBAL CHALLENGES AND OPPORTUNITIES IN 2024

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Abstract: Purpose: A key aspect of neuropsychiatric drug development in 2024 is the commitment to patient centricity. The mandatory provision of Plain Language Summaries (PLS) throughout Europe embraces patient centricity. The recent voluntary commitment in North America is commendable.

Research sites, sponsors, CROs, IRBs and patient advocacy groups have publicly endorsed the importance of PLS. As the promise of PLS is being fulfilled in the EU, we've looked at the global landscape to highlight challenges and opportunities with the wider implementation of PLS.

Content: The major obstacles to implementation are different on different continents. There was one common theme outside of the EU. None of the regulatory agencies in Africa, Asia, Australia and South America has mandated the provision of PLS. In the US, the FDA has published Patient-Focused Drug Development (PFDD) as four Guidance Documents. While these are suggestive in advocating for PLS, they are not mandatory.

Methods: Here in the US we conducted an emailed survey of well-established CNS Research Sites asking about their most recent experience with, or access to, PLS. For the rest-of-the-world, we conducted online searches of both pertinent scientific publications, as well as investigating the applicable regulatory websites, such as Australia's Therapeutic Goods Administration (TGA). In Africa, Asia and South America we looked on regulatory websites for countries like Nigeria, Japan and Brazil. In early-2024, we could not identify any mandatory regulatory requirement for PLS outside of the EU.

Results: Africa: Challenges = As many as 3,000 different languages spoken in Africa. In 2023, only 2.2% of clinical trials were conducted in Africa, while Africa represents 17% of the world's population. Opportunities = Africa represents 25% of the world's total disease burden.

Asia: Challenges = More than 2,000 different languages. In Japan, it is strictly forbidden for any pharmaceutical company to communicate directly with any patient. Opportunities = Medical affairs representatives from domestic and global Japanese pharma companies acknowledge both the importance and potential value of PLS. Australia: Challenges = The indigenous Australians speak 250 different languages; however, they comprise a very small percentage of clinical trial participants. Opportunities = In 2022, the Government Department of Health published PLS National Guidelines to improve the coordination of treatment and support of patients. They fell short of mandating PLS for clinical trial participants; 89.8% of Australians speak English. South America: Challenges = The lack of any current regulatory-related mandate for PLS is the only apparent hurdle. Opportunities = All 440 million residents speak one of only two languages: Spanish and/or Portuguese. USA: Challenges = The lack of FDA-mandated PLS, plus contrasting corporate cultures remain as hurdles in 2024. Opportunities = Non-profit and For-profit IRBs, along with an array of third-party providers are now experienced and capable of delivering effective PLS.

Importance: We will present the ten key elements of a Layperson Summary as well as the ten positive primary outcomes from an effective PLS. From a cost-effective/return-on-investment perspective, PLS are a win-win-win! We have identified (at least) three Pharma companies that have voluntarily and substantively embraced the promise of PLS and patient centricity.

W57. CONTEMPORARY ESTIMATES OF THE DIRECT MEDICAL COST BURDEN OF TREATMENT-RESISTANT DEPRESSION

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Abstract Background: Treatment-Resistant Depression (TRD) is a condition in which individuals with Major Depressive Disorder (MDD) fail to respond to two or more treatments of adequate dose and duration within the same depressive episode. This study seeks to update prior work on the direct medical cost burden of TRD with more contemporary economic data, given changes in care patterns and disease burden that may have emerged alongside new treatment innovations and the global COVID-19 pandemic (Amos et al., 2018; Sussman et al., 2019).

Methods: Adults with commercial insurance in the United States between ages 18 and 64 with MDD were identified between 1/1/2017 and 12/31/2022 within Merative™ MarketScan® Commercial and Medicare Supplemental Databases. Patients who failed at least 2 MDD treatment agents of adequate dose and duration within 2 years of their first antidepressant treatment were considered to have TRD. Patients with TRD were matched 1:1 to patients with non-TRD MDD on demographic (age, sex, index year, region, plan type) and clinical characteristics (comorbidities). On the matched cohorts, total all-cause, mental health, non-mental health, and pharmacy costs (insurance payments, US$2023) per patient per year were estimated through a generalized linear model (GLM) adjusting for baseline total direct costs.

Results: A total of 23,909 patients with TRD and 459,260 patients with non-TRD MDD were identified; with exact, 1:1 matching, 23,426 TRD patients were matched to 23,426 non-TRD MDD patients. Within the post-match samples, the mean (SD) age was 41 (13) years and 72.8% of patients were female in both cohorts; the mean follow-up time was 1.57 years in the MDD cohort and 1.71 in the non-MDD TRD cohort. The mean, unadjusted all-cause costs per year in the TRD cohort were $25,931 ($3,942 mental health, $15,444 non-mental health, $6,545 pharmacy) and in the non-TRD MDD cohort were $17,591 ($1,363 mental health, $11,911 non-mental health, $4,317 pharmacy). Adjusted costs were statistically significantly higher in the TRD cohort compared to the non-TRD MDD cohort (p LESS THAN 0.0001): mean (SE) difference in total costs was $6,977 ($383), $2,528 ($107) for mental health costs, $2,496 ($306) for non-mental health costs, and $1,892 ($117) for pharmacy costs.

Conclusions: This study provides updated estimates of the direct medical economic burden among adults with TRD and non-TRD MDD. Results from this work corroborate prior research in this area on the incremental economic burden of TRD (Amos et al., 2018; Sussman et al., 2019) and underscore the need for persistent innovation and access to care for this difficult-to-treat patient population.

W58. AN EEG-BASED, MACHINE LEARNING BIOMARKER TO IDENTIFY RESPONSIVE VS. NON-RESPONSIVE SUBJECTS IN AN MDD CLINICAL TRIAL: EARLY VALIDATION DATA FROM THE EMBARC AND ROTTCO STUDIES

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Abstract: Introduction: The search for predictors of treatment response in psychiatric disorders has historically relied on baseline clinical and demographic characteristics. Among these biomarkers, EEG paradigms have shown promise in subgrouping patients, either in terms of distinct biotypes or in relation to treatment response underscoring the potential of EEG to represent a relatively inexpensive, non-invasive approach to enhance treatment efficacy. This study aimed to identify major depressive disorder (MDD) subtypes through EEG-based functional connectivity analysis, utilizing resting-state data to predict treatment outcomes. To achieve this, we utilized a proprietary machine learning based approach to generate patient clusters and examined how these clusters correlated with clinical change. By applying clustering algorithms to EEG data, we aim to reveal neurophysiological differences among MDD subtypes, potentially guiding more effective treatment decisions and clinical trial sample enrichment.

Methods: We conducted a post-hoc analysis using baseline scalp EEG data from the EMBARC trial, which investigated sertraline's efficacy in treating MDD. We employed unsupervised machine learning, a data-driven approach that identifies patterns and structures in data without prior labeling, using K-means clustering which is a method of partitioning data into distinct groups based on intrinsic characteristics to identify MDD subtypes based on EEG functional connectivity features. Cohen's d effect sizes and p-values were calculated for each subject's total HAMD-17 score changes from baseline (Week 0) to the end of Stage I (Week 8), along with HAMD-17 item analyses. Validation procedures, including cross-site assessments, were performed to assess the robustness of the findings.

Results: Of the 218 patients from the EMBARC dataset included in our analysis, three distinct MDD subtypes (subtype 1, subtype 2, and subtype 3) were identified. Approximately 48% of patients belonged to subtype 1 (n=105) where there was a significant ($p < .05$) treatment response to sertraline (n=51) compared to placebo (n=54) (Cohen's $d = 1.235$, $p < 0.0001$). In contrast, subtype 2 patients (approximately 35% of the total population) did not respond favorably to sertraline. Surprisingly, subtype 3 (comprising around 19% of patients) exhibited a larger response to placebo than sertraline (Cohen's $d = -1.447$, $p < 0.0003$), with specific HAMD-17 items showing notable differences. Validation analyses, including ten-fold cross-validation, demonstrated high consistency in the findings of the EEG-informed machine learning methodology, evidenced by a 99.2% subtype membership consistency.

Conclusions: Utilizing EEG functional connectivity features and unsupervised machine learning continues to uncover identify patient subtypes with significantly different treatment responses in MDD. This technology has the potential to detect subpopulations that are likely to have lower responses on placebo, offering the promise of reducing trial failure rates, sample sizes, costs, and enrollment times. Ongoing research aims to validate these findings across additional MDD and CNS datasets.

W59. EFFECT OF LEMBOREXANT ON SLEEP ARCHITECTURE IN ADULT AND ELDERLY PARTICIPANTS WITH MODERATE TO SEVERE CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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Abstract Background: Patients with chronic obstructive pulmonary disease (COPD) commonly experience disruption of sleep and, accordingly, negative impacts on sleep architecture. These effects can include reduction and temporal redistribution of rapid eye movement (REM) and non-REM sleep. Lemborexant (LEM) is a competitive dual orexin receptor antagonist approved to treat adults with insomnia. In Study E2006-G000-304 (NCT02783729), a pivotal phase 3 study of older adults with insomnia, LEM treatment increased total sleep time (TST), with increases in REM sleep. Study E2006-A001-113 (Study 113; NCT04647383) investigated the respiratory safety of LEM vs placebo (PBO) in adult and elderly participants with moderate to severe COPD. There was no adverse impact on peripheral oxygen saturation and the apnea-hypopnea index during TST on day 8 of daily treatment for participants who received LEM 10 mg (LEM10) vs PBO, demonstrating respiratory safety with single and multiple dosing. This post hoc analysis of Study 113 evaluated sleep architecture in participants with moderate to severe COPD and without insomnia who received LEM10.

Methods: Study 113 was a multicenter, randomized, double-blind, PBO-controlled, 2-period crossover study in adult participants with moderate to severe COPD and an apnea-hypopnea index <15 events/h. Participants were screened for COPD severity by spirometry per Global Initiative for Obstructive Lung Disease recommendations. Participants were randomized to two 8-night treatment periods with LEM10 or PBO (separated by ≥14 d). In-laboratory polysomnography (PSG) was performed at screening, on day 1 (D1; after a single bedtime dose), and day 8 (D8; after multiple bedtime doses) during both treatment periods to assess non-REM (N1, N2, N3, and total) and REM sleep durations along with TST (duration of sleep from sleep onset [latency to persistent sleep] until awakening) and REM latency (time from sleep onset to REM onset).

Results: The analysis set comprised 30 participants with moderate to severe COPD, mean (SD) age 69.2 (6.3) y, and 21 (70.0%) female. Five (16.7%) participants had severe COPD and 25 (83.3%) had moderate COPD. On both days, TST was significantly higher with LEM10 vs PBO: least squares mean (LSM; standard error [SE]) in minutes on D1: 388.90 (12.37) vs 319.52 (12.37); P < 0.0001; D8: 370.05 (13.69) vs 332.94 (13.69); P=0.003. Total non-REM sleep was significantly higher only on D1 with LEM10 vs PBO: LSM (SE) on D1: 298.32 (8.87) vs 261.55 (8.87); P < 0.0001; D8: 283.78 (10.46) vs 269.90 (10.46); P=0.145. Total REM sleep was significantly higher with LEM10 vs PBO on both D1 and D8: LSM (SE) on D1: 90.58 (7.20) vs 57.97 (7.20); P < 0.0001; D8: 86.27 (6.92) vs 63.04 (6.92); P=0.001. REM latency was lower on D1 and was significantly lower on D8 for LEM10 vs PBO: LSM (SE) in minutes on D1: 100.44 (18.16) vs 129.14 (18.31); P=0.057; D8: 94.49 (18.17) vs 135.54 (18.77); P=0.022. LEM was well tolerated; most treatment-emergent adverse events were mild, and no new safety signals were observed.

Conclusion: In participants with moderate to severe COPD but without confirmed insomnia, LEM increased total sleep, non-REM, and REM sleep compared with PBO as assessed after single or multiple doses of LEM. In conjunction with evidence of respiratory safety, LEM may be a useful option for the treatment of insomnia in patients with moderate to severe COPD.

SPONSOR: Eisai Inc.

W60. NONCLINICAL STUDIES OF ABUSE POTENTIAL WITH DUAL OREXIN RECEPTOR ANTAGONISTS: CONCORDANCE WITH REAL-WORLD USE

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Abstract Background: Approved dual orexin antagonists (DORAs; lemborexant, suvorexant, daridorexant) underwent determination of abuse potential prior to regulatory approval in the United States. Nonclinical data did not indicate potential for abuse of any of the 3 DORAs in humans. However, human abuse potential (HAP) studies showed no difference in drug liking between the DORAs and the active comparator (with established abuse potential), zolpidem, in recreational sedative users who were able to recognize and like either zolpidem alone (suvorexant) or both zolpidem and suvorexant (lemborexant and daridorexant). Based largely on the HAP studies, the 3 DORAs were placed into Schedule 4 (CIV), the same controlled class as GABAergic hypnotics. At the time of approvals, there were no postmarketing data from the community to support a low predicted abuse risk based on the nonclinical studies. Currently, there are more than 8 years of postmarketing safety data from the 3 DORAs, indicating lower abuse risks compared with other CIV hypnotics.

Methods: Adverse events with the preferred terms (PTs) of drug withdrawal syndrome, drug abuse, and drug dependence were evaluated from Eisai's ongoing global postmarketing safety surveillance system for lemborexant in the United States, Canada, and Japan (Dec 20, 2019–Sep 30, 2023) and the FDA Adverse Event Reporting System (FAERS) from suspect cases (Jan 1, 2015–June 30, 2023). In FAERS, reports of those PTs from DORAs were compared with zolpidem and with benzodiazepines approved for patients with insomnia (estazolam, temazepam, triazolam).

Results: Since lemborexant's marketing approval, there have been a small number of cases with the 3 PTs of interest received. Given the number of patients exposed postmarketing (approximately 475 million patient days) and the number of reports (73) related to these 3 PTs, the calculated reporting rate corresponds to approximately 0.15 cases per million patient days of global exposure. Of 10,202 reports for DORAs in FAERS, the percentages of reports for PTs related to drug withdrawal syndrome, drug abuse, and drug dependence were 0.05%, 0.02%, and 0.1%, respectively. These data match the findings in the pivotal studies programs for the 3 DORAs, where no dependence was observed in the insomnia patient population. To that end, none of the DORA labels contain a warning about dependence. Conversely, reports in FAERS for the benzodiazepines (5534 reports) were 0.8%, 12.9%, and 3.7%, respectively, and 1.0%, 9.1%, and 5.3% for zolpidem (18,330 reports), respectively.

Conclusion: Data from these sources suggest that relying exclusively on HAP studies for scheduling the DORAs appears to overestimate their potential for abuse in the community. These findings are in line with research that suggests abuse potential may be well predicted by the results of the nonclinical studies and by other national surveillance systems, which also suggest that the DORAs do not pose meaningful abuse potential and related risks.

SPONSOR: Eisai, Inc

W61. SELTOREXANT, ADJUNCTIVE TO ANTIDEPRESSANTS, IN ADULTS WITH MDD WITH INSOMNIA SYMPTOMS: RESULTS OF A DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED STUDY

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Abstract Background: Seltorexant, a first-in-class, potent, selective orexin-2 receptor antagonist, normalizes manifestation of hyperarousal and enhances physiological sleep. This phase 3 study (NCT04533529) compared the efficacy/safety of seltorexant to placebo, each adjunctive to background SSRI/SNRI, for improving depressive symptoms in patients with major depressive disorder (MDD) with insomnia symptoms (IS).

Methods: This was a 6-week, multicenter, double-blind (DB), randomized, placebo-controlled study of adults (18-74 years) with a primary DSM 5 diagnosis of MDD without psychotic features. Participants had Hamilton Depression Rating Scale total scores ≥20 and ≥18 at first and second screening interviews, respectively, and an inadequate response to 1-2 antidepressants (SSRI/SNRI) administered at an adequate stable dose and duration (≥6 weeks but ≤24 months) in the current episode. Eligible participants were randomized 1:1 to receive seltorexant 20 mg or matching placebo for 6 weeks, while continuing their baseline SSRI/SNRI. The primary efficacy endpoint was changed from baseline to day 43 in Montgomery-Åsberg Depression Rating Scale (MADRS) total score. Key secondary efficacy endpoints were changes from baseline to day 43 in MADRS without sleep item (MADRS-WOSI) total score and Patient Reported Outcome Measurement Information System-Sleep Disturbance (PROMIS-SD) T-score. Efficacy analyses were conducted via mixed effects models for repeated measures.

Results: 588 participants with MDD were randomized (seltorexant: n=284 [216 with IS]; placebo: n=304 [228 with IS]), of which 586 received ≥1 dose of study drug and were included in the DB safety analysis set (mean age 45.1 years, 77.1% white, 76.6% female). 419 participants with MDD with IS who received ≥1 dose of DB study drug and had a baseline MADRS total score ≥24 were included in the DB efficacy analysis set. The primary efficacy endpoint significantly improved with seltorexant versus placebo at day 43 (least squares mean difference [95% CI] in MADRS total score: -2.6 [-4.53, -0.74]; 2-sided p=0.007). Key secondary endpoints also significantly improved with seltorexant at day 43 (MADRS-WOSI total score: -2.0 [-3.75, -0.28]; 2-sided p=0.023, and PROMIS-SD T-score: -3.7 [-5.48, -2.00]; 2-sided p LESS THAN 0.001). Treatment-emergent adverse events (TEAEs) were reported for 36.0% of seltorexant and 40.3% of placebo recipients. Few participants (seltorexant: 6/283 [2.1%]; placebo: 7/303 [2.3%]) discontinued study drug due to TEAEs. One participant in each group experienced a serious TEAE(s) in the DB phase, all deemed unrelated to study drug.

Conclusions: Seltorexant showed statistically significant and clinically meaningful antidepressant effects, beyond improvement of insomnia symptoms, in patients with MDD with IS who had experienced inadequate response to SSRI/SNRI. Seltorexant demonstrated a safety profile similar to placebo.

W62. BRIDGING THE EFFICACY-EFFECTIVENESS DIVIDE: COMPARING INTRANASAL ESKETAMINE FOR TREATMENT RESISTANT DEPRESSION IN THE CLINICAL TRIAL VERSUS REAL WORLD SETTING

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Abstract: Introduction/Objectives: The Food and Drug Administration (FDA) approved Janssen Pharmaceutical's application for new drug approval for intranasal esketamine (Spravato), in conjunction with an oral antidepressant, for treatment resistant depression (TRD) in March 2019. While intranasal esketamine has been available to clinicians in approved treatment centers for several years, few reports have appeared documenting the effectiveness of intranasal esketamine treatment for patients with TRD in clinical settings. In the present report, we compare results of intranasal esketamine treatment in patients at an approved esketamine clinical site to results reported in pivotal trial studies known as SUSTAIN-1 conducted by Janssen Pharmaceuticals.

Methods: This analysis was comprised of two patient groups. Group one entailed a retrospective analysis of results obtained from 50 consecutive TRD patients enrolled in an intranasal esketamine treatment program at the Institute of Living (IOL), Hartford, CT. Eligibility for treatment in the IOL program involved a diagnosis of treatment resistant depression with at least two failed antidepressant drug trials in the present episode. Patients had depression severity scores determined with the MADRS at the baseline visit and at each treatment session with intranasal esketamine, with the treatment protocol following the FDA REMS guidelines. Treatment outcome assessment was based on a comparison of MADRS ratings at baseline and at four weeks of treatment. Group two involved subjects enrolled in the IND phase of the RCTs conducted for regulatory approval, referred to as SUSTAIN-1, with 437 TRD patients initially being enrolled. Access to data on subjects enrolled in SUSTAIN-1 was made possible through the Yale University Open Data Access Project. Data were available on MADRS scores at baseline and at four weeks of intranasal esketamine treatment in the TRD patients participating in the SUSTAIN-1 IND phase. Descriptive statistics between the IOL and SUSTAIN-1 data on MADRS scores at baseline and week 4 as well as within-patient change in MADRS were compared. An equivalence analysis was conducted to evaluate the comparability of results obtained in the two patient groups.

Results: For the IOL TRD patients, the mean MADRS score at baseline was 35.3±5.3 (SD), and at four weeks of intranasal esketamine treatment, was 15.5±8.7, resulting in a within-patient mean reduction in depression severity of 20.4±8.3. For the SUSTAIN-1 group, the mean MADRS score at baseline was 37.7±5.5 and at four weeks was 14.4±11.3 for a within-patient reduction in depression severity with intranasal esketamine treatment of 23.4±12.4. Using a 50% reduction in MADRS score from baseline to four weeks of treatment to define treatment response, 64.1% of the patients in the IOL cohort and 69.8% of SUSTAIN-1 participants demonstrated a response to treatment with intranasal esketamine. Comparison of the IOL data for treatment response in TRD patients to the results obtained in the SUSTAIN-1 IND phase demonstrated that the IOL patient response data are equivalent to the RCT SUSTAIN-1 data ($p = 0.031$).

Discussion: The results obtained from this retrospective observational analysis based on data obtained from a clinical intranasal esketamine treatment program demonstrate strong external

validity for the effectiveness of intranasal esketamine in the treatment of TRD in a real world setting.

W63. ANALYSIS OF CORRELATION OF THE CLINICAL AND PATIENT GLOBAL IMPRESSION OF IMPROVEMENT SCALES IN ACUTE SCHIZOPHRENIA CLINICAL TRIALS

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Abstract: Introduction: The CGI-I and the PGI-I scales are often used as outcome measures of efficacy in clinical trials. Studies assessing treatment efficacy in acute schizophrenia population face additional challenges due to the complexity of the disorder and diversity of the individual experiences. This study explores the correlation between the CGI-I and the PGI-I scales in subjects with acute Schizophrenia.

Methods: The data from two double-blind, placebo-controlled studies of subjects with acute exacerbation of schizophrenia was used for this analysis. A total of one hundred and seventy-seven visits from fifty-five adult individuals participating in these trials were evaluated. At each of visits the clinician/rater completed the CGI-I and the subjects completed the PGI-I. Pearson correlation coefficient was calculated for the two scales (CGI-I/PGI-I).

Results: The statistical analysis indicated that there is a significant medium positive correlation between the CGI-I and the PGI-I, ($r(175) = .403$, $p < .001$). However, in over 47% of the visits (N=83), subjects reported significantly greater improvement of symptoms compared to the clinicians/raters. Conversely, clinicians/raters rated significantly greater improvement of symptoms in 23% of the visits compared to subject's perceptions based on their ratings. Overall, in 23% of visits (N=40) there was at least a 2 points difference between the CGI-I and the PGI-I scores at the same time point. The study findings provide insight into the potential impact of self-reported measures of Schizophrenia symptoms in clinical trials outcome.

Conclusion: This study shows that the clinician rated CGI-I gives an objective evaluation of symptoms but may not completely capture the multifaced nature of patients' experiences with acute Schizophrenia. Discords between clinician and patient viewpoints poses an obstacle, possibly leading to inconsistencies in the reported scores. Patients' subjective perception of improvement, as measured by the PGI-I, delivered important insights but can be predisposed by factors such as social functioning, cognition, quality of life and insight into illness, frequently going beyond clinical symptoms. The study results highlight the importance of bearing in mind both clinician and patient perspectives in clinical trial assessments, as well as the need for further researching and understanding of treatment outcomes in acute Schizophrenia clinical trials. Additional research is needed to explore the implications of these findings for clinical practice and the expansion of new treatment for individuals with this condition.

Full Disclosure of Author Conflicts: All authors have no conflicts of interest or bias in the conclusions of the current investigation or promotion of the current study results.

W64. SEMAGLUTIDE FOR THE TREATMENT OF ANTIPSYCHOTIC-ASSOCIATED WEIGHT GAIN IN PATIENTS NOT RESPONDING TO METFORMIN – A CASESERIES

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Abstract Background and Objective: While antipsychotic (AP) medications are considered the cornerstone of treatment in schizophrenia and other psychiatric conditions, contributing effects of these medications on weight gain have been well-established. Comorbid obesity among individuals with severe mental illness (SMI) have been associated with poorer quality of life, barriers to social engagement, worse adherence, and impaired cognition. Despite this, the available treatment strategies for managing this growing problem are significantly lacking. At present, metformin has the most evidence for modest weight gain mitigation in individuals with SMI who experience antipsychotic associated weight gain (AAWG). However, it is effective in only approximately 20% of patients, with no clear recommendations for the subgroup failing to respond to metformin. Among agents approved for chronic weight management in Canada, glucagon-like peptide-1 receptor agonists (GLP-1RAs) are associated with reductions in cardiovascular mortality, with the recent addition of once-weekly semaglutide for this indication. The long-acting, once-weekly formulation has shown promising preliminary evidence for both effectiveness and tolerability. Therefore, in this case series involving the SMI population, the primary objective was to study changes in weight over 12 months following the initiation of semaglutide among metformin non-responders.

Methods: A retrospective chart review was conducted for individuals between 2019 and 2021, in the Mental Health and Metabolism clinic at the Center for Addiction and Mental Health (CAMH) in Toronto, Canada. The inclusion criteria consisted of patients who were on a stable dose of an antipsychotic medication, who failed to lose > 5% body weight on metformin (highest tolerated dose) at the end of 3 months or those who continued to meet criteria for metabolic syndrome at the end of 3 months. They were then initiated on semaglutide of up to a 2 mg dose per week. All demographics and metabolic data were collected at baseline, 3, 6 and 12 months.

Results: Twelve patients in total were included with a mean age of 36.09 ± 13.32 years, who were on a mean semaglutide dose of 0.71 ± 0.47 mg/week at the end of 12 months. At baseline, the mean weight was 111.4 ± 31.7 kg, and the BMI was 36.7 ± 8.2 kg/m2 with a mean waist circumference of 118.1 ± 19.3 cm. After initiation of semaglutide, weight loss of 4.56 ± 3.15 kg ($p < 0.001$) was noted at 3 months, 5.16 ± 6.27 kg ($p = 0.04$) at 6 months, and 8.67 ± 9 kg ($p = 0.04$) at 12 months. No serious adverse events were reported on the medication, with some experiencing tolerable gastrointestinal side-effects which subsided with time.

Discussion and Relevance: This case series from a naturalistic, clinical setting suggests that among metformin non-responders, semaglutide appears to be effective in reducing AAWG. However, well-powered randomized control trials investigating semaglutide for AAWG in the SMI population are required.

W65. EFFECT OF ULOTARONT ON BRAIN DOPAMINE SYNTHESIS CAPACITY IN SUBJECTS WITH SCHIZOPHRENIA ON STABLE DOSES OF A D2 ANTIPSYCHOTIC: RESULTS OF AN 18F-DOPA PET STUDY

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Abstract Background: 18F-DOPA PET studies report higher striatal dopamine (DA) synthesis capacity is associated with symptoms of psychosis and is correlated with illness severity [1]. In a mouse model, ketamine-induced elevations in DA synthesis capacity were reduced by single doses of ulotaront (3 mg/kg i.p.) with no effect on baseline DA synthesis capacity [2]. Ulotaront is trace amine-associated receptor 1 (TAAR1) agonist with 5-HT1A activity that has demonstrated efficacy in a Phase 2 trial in patients with schizophrenia [3]. The aim of the current study was to evaluate the effect of ulotaront adjunctive to a D2 antipsychotic on brain DA synthesis capacity, as measured by 18F-DOPA PET imaging, in adults with schizophrenia.

Methods: Subjects, ages 18-45, were enrolled who met DSM-5 criteria for schizophrenia and were on a stable dose of a D2 antipsychotic for a ≥3 weeks prior to screening. At screen, an 18F-DOPA PET scan was performed. Subjects were continued on their antipsychotic, and treatment with ulotaront was added for 14 days at an initial dose of 50 mg/d for 3 days followed by 75 mg/d for the remaining time period. On Day 14, the 18F-DOPA PET scan was performed 2-4 h after the final dose. The primary endpoint was change from baseline in DA synthesis capacity in the striatum at day 14 by 18F-DOPA PET. Imaging data were analyzed with Patlak modelling with cerebellum as a reference region, resulting in the influx constant Kicer reflecting DA synthesis capacity. Averaged regional Kicer values were calculated and correlated with efficacy measures (PANSS total and subscale scores). Change from baseline in DA synthesis was calculated and a repeated measures ANOVA was used to test treatment, and treatment by region, interaction effects.

Results: 22 patients with schizophrenia were enrolled; 19 had useable baseline and day 14 scans: male (n=14), female (n=5); mean age, 32.9; baseline mean (SD) PANSS total 79.3 (7.3) and PANSS positive subscale 19.2 (4.6). There was a significant effect of treatment ($p < 0.05$) and striatal subregion ($p < 0.05$) on Kicer but no treatment by subregion interaction ($p > 0.8$). Mean percent changes from baseline, and respective treatment effect size were: whole striatum= -3.98% (95% CI: -8.68%, 0.72%) and Cohen's d= -0.46 (95% CI: -0.97, 0.05), associative striatum= -3.38% (95% CI: -8.09, 1.34) and Cohen's d= -0.39 (95% CI: -0.89, 0.11) ; motor striatum= -3.89% (95% CI: -9.61, 1.81%) and d= -0.39 (95% CI: -0.89, 0.11); and limbic striatum= -5.79% (95% CI: -9.66, -1.92%) and d= -0.74 (95% CI: -1.28, -0.19). The mean reduction in DA synthesis capacity for all 3 striatal subregions was greater than the estimated minimal threshold (0.0005/min) likely to be clinically meaningful. There was a significant moderate correlation between change in striatal 18F-DOPA Kicer and change in

Marder Positive Factor score on the PANSS (r=0.5, $p < 0.05$) but no significant relationship with change in PANSS total symptom score (r=0.2, $p > 0.05$).

Conclusions: Consistent with preclinical findings, this study found that 14 days of treatment of patients with schizophrenia with ulotaront added to a stable dose of a D2 antipsychotic resulted in potentially clinically meaningful reductions in dopamine synthesis capacity in the striatum that were correlated with a reduction in the severity of the PANSS-positive subscale score. These results, despite stable baseline treatment with a D2 antipsychotic, provide confirmation of the potential efficacy of the novel TAAR1 agonist mechanism of action of ulotaront.

W66. COMPARISON OF AUGMENTATION WITH ARIPIPRAZOLE OR REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION VERSUS SWITCHING TO THE ANTIDEPRESSANT VENLAFAXINE ON QUALITY OF LIFE AND COGNITION IN SUBJECTS WITH TREATMENT RESISTANT DEPRESSION

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Abstract Background: Treatment-resistant depression (TRD) is a debilitating illness that impairs health-related quality of life (HRQOL) and cognition. Recently, quality of life and cognition have emerged as target outcomes for MDD treatments aimed to achieve full recovery. **Objective:** This study compared the impact of augmenting antidepressants with aripiprazole or repetitive transcranial magnetic stimulation (rTMS) versus switching to the antidepressant

venlafaxine (or duloxetine for those not eligible to receive venlafaxine) on quality of life and cognition in patients with TRD.

Methods: In a pre-defined secondary analysis of a multi-site, open-label trial, 278 TRD patients with inadequate response to two or more antidepressants, were randomly assigned to one of three treatment arms (aripiprazole n=92; rTMS=70; venlafaxine/duloxetine=98) in a 1:1:1 ratio for 8 weeks in an outpatient setting. Quality of life was assessed using the short form of the quality-of-life enjoyment satisfaction scale (Q-LES-Q-SF). Cognition was evaluated with the Cognitive and Physical Functioning Questionnaire (CPFQ). A mixed-effects model with repeated measures was employed for the analysis.

Results: 260 randomized subjects with at least one post-baseline MADRS assessment were included in the analysis. Augmentation with aripiprazole demonstrated superiority over switching to venlafaxine/duloxetine on the Q-LES-Q-SF (estimate=3.51; SE 1.4; 95% CI: [0.76, 6.26], p=0.012). At week 8, the mean model estimated change in the Q-LES-Q-SF scores for the aripiprazole group was 12.98 (SE=0.9), whereas the mean model estimated change for the venlafaxine group was 10.66 (SE=0.9.). At week 8, the mean model estimated change in the Q-LES-Q-SF scores for the rTMS group was 13.83 (SE=1.0); this change was not statistically significant superior to venlafaxine ($p > 0.2$). Neither aripiprazole nor rTMS demonstrated significant differences compared to the venlafaxine/duloxetine switch group in terms of cognitive outcomes as measured by CPFQ scale ($p > 0.5$).

Conclusion: Augmentation with aripiprazole, but not rTMS, improved quality of life significantly versus switching antidepressants in TRD patients. However, rTMS showed greater numerical improvements in secondary and tertiary outcomes compared to the other groups. Differences in sample size for each group may have contributed to lack of statistically significant difference for the rTMS versus venlafaxine/duloxetine comparison.

W67. EFFICACY AND SAFETY OF XEN1101, A NOVEL, KV7 POTASSIUM CHANNEL OPENER IN ADULTS WITH MODERATE TO SEVERE MAJOR DEPRESSIVE DISORDER: RESULTS FROM THE PHASE 2 X-NOVA STUDY

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Abstract Background: Major depressive disorder (MDD) remains a significant public health concern globally, with 1 in 3 patients experiencing inadequate responses to initial antidepressant (AD) therapy. While the pathophysiology of MDD is partially elucidated, the complete spectrum of biologic pathways contributing to MDD is yet to be fully understood. Novel treatment approaches targeting distinct pathways are warranted to address this unmet need. Voltage-gated KCNQ-type potassium channels (Kv) regulate cell membrane excitability.

Certain Kv7 channel openers have been shown to confer seizure reduction (Khan R et al., 2024) and have promising results in preclinical and clinical studies for depressive-like behavior in animal models and depression in patients, respectively (Friedman AK et al., 2016; Costi S et al., 2021). XEN1101 is a novel, potent, Kv7.2/7.3-specific potassium channel opener in development for the treatment of epilepsy and MDD.

Methods: The X-NOVA trial was a multicenter, randomized, double-blind, placebo-controlled, proof-of-concept Phase 2 study conducted across 20 sites in the United States. Adults aged 18–65 years with moderate to severe MDD and anhedonia were randomized 1:1:1 to receive XEN1101 at doses of 10 mg, 20 mg, or placebo (PBO) once daily (QD) with food without titration. The primary efficacy endpoint was the change in Montgomery-Åsberg Depression Rating Scale (MADRS) score from baseline at week 6. A key secondary endpoint included changes in the Snaith-Hamilton Pleasure Scale (SHAPS) score, and exploratory endpoints included the 17-Item Hamilton Depression Rating Scale (HAM-D17) score and the Clinical Global Impression of Improvement (CGI-I) score at week 6.

Results: Of the 168 randomized patients, 164 comprised the modified intent-to-treat population. XEN1101 demonstrated a dose-dependent reduction in MADRS scores from baseline at week 6 compared to placebo (least squares mean point reduction: 10 mg (−15.61), 20 mg (−16.94), PBO (−13.90), with the 20 mg dose showing a clinically meaningful difference (Duru G et al., 2008) of 3.04 points between PBO and XEN1101, which was not statistically significant (P=0.135). Statistically significant improvements were observed in HAM-D17 (−10.18 vs −13.26; P=0.042) and SHAPS (−5.30 vs −7.77; P=0.046), as well as at least minimally improved depressive symptoms by CGI-I (P=0.004) in the 20 mg group compared to placebo. Early onset of efficacy was noted at week 1 in the 20 mg group for MADRS change (–2.66; P=0.047). XEN1101 was generally well tolerated, with no serious adverse events reported in the treatment groups. The incidence of treatment-emergent adverse events was 52% and 66% in the 10 mg and 20 mg groups, respectively, compared to PBO (60%). XEN1101 was not associated with notable weight gain; patients did not report notable sexual dysfunction.

Conclusion: Despite not achieving statistical significance in its primary endpoint, XEN1101 demonstrated a clinically meaningful reduction of depression measured by the MADRS, a significant reduction in HAMD-17, an early onset of action, a significant reduction in anhedonia, and a potentially differentiated safety profile compared to other ADs. The X-NOVA results are particularly meaningful given that there was a 2 in 3 chance of receiving active treatment, which has been previously shown to increase the placebo response (Papakostos GI, et al. 2009). A Phase 3 clinical program is being planned in 2024 to continue to explore XEN1101 in MDD.

Funding: This study was funded by Xenon Pharmaceuticals Inc.

W68. THE PRICE TO PAY FOR MENTAL WELLNESS: MITIGATING THE CARDIO-METABOLIC ADVERSE EFFECTS OF PSYCHOTROPICS ON PATIENTS BY CO-PRESCRIBING SEMAGLUTIDE

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Abstract: Purpose: Managing psychiatric illness particularly severe mental illness such as schizophrenia spectrum and mood disorders on a long-term basis with many psychotropics often results in patients developing significant cardio-metabolic syndrome. Several

mechanisms have been postulated to be responsible for this, including increased appetite and hormonal abnormalities. While the co-prescription of metformin has been tried successfully in some cases, many patients continue to develop abdominal obesity, insulin-resistant diabetes mellitus, dyslipidaemia and high blood pressure when prescribed psychotropics. These common but preventable conditions can increase the risk for stroke, myocardial infarction and atherosclerotic heart disease and result in increased morbidity and mortality. While lifestyle modifications are recommended for these patients as a first-line they are not practical to implement for many patients in our population in the South Bronx due to socio-economic factors. For many patients, cardio-metabolic syndrome can be the heavy price to pay for maintaining mental wellness and psychiatric stability.

Methodology: We would like to explore the feasibility of prescribing the GLP-1 agonist semaglutide to select patients at the Bronxcare inpatient psychiatric unit providing informed consent and meeting eligibility criteria, in order to mitigate this adverse effect of psychotropics. We propose to design a prospective cohort study.We plan to encourage them to continue taking this drug on outpatient basis after discharge from the inpatient psychiatric unit and arrange close follow-up of these patients at our outpatient clinic. Eligibility criteria would include male as well as non-pregnant, non-lactating females between 18- 59 years of age who are on those long-term psychotropics with a known moderate to severe propensity to cause weight gain. Among them, patients with a basal metabolic index of more than 27kg/m2 and at least one weight-related condition such as high blood pressure, type 2 diabetes or high cholesterol would be considered eligible. In addition, merely having a BMI of 30 kg/m2 or greater would make one meet eligibility criteria even in the absence of weight-related conditions. We plan to follow these patients regularly and measure long-term tangible outcomes at baseline, 6 months, 12 months and 24 months while actively monitoring for side effects. This would include both mental health measures of psychiatric decompensation through psychiatric rating scales such as Brief Psychiatric Rating Scale (BPRS), Montgomery- Asberg Depression Rating Scale (MADRS), Young Mania Rating Scale (YMRS), Mood Disorder Questionnaire (MDQ) as well as bio-markers of cardio-metabolic syndrome such as weight, waist circumference, blood pressure, fasting blood sugar and haemoglobin A1c, triglyceride levels, high-density lipoprotein cholesterol.

Hypothesis: We hypothesize that close follow-up will result in improved psychiatric outcomes, enhanced adherence to psychotropics, and reduced treatment non-adherence stemming from cardio-metabolic concerns. Additionally, we anticipate observing improved cardio-metabolic outcomes with each successive outpatient visit.

Importance: Recognizing the interconnection of body and mind in overall wellness, our study seeks to extend the benefits of semaglutide to individuals with psychiatric illnesses on long-term psychotropics. We aim to enhance the mental and physical health of patients in the South Bronx, emphasizing the importance of holistic care.

W69. SURVEY STUDY: EXPLORING THE FEASIBILITY AND ACCEPTABILITY OF TRANSCRANIAL MAGNETIC STIMULATION THERAPY (TMS) IN PREGNANT INDIVIDUALS WITH DEPRESSION AND /OR SUBSTANCE USE DISORDER (SUD)

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Abstract: Objective: Transcranial magnetic stimulation (TMS) is a non-invasive, well-tolerated, and highly effective Federal Drug Administration approved intervention for depression and substance use disorder (SUD) for non-pregnant individuals. The objective of this study was to determine knowledge and acceptability of TMS among peripartum individuals with SUD.
Methods: We conducted an anonymous survey of pregnant and postpartum individuals with SUD receiving care at a single center's multi-disciplinary perinatal addiction clinic. We developed a survey to explore knowledge and acceptability of TMS in pregnant individuals with SUD and/or mood disorders. Descriptive statistics were used to summarize results.
Results: We collected 75 surveys from May 2023 to September 2023 (response rate 87.2%). In this cohort, most (N=50, 66.6%) were between 26-34 years of age. Most participants (N=59, 78%) identified as white, 12 (16%) as Hispanic, and 6 (8%) as African American. Most were pregnant (N=56, 74.7%) at time of survey. A majority (N=57, 76%) had used at least once substance in the past year, 49 (65.3%) were currently receiving SUD treatment. Of those who reported a mental health diagnosis (N=70, 93.3%), 42 (60%) were currently receiving mental health treatment. With respect to TMS, 45 (60%) participants were interested in TMS as therapy for SUD and 51 (68%) were interested in TMS therapy for depression for perinatal depression.
Conclusion: These preliminary data suggest acceptability and feasibility of TMS as treatment modality for SUD or mental health in this population.

W70. A CASE SERIES OF COVID-ENCEPHALOPATHY IMAGED WITH FMRI AND TREATED WITH NEAR INFRARED LIGHT

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Abstract: 5 patients presented with decreased cognitive function after bouts of infection via COVID-19. Adjacent symptoms included decreased executive function, memory impairment, labile mood, and loss of olfaction. Patients underwent advanced MRI scans of the brain including arterial spin labeling (ASL) functional MRI (fMRI) sequences: the resulting images conveyed reduced signal of the right prefrontal region, frequently in the orbitofrontal region superior to the bilateral olfactory bulbs. Additionally, blood oxygen level dependent (BOLD) sequences of the brain demonstrated a diminished signal in the anterior component of the default mode network (DMN). Patients were diagnosed with post-COVID Encephalopathy after receiving neurological examinations. Baseline self-report measures were obtained, and baseline neurocognitive test outcomes were recorded. Near Infrared (NIR) light therapy was administered with the bilateral orbitofrontal and dorsolateral prefrontal cortices as the primary targets. 4 patients were treated only at the bilateral orbitofrontal cortices while 1 patient was treated at both targets with the intention of increasing blood flow and functioning of the selected regions. After 8 treatments of NIR light therapy, patients exhibited improvement in scoring of both self-report measures and neurocognitive testing, and one patient underwent repeat fMRI sequences with the ASL of their prefrontal region returning to normal. This series of cases illustrates advanced imaging's potential in revealing the neurological deficits derived

from COVID-19, as well as the efficacy of NIR light therapy in the treatment of post-COVID encephalopathy.

W71. THE PROPRANOLOL PROBLEM: MIXED RESULTS IN THE TREATMENT OF TRAUMA-RELATED DISORDERS

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Abstract: Propranolol, a non-selective beta-adrenergic receptor antagonist, has been intensively studied in both its efficacy and effectiveness in the treatment of trauma-related disorders in animals and humans such as acute stress disorder (ASD) and post-traumatic stress disorder (PTSD). Initial research had found promising results in the reduction of Pavlovian-conditioned fear response in mice as indicated by anxiety-like behaviors such as freezing. These positive results were only with the administration of propranolol occurring after the conditioning (secondary treatment), not prophylactically. With relatively strong preliminary data, human trials were pursued in hospital settings with mixed, but mostly nonsignificant results as well as inadequate sample sizes for robust analyses. The trials that were successful in detecting effects of propranolol in the reduction of trauma-related disorders followed trauma-narrative memory reconsolidation protocols. There are a number of working theories from multiple different systematic reviews, meta-analyses, and randomized control trials (both single and double blinded) that offer some explanations for these perplexing results, but most have satisfactorily been addressed in subsequent research. This review will aggregate, analyze, and present existing data and research on both animals and humans in propranolol's treatment of trauma-related disorders with the goal of highlighting trends in research design, data, and study limitations to better inform future research on this substance.

W72. DOUBLE-BLIND, PLACEBO-CONTROLLED MULTIPLE ASCENDING DOSE STUDY OF BXCL501 WITH CONCOMITANT TREATMENT WITH ANTI-DEPRESSANT IN HEALTHY VOLUNTEERS

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Abstract Background: Sublingual dexmedetomidine (BXCL501) is an orally dissolving film formulation of dexmedetomidine (Dex), a selective alpha2-adrenergic receptor agonist. Alpha2-adrenergic receptor agonists are approved for ADHD, opioid withdrawal and hypertension, indications associated with highly aroused and agitated state. Dex is more potent with greater intrinsic activity than other alpha2-adrenergic agonists (e.g. clonidine, guanfacine and lofexidine). BXCL501 is approved for the acute treatment (single dose) of agitation associated with schizophrenia and bipolar disorders based on evidence of safety and efficacy in Phase 3 studies. It is currently being investigated for the treatment of agitation associated with Alzheimer's dementia.

Methods: This study evaluated the safety, tolerability and pharmacokinetics of BXCL501 (daily doses ranging from 30 to 140 mcg) in healthy volunteers for up to 7 days, with 3 days of safety follow-up. Participants were randomized 1:1 to receive BXCL501 or matching placebo. In 6 cohorts (N = 112), BXCL501doses (30, 60, 80, 120 mcg) or placebo were administered every morning (qAM) or split doses of 30 mcg qAM + 60 mcg every evening

(qHS) and 40 mcg qAM + 80 mcg qHS. Cohort 7 participants (N = 13) received an SNRI anti-depressant, 30 mg duloxetine BID and BXCL501 split dose 60 mcg qAM and 80 mcg qHS or placebo.

The majority (94%) of participants who were randomized and dosed completed the study. Participants were aged 21 to 77 years (mean 42 years), male (79%) and African American (62%) or white (36%). With repeat daily dosing, peak plasma concentrations and plasma exposure of Dex increased with the dose between 30 to120 mcg of BXCL501 (qAM). Dex was eliminated with a short half-life of about 2 to 3 hours with no accumulation observed with single or split dosing regimen during 7 days of treatment.

Results: No deaths, serious adverse events or AEs leading to discontinuation were reported. Overall treatment-emergent AEs (TEAEs) reported during the treatment period were mostly mild or moderate intensity and reported in 38% of participants in pooled placebo group, 33% in 30 mcg qAM group, 92% in 60 mcg group, 46% in 30 mcg qAM + 60 mcg qHS group, 42% in 40 mcg qAM + 80 mcg qHS group, 69% in 80 mcg qAM group, 67% in 120 mcg qAM group and 63% in duloxetine + BXCL501 group. The most frequent TEAEs related to BXCL501 were hypotension and orthostatic hypotension (together 32%), then dizziness, headache, paresthesia, somnolence (together 14%) and lack of satiety (6%). The most frequent TEAEs related to duloxetine were hypotension and orthostatic hypotension (together 31%) and abdominal pain and constipation (together 15%). Changes in ECG numeric parameters were observed in some of the groups, but no dose-related relationship or clinically relevant pattern were observed. While orthostatic hypotension was observed across all groups, the AE was mild to moderate in intensity and did not lead to study discontinuation. During post-treatment follow-up, no participants experienced symptoms to suggest a withdrawal syndrome.

Conclusions: This study confirmed the safety, tolerability and PK profile of BXCL501 with repeated dosing across a range of doses. Concomitant administration of BXCL501 (split doses) with an anti-depressant which increases both serotonergic and noradrenergic signaling was well tolerated. These data provide initial support that adjunctive BXCL501 could be a potential treatment option for acute conditions of distress (e.g. opioid withdrawal syndrome, acute stress, post-partum depression).

W73. NAVACAPRANT, A NOVEL AND SELECTIVE KAPPA OPIOID RECEPTOR ANTAGONIST, IMPROVES SYMPTOMS OF MAJOR DEPRESSIVE DISORDER IN A PHASE 2 TRIAL, INCLUDING IN PARTICIPANTS WITH COMORBID ANXIETY AT BASELINE

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Abstract: Introduction: Major depressive disorder (MDD) affects over 21 million U.S. adults and is a leading cause of disability, morbidity, and mortality. Anhedonia and anxiety are common presenting symptoms that are linked to more severe MDD and poorer response to antidepressant treatment. In MDD patients with anxiety, remission rates are lower and remission takes longer to achieve than in those without anxiety. New targeted therapies are needed to treat MDD, while also improving tolerability over current antidepressants. Kappa opioid receptors (KORs) are novel targets abundantly expressed in brain circuits regulating

reward, motivation, stress, and anxiety. KOR antagonists are believed to restore the regulation of multiple neurotransmitters that play a role in regulating mood, reward, cognition, and behavior. Navacaprant (NMRA-140, BTRX-335140) is a novel, potent, and highly selective KOR antagonist with promising efficacy and safety findings in a recent Phase 2 study in adults with MDD. To further characterize the efficacy of navacaprant, efficacy data for depressive symptoms and anhedonia were analyzed in a subgroup of participants with moderate-to-severe anxiety in this Phase 2 study.

Methods: Participants (18-65 y) were randomized 1:1 to 8 weeks of once-daily oral navacaprant (80 mg) or placebo in this randomized, double-blind, placebo-controlled study. A subgroup analysis assessed study outcomes in participants with a baseline Hamilton Anxiety Rating Scale (HAM-A) score equal to or above the median of 17. Outcomes included change from baseline (CFB) to Weeks 4 and 8 in 17-item Hamilton Depression Rating Scale (HAMD-17), HAMD-17 response rates (≥50% decrease from baseline), HAMD-17 remission rates (score ≤7), and Snaith-Hamilton Pleasure Scale (SHAPS). Since ≥10% of patients had missing data, a prespecified last-observation-carried-forward (LOCF) analysis was used to assess outcomes in this subgroup. P values were not corrected for multiplicity.

Results: In participants with moderate-to-severe anxiety (baseline HAM-A ≥17, navacaprant n=48, placebo n=45), the CFB in HAMD-17 with navacaprant was statistically significant vs placebo at Week 4 (least squares mean difference, LSMD [SE], -3.8 [1.22], P=0.002) but not at Week 8 (-2.7 [1.38], P=0.052). For HAMD-17 response rate, navacaprant showed a numerical advantage vs placebo at Week 4 (rate difference [95% CI], 13.2% [-5.0–31.4%], P=0.164, number needed to treat [NNT]=8) and a statistically significant advantage at Week 8 (21.4% [2.5–40.3%], P=0.032, NNT=5). For HAMD-17 remission rate, navacaprant was associated with statistically significant improvement vs placebo at both timepoints (rate difference [95% CI], 14.3% [1.7–26.9%], P=0.034, NNT=7) and (16.3% [2.3–30.2%], P=0.029, NNT=7). The CFB in SHAPS with navacaprant was statistically significant vs placebo at both timepoints (LSMD [SE], -3.7 [1.32], P=0.007) and (-4.5 [1.39], P=0.002). Most frequently reported AEs included headache (4.9% both) and nausea (4.9% navacaprant, 1.0% placebo); no serious AEs were reported with navacaprant.

Conclusions: Navacaprant was associated with statistically significant improvements compared to placebo in symptoms of depression, including anhedonia, following 8 weeks of treatment in participants with moderate-to-severe anxiety at baseline, a population that often experiences poorer acute outcomes. These findings support the further development of navacaprant as an antidepressant monotherapy.

W74. PROPENSITY WEIGHTED APPROACH TO CONTROL THE CONFOUNDING EFFECT OF UNBALANCED DISTRIBUTION OF PLACEBO RESPONDERS ON THE TREATMENT EFFECT IN PSYCHIATRIC CLINICAL TRIALS: AN ARTIFICIAL INTELLIGENCE DRIVEN TRIAL SIMULATION STUDY

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Abstract Background: Randomized, placebo-controlled clinical trials (RCT) are the gold-standard approach for assessing treatment effect (TE=baseline corrected difference of clinical scores in active and placebo arms). The uncontrolled baseline distribution of the individuals' probability of showing improvements due to expectancies of positive treatment outcomes (PE)

can lead to biased estimates of TE as the conventional study designs and statistical approaches don't account for unbalanced baseline distribution of confounding factors such as PE. In this framework, clinical trial simulation (CTS) allows for running multiple trial protocols (scenarios) and to identify alternative and more generalizable approaches for analyzing and reporting RCT results.
Recently a novel methodology was proposed for assessing TE conditional to PE [Transl.Psychiatry. 2023 Apr 29;13(1):141]. Individual PE was estimated using artificial intelligence (AI). The inverse of PE was used as a weight in the MMRM analysis (PSW) to assess TE by controlling the potential confounding effects of unbalanced PE distributions. The objective of the present analysis was to compare the outcomes of PSW and reference non-weighted analysis (NW) using simulated RCTs characterized by different baseline PE distributions.

Methods: CTSs were conducted using data from two placebo-controlled 3-arm RCTs to evaluate paroxetine CR (12.5 and 25 mg) in major depressive disorders. The analysis was organized into 4 steps: 1. The baseline PE was estimated in each study and treatment arm using AI applied to screening and baseline HAMD-17 scores. 2. The impact of different distributions of PE on TE estimate was assessed in 5 simulation scenarios (Si) with different proportions of subjects in 4 classes of PE: 1: < 25%, 2:0.25%-0.5%, 3:0.5%-0.75%, and 4. > 0.75%. S1: 25% of subjects were allocated in each class, S2-3 35% and 45% of subjects were allocated in classes 3-4, S4-5 35% and 45% of subjects were allocated in classes 1-2. In the other classes, an equal number of subjects was allocated for a total of 170 subjects/arm. 3. For each scenario, twenty RCTs were simulated using a Monte-Carlo approach by resampling the original individual HAMD-17 scores associated with different individual propensity values 4. Two MMRM analyses were conducted on the data of each scenario using the PSW and NW methodology.

Results: The results of the analyses (mean TEs estimated in the 20 replicates of the RCTs) indicated a strong impact of the PE distribution on the estimated TE in the NW analysis. The TEs estimated with PSW analysis were substantially insensitive to the distribution of PE. In particular:

•TEs were significantly larger in the PSW with respect to the NW analysis in the low and high-dose groups.

•TEs were significantly lower in the NW with respect to the PSW analysis in scenarios with 35% and 45% of subjects in class $p > 0.75$

•TEs were significantly larger in the NW with respect to the PSW analysis in simulations with 35% and 45% of subjects in class $p < 0.25$.

•TEs were similar in each simulation scenario irrespectively to the PE distribution in the PSW analyses

Conclusions: A strong correlation between PE distribution and assessment of TE was detected in NW analysis. The PSW analysis better controlled the baseline unbalance of PE and provided similar results in different simulation scenarios. These findings emphasize the potential interest of PSW to become the reference approach for analyzing RCTs.

W75. LEMBOREXANT AUGMENTATION OF NALTREXONE FOR ALCOHOL CRAVING AND SLEEP: A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY

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Abstract: Pharmacological interventions for alcohol use disorder (AUD) include FDA approved medications such as naltrexone that have demonstrated efficacy in reducing alcohol cravings, consumption, and likelihood of relapse. However, there is significant variability in response to treatment due to persistent symptoms such as cravings and insomnia. In this study, we focus on the orexin system, which has been implicated in behaviors such as feeding, sleep-wake cycle, motivation, and reward associated with food, sex and substances including alcohol. Orexin receptors have been shown to modulate addictive behaviors and arousal in animals. In humans, orexin antagonists are approved for treatment of insomnia. Multiple animal studies have demonstrated efficacy of orexin antagonists in reducing alcohol craving, self-administration, and reinstatement of alcohol use induced by cues and stress.
We have completed a randomized, double-blind, placebo-controlled pilot trial of naltrexone plus placebo versus naltrexone plus lemborexant augmentation conducted at The Menninger Clinic on 8 inpatients with alcohol use disorder and insomnia over 2 to 4 weeks. We measured cue-induced cravings using virtual reality and Alcohol Urge Questionaire and non-cued cravings using the Penn Alcohol Cravings Scale. Secondary measures will include sleep parameters using an actigraph measuring total sleep time, sleep latency, wake after sleep onset, sleep efficiency, and patient report measures using the Insomnia Severity Index, the Pittsburg Sleep Quality Index and the Epsworth Sleepiness Scale. Other measures will include anxiety, depression, and suicide risk using self-report questionnaires. H1: we hypothesize that the group receiving naltrexone plus lemborexant augmentation will have a greater decrease in cue-induced and non-cued alcohol craving scores than naltrexone alone. H2: we hypothesize that the group receiving naltrexone combined with lemborexant will experience a greater improvement on subjective and objective sleep measures, as well as depression, anxiety, and suicide risk.

W76. AN ALGORITHMIC MODEL FOR THE RISK OF NEW-ONSET SCHIZOPHRENIA IN YOUNG CANNABIS USERS

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Abstract: The present study is to develop a mathematical model to estimate the incidence of new cases of schizophrenia in adolescents as a result of cannabis use. The equation is a logistic function, which models the growth of a population with a limiting value as a carrying capacity. The most important observation is that the curves estimated, are steeper and higher for frequent cannabis users than for infrequent or never users, and for males than for females. The curves also shift to the left with earlier age of first cannabis use, indicating a higher risk of schizophrenia at younger ages. According to the calculations, we can extrapolate new-onset schizophrenia cases by creating a scenario in which 5% of adolescents aged 15-18 years are cannabis users. This means that there are 1.25% of cannabis users in each age group. Second, we assume that cannabis users are equally divided between high and low frequency users. This means that in each age group there are 0.625% high-frequency users and 0.625% low-

frequency users. Third, we assume that the sex ratio of cannabis users is the same as in the general population, which is about 51% male and 49% female.
Using these assumptions, we can calculate the number of new cases of schizophrenia in each age group by multiplying the cumulative incidence of schizophrenia by the number of cannabis users in that age group. For example, among frequent male cannabis users aged 15, the number of new schizophrenia episodes is 0.06×0.00625×100,000=37.5, where 0.06 is the cumulative incidence of schizophrenia among frequent male cannabis users aged 15, 0.00625 is the proportion of frequent male cannabis users in the population, and 100 000 is the total population. According to these calculations, the total number of new schizophrenia episodes in a population of 100,000 adolescents aged 15-18 years in which 5% are cannabis users is 585. This is more than 10 times higher than the number of new schizophrenia episodes in the same population in which no one uses cannabis, which is 50.

W77. USING EXPERIMENTAL DATA TO GUIDE PSYCHOTHERAPEUTIC APPLICATIONS OF DISSOCIATIVE AND PSYCHEDELIC MEDICATIONS

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Abstract: Classic psychedelics (e.g., psilocybin, lysergic acid diethylamide) and N-methyl-D-aspartate (NMDA) receptor-mediated dissociatives (e.g., ketamine) are being investigated for a growing number of applications in psychiatry. These pharmacological drug classes have been likened for their potential to achieve rapid benefits after a transient psychoactive period and converging on downstream mechanisms of glutamate-driven neuroplasticity. Of particular interest, models of drug-assisted therapy are being explored as a strategy for optimizing treatment with these interventions (1). However, there has been little research to date on how best to combine drug and psychotherapeutic support. Even less is known about how specific properties of classic psychedelics and dissociatives could inform the varieties of support provided for each.
Dextromethorphan (DXM), like ketamine, is a noncompetitive NMDA-receptor antagonist that elicits subjective experiences of dissociation/disembodiment at sufficiently high doses. Our team at the Johns Hopkins Behavioral Pharmacology Research Unit (BPRU) conducted a series of investigations to examine the effects of placebo, DXM 400mg/70kg, and three doses of psilocybin (10, 20, and 30mg/70kg). These drugs were administered to 20 hallucinogen-experienced but otherwise healthy volunteers, using a double blind, within-subjects, crossover design and experimental conditions that are typical of therapeutic psychedelic trials. Significant efforts were taken to mask drug conditions and later assessed. Previous reports of this dataset have contributed to scientific knowledge of the subjective, behavioral, cognitive, physiological, and most recently, psychological effects of these drugs (2).

Here, we synthesize key findings across these studies and present new, unpublished data relevant to psychotherapeutic applications of DXM and psilocybin, and to dissociative- and psychedelic-assisted therapies, more broadly. Experiences of both DXM and psilocybin were rated as personally meaningful, spiritually significant, psychologically challenging, and psychologically insightful compared to placebo. Medium and high doses of psilocybin contributed to positive changes in attitudes toward life, attitudes toward self, mood, relationships, behavior, and spirituality after 1 week. DXM also seemed capable of similar effects when used under the same conditions. Ratings of acute drug experiences predicted

positive changes at 1 week, particularly for the medium dose of psilocybin. For DXM, ratings of dosing sessions as personally meaningful (vs spiritually significant or psychologically insightful) were most predictive of enduring psychological changes. Compared to psilocybin, DXM was associated with greater disembodiment, physical discomfort, impairment of episodic memory, and being experienced acutely as "less real."

This study has several limitations, including the challenge of translating these results to clinical, hallucinogen-naive populations. Nonetheless, these data suggest the value of supportive preparation, dosing support, and aftercare with dissociative-based therapies as a strategy for treatment optimization. While some of these methods may overlap with those utilized across therapeutic psychedelic trials, there also appear to be areas of critical divergence for dissociative therapies, based on a unique subjective and cognitive profile for this drug class as demonstrated here.

W78. BRAIN AND PERIPHERAL TISSUE DISTRIBUTION OF INTRANASAL RADIOLABELED ITRUVONE (PH10) IN LABORATORY RATS

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Abstract Background: Itruvone (PH10, pregn-4-en-20-yne-3-one) is an odorless and tasteless investigational synthetic neuroactive steroid formulated as a nasal spray. Itruvone activates chemosensory neurons in the nasal passages to impact fundamental olfactory-amygdala neural circuits involved in the pathophysiology of depression. In a randomized, double-blind, placebo-controlled Phase 2A study, itruvone monotherapy (daily dose of 6.4 µg) was found to be significantly superior to placebo as early as Week 1 and sustained to Week 8 for the treatment of major depressive disorder1 (P=0.022, ES 0.95 at Week 8). Stimulation of the limbic amygdala increases the activity of the sympathetic autonomic nervous system and the release of catecholamines from the midbrain. The objective of the present study was to determine the brain and peripheral tissue distribution following a single intranasal dose administration of 92.4 µg/rat radiolabeled itruvone (14C-itruvone) to naïve male and female laboratory rats.

Methods: Male and Female Long Evans rats 10 to 13 weeks old and weighing between 231 to 325 g at initiation of dosing were used. Animals were euthanized at 15 minutes, 60 minutes, and 6, 24, 72, and 168 hours after intranasal dosing of radiolabeled itruvone and subjected to whole-body autoradiography. Whole-body sagittal plane 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. Whole blood was taken by cardiac puncture to measure blood and plasma levels of 14C-itruvone using liquid scintillation counting (LSC).

Results: One male and one female rat were used for autoradiographic analysis at each time point. A single intranasal administration of 14C-itruvone was largely confined to the nasal passages and digestive system, with low or undetectable 14C-itruvone uptake in either peripheral (e.g., blood and blood plasma, kidney, pancreas testes/uterus) or central nervous system (CNS: olfactory lobes, cerebrum, cerebellum, and spinal cord) tissue at all time points-from 15 minutes to 168 hours after intranasal administration. Blood and plasma concentrations (ng Equivalents 14C-itruvone/g, where the lower limit of detection was < 9.4 ng-eq/g), as measured by LSC, were also low, peaking at 15 minutes in males (12.3 and 21.3 ng-eq/g, respectively) and at 1 hour in female rats (88.4 and 145 ng-eq/g, respectively).

Discussion: Overall, the data further support the proposed mechanism of action whereby itruvone binds to receptors of peripheral sensory neurons in the nasal cavity, rather than neuronal receptors in the brain, thereby limiting transport of molecules to the circulatory system, minimizing both potential blood-brain barrier penetration and systemic exposure. When combined with preclinical electrophysiology data demonstrating that the mechanism of action of itruvone does not involve direct activation of GABA-A receptors2, the current evidence suggests that itruvone has the potential to achieve antidepressant effects while avoiding benzodiazepine- or antidepressant-associated side effects such as weight gain, sexual dysfunction, and sedation or psychotomimetic side effects and safety concerns potentially associated with intravenous or intranasal ketamine therapy. The efficacy, safety, and tolerability of itruvone monotherapy in the treatment of major depressive disorder will be further evaluated in a planned Phase 2B study.

W79. LONG-TERM SAFETY AND EFFICACY OF ESMETHADONE IN PATIENTS WITH MAJOR DEPRESSIVE DISORDER: FINDINGS FROM A 12-MONTH OPEN-LABEL STUDY

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Abstract Background: Esmethadone (REL-1017) is an N-methyl-D-aspartate receptor (NMDAR) uncompetitive antagonist antidepressant candidate. In placebo-controlled, double-blind, randomized studies, adjunctive treatment with esmethadone showed promising efficacy and safety results in patients with major depressive disorder (MDD) and an inadequate response to standard antidepressants.

Methods: This 12-month, open-label safety and efficacy study of oral 25 mg esmethadone once daily included patients with MDD who had completed one of three double-blind 4-week esmethadone studies (Study REL-1017-301 and study REL-1017-302 investigated esmethadone as adjunctive treatment; study REL-1017-303 investigated esmethadone as monotherapy), and also included patients with MDD without prior participation in randomized esmethadone studies (de novo patients). Safety assessments included recording all adverse events (AEs), clinical laboratory measures, vital signs, electrocardiogram (ECG), and scores of the Columbia Suicide Severity Rating Scale (CSSRS). Efficacy was measured using the Montgomery-Åsberg Depression Rating Scale (MADRS10), the Clinical Global Impressions of Improvement (CGI-I) and Severity (CGI-S), and the Hamilton Anxiety Rating Scale (HAM-A). Baseline scores for patients from the 4-week studies were recorded prior to the first double-blind dose, and for de novo patients, prior to the first open-label dose. The Safety Population (SP) included all enrolled and dosed patients; the Full Analysis Set (FAS) included all treated patients with at least one efficacy assessment during the open label study.

Results: The SP included 618 patients; FAS consisted of 582 patients, including 202 de novo patients. For the SP, the mean standard deviation (SD) age was 42.9 (13.5) years, and the mean (SD) baseline MADRS score was 34.5 (4.7). There were no deaths and no treatment related

serious AEs. The most common AEs were headache (4.4%), nausea (4.0%), and dizziness (2.4%); 3% of SP discontinued because of treatment-related AEs. The majority of AEs were transient and mild or moderate in intensity. and. There were no signals for meaningful neurological, cardiovascular, hepatic, renal or metabolic or sexual side effects and no worsening in CSSRS scores. There were no AEs related to QTc prolongation and no signals for abuse potential. In the FAS population, mean (SD) change from baseline (CFB) for the MADRS was - 20.7 (10.5), -20.0 (10.7), -21.2 (11.4), and -21.8 (10.1) at 3, 6, 9, and 12 months, respectively. In the de novo population, mean CFB for the MADRS was -20.0 (10.2), -18.9 (10.8), -18.8 (10.3), and -23.8 (9.5) at 3, 6, 9, and 12 months, respectively. In the FAS group, the CGI-S score decreased from 4.8 (0.6) at baseline to 2.5 (1.2) at month 12, and in the de novo group from 4.8 (0.6) to 2.4 (1.2). HAM-A score decreased from baseline of 20.6 (5.9) to 10.0 (7.1) in the FAS group and from baseline of 20.6 (5.9) to 10.6 (7.4) in the de novo group at month 12. CGI-I scores at 12 months were improved (score of < 3) in 89.1% of the FAS group and 96.5% of de novo patients. In the FAS group, response and remission rates at 12 months were 69.5% and 49.0%, respectively, and in the de novo group were 77.2% and 54.4%.

Conclusions: Long-term treatment with esmethadone was well tolerated with no signal for meaningful neurological, cardiovascular, metabolic or sexual side effects. No new safety concerns were identified. Patients showed a mean CFB in MADRS scores of approximately -20 points, with consistent improvements in CGI-S, CGI-I, and HAM-A scores. The antidepressant efficacy of esmethadone was sustained over 12 months.

W80. EFFICACY AND SAFETY OF ESKETAMINE NASAL SPRAY AS MONOTHERAPY IN ADULTS WITH TREATMENT-RESISTANT DEPRESSION: A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY

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Abstract Background: Esketamine (ESK) nasal spray is approved in 75 countries as adjunctive treatment with oral antidepressant (OAD) for treatment-resistant depression (TRD). However, whether ESK is efficacious as a monotherapy for TRD patients is not known. Considering the suboptimal effect of standard of care OADs for many patients in the TRD population and their associated side effects, the effectiveness of ESK as monotherapy is an important question that could inform clinical practice. This study assessed efficacy and safety of ESK monotherapy compared to placebo (PBO) in adults with TRD.

Methods: This randomized, double-blind (DB), multicenter, PBO-controlled study (NCT04599855) enrolled adults with recurrent or single (duration ≥2 years) episode of major depressive disorder (DSM-5 criteria) without psychotic features (Mini International Neuropsychiatric Interview) and who scored ≥34 on the Inventory of Depressive Symptomatology-Clinician rated, 30-item (IDS-C30) scale. Participants must have had nonresponse (≤25% improvement) to ≥2 OADs during the current depressive episode. All participants had a ≥2-week OAD-free period and were then randomized 2:1:1 to receive either PBO or fixed dose ESK (56 or 84 mg) twice-weekly for 4 weeks. The full efficacy analysis set included participants meeting the following criteria: Montgomery-Asberg Depression Rating Scale (MADRS) total score ≥28 at Screening Weeks 1, 2 and Day 1 (pre-randomization) and ≤25% improvement in MADRS total score from Screening Week 1 to Day 1; received at least 1 dose of DB study intervention. Primary endpoint was change in MADRS total score from

baseline to Day 28. Key secondary endpoint was change in MADRS total score from baseline to Day 2 post first dose. Safety was monitored throughout the study. Primary and key secondary endpoints were analyzed using a mixed-effects model with repeated measures and a predefined testing hierarchy to control for multiplicity.

Results: Full efficacy analysis set was 378 adults (ESK: 56 mg, 86; 84 mg, 95; PBO: 197). Participant mean age was 45.4 years (9.8% ≥65 years), majority (61.1%) were female. At baseline, mean IDS-C30 score was 45.8, and mean MADRS total score was 37.3. Mean (SD) change from baseline to Day 28 in MADRS total score was: ESK 56 mg, −12.7 (11.82); ESK 84 mg, −13.9 (11.89); PBO, −7.0 (10.07). Differences for both ESK groups compared to PBO were statistically significant (2-sided $p < 0.001$). At Day 28, Least-square (LS) mean difference (SE) between ESK and placebo was −5.1 (1.42) and −6.8 (1.38) for 56 mg and 84 mg, respectively. At Day 2, differences in ESK 56 mg group (2-sided p=0.004) and ESK 84 mg group (2-sided p=0.006) were also significant compared to PBO group. At Day 2, LS mean difference (SE) between ESK, and placebo was −3.8 (1.29) and −3.4 (1.24) for 56 mg and 84 mg, respectively. The most common (≥10%) treatment-emergent adverse events during the DB phase for combined ESK groups were nausea, dissociation, dizziness and headache.

Conclusion: The results of this 4-week controlled study show a statistically significant and clinically meaningful improvement of depressive symptoms as early as Day 2 after the first dose with ESK monotherapy (56 and 84 mg doses). No new safety signals were identified. These results provide important new data to inform treatment options for patients with TRD receiving ESK.

W81. HOW SHOULD WE MEASURE SLEEP AND CIRCADIAN RHYTHM IN ADOLESCENTS AND YOUNG ADULTS WITH PSYCHOSIS SPECTRUM SYMPTOMS?

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Abstract Objectives: Sleep and circadian rhythms are potentially modifiable biological targets that are disrupted in adolescents and young adults with subthreshold and threshold psychosis. In a preliminary study, we sought to determine cross-sectional correlations between different methods of assessment and psychiatric symptoms in youth with psychosis spectrum symptoms.
Methods: We measured sleep and the circadian rhythm for 7 days in youth ages 16-30 with psychosis spectrum symptoms within the past year or a threshold psychotic disorder diagnosis. Additionally, enrollment required at least mild sleep disturbances, defined as a Structured Interview for Psychosis-Risk Syndromes (SIPS) item G1 (SIPSG1) >=1. Sleep and circadian rhythm were measured using 4 modalities: 1) wrist actigraphy (also known as accelerometry), 2) a clinician-rated sleep scale (SIPSG1), 3) self-reported sleep scales on the Patient-Reported Outcomes Measurement Information System (PROMIS), and 4) sleep diaries.

Results: The mean age of the study sample was 21.8 (Standard Deviation (SD) = 4.41) years old, and 57% (n = 12) of participants were female. Self-reported race/ethnicities of the sample were: 48% (n = 10) non-Hispanic Black, 38% (n = 8) non-Hispanic White, 15% (n=3) other. The mean 18-item Brief Psychiatric Rating Scale (BPRS18) score for the past week was 30.6 (SD = 15.53). 29% (n = 6) had a diagnosed threshold psychotic disorder, and 29% (n= 6) were

prescribed antipsychotic medications. Clinician-rated sleep disturbances on SIPSG1 had a mean of 2.71 (SD=1.45).

Clinician-rated sleep disturbances SIPSG1 was significantly correlated with self- reported PROMIS sleep related impairment ($r = 0.66$, $p = 0.03$) and disturbances ($r = 0.79$, $p < 0.001$). However, self-reported healthy sleep habits (PROMIS sleep practices) were not associated with PROMIS self-reported sleep disturbances or impairments. Actigraphy measures were not associated with self-reported, clinician- rated, or sleep diary measures.

There was a positive correlation between the psychiatric symptoms on the BPRS18 and PROMIS sleep-related impairment ($r = 0.60$, $p < .01$).

Conclusions: Measuring sleep and circadian rhythm in adolescents and young adults with psychosis spectrum symptoms is feasible, but there were inconsistencies among the 4 modalities of measurement investigated.

W82. EXPLORING NON-US RATER WORK STRESS AND BURNOUT: HOW CAN WE DO BETTER TO PRESERVE OUR PRIMARY ENDPOINT EVALUATORS?

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Abstract: Introduction: Psychiatric and neurological clinical trials face a myriad of challenges navigating research and development (R and D) and have some of the lowest probability of success rates (Zhu, 2020; Thomas, 2021). Skilled psychometric raters are crucial to the success of such clinical trials as they are responsible for collecting primary efficacy endpoint data. Proficient raters require vigorous vetting and continuous training, leading them to become experts in their role as an endpoint evaluator and with increased experience make them quite difficult to replace. It is therefore vital to increase our understanding of the unique job-related stressors raters experience, including burnout, and how these may negatively impact their performance. Supporting rater wellbeing and longevity is key to the future success of our industry. Despite their distinctive and critical role, rater-centric investigations of work stress or burnout were not found in a review of the current literature.

Methods: The Site Rater Stressors Survey (SRSS) was specifically developed for the current study to assess factors related to job stress and burnout from a rater perspective. Development of the survey incorporated input from leaders at the site-level and at rater training and surveillance companies ensuring content and face validity. The instrument was written in English, took about 10 minutes to complete and contained 39 items covering demographics and questions assessing perceptions of various job-related tasks. Likert-type items assessed stress associated with rater tasks (18 items), burnout frequency and severity (2 items), job stress impact to work performance (4 items), and 3 open-ended questions soliciting additional feedback. Three rater training vendors distributed the SRSS to raters within their database who completed rater training. Raters were informed of the survey, its purpose, how their contact information was obtained and that their participation was voluntary and anonymous.

Results: The SRSS was completed by 209 OUS raters (in Canada, Mexico, South America, Europe, Southeast Asia, Russia and Africa). Job-related tasks with the highest levels of stress reported were vendor-related troubleshooting of digital technology, vendor training that

seemed inconsistent, and having limited resources at the site to effectively complete the workload. Almost half (46.6%) of the raters reported experiencing burnout at least sometimes, and a majority (88%) reported that burnout had a negative impact on their ratings. Over two-thirds (68.9%) of raters reported some level of interference from stress and burnout in their role as a rater, and 27% said they would likely to leave their job if they were presented with another offer.

Discussion: Raters possess a highly specialized and essential role that substantially contributes to the success of psychiatric and neurological clinical trials. However, the data presented here indicates that these raters experience a significant level of job-related stress and burnout that has a high likelihood of impacting the overall quality of their work. This poster will further explore the stressors that may lead to a decline in rater work performance. We will also discuss various strategies that clinical trial stakeholders may employ in efforts to reduce work-related stress and burnout experienced by raters.

W83. USE OF A NOVEL PHARMACOGENOMIC BIOMARKER TO ENRICH RESPONDERS FOR LIAFENSINE IN TREATMENT-RESISTANT DEPRESSION PATIENTS IN A PHASE 2B CLINICAL STUDY

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Abstract: Introduction: For most disorders, only subpopulations are responsive to approved drugs. For example, the typical response rate is about 60% for diabetes and as low as 25% for many approved drugs in oncology. For major depressive disorder, the STAR*D study suggests that approximately 35% of depressed patients are responsive to their initial antidepressant treatment. In some fields, such as oncology, it has become commonplace to use genetic biomarkers to select which patients a drug is most likely to be efficacious in, and many regulatory approvals are based on this.

Given the diversity of drug responsiveness in psychiatry patients, there is a great interest in identifying biomarkers for responsive subpopulations. A corollary is that drugs under development may have failed because the original studies did not focus on the correct subgroup of patients. Identifying biomarkers from existing data of previous clinical trials may lead to the discovery of responsive subpopulations and allow medications to be retargeted.

The current work is based on the prior clinical development program for liafensine (DB104) in treatment-resistant depression (TRD). These studies failed to demonstrate the superiority of liafensine to standard of care (SOC).

Using blood samples and clinical data from these past clinical studies and a novel genomic biomarker discovery platform (based on whole genome sequencing and artificial intelligence), a new biomarker, named Denovo Genomic Marker 4 (DGM4™) correlating with liafensine efficacy in TRD patients was discovered. A new randomized, double blind, placebo controlled Phase 2b study (ENLIGHTEN) was conducted using this biomarker to enrich the patients to prospectively validate the biomarker hypothesis.

ENLIGHTEN Study (Phase 2b) DGM4 status of the patient to enrich the study population with DGM4-positive TRD patients who were randomized to one of the 3 treatment arms: placebo, liafensine 1 mg per day, and liafensine 2 mg per day in a 1:1:1 ratio. The 6-week treatment period was followed by a 28-day follow-up primarily for safety monitoring. The primary endpoint was the change in Montgomery Åsberg Depression Rating Scale (MADRS) score

from baseline to Week 6. Several novel methods were used for patient enrollment and management during the study.

Results: The study enrolled a total of 197 TRD patients (188 DGM4-positive treated). All endpoints were successfully met. DGM4-positive patients who received liafensine demonstrated a highly significant improvement in MADRS over the 6-week treatment period compared to those who received placebo (mean change –15.4 ± 0.9 in the combined liafensine arms vs. –11.0 ± 1.3 in the placebo arm, p = 0.0056). Similarly, change in Clinical Global Impressions Scale-Severity (CGI-S) from baseline was –1.5 in the combined liafensine arms vs. –1.1 in the placebo arm (p = 0.0189); Clinical Global Impressions Scale-Improvement (CGI-I) was 2.3 in the combined liafensine arms vs. 2.9 in the placebo arm (p = 0.0026); change in Sheehan Disability Scale (SDS) from baseline was –11.5 in the combined liafensine arms vs. –8.4 in the placebo arm (p = 0.05). The most common adverse events with liafensine treatment were nausea (12.9%), headache (12.1%), constipation (10.5%), and somnolence (8.9%). Overall, liafensine was highly efficacious and well tolerated in DGM4 positive patients.

Discussion: This groundbreaking study was the first successful use of a genetic biomarker in a controlled CNS clinical trial to identify patients with a psychiatric disorder for drug response, and the results confirmed the predicted outcomes. This marks the beginning of a new era of a more efficient way of developing new antidepressants, and potentially therapies for other CNS diseases.

W84. A REVIEW OF RECENT TRENDS IN SOCIODEMOGRAPHIC COMPOSITION AMONG ASCP MEMBERS, LEADERS, AND MEETING ATTENDEES

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Abstract: The literature highlights the pervasive impact of discrimination and implicit bias in academia, which can hinder the participation and advancement of individuals from underrepresented groups, particularly in scientific fields. These barriers highlight the importance of initiatives supporting diversity, equity, and inclusion (DEI). Therefore, the American Society of Clinical Psychopharmacology (ASCP) has actively worked to promote DEI in its membership and participation.

For this study, we analyzed sociodemographic shifts, including an assessment of underrepresented minorities (URM) representation, among ASCP membership from 2018 to 2023. Leadership composition and meeting attendees' demographics were also assessed. We collected sociodemographic data from the ASCP records including sex and gender distribution, and ethnic diversity. The data were analyzed using descriptive statistics, linear regression, and ANOVA to determine the pattern and statistical significance of the sociodemographic changes over the past 6 years.

In 2023, ASCP had 1,113 members (male: 63.79%, female: 33.78%, and other: 0.9%), 195 in leadership positions (male: 63.59%, female: 36.41%), and on average 333 individuals attended the spring, fall, and annual meetings (male: 54.27%, female: 43.61%, and other: 2.12%). From 2018 to 2023, the membership composition did not change significantly, although there was a moderately strong correlation ($R2 > 0.5$) showing an increase in the proportion of male members (slope=0.88, p=0.104) and a decrease in female members (slope=-1.24, p=0.057). Over the same period, the leadership configuration changed significantly, showing an increase in the proportion of members identifying as Asian (slope=-1.24, p=0.057, R2=0.72) and a concomitant decrease in the proportion of members who identify as White European (slope=-1.92, p=0.006, R2=0.88). The sociodemographic characteristics of the attendees has also changed significantly over time, showing a decrease in age (slope=-0.70, p=0.02, R2=0.79), an increase in female attendees (slope=0.44, p=0.01, R2=0.82), a decrease in the proportion of attendees identifying as White European (slope=-2.03, p=0.001, R2=0.84), and a significantly higher proportion of URM attendees (15% in 2018 vs 21% in 2023, p=0.016). There were also non-significant changes, with moderately strong correlations ($R2 > 0.5$) indicating a decrease in the proportion of male attendees (slope=-0.64, p=0.070) and an increase in the proportion of attendees identifying as Asian (slope=0.98, p=0.072) since 2018. Additionally, starting in 2023, to better understand the sociodemographic characteristics of their membership, leadership, and attendees, ASCP expanded the "other" sex and gender category to include gender fluid (0.09%), non-binary (0.09%), prefer to self-describe (0.09%), and prefer not to answer (0.63%); and the "other" ethnicity category to include Black (0.45%), Black African (0.45%), Asian American (0.9%), Middle Eastern (1.17%), Multi-race (0.54%), Native Alaskan (0.18%), prefer to self-describe (4.22%), and prefer not to answer (1.44%).

Efforts to enhance diversity in academia are essential for fostering inclusive, productive, and welcoming environments. Initiatives such as the ASCP Inclusivity Committee aim to enhance diversity in research, leadership, membership, and participant representation. The importance of DEI extends beyond academia to clinical and translational science, where diversity among researchers and trial participants can help address health disparities. These results show that although significant improvements have been achieved over the past 5 years, more work is needed to foster inclusivity at ASCP.

W85. USING ACTIVE AND PASSIVE DIGITAL PHENOTYPING TO AUGMENT EFFICACY ASSESSMENTS IN AN EARLY-STAGE DRUG DEVELOPMENT PROGRAM

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Abstract Background: Early-stage drug development requires balancing cost and optimization of data collection. Blinded trials may not always be feasible and the risks of placebo effects may need to be accepted in order to detect beneficial elements of a novel compound. One strategy to reduce risk, by increasing density of data collection and collecting data less susceptible to placebo effects, involves technology-based approaches to collect densely sampled active and passive data. Passively collected data such as activity and sleep seem less vulnerable to participant-driven placebo effects. Some actively sampled data are not transparently related to efficacy, such as engagement in positive activities that are more

common when participants are less symptomatic. Here we present the results of an open-label treatment study of a "ANC-501", a V1b receptor antagonist in participants with Major Depressive Disorder. Sampling with passive and active technology-based assessments occurred daily and clinical ratings were dispersed at standard clinical trials intervals.

Methods: In this study, 13 participants were treated with ANC-501 50mg adjunctive to ongoing antidepressant medication in a non-blinded design for 8 weeks. Standard clinical ratings of depression (MADRS) and anxiety (HAM-A) were collected at days 1, 8, 15, 29, 43, and 56. During the protocol, participants also answered ecological momentary assessment (EMA) surveys, 2 times per day, 7 days per week, as well as wearing an actigraph smartband which measured daily steps and daytime and night-time sleep data. EMA surveys queried depression (HAM-D 6) and Anxiety (GAD7) as well as a previously validated survey of daily activities which included location (Home vs away), social context (alone vs. with someone), productive and unproductive home-based activities and away from home activities. Data analyses included changes in symptoms based on in-person and EMA assessments as well as EMA-based assessments of activities, sleep, and daily steps. Concurrent and lagged analyses were used to determine if EMA and actigraphy-based assessments converged with and predicted later changes in symptoms.

Results: A total of 658 EMA surveys were collected as well as 184 patient-days of actigraphy. In person and EMA based ratings of depression improved to day 56, all $p < .02$. The effect sizes for improvements in depression were $d=1.8$ for in person ratings and $d=1.3$ for EMA. EMA depression ratings correlated with clinical ratings at all assessments (all r's >.05) and both clinical and EMA depression ratings correlated with concurrent step counts ($p < .05$). Changes in EMA-rated depression up to days 15 and 29 predicted changes in clinical ratings at days 43 and 56 (all $r > .45$). Productive activities significantly increased over time ($p=.02$) and these increases from baseline to days 8, 15, and 29 predicted clinical ratings of depression at later assessments. Total minutes of sleep improved over the protocol, due to significant increases in nighttime sleep, $X2(7)=24.98$, $p < .001$.

Implications: Even in a small unblinded trial, passive and active digital phenotyping converged with and predicted clinical ratings. Digital phenotyping that is not transparently related to efficacy assessments (sleep, productive activities, step counts) correlated with concurrent clinical ratings and predicted later clinical changes. Thus, digital phenotyping data anticipated later clinical outcomes, validating these ratings in terms of sampling the behavior that precedes the dispersed ratings. These data suggest that low-cost, technology-based assessments can efficiently provide high volumes of unbiased information that could never be collected by an in-person assessment strategy.

W86. LOW LONG-TERM RISK OF EPS WITH MUSCARINIC AGONIST KARXT (XANOMELINE AND TROSPIUM)

Keisha Novak[1], Carolyn Watson[1], Amy Claxton[1], Ronald Marcus[1], Stephen K. Brannan[1], Colin Sauder[1]*

[1]Karuna Therapeutics

Abstract Background: Atypical antipsychotics can induce extrapyramidal symptoms (EPS), contributing to overall side-effect burden. KarXT (xanomeline and trospium chloride) is an investigational therapy targeting muscarinic receptors and lacking D2 dopamine receptor

binding that shows promise for treating schizophrenia without many of the side effects associated with current treatments. Here, we further characterize EPS rates across 52-week long-term clinical trials in KarXT.

Methods: EMERGENT-1 (NCT03697252), EMERGENT-2 (NCT04659161), and EMERGENT-3 (NCT04738123) were 5-week, randomized, double-blind, placebo-controlled, inpatient trials in people with schizophrenia. Treatment-emergent adverse events (TEAEs) associated with EPS from the safety populations, defined as all participants who received □1 dose of trial medication, were pooled. EPS were assessed by examining change from baseline on the Simpson-Angus Scale (SAS), Barnes Akathisia Rating Scale (BARS), and Abnormal Involuntary Movement Scale (AIMS). Additional interim data from the long-term, 52-week EMERGENT 4 (NCT04659174) and EMERGENT 5 (NCT04820309) open-label safety/tolerability studies are reported here.

Results: In the 5-week pivotal studies, rates of EPS TEAEs were 3.2% and 0.9% among KarXT (N=340) and placebo (N=343), respectively. Among EPS TEAEs, incidence of treatment-related EPS AEs were 1.5% among KarXT and 0.3%, in placebo. Among the long-term 52-week studies (N=674), rates were lower than the 5-week studies, with 1.6% of KarXT participants reporting an EPS TEAE. The incidence of EPS AEs deemed to be treatment-related was 1.0%; the most commonly reported treatment-related EPS AE was akathisia (0.6%). Across both studies, incidence of dose reduction and treatment discontinuation due to EPS TEAE were ≤0.7%. Most EPS TEAEs were mild, resolved during treatment without dose changes or discontinuation, and were not accompanied by corresponding elevations in EPS assessment scales (SAS, BARS, AIMS).

Conclusions: The incidence of TEAEs associated with EPS with KarXT was low and not associated with increased scores on EPS scales across short term and long-term studies. These results, combined with the robust efficacy of KarXT in trials to date, suggest that KarXT is not associated with akathisia or EPS.

W87. OXYBUTYNIN IS EFFECTIVE ON METHADONE- INDUCED HYPERHIDROSIS TREATMENT: A CASE REPORT

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Abstract: Methadone is a synthetic opioid with the longest history of use for opioid use disorder treatment, having been used since 1947. methadone maintenance treatment (MMT) is a long-term and slow-onset substitution therapy, which needs complete medication adherence to achieve optimal outcomes. Hyperhidrosis is a common adverse effect experienced by patients using methadone as opioid replacement therapy; research has suggested the rate may be as high as 45%. Sweat glands are enervated by the sympathetic nervous system, activated via muscarinic receptors, and it is not surprising that an anti-muscarinic would antagonize perspiration through its peripheral action on exocrine glands. Oxybutynin is an anticholinergic medication able to antagonize the M1, M2, and M3 subtypes of the muscarinic acetylcholine receptor. It is generally used to relieve urinary and bladder difficulties. In the second half of the last decade, specific treatment with oxybutynin began to be reported for treatment of hyperhidrosis. This condition could be one of the barriers to methadone maintenance treatment adherence. On the other hand, reducing or discontinuing methadone might result in withdrawal

symptoms and relapse. Hence, optimizing the treatment and improvement of compliance require addressing and taking care of side and adverse effects of methadone.

Case Description: The patient was a 27-year-old single male with no prior medical or psychiatric history who was maintained on methadone 180 mg daily, when he was no longer reported his withdrawal symptoms and craving for opioid use. Before starting methadone maintenance treatment, the patient was misusing Percocet for the past 6 years, which was introduced by his friends. He also admitted to smoking 1 joint of Marijuana and occasional misusing half a tablet of Xanax 2 mg to self-treat his anxiety. All urine tests were positive for Methadone, also for Cannabis and Benzodiazepine consistently on every 2-week basis. Serum methadone level was measured 3 hours after methadone administration to determine adequate plasma concentrations of methadone and it was 1200 ng/ml (normal range of 100-400 ng/ml).

The patient did not show or endorse any other symptoms of opioid withdrawal, including nausea, vomiting, body ache, dilated pupils, insomnia, etc. Review of systems and physical exam findings were unremarkable for any symptoms of thyroid disease, diabetes, autonomic disorders, infection, or malignancy which were compatible with blood work lab results.

The patient had no medical conditions and did not take any medication other than methadone. While the patient had self-reporting of social anxiety and depression, he was screened and evaluated carefully and was diagnosed with substance-induced mood disorder including depression and anxiety. These conditions were managed successfully by prescribing Escitalopram 20 mg daily and he did not endorse anxiety when sweating occurred. The patient reported excessive sweating in both axillae, face and on both palms, which only began after receiving methadone and interfered with his occupational, relationship and other social activities. The patient denied having this symptom during the time of missing the methadone dose for a day due to his floating work schedule. He was educated and recommended treating w ith Oxybutynin to reduce his hyperhidrosis. All indications, risks and benefits of medication were explained, and he expressed his strong desire to start on this medication. He had an informed consent discussion before onset of medication. After obtaining consent, he was placed on Oxybutynin 5 mg twice daily, which resulted in the complete cessation of the hyperhidrosis within a few days of starting the medication.

Conclusion and Discussion: There are a few cases treated for opioid-induced sweating described in previous studies. Mercadnate reported that morphine-induced sweating was treated adequately with hyoscine butylbromide.

Biperiden, is an anticholinergic medication which has been used to treat methadone-induced diaphoresis and sweating in 3 cases, while Al-Adwani described the successful management of opioid-induced hyperhidrosis by an antihis tamine, desloratidine, and most recent case who was treated successfully with Oxybutynin 5 mg QID for methadone-induced hyperhidrosis reported in 2017.

Sweating remains a rare occurrence in clinical practice and under-recognition of this side effect may lead to patient discomfort as well as failure in treatment compliance. Hence, a careful history inquiring about additional symptoms, review of systems for underlying medical comorbidities, medication history and frequent urine toxicology screening can be useful to rule out other possible causes of hyperhidrosis.

This study supports the prior case report finding about treatment of methadone- induced hyperhidrosis with oxybutynin. The present case proposes that oxybutynin 5 mg oral tablet twice daily) can be very effective and merits consideration in patients with methadone-induced

hyperhidrosis and help methadone clinic and health care providers to diagnose and treat one of the less recognized adverse effects of methadone.

W88. DOES ASSOCIATION BETWEEN PROBLEMATIC SUBSTANCE USE AND SUICIDAL IDEATION IN YOUTHS DIFFER BASED ON SEX?

Sofia Alcasey[*1], Taylor Helmbrecht[1], McKenna Dougherty[1], Teresa Slettebo[1], Isabella Huddleston[1], Alyssa Serrano[1], Ann Brindley House[1], Elizabeth Dedrick[1], Sidarth Wakhlu[1], Abu Minhajuddin[1], Manish Jha[1], Madhukar H. Trivedi[1]*

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Abstract: Aim: Epidemiological studies suggest that presence of substance use disorders in adolescents and adults is associated with higher likelihood of active suicidal ideation (SI). However, whether this association differs based on sex remains unknown. In this report, we aimed to evaluated whether the association between problematic substance use and SI differs based on sex.

Methods: Youths aged 10 to 18 years who were receiving outpatient care in a primary care or psychiatric setting with measures of problematic substance use and SI were included (N=581; n=393 females and n=188 males). Problematic substance use was defined as core of 2 or more on the Car, Relax, Alone, Forget, Friends, Trouble (CRAFFT) scale version 2.1. Self-reported active SI was evaluated with the suicidal thoughts factor of the Concise Health Risk Tracking (CHRT) Scale which includes the following items that are rated from "strong disagree" to "strongly agree" on a 5-point Likert scale: "I have been having thoughts of killing myself;" "I have thoughts about how I might kill myself;" and "I have a plan to kill myself." Overall depression and anxiety severity were assessed with 9-item Patient Health Questionnaire (PHQ-9) and 7-item Generalized Anxiety Disorder (GAD-7) scales, respectively.

Results: Problematic substance use rates were 14.2% (56/393) and 17.6% (33/188) in females and males, respectively. Mean (standard deviation) scores of CHRT SI items for males and females with problematic substance use were 4.7 (2.8) and 3.9 (2.8), respectively while among those without problematic substance use were 3.2 (3.0) and 1.9 (2.6) respectively. The Cohen's d effect size of difference in SI between those with versus without problematic substance use in males and females were 1.07 ($p < 0.0001$) and 0.24 ($p=0.076$). Furthermore, there was a significant problematic substance use-by-sex interaction in predicting SI ($p=0.018$) even after controlling for age, race, PHQ-9 and GAD-7.

Conclusion: In this sample of youths receiving treatment in primary care or psychiatric clinics, presence of problematic substance use was associated with significantly higher levels of SI in males but not in females.

W89. A RANDOMIZED, DOUBLE-BLIND CONTROLLED COMPARISON OF NRX-101 (D-CYCLOSERINE/LURASIDONE) TO LURASIDONE FOR ADULTS WITH BIPOLAR DEPRESSION AND SUBACUTE SUICIDAL IDEATION OR BEHAVIOR

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Abstract: Patients with Bipolar Disorder (BP) have a suicide rate that is 10- to 30-fold higher than the population. Because one-fifth of untreated BP patients complete suicide and up to 60% may attempt suicide, new pharmacological treatment interventions are necessary to address this significant unmet medical need. NRX-101 is a fixed dose combination of D-cycloserine and lurasidone. In a Phase 2 trial in patients with bipolar depression and severe suicidal ideation initially stabilized with subanesthetic doses of ketamine, oral NRX-101 demonstrated reduced depression and suicidal ideation compared to lurasidone alone. Based on these findings, the FDA awarded Breakthrough Therapy Designation to NRX101 and granted a Special Protocol Agreement (SPA) for a registrational trial. Pursuant to the SPA, we conducted a multicenter, randomized, stratified, double-blind, parallel-group, two-arm outpatient study comparing NRX-101 (d-cycloserine and lurasidone) to lurasidone (and placebo) in a 1:1 ratio for the treatment of bipolar depression in participants with subacute suicidal ideation or behavior who do not require hospitalization. Key inclusion criteria included a diagnosis of BD I or II, on current treatment for BD, confirmed active suicidal ideation without the intention to act corresponding to an answer of 'Yes' on item 3 and/or item 4 on the Columbia Suicide Severity Rating Scale (C-SSRS) and a total score ≥30 on the Montgomery-Asberg Depression Rating Scale (MADRS). Key exclusion criteria included a history of schizophrenia or schizoaffective disorder or any history of psychotic symptoms when not in an acute bipolar mood episode, a lifetime history of phencyclidine/ketamine drug abuse, failed use of ketamine for depression or suicidality, or dementia, delirium, amnestic, or any other cognitive disorder. Full inclusion and exclusion criteria can be found on clinicaltrials.gov NCT03395392. The primary endpoint was change from baseline over 42 days in MADRS total score. Key secondary endpoints were change from baseline over 42 days in Clinical Global Impression for Severity of Suicidality (CGI-SS) and time to treatment failure in each arm. All rating sessions for MADRS and C-SSRS were recorded as audio files and reviewed by central master-raters. Any MADRS total score that differed by more than three points from the master-rater score was deemed non-congruent and was independently adjudicated. The Mixed-Effect Model Repeated Measure (MMRM) will be the primary analysis for the primary efficacy endpoint. All primary analyses will be in the modified Intent-To-Treat (mITT) population as primary and repeated in the Per Protocol population if > 5 percent are excluded. The study met enrollment goals of 74 patients. Database lock will occur in April 2024. Trial efficacy and safety data and rater congruence results will be presented for the first time at the ASCP.

W90. IS THE MAGNITUDE OF THE PSYCHEDELIC EXPERIENCE ASSOCIATED WITH DEPRESSIVE IMPROVEMENT?

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Abstract Introduction: Is a psychedelic experience necessary for the improvement in mood state? We examined the relationship between the magnitude of the psychedelic experience and psychedelic treatment outcomes from studies in severe treatment-resistant depression (P-TRD) and bipolar type II depression (BPII).

Methods: N = 25 adults (n = 12 P-TRD, n = 13 BPII) withdrew from psychotropic medications and completed three psychedelic preparation sessions before receiving a 25mg dose of a proprietary synthetic psilocybin compound (COMP360). Participants completed the Five-Dimensional Altered States of Consciousness scale (5D-ASC), which captures magnitude and intensity of a psychedelic experience, immediately after their psilocybin dosing session,

followed by three integration sessions. The differences between MADRS scores at Baseline and 3 weeks post-dosing were used to assess the degree of response.

Results: Overall intensity of the psychedelic experience, as evidenced by cumulative 5D-ASC scores, was not associated with a change in MADRS scores (r = -.27, p = .187). A subscale, visionary restructuralization (VRS), which captures psychedelic imagery, was most strongly associated with change in MADRS score (r = -.43, p = .033), followed by oceanic boundlessness (OBN) (r = -.343, p = .093), which captures derealization phenomena. These findings were consistent across both diagnostic groups.

Discussion: There was a statistically significant correlation between the intensity of psychedelic imagery (VRS) and psychedelic treatment outcomes. It is unclear whether a psychedelic experience is necessary for symptom improvement or a biomarker for the intensity of the biologic effects of psychedelics on serotonergic neurons.

W91. ROPANICANT (SUVN-911), A α4β2 RECEPTOR ANTAGONIST: A PHASE-2 STUDY EVALUATING THE SAFETY AND EFFICACY IN PARTICIPANTS WITH MODERATE TO SEVERE MAJOR DEPRESSIVE DISORDER

Ramakrishna Nirogi[1], Veera Raghava Chowdary Palacharla[1], Vijay Benade[1], Jyothsna Ravula[1], Satish Jetta[1], Vinod Kumar Goyal[1], Abdul Rasheed Mohammed[1], Ramkumar Subramanian[1], Santosh Kumar Pandey[1], Pradeep Jayarajan[1], Anil Shinde[1]*

[1]Suven Life Sciences

Abstract: Ropanicant (SUVN-911) is a potent and selective α4β2 nicotinic acetylcholine receptor (nAChR) antagonist and has demonstrated more than 100 fold selectivity against over 70 receptors which include closely related α3β4 nAChR receptors, GPCRs, ion channels, enzymes, peptides, steroids, second messengers, growth factors, and prostaglandins (Caliper Life Sciences Inc.). Ropanicant showed good oral bioavailability in preclinical species (rats, mice, and dogs). Upon oral administration in rats, it showed good brain exposures that translated well into dose-dependent receptor occupancy at α4β2 receptors. Good oral exposures translated into robust antidepressant-like effects in animal models, and increased cortical serotonin and norepinephrine levels. It showed a faster onset of antidepressant activity, enhanced cognitive function, and did not induce sexual dysfunctions in animal models thus, major limitations of the currently used antidepressants. Non-clinical safety of ropanicant has been established in a battery of safety pharmacology, genotoxicity, and general toxicity studies. Ropanicant was well tolerated and safe up to the highest tested dose of 60 mg single dose and 45 mg once daily for 14 days in healthy subjects. An open-label parallel-group study to evaluate the safety and efficacy of ropanicant in participants with moderate to severe major depressive disorder (MDD) is currently ongoing at several study centers in the USA (NCT06126497). The primary objective of the study is to evaluate the safety of ropanicant in participants with MDD. The secondary objectives include the assessment of ropanicant treatment in reducing depressive symptoms and the evaluation of its pharmacokinetics in MDD patients. Approximately 36 participants will be randomized to receive ropanicant either 45 mg QD, 30 mg BID, or 45 mg BID in a ratio of 1:1:1. Following a screening period of up to 4 weeks, participants will be treated for 2 weeks. Safety assessments will include adverse events, physical examination, vital signs, ECG, clinical laboratory tests, and suicidal ideation/behavior evaluation by Columbia Suicidal Severity Rating Scale (C-SSRS). The efficacy assessments will include change from baseline in Montgomery–Asberg Depression Rating Scale (MADRS) and Clinical Global Impression of severity (CGI-S). Pharmacokinetics will be evaluated on day

1 and day 14 in subjects receiving BID dosing. This open-label study will be a preface to a future double-blind placebo-controlled study of ropanicant in participants with MDD. Demographics and baseline characteristics of the recruited subjects will be presented during the conference.

W92. OPTIMAL DOSAGE OF PSILOCYBIN IN THE TREATMENT OF MOOD DISORDERS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Abstract Background: Depression is a major psychiatric disorder associated with substantial morbidity and mortality affecting more than 260 million people worldwide. First-line treatments include pharmacotherapy and psychotherapy although approximately 30% of patients would not respond to multiple trials meeting criteria for Treatment-Resistant Depression (TRD). Novel treatment strategies have been proposed ranging from medication combinations to ketamine and lately Psilocybin has shown potential efficacy for mood disorders although inconsistencies regarding dose and duration of treatment need to be elucidated. Here we aimed to appraise the current evidence on the optimal dosages of Psilocybin in the treatment of mood disorders.

Methods: Major databases were searched for randomized controlled trials (RCTs), open-label trials, and observational studies that reported the use of psilocybin as adjunctive or monotherapy for adult patients with mood disorders. The protocol was registered under PROSPERO (CRD42023388587). The search dates for the updated dataset will be revised to incorporate the most recent studies published in 2023-24.

Results: A total of 8769 abstracts were screened and 108 articles were selected for full-text review. Four studies (101 major depressive disorder [MDD] and 20 treatment-resistant depression [TRD] patients) including three RCTs (n= 101), and one open-label prospective (n=20) study met the study criteria. Study duration ranged from 4 to 52 weeks with a daily psilocybin dose of 10-25 mg/day. Depressive symptoms were assessed from 1 week to 12 months post-treatment, with the Beck Depression Inventory 1A (BDI-1A), the 17-item Hamilton Depression Rating Scale (HAM-D-17), the Montgomery Asberg Depression Rating Scale (MADRS), GRID-Hamilton Depression Rating Scale (GRID-HAMD), and self-rated QIDS-SR16 as primary and secondary outcome measures. Studies reported a significant improvement in mood symptoms although there were inconsistencies between dose and efficacy. Overall psilocybin was well tolerated with no major significant side effects.

Conclusions: Limited conclusions can be drawn about optimal dosages of psilocybin in mood disorders, but overall tolerability was good, and depressive symptoms improved rapidly after treatment onset remained significant for weeks post-treatment. Psilocybin represents a promising paradigm for MDD-TRD. Further studies with larger sample sizes are warranted.

W93. BEYOND RESPONSE AND REMISSION: USING TIME TO DISCONTINUATION AS AN OUTCOME OF KETAMINE TREATMENT FOR DEPRESSION

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[1]*Mayo Clinic*

Abstract: Background: Intravenous (IV) ketamine has become an increasingly available treatment option for major depressive disorder. The response and remission rates have ranged from 36-70% and 13-43%, respectively. However, response and remission rates typically apply to an acute course of treatment, and ketamine has a high relapse rate, making maintenance treatments necessary. In this study, we investigated the time to discontinuation as another outcome measure.

Method: Adult patients with major depressive disorder or bipolar depression who were treated with at least 1 IV ketamine infusion (0.5 mg/kg body weight) at the Mayo Mood Clinic between 6/1/2018 and 11/30/2023 were included. A Quick Inventory of Depressive Symptoms Self-Rated 16 items (QIDS-SR16) was administered on the day of each treatment, and patients were asked to complete another QIDS-SR16 the day after treatment. The score on the day after treatment was used as the endpoint score of an acute course. Response (change in QIDS-SR16≥50%) and remission (QIDS-SR16≤5) were calculated. Kaplan-Meier analysis for the time to discontinuation for all patients and for those who continued after the acute course was performed. BlueSky Statistics v10.3.1 (Chicago, IL) was used.

Results: Eighty-two patients (mean age 47.1 years, 67.1% female) were included. Baseline (±SD) QIDS-SR16 was 18.2±4.1, and ending QIDS-SR16 was 9.7±5.8. The median number of treatments in the acute course was 3, and resulting response and remission rates were 48.8% (n=40) and 11.0% (n=9), respectively. The median follow-up duration was 43.2 months. Kaplan-Meier analysis showed that 50% had discontinued by 2.1 months after starting treatment. Fifty-three (64.6%) patients continued to maintenance, indicating they and/or the clinician felt that they had received sufficient benefit to continue. Of those 53, 50% discontinued by approximately 21.7 months. Their mean time in acute and maintenance treatment was 21.1 months (median 10.4, range 0.43 to 74.5 months). By the end of the study period, 22 of 82 (26.8%) patients remained actively receiving maintenance ketamine.

Conclusions: In our clinic, for every patient who received at least 1 IV ketamine treatment, half stopped by 2.1 months, and of those who continued to maintenance, half stopped by 21.7 months (1.8 years). Overall, approximately 27% of patients who started ketamine were still receiving maintenance. The time to discontinuation is frequently the patient's decision, and indicates when they feel there is not enough benefit to continue treatments. It adds meaningful information when discussing IV ketamine outcomes with patients, and can help clinicians plan duration of treatments and further define the role of ketamine for major depression and bipolar depression.

W94. SAFETY AND TOLERABILITY OF BHV-7000, A NOVEL KV7 POTASSIUM CHANNEL ACTIVATOR: RESULTS FROM PHASE 1 SINGLE AND MULTIPLE ASCENDING DOSE STUDIES

Bharat Awsare[1], Azim Munivar[*1], Eric Ashbrenner[1], Heather Sevinsky[1], Michael Bozik[1], Steven Dworetzky[1], Lia Donahue[1], Randall Killingsworth[1], Bruno Francoeur[2], Irfan Qureshi[1]*

[1]Biohaven Pharmaceuticals, [2]Syneos Health

Abstract: Introduction: BHV-7000 is a novel, small molecule, selective activator of Kv7.2/7.3 potassium channels. Kv7 activation normalizes the pathological hyperexcitability that contributes to depression and has demonstrated efficacy in multiple preclinical models.

Clinical proof-of-concept studies with Kv7 activators have demonstrated antidepressant activity and provide support for Kv7 activation as a novel treatment for depression and anhedonia. The Kv7 channel is also a compelling target for bipolar disorder; human genetics link Kv7 to risk of bipolar disorder, and preclinical models show Kv7 activation corrects disease-related phenotypes and behaviors. The objectives of these Phase 1 single ascending dose (SAD) and multiple ascending dose (MAD) studies were to evaluate the safety and tolerability of BHV-7000.

Methods: These double-blind, placebo controlled, sequential SAD/MAD studies enrolled healthy adults aged 18-55 years. SAD subjects were randomized 3:1 to BHV-7000 (4, 10, 25, 50, or 100 mg) or placebo. MAD subjects were randomized 3:1 to BHV-7000 (10, 25, 40, 80, or 120 mg daily) or placebo, and treated for 15 days. Safety evaluations included adverse event (AE) monitoring, clinical laboratory tests, vital signs, ECGs, physical examinations, and suicidality tracking. A Safety Review Committee assessed the safety and tolerability after completion of each dose level prior to dose escalation.

Results: Across the SAD and MAD studies, 77 subjects received BHV-7000 (N = 58) or placebo (N = 19). SAD cohorts included 39 subjects randomized to BHV-7000 (n = 29) or placebo (n = 10); MAD cohorts included 38 subjects randomized to BHV-7000 (n = 29) or placebo (n = 9). The mean age was approximately 40 years; the majority of subjects were male and white. Adverse events occurring in ≥ 2 BHV-7000 treated subjects (BHV-7000 vs placebo) in the SAD cohorts were headache [3/29 (10.3%) vs 0/10 (0%)] and abdominal discomfort [2/29 (6.9%) vs 0/10 (0%)]; and in the MAD cohorts were headache [6/29 (20.7%) vs 3/9 (33.3%)], back pain [6/29 (20.7%) vs 0/9 (0%)], constipation [3/29 (10.3%) vs 3/9 (33.3%)], dizziness [3/29 (10.3%) vs 2/9 (22.2%)], abdominal pain [2/29 (6.9%) vs 1/9 (11.1%)], and fatigue [2/29 (6.9%) vs 2/9 (22.2%)]. There were low rates of CNS-related AEs; no somnolence was reported. The majority of AEs were mild and resolved spontaneously. There were no deaths, serious AEs, severe AEs, or dose-limiting toxicities. There were no clinically meaningful trends or treatment-related findings for laboratory values, vital signs, ECGs, or suicidality.

Conclusion: BHV-7000 was well tolerated at single doses up to 100 mg and multiple doses up to 120 mg daily for 15 days. These findings support further clinical development of BHV-7000 which offers a new mechanism of action and potential for better tolerability among existing treatments for major depressive disorder and bipolar disorder.

W95. TWO RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIALS OF TRORILUZOLE, A NOVEL GLUTAMATE MODULATING AGENT, IN OBSESSIVE-COMPULSIVE DISORDER

Azim Munivar[*1], Stephen Kaplita[1], Kimberly Gentile[1], Lia Donahue[1], Deborah Smith[1], Tim McCormack[1], Christopher Jensen[1], Irfan Qureshi[1], Vladimir Coric[1]*

[1]*Biohaven Pharmaceuticals*

Abstract: Introduction: Few patients with obsessive-compulsive disorder (OCD) experience a complete response to serotonergic and dopaminergic therapies, suggesting other neurochemical systems are involved in OCD pathophysiology. Preclinical, clinical, genetic, and neuroimaging studies implicate glutamatergic hyperactivity in the pathogenesis of OCD. Troriluzole, a novel glutamate modulating agent, may normalize synaptic glutamate levels by increasing expression and function of glutamate transporters and by decreasing presynaptic

glutamate release. Troriluzole is designed to provide enhanced bioavailability, eliminate the need for fasting, enable once-daily dosing, reduce first pass metabolism, and minimize hepatotoxicity relative to its active metabolite, riluzole. A Phase 2 study of troriluzole in OCD demonstrated consistent treatment benefit at all timepoints. Patients with more severe OCD symptoms at baseline also demonstrated larger treatment effects. These results informed the development of 2 ongoing Phase 3 clinical trials. Herein we describe the demographic and baseline characteristics for these studies.

Methods: These are two identical Phase 3 randomized, double-blind, placebo-controlled trials evaluating adjunctive troriluzole 280 mg daily in up to 700 adults for 10 weeks. Subjects have a history of OCD for ≥1 year with inadequate response to an ongoing standard of care medication, defined as a Yale-Brown Obsessive Compulsive Score (Y-BOCS) ≥ 22 at screening and baseline. The primary endpoint is change from baseline in Y-BOCS. Preliminary demographics and baseline characteristics were analyzed as of January 2024.

Results: Across the two Phase 3 studies, mean (SD) age was 37.8 (13.19) years. Mean (SD) baseline Y-BOCS was 27.4 (3.56). The majority of subjects were female (65%) and white (82%); The proportion of subjects reporting 2-10, 11-20, and 21+ years of OCD history was 42%, 18%, and 17%, respectively.

Conclusion: These two Phase 3 clinical trials are evaluating troriluzole in a population with moderate-to-severe OCD symptoms despite standard of care therapy. These results underscore the incomplete efficacy of available therapies which are also associated with sexual dysfunction, metabolic syndrome, and extrapyramidal symptoms. If troriluzole proves to be safe and efficacious, this will be the first novel mechanism of action in OCD in over 20 years and an important breakthrough for the millions of patients suffering from this disorder.

Thursday, May 30, 2024

Poster Session II with Lunch

T1. RETROSPECTIVE ANALYSIS OF KETAMINE INTRAVENOUS THERAPY OUTCOMES AT A LARGE ACADEMIC CENTER

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Abstract: Major Depressive Disorder (MDD) are psychiatric disorders that affect over 280 million people worldwide. Standard treatments fail patients with treatment-resistant depression (TRD) leading to years of suffering. Intravenous ketamine is an intervention for patients with TRD as it is associated with rapid improvement of mood and suicidal ideation (SI).

We analyzed 278 outpatients with MDD who completed at least six intravenous ketamine treatments at Massachusetts General Hospital over 5 years (2018-2023). Age range was 18-84 (mean 42.6), treated if they failed 4 or more prior treatment trials. Patients were female (51%), Caucasian (89.5%). Current moderate to SUD and history of psychosis were excluded. Over 2/3 of patients have comorbid diagnoses (PTSD, OCD, GAD, and/or ADHD). Over 70% of patients endorsed SI at baseline. Approximately 130 patients are currently on intravenous ketamine maintenance therapy.

Patients filled out a QIDS-16, a self-rated scale of depression symptom severity, on the day of treatment prior to their infusion. Therefore, scores reflect their relatively worst symptomatology as they have had the longest time since their previous treatment. Response was defined as 50% improvement from baseline and remission was defined as a QIDS-16 score of 5 or less.

Induction consists of biweekly infusions for three weeks (six treatments), followed by maintenance adjusted as needed for each patient. Dosing starts at 0.5mg/kg and is subsequently escalated based on efficacy and tolerability (range 0.5-2.4mg/kg). Patients that did not respond to a dose of 1.0mg/kg were further escalated to facilitate improvement in symptoms and increased interval duration between treatments.

We monitored blood pressure (mmHg), heart rate (bpm), and oxygen saturation at 20 minutes intervals. Hypertension and tachycardia were the most common side effects, with nausea and treatment-emergent anxiety following. Side effects were managed with benzodiazepines, antiemetics, and beta-blockers to ensure safety. Here we present our outcomes with a focus on the timeline of response, efficacy, frequency of maintenance and interval duration, adverse events, and side effect management.

T2. INTEGRATION OF BLOOD-DERIVED AND BRAIN-DERIVED BIOMARKERS FOR PREDICTING STAGE 2 REMISSION STATUS IN EMBARC STUDY SUBJECTS WITH MAJOR DEPRESSIVE DISORDER

Milica Barac[*1], Caroline Grant[1], Taryn Mayes[2], Thomas Carmody[2], Abu Minhajuddin[2], Russell Toll[2], Cherise Chin Fatt[2], Paul Croarkin[1], William Bobo[1], Manish Jha[2], Arjun Athreya[1], Madhukar Trivedi[2]*

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Abstract Background: Only one-third of patients with Major Depressive Disorder (MDD) remit to first-line antidepressant therapies. Previous studies have demonstrated the utility of brain-derived markers and blood-derived markers individually for predicting outcomes to pharmacotherapy in patients with MDD. This work aimed to determine whether machine learning (ML) techniques which harness the joint power of blood- and brain-derived biomarkers may improve predictions of remission in patients with MDD.

Methods: This study included patients with MDD and clinical remission status at 16 weeks (N = 90) from the 'Establishing Moderators and Biosignatures of Antidepressant Response for Clinical Care for Depression' (EMBARC) study. Patients were initially treated with Sertraline (N=40) or Placebo (N=50), and depending on response status at 8 weeks of therapy, their therapy was maintained (Sertraline responders) or switched (to Sertraline, if a non-responder to placebo, or to Bupropion, if a non-responder to Sertraline). Resting state functional magnetic resonance imaging (fMRI), brain electroencephalogram (EEG), plasma protein, and clinical items (N=8,949 items total) collected at baseline were used as predictors. EEG features collected at 1-week of therapy and changes from baseline to 1 week were also included as predictors. Feature selection was performed utilizing the Boruta algorithm which predicted remission status at 8 weeks of treatment. Selected features were incorporated into several supervised ML approaches (random forest, penalized regression, naïve bayes, K-nearest neighbors) and predictability of remission status at 16 weeks was assessed by area under the receiver operating characteristic curve (AUC). Nested cross-validation was used to train and test models, with 75% of the sample allocated for training. Fifteen random training and testing splits were created, and the results presented were averaged across the splits.

Results: Boruta feature selection yielded 24 baseline features for predicting remission of MDD at week 16 of treatment. The highest AUC was achieved by random-forest based integration of clinical, blood, and fMRI brain connectivity measures (mean AUC [95% CI] = 70.33 [0.64-0.76]). Sensitivity was 0.89 [0.84-0.94], and specificity was 0.6416 [0.56-0.72]. In addition to the baseline depression severity, four fMRI features and MIP-3b/CCL19 (Macrophage Inflammatory Protein-3 beta) were top predictors of remission. Two of the top fMRI features represented functional connectivity between the right hemisphere default mode network and (i) the left hemisphere default mode network inferior orbitofrontal and (ii) the visual network calcarine regions.

Conclusions: Baseline blood-derived protein and fMRI features together established predictability of MDD remission at 16 weeks. Future work will aim to elucidate potential mechanisms contributing to improved predictability.

T3. USE OF BIOMARKERS TO IDENTIFY TREATMENT FOR PYSCHIATRIC PATIENTS

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Abstract: This presentation serves as an introductory guide to the field of machine learning with a focus on practical applications in the medical domain. It explores various regression models within the context of supervised learning, aiming to provide healthcare professionals and researchers with valuable insights into this important area. Supervised learning is approached through the perspective of outcome measurement (Y) and a vector of predictor measurements, which are essential in solving medical prediction problems. The outcome variable Y is divided into two distinct categories: 1) regression, where Y represents quantitative values, and 2) classification, where Y encompasses finite, unordered sets, such as predicting patient responses to pharmacological treatments or classifying patients based on medical scores like MADRS(Montgomery-Asberg Depression Rating Scale).
Training data, consisting of pairs of predictor and outcome variables, forms the basis for machine learning models, enabling them to predict unseen cases and identify critical factors influencing medical outcomes.This presentation emphasizes the importance of assessing prediction quality and the search for an ideal prediction function, f(x). It also discusses model accuracy, introducing concepts such as training error bias and test error, and explains the trade-offs between model complexity, bias, and variance, all within the context of medical applications. This naturally leads to the Bias-Variance decomposition, an essential framework for healthcare professionals and researchers to comprehend predictive model performance.

Parametric and structured models, such as linear models, are defined and dissected, with a focus on how they can be used to minimize training error in the medical context. The presentation contrasts regularization techniques like LASSO and ridge regression with best subset selection, highlighting the utility of LASSO in high-dimensional medical regression when dealing with sparse data. Geometric interpretations of LASSO and forward stepwise regression are provided, accompanied by practical examples from medical research.

Keywords: Machine Learning, Supervised Learning, Medical Applications, Regression Models, Model Accuracy, Predictor Variables, LASSO, Ridge Regression, Healthcare, K-NN Algorithm, Bias-Variance Decomposition, Linear Models.

T4. GLUCAGON-LIKE PEPTIDE-1 (GLP-1) RECEPTOR AGONISM AS A POTENTIAL PHARMACOTHERAPY FOR ALCOHOL USE DISORDER: CONVERGING EVIDENCE FROM RODENT AND EARLY HUMAN STUDIES

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Abstract: Consistent with the role of the glucagon-like peptide-1 (GLP-1) system in alcohol seeking and consummatory behaviors, evidence from preclinical experiments, preliminary clinical studies, and anecdotal reports suggest that GLP-1 receptor agonists (GLP-1RAs) - already approved for treating type 2 diabetes mellitus and obesity - may represent promising pharmacotherapeutic options for alcohol use disorder (AUD). Recently developed GLP-1RAs such as semaglutide are gaining significant traction as they are more potent and have longer half-lives and higher affinity for the GLP-1R, compared to the first generation of GLP-1RAs. In a series of rodent experiments, we tested the effects of semaglutide on binge-like and dependence-induced drinking in male and female mice and rats. Semaglutide dose-dependently

reduced alcohol intake in both paradigms and species, with no sex differences. Electrophysiology experiments on brain slices suggested that semaglutide enhances GABA release from the central amygdala and infralimbic cortex neurons. Next, in a real-world cohort study, we examined the association between GLP-RAs receipt and change in alcohol use. We extracted data from the Veterans Aging Cohort Study (VACS) national cohort, which includes ~13.5 million veterans who ever received care in the Department of Veterans Affairs, the largest integrated healthcare system in the US. A total of 28,996 GLP-1RA initiators were propensity score matched 1:1 to two comparator groups: individuals initiating dipeptidyl peptidase 4 (DPP-4) inhibitors (active comparator) and those receiving neither GLP-1RAs or DPP-4 inhibitors (unexposed). DPP-4 inhibitors are also approved for treating type 2 diabetes mellitus and boost the endogenous GLP-1 by blocking its degradation. Changes in pre- to post-index Alcohol Use Disorder Identification Test – Consumption (AUDIT-C) scores were compared between groups, using difference-in-difference (DiD) analyses. Results showed that GLP-1RA recipients had significantly greater reductions in AUDIT-C scores over time compared with unexposed (DiD: 0.09; 95% CI: 0.03, 0.14) and DPP-4 inhibitor recipients (DiD: 0.11; 95% CI: 0.05, 0.17). Stronger DiD estimates were found among individuals with AUD or hazardous/binge drinking: 0.51 (95% CI: 0.29, 0.72) and 1.38 (95% CI: 1.07, 1.69) for GLP-1RA vs. unexposed and 0.65 (95% CI: 0.43, 0.88) and 1.00 (95% CI: 0.68, 1.33) for GLP-1 vs. DPP-4 inhibitor comparisons. Comparing DPP-4 inhibitors recipients to unexposed showed no association with changes in AUDIT-C scores (DiD: 0.02; 95% CI: -0.02, 0.05), indicating our GLP-1RA results were not affected by residual confounding. Together, these data from rodent and human pharmacoepidemiological studies provide converging evidence in support of testing GLP-1RAs in patients with AUD. Given the known safety profile and widespread prescription of these medications, if shown to be efficacious in clinical trials, GLP-1RAs have the potential to be a successfully repurposed for AUD treatment.

T5. LATE NIGHT LEADS: EXPLORING THE RELATIONSHIP BETWEEN CALLBACK TIMES AND MDD SYMPTOMATOLOGY FOR LATE NIGHT APPLICATIONS AND IMPLICATIONS FOR RECRUITMENT AND PLACEBO RESPONSE

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Abstract: Introduction: From the 1980's to the 2000's, placebo response in Major Depressive Disorder (MDD) trials increased by approximately 7% per decade. The increase in placebo response has decreased the likelihood that an investigational antidepressant will have a statistically significant drug response and increased the likelihood for a type II error—falsely deciding that a drug doesn't work when it really does. Per Fava et al, one of the variables correlated with placebo response with clinical MDD trial participants is a lack of the melancholic features of major depressive disorder (MDD), such as anhedonia, weight loss, and insomnia. If a lack of melancholic features is correlated with placebo response, then the presence of melancholic features should be correlated with less placebo response, and insomnia (which can theoretically be identified through the recruitment process) should be correlated with less placebo response as well. Therefore, recognizing participants with insomnia through the recruitment process, and prioritizing their enrollment into clinical MDD trials should decrease placebo response and type II error. This study aims to explore MDD symptomatology for participants who apply for MDD trials between the hours of 12am to 6am, and the implications for callback recruitment practices.

Methods: Our sample consisted of two groups of participants, group A and group B. Group A consisted of participants who clicked on ads six months prior to 26MAR2023, and group B consisted of participants who clicked on ads six months after 26MAR2023. Each group was subdivided into four six-hour subgroups, from 12am-6am, 6am-12pm, 12pm to 6pm, and 6pm to 12am. For group A, we designated the subgroups as A1, A2, A3, and A4, and B1, B2, B3, and B4. Inferential analyses focused on a series of four-way analyses of variance (ANOVA) comparing A1 to A2, A3, and A4, and B1 to B2, B3, and B4, to examine how callback times affect PHQ9 scores (total and individual question scores) at prescreen for the four different subgroups.

Results: The time of day of application was significantly associated with sleep problems for participants that were called back at 8am (group A), such that those participants who applied between 12am and 6am (A1) had higher rates of sleep problems that those than those who applied between 6am and 12pm (group A2) (p=0.02). This association did not hold true for participants who were called back at 12pm (group B). The time of day of application was significantly associated with psychomotor symptoms for participants that were called back at 12pm (group B) (p=0.03), however, since none of the pairwise comparisons among the group B subgroups were statistically significant, it's impossible to say if subgroup B1 experienced more psychomotor symptoms than subgroup B2, B3, or B4.

Conclusion: Callbacks starting at 8am to participants who click on ads for depression trials between the hours of 12am and 6am is associated with participants who are experiencing sleep problems, whereas callbacks starting at 12pm to participants who click on ads for depression trials between the hours of 12am and 6am is associated with participants who are experiencing psychomotor symptoms. Though both question #3 and #8 on the PHQ9 are compound items, we hypothesize that group A is more likely to suffer from insomnia and group B is more likely to suffer from psychomotor retardation, however further research would be required to substantiate these claims. Given insomnia is a core feature of melancholic features, we conclude that callbacks at 8am rather than 12pm are more likely to identify participants suffering from MDD with melancholic features.

T6. AZAPIRONE ABUSE AND MISUSE: A REVIEW

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Abstract Background: Azapirone-class drugs (e.g., buspirone, ipsapirone) are mainly used as treatments for anxiety disorders via their partial agonist effects on 5-HT1A receptors. They are thought to have a low potential for misuse-dependence and are considered safe treatment options compared to benzodiazepines. However, recent evidence suggesting the contrary has raised concerns about their safety. This review aims to elucidate the current evidence on the abuse and misuse potential of azapirones, with a focus on informing prescription patterns to better personalize care.

Methods: A Prisma-compliant systematic search of Pubmed and Web of Science followed by bibliographic searches of included articles were conducted to identify peer-reviewed publications published before February 2024 reporting the abuse and misuse of azapirones (as the sole ingestant) in humans. Extracted characteristics included author(s); year of publication; study design; geographic location; setting; participant characteristics; nature of abuse/misuse;

subjective effects experienced; adverse events; and other relevant information. A summary of personal experiences of users from online forums is included.

Results: Sixteen publications including case reports (n=6) and clinical studies (n=10) were included. Clinical studies reported that azapirone use is not associated with key features of abuse or misuse such as subjective rewarding effects, tolerance, and withdrawal, albeit some of the reports acknowledged that that abuse of azapirones occurs but is uncommon in the real-world setting. On the other hand, all case reports described azapirone abuse, involving patients with a history of incarceration and substance use disorder who were nasally ingesting the drug to achieve a sedative effect. Personal experiences of users from online forums described similar sedating sensations in addition to adverse effects. While the effects of azapirone overdose are generally non-lethal, it can cause seizures, dizziness, drowsiness, and gastrointestinal symptoms.

Conclusions: Azapirones demonstrate potential for abuse and misuse, particularly among those with a history of incarceration and substance use disorder. This misuse may stem from behavioral factors rather than purely pharmacologically factors. Overdose is generally non-lethal but can result in adverse effects. Recognizing these high-risk populations is crucial for personalized care strategies aimed at mitigating misuse. Further research focused on identifying and preventing azapirone abuse and misuse is imperative to ensure the safe and effective treatment of anxiety disorders in vulnerable populations.

T7. EFFICACY OF BREXPIPRAZOLE IN COMBINATION WITH SERTRALINE FOR PATIENTS WITH POST-TRAUMATIC STRESS DISORDER: SUMMARY OF DATA FROM PHASE 2 AND PHASE 3 RANDOMIZED CLINICAL TRIALS

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Abstract Background: Existing pharmacotherapies for post-traumatic stress disorder (PTSD) have demonstrated modest and inconsistent outcomes in clinical trials. An unmet need remains for a pharmacotherapy that has a consistent efficacy profile and is well tolerated. The efficacy and safety of combination therapy with brexpiprazole + sertraline for patients with PTSD have been evaluated in three clinical trials. The aim of this report is to summarize the efficacy data from each of the three trials (full safety data will be summarized elsewhere at ASCP 2024).

Methods: The three randomized, controlled, double-blind trials, conducted in the US, were Trial 061 (Phase 2; NCT03033069), Trial 071 (Phase 3; NCT04124614), and Trial 072 (Phase 3; NCT04174170). The trials enrolled male and female outpatients, aged 18–65 years, who had a Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) diagnosis of PTSD and symptoms for ≥6 months. Each trial included a 1-week placebo run-in phase followed by an 11-week randomized treatment phase. In Trial 061, patients were randomized 1:1:1:1 to flexible-dose brexpiprazole 1–3 mg/day + sertraline 100–200 mg/day, flexible-dose brexpiprazole 1–3 mg/day + placebo, flexible-dose sertraline 100–200 mg/day + placebo, or placebo (double dummy). In Trial 071, patients were randomized 1:1 to flexible-dose brexpiprazole 2–3 mg/day + fixed-dose sertraline 150 mg/day, or fixed-dose sertraline 150 mg/day + placebo. In Trial 072, patients were randomized 1:1:1 to fixed-dose brexpiprazole 2

mg/day + sertraline 150 mg/day, fixed-dose brexpiprazole 3 mg/day + sertraline 150 mg/day, or fixed-dose sertraline 150 mg/day + placebo. In the flexible-dose trials, the dose of brexpiprazole (and sertraline in Trial 061 only) could be adjusted to optimize efficacy and safety/tolerability. The primary endpoint in each trial was the least squares (LS) mean change in Clinician Administered PTSD Scale for DSM-5 (CAPS-5) Total score from baseline (randomization) to Week 10. Safety and tolerability were also assessed.

Results: A total of 1,290 patients were randomized (Trial 061, n=321; Trial 071, n=416; Trial 072, n=553). In Trial 061, the LS mean change from baseline (randomization) to Week 10 in CAPS-5 Total score was -16.4 with brexpiprazole + sertraline (p=0.011 versus sertraline + placebo), -12.2 with brexpiprazole + placebo, -11.4 with sertraline + placebo, and -10.5 with placebo. In Trial 071, the LS mean change was -19.2 with brexpiprazole + sertraline (p=0.0007 versus sertraline + placebo), and -13.6 with sertraline + placebo. In Trial 072, the LS mean change was -16.5 with brexpiprazole 2 mg/day + sertraline (p=0.52 versus sertraline + placebo), -18.3 with brexpiprazole 3 mg/day + sertraline (p=0.66 versus sertraline + placebo), and -17.6 with sertraline + placebo. There were no unexpected safety or tolerability outcomes with brexpiprazole + sertraline.

Conclusion: In Trial 061 and 071, on the primary endpoint, the combination of brexpiprazole + sertraline was more effective than sertraline alone. In Trial 072, whilst the primary endpoint was not met, improvements from baseline in symptoms of PTSD with brexpiprazole + sertraline combination therapy were consistent with Trials 061 and 071. Overall, results from three clinical trials indicate that brexpiprazole + sertraline combination therapy is associated with a consistent and clinically relevant improvement from baseline in symptoms of PTSD.

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T8. ZIPRASIDONE AND PREGNANCY: PRELIMINARY DATA FROM THE MGH NATIONAL PREGNANCY REGISTRY FOR PSYCHIATRIC MEDICATIONS

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Abstract Background: Since its FDA approval in 2001, ziprasidone has been used for the treatment of schizophrenia and bipolar disorder, although pregnancy safety data in humans has been lacking. The goal of the current analysis was to determine the risk of major malformations among infants exposed to ziprasidone during pregnancy compared to a group of non-exposed infants.

Methods: The National Pregnancy Registry for Psychiatric Medications (NPRPM) is a prospective pharmacovigilance program in which pregnant women are enrolled and interviewed during pregnancy and the postpartum period. Enrollment is ongoing. Labor and delivery and pediatric medical records were screened for evidence of major malformations followed by adjudication by a blinded dysmorphologist. Infants with first trimester exposure to ziprasidone were compared to controls without second-generation antipsychotic exposure.

Results: As of January 17, 2024, 3,444 women have enrolled in the study. At the time of data extraction, 55 ziprasidone-exposed infants and 1538 infants in the comparison group were eligible for these analyses. There were 2 major malformations associated with ziprasidone exposure in the first trimester. The absolute risk for major malformations in the exposure group was 3.64% (95% CI: 0.44, 12.53) for ziprasidone compared to 1.11% (95% CI: 0.65, 1.76) in the control group.

Implications: Although these preliminary data suggest a possible increased risk of major malformations with first-trimester exposure to ziprasidone, this risk, thus far, does not meet the threshold of a major teratogen such as valproic acid. A greater number of ziprasidone pregnancy exposures are needed for a more precise understanding of its reproductive safety profile.

T9. THE NATIONAL PREGNANCY REGISTRY FOR PSYCHIATRIC MEDICATIONS: RISK OF MAJOR MALFORMATIONS FOLLOWING FETAL EXPOSURE TO SECOND GENERATION ANTIPSYCHOTICS

Lee Cohen[*1], Marlene Freeman[1], Parker Killenberg[1], Ellen Sojka[1], Caroline Frisch[1], Audrey Reuman[1], Maya Verghese[1], Hannah Yoon[1], David Chitayat[2], Sonia Hernández-Díaz[3], Adele Viguera[4]*

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Abstract: Purpose: The Massachusetts General Hospital National Pregnancy Registry for Psychiatric Medications (NPRPM) is a longitudinal prospective research study which systematically gathers reproductive safety data on psychotropic use during pregnancy. Second generation antipsychotics (SGAs) are commonly used in reproductive-aged women to treat psychiatric disorders, such as bipolar disorder and major depressive disorder. The NPRPM's primary outcome of interest is major malformations following first trimester SGA-exposure, with data informing the care of reproductive-aged women with psychiatric histories.

Methodology: The NPRPM prospectively collects data from pregnant women, aged 18-45 years, with histories of psychiatric disorders. Three phone interviews are conducted to ascertain information on the mothers and babies, two of which occur during pregnancy and the final interview occurs three months postpartum. Enrollment and longitudinal follow-up of participants are ongoing. In this analysis, exposure is defined as SGA-use during the first trimester of pregnancy as reported by the participant. The control group consists of women who did not use an SGA at any point during pregnancy. Participants exposed to SGAs in the second and/or third trimester but not the first trimester were excluded from analysis. Prenatal exposure to psychotropics other than SGAs does not exclude participants from either the exposure or control groups. Major malformations are identified through a multi-step process: pertinent information is abstracted from medical records, and potential malformation cases are then adjudicated by a dysmorphologist blinded to psychiatric diagnoses and drug exposure.

Results: As of January 24th, 2024, 3467 women were enrolled in the NPRPM, including 1238 in the exposure group and 2229 in the comparison group. Medical records were obtained for 77% of participants. A total of 2492 participants (918 exposed to an SGA in the first trimester,

1574 unexposed to an SGA during pregnancy) completed the postpartum interview and were eligible for analysis. Of 918 infants in the exposure group, 26 confirmed major malformations were identified. In the control group of 1574 infants, 20 malformations were identified. No consistent pattern of malformation was seen in either group. The absolute risk of major malformations was 2.75% in the exposure group and 1.12% in the comparison group. No specific patterns of major malformations were observed in either group.

Importance: According to CDC national data, the prevalence of major malformations is approximately 3% among all live births in the United States. In this analysis, the absolute risk of neonatal major malformations was similar at 2.75% in the exposed group, while it was lower at 1.12% in the unexposed group compared to this external reference. The low absolute risk in our unexposed group could be attributed to random error or increased rates of healthy behaviors compared to the general population of reproductive-aged women. This highlights the need for a larger sample size.

This new estimate supports earlier preliminary data indicating that SGAs are unlikely to

have a teratogenic effect on the level of valproic acid or thalidomide. Ongoing data collection through the Registry is critical in defining the risk estimate more precisely and reducing uncertainty.

T10. EFFECT SIZE DEFLATION AS A FUNCTION OF SAMPLE SIZE IN ADJUNCTIVE TREATMENT TRIALS FOR NEGATIVE SYMPTOMS IN SCHIZOPHRENIA

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Abstract Background: Negative symptoms of schizophrenia typically persist despite treatment with best available medications for schizophrenia. Clinical studies have evaluated the effects of multiple compounds for adjunctive use across a range of mechanisms of action, but no approved compounds are yet available. A major challenge in the development of adjunctive treatments has been replicating the results of promising single-trial studies in multi-center investigations. It has recently been shown in monotherapy studies of schizophrenia that placebo effects scale differentially with sample size than treatment effects. Here, we investigated size-related placebo effects in multicenter clinical trials of adjunctive medications, and modeled their effects on sample size calculations and clinical trial design.

Methods: Using Pubmed and clinicaltrials.gov, we conducted a literature search of treatment studies of a non-antipsychotic compound adjunctive to antipsychotics in non-acute schizophrenia in which change in negative symptoms was reported, operationalized as mechanisms of action (MOA) with 5 or more total studies, including at least one multi-center study with ≥3 sites. The last search was in August 2022. Meta-analysis and meta-regression analyses were conducted with sample size as a covariate.

Results: 161 drug vs. placebo comparisons across 127 studies with 13,119 unique participants across 8 mechanisms of action (MoA, per study n=103.1±143.7, range 8 to 705). 5,195 were allocated to the placebo groups, and 7924 to the drug groups. Studies were published between 1992 and 2022. 63 comparisons were multi-center (39.1%.

Across MoA, the magnitude of the placebo response scaled with both sample size or site to a greater extent than treatment response, leading to a significant reduction in trial effect size with sample size and number of treatment sites ($p < 0.001$). Significant results across MoA were obtained preferentially with sample sizes in the range of 30 to 150 individuals. Other factors contributing to reduced effect size include percentage of academic sites, industry sponsorship and year of publication. Critical sample sizes for potential studies were then modeled based upon the concept of effect size deflation by sample size. These models demonstrated that given present sample-size vs. placebo effect magnitude, largest power is obtained for studies with < 100 individuals, and that no studies can be designed to achieve a power of > .8 to detect a moderate (d=.05) magnitude clinical effect.

Discussion: These findings demonstrate the consequences of placebo-effect scaling by sample size within adjunctive clinical for negative symptoms and demonstrate the need to incorporate realistic sample-size penalties in power calculations for multi-center clinical trials. In specific, they argue for moderate size studies with limited number of performance sites. The findings also highlight the significant meta-analytic findings for several existing mechanisms including 5-HT3R, anti-inflammatory, anti-depressant and NMDAR modulator mechanisms, which may serve as useful adjuncts to antipsychotic medication.

T11. A RANDOMIZED, DOUBLE-BLIND, ACTIVE COMPARATOR-CONTROLLED, PHASE 3 STUDY TO EVALUATE THE LONG-TERM SAFETY AND TOLERABILITY OF ULOTARONT IN PATIENTS WITH SCHIZOPHRENIA

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Abstract Background: Ulotaront is a trace amine-associated receptor 1 (TAAR1) agonist with 5-HT1A agonist activity that lacks direct D2 and 5-HT2A receptor antagonism. Ulotaront is in clinical development for the treatment of schizophrenia. The pharmacological, safety and tolerability profile of ulotaront appears to be distinct from atypical antipsychotics based on preclinical [1,2] and clinical [3, 4, 5] data demonstrating minimal to no association with extrapyramidal symptoms (EPS), no prolactin effects, and a potentially favorable metabolic profile. The current study was designed to evaluate the long-term safety and tolerability of ulotaront, for ulotaront as a novel treatment for schizophrenia. Exploratory analyses were included to compare ulotaront to an atypical antipsychotic (quetiapine XR).

Methods: This was a multicenter, randomized (in a 2:1 ratio), double-blind, parallel-group, 52-week, flexible-dose study evaluating the safety and tolerability of ulotaront (50-100 mg/d) versus quetiapine XR (QXR; 400-800 mg/d), in adult patients with a DSM-5 diagnosis of schizophrenia who were clinically stable for ≥8 weeks prior to screening and had a PANSS total score ≤80 at study entry. Patients who were treatment resistant to antipsychotic medication or who had a history of inadequate response or intolerability to quetiapine or quetiapine XR were excluded from study entry. The primary study outcomes were safety related, including incidence of overall adverse events (AEs), serious adverse events (SAEs), AEs leading to discontinuation, change from Baseline in body mass index (BMI) and waist circumference, clinical laboratory tests, and ECG parameters.

Results: In the safety population treated with ulotaront (N=201) and QXR (N=102), total discontinuations were 47.8% vs. 44.1%, respectively, and AEs leading to study discontinuation were 22% vs. 21%. The most common AEs for ulotaront vs. QXR (≥10% in either group) were somnolence (6.0% vs. 20.6%), insomnia (14.9% vs. 10.8%), schizophrenia (14.4% vs. 5.9%), anxiety (13.9% vs. 9.8%), constipation (3.5% vs. 11.8%), and weight increase (4.0% vs. 10.8%). Mean changes from Baseline to Week 52 in weight-associated parameters for ulotaront vs. QXR were as follows: weight (-1.2 vs. +1.4 kg; $p < 0.001$), BMI (-0.4 vs. +0.5 kg/m2; $p < 0.001$), and waist circumference (-1.4 vs. +1.4 cm; $p < 0.05$). There was no clinically-significant Baseline to Week 52 changes in either treatment group in laboratory (including glycemic indices, lipids, prolactin) or vital sign parameters. In secondary effectiveness measures (PANSS total and subscale scores), there were no significant differences in change from Baseline to Week 52, or to any intermediate time-point, between ulotaront and QXR.

Conclusions: The results of this study extend the findings from a previously-reported 6-month Phase 2 study to 52 weeks [4], demonstrating that long-term treatment with ulotaront is safe and well-tolerated with no unexpected adverse effects for this novel TAAR1 agonist class drug. The notable lack of adverse effects of ulotaront on lipids and glycemic indices, and the significant reduction in weight and waist circumference, are consistent with preclinical research suggesting that ulotaront improves glycemic control and reduces body weight in rodent models of diabetes, obesity, and iatrogenic weight gain [2].

T12. DETERMINANTS OF BURDEN AND PSYCHOSOCIAL FUNCTIONING AMONG CARE PARTNERS OF CIVILIAN PATIENTS LIVING WITH PTSD

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Abstract Background: Post-traumatic stress disorder (PTSD) is a mental health condition that is triggered by either experiencing or witnessing a traumatic event. Care partners of civilian PTSD patients can be significantly impacted by their relationship with the patient, as well as time-dependent, developmental, physical, and social burdens that place them at risk of increased distress. There is limited research exploring factors that effectively predict a higher level of burden or significant impairment in psychosocial functioning among care partners.

Methodology: A cohort of 250 care partners supporting individuals formally diagnosed with PTSD were recruited to complete a 30-minute survey covering demographics, patient characteristics, and utilized two validated scales, the Zarit Burden Interview (ZBI) (scoring range: 0-88; 4 levels of severity level), and the Brief Inventory of Psychosocial Functioning (B-IPF) (scoring range: 0-100; 5 levels of impairment). The ZBI assesses care partner burden and the B-IPF assesses PTSD-related psychosocial functional impairment. Independent Simple Ordinary Least Squared Regressions were performed to assess the linear effects between individual predictor variables and ZBI and B-IPF total scores.

Results: Care partners of PTSD patients with anxiety disorders had an average B-IPF and ZBI score that was 17.6 and 8.3 points higher, respectively, than care partners of PTSD patients with no anxiety disorders (B-IPF: $p < 0.001$, ZBI: $p < 0.001$). Care partners of patients with depressive disorders exhibited an average score of 21.5 B-IPF and 13.8 ZBI points higher

compared to care partners of patients with no depressive disorders (B-IPF: $p < 0.001$, ZBI: $p < 0.001$). Care partners that are friends of the patient exhibited an average score of 16.5 B-IPF and 4.4 ZBI points lower than that of spousal care partners (B-IPF: $p < 0.001$, ZBI: $p < 0.05$). Care partners of patients with commercial insurance had an average of 5.3 ZBI points lower than that of care partners of Medicare patients ($p < 0.05$). Female care partners, on average, had higher burden and psychosocial impairment than male care partners (ZBI: $\beta = 4.6$ $p < 0.01$, B-IPF: $\beta = 8.3$ $p < 0.01$). Care partners that were unemployed due to care giving scored 12.2 ZBI points and 20.1 B-IPF points higher, on average, compared to employed care partners (ZBI: $p < 0.001$, B-IPF: $p < 0.001$). Care partners that lived with the patient experienced higher ZBI and B-IPF scores compared to care partners that did not live with the patient (ZBI: $\beta = 5.2$ $p < 0.001$, B-IPF: $\beta = 15.7$ $p < 0.001$). Care partners of patients receiving pharmacotherapy and psychotherapy experience higher ZBI and B-IPF scores, compared to care partners of patients only receiving pharmacotherapy (ZBI: $\beta = 9.1$ $p < 0.001$, B-IPF: $\beta = 11.5$ $p < 0.001$).

Conclusion: Care partners caring for PTSD patients with comorbid mental health conditions appear to bear significant burden. Additionally, the relationship between the patient and primary care partners, severity of PTSD symptoms, and presence of insurance also appear to be major drivers. Understanding the economic burden of these specific factors may drive the development of new care partner-focused solutions.

T13. THE BRIEF INVENTORY OF PSYCHOSOCIAL FUNCTIONING AND ZARIT BURDEN INTERVIEW ARE STRONGLY CORRELATED MEASURES FOR USE IN CARE PARTNERS OF CIVILIAN INDIVIDUALS WITH POST-TRAUMATIC STRESS DISORDER

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Abstract Background: The Zarit Burden Interview (ZBI) is a widely used, 22-item, self-report measure that assesses caregiver or care partner burden but has not been used for care partners of individuals with post-traumatic stress disorder (PTSD). The Brief Inventory of Psychosocial Functioning (B-IPF) is a 7-item self-report measure that assesses PTSD-related psychosocial functional impairment and was developed as an abridged version of the Inventory of Psychosocial Functioning (IPF) for use in settings where time is a major consideration. This research aims to evaluate the relationship between the ZBI and B-IPF and establish their use to measure burden in care partners of individuals with PTSD.

Methodology: A cohort of 250 care partners of individuals with PTSD in the United States completed a 30-minute online survey that included the 22-item ZBI and 7-item B-IPF to measure the level of care partner burden and impact on psychosocial functioning. Correlation analysis was conducted to evaluate the relationship and association between the ZBI and B-IPF based on their total scores, ZBI two-factor model, and individual items. A Shapiro-Wilks test was conducted to assess the normality of the ZBI and B-IPF survey response distributions (ZBI: $p < 0.001$, B-IPF: $p < 0.001$). As a result of the normality test, a Spearman's Rank Correlation was performed to measure the strength of association between the two surveys.

Results: Of the care partners surveyed, the average total ZBI score was 27.10 out of 88 (SD: 12.51) with 47% of care partners experiencing "mild to moderate" levels of burden. The average total B-IPF score was 40.47 out of 100 (SD: 22.19) with 34% of care partners experiencing "moderate" impairment on their psychosocial functioning. The total scores of the B-IPF and ZBI are strongly correlated ($\rho = 0.8$) and the role strain dimension of the ZBI had the highest correlation with the friendships and socializing domain of the B-IPF ($\rho = 0.77$). The personal strain factor of the ZBI was strongly correlated with the family relationships domain of the B-IPF ($\rho = 0.68$). Additionally, the friendships and socializing domain of the B-IPF was strongly correlated with several individual items of the ZBI including lack of time for self ($\rho = 0.64$) and lack of privacy due to patient ($\rho = 0.65$).

Conclusion: Care partners of individuals with PTSD experience burden as well as impairment of their psychosocial functioning as measured by the ZBI and B-IPF, demonstrating the need for awareness of the disease burden PTSD can have on care partners. The ZBI and B-IPF are strongly correlated measures with the ZBI role strain dimension and B-IPF day-to-day activity domain having the highest correlation. In settings where employing the full 22-item ZBI is difficult, the B-IPF can be more easily administered to measure burden on care partners of individuals with PTSD more broadly beyond its validated use for impairment on psychosocial functioning.

T14. APIMOSTINEL, A NOVEL NMDAR MODULATOR WITH RAPID-ACTING, SUSTAINED EFFECTS AND FAVORABLE DRUG-LIKE PROPERTIES: PRECLINICAL STUDIES

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Abstract Background: NMDA receptor (NMDAR) modulation is an emerging rapid-acting pharmacological mechanism for treating neuropsychiatric disease, with recent FDA approvals of Spravato® and Auvelity®. Herein, we investigated the in vitro and in vivo pharmacology of apimostinel, a novel NMDAR positive allosteric modulator currently undergoing clinical investigation for depression.

Method: Apimostinel induced potentiation of NMDA receptor current was measures in HEK cells expressing human GRIN2A-or GRIN2B-containing receptors. In vivo, resting medial prefrontal qEEG alpha power was measured. Apimostinel's pharmacodynamic effect upon metaplasticity, via NMDAR-dependent long-term potentiation (LTP) in the medial prefrontal cortex, was measured in freely behaving rats 1 hr., 1 week, and 2 weeks post-dose, and after 7 daily doses. A chronic unpredictable stress (CUS) protocol was used to determine antidepressant-like effects of apimostinel.

Results: Apimostinel enhanced activation of recombinant GRIN2A and GRIN2B-containing NMDA receptors with a modest potency preference for GRIN2A relative to GRIN2B. Apimostinel increased cortical qEEG alpha power, a biomarker of NMDAR activation, in correlation with CSF exposures that potentiate NMDARs. Apimostinel treatment acutely enhanced in vivo LTP formation and metaplasticity for approximately 7 days following a single dose. Repeat low dose (0.1, and 1 mg/kg IV) of apimostinel produced a larger enhancement of

EEG alpha power and lead to a larger and longer lasting facilitation of Metaplasticity (14 days) as compared to a single dose. However, repeat high dose apimostinel (10 mg/kg IV) failed to enhance metaplasticity as compared to vehicle, and produced a weaker enhancement of alpha as compared to a single dose. In the CUS assay, apimostinel produced robust and sustained antidepressant-like effects without ketamine-like dissociative side effects and exhibited superior potency and therapeutic rage (0.01- > 1 mg/kg) versus ketamine.

Conclusions: Apimostinel is a novel NMDAR modulator that enhances activation of GRIN2A and GRIN2B-containg recombinant receptors. It demonstrates rapid and sustained single-dose enhancement of plasticity, with superior safety versus NMDAR antagonists like ketamine. Repeat low dose apimostinel produces an optimal effect on metaplasticity and alpha power. A strong correlation of apimostinel drug exposure across NMDAR potentiation, qEEG biomarkers, metaplastic effects, and antidepressant-like response provides compelling rationale for clinical evaluation across neuropsychiatric disorders.

T15. IMPACT OF TIME TO BREXPIPRAZOLE INITIATION ON HEALTHCARE RESOURCE UTILIZATION AND COST FOR MAJOR DEPRESSIVE DISORDER: – A US REAL-WORLD STUDY

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Abstract Background: Brexpiprazole is an oral atypical antipsychotic indicated for adjunctive treatment of adults diagnosed with (MDD). Latest real-world evidence focused on the economic impact related to utilization and timing of initiation of brexpiprazole in adults with MDD can support informed decision-making.

Objectives: To assess the timing of brexpiprazole initiation, its impact on healthcare resource utilization (HCRU), and cost for adjunctive treatment of adults with MDD in real-world practice.

Methods: This retrospective cohort study was conducted using deidentified MerativeTM MarketScan® commercial claims data in the US (Jan 2013 to Dec 2021). Adults (≥18 years) with MDD were identified by using validated ICD-9 and ICD-10-CM codes with ≥1 inpatient or ≥2 outpatient visits. Adjunct brexpiprazole users were classified as late initiators if they were initiated later than ≥1 year after antidepressant (ADT) following MDD diagnosis (1, 2). Brexpiprazole initiation within 1 year after first ADT was further categorized into two groups (≤60 and > 60–365 days) based on outpatient visit trends from a Poisson regression model, using nonlinear splines. Overall and MDD-specific HCRU and adjusted cost, 1 year post brexpiprazole initiation (index date), was used as the outcome of this study. A negative binomial regression was used to model HCRU; a generalized linear model with gamma distribution and log link was used to calculate adjusted annualized cost related to HCRU. Alpha < 0.05 was considered statistically significant.

Results: Overall, 1226 adults with MDD and adjunct brexpiprazole users were identified. The median age was 47 years (IQR 36–55). No statistically significant differences were observed across three categories of brexpiprazole users and baseline covariates except gender. In a multivariable adjusted model, compared to those with brexpiprazole initiation ≤60 days post first ADT, late initiators were strongly associated with MDD-specific outpatient visits (adjusted IRR=1.32, 95% CI 1.08–1.62, p=0.006). From adjusted generalized linear model for

1 year cost following index date, late initiators had significantly higher annualized total cost ($12,785) compared with those initiating brexpiprazole within 60 days ($8036), p=0.0009.

Conclusion: In this analysis of over 1000 adults, late initiation of brexpiprazole beyond 1 year after first ADT was associated with significantly higher outpatient healthcare utilization and cost in real-world practice. Early intervention with adjunct brexpiprazole may reduce HCRU burden and cost among adults with MDD.

T16. EFFECT OF BEDTIME SUBLINGUAL CYCLOBENZAPRINE (TNX-102 SL) ON PAIN, SLEEP, FATIGUE AND COGNITION IN FIBROMYALGIA-TYPE LONG COVID: RESULTS OF A DOUBLE-BLIND RANDOMIZED PROOF-OF-CONCEPT PHASE 2 STUDY

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Abstract: Fibromyalgia (FM)-type Long COVID is a common chronic nociplastic syndrome characterized by widespread pain, nonrestorative sleep, fatigue, and cognitive dysfunction, and by functional impairment. TNX-102 SL is a sublingual, transmucosal formulation of cyclobenzaprine (CBP) designed for bedtime administration to improve sleep quality. CBP is a tricyclic antagonist of 5-HT2A, α1 adrenergic, H1 histaminergic, and M1 muscarinic receptors. The mechanistic hypothesis for bedtime TNX-102 SL is that improving sleep quality in FM-type Long COVID can lead to syndromal improvement. In this Phase 2 trial, PREVAIL, TNX-102 SL treatment resulted in numerical improvements in pain, sleep quality, fatigue, and cognition.

PREVAIL was a placebo-controlled proof-of-concept trial at 19 U.S. sites. The study enrolled Long COVID patients with multi-site pain as captured by a modified Michigan Body Map. Although initial planned N was 470, recruitment was stopped early for business reasons; and a total of 63 patients were randomized to TNX-102 SL 2.8 mg for two weeks, followed by 5.6 mg for 12 weeks (n=32) or to matching placebo for 14 weeks (n=31). The primary endpoint was Week 14 change from baseline in weekly average of daily diary worst Long COVID numerical rating scale (NRS) pain scores, analyzed by mixed model repeated measures. Other measures included daily sleep quality; PROMIS Fatigue, Cognitive Function - Abilities, and Sleep Disturbance T-scores; Insomnia Severity Index (ISI); Sheehan Disability Scale (SDS); and Patient Global Impression of Change (PGIC).

TNX-102 SL had a small numeric advantage over placebo on the pain primary (least squares (LS) mean (SE) change in TNX-102 SL -2.2 (0.34), and PBO -2.0 (0.35), difference of −0.2 (0.49) NRS units, p=0.74, effect size [ES] = 0.08). Clinically meaningful activity was observed in PGIC response rates (‘very much improved’ or ‘much improved’) for TNX-102 SL versus placebo at week 6 (31.3% vs. 9.7%), week 10 (28.1% vs. 12.9%), and week 14 (34.4% vs. 16.1%). TNX-102 SL treatment also showed activity (ES > 0.20) in PROMIS Fatigue (ES=0.50), sleep quality diary (ES=0.23), PROMIS Sleep Disturbance (ES=0.32), the ISI (ES=0.24), the SDS (ES=0.26), and the PROMIS Cognitive scale (ES=0.21). TNX-102 SL demonstrated a favorable tolerability profile with no new safety signals or serious adverse events. The local administration site reaction of oral hypoaesthesia was the most common AE with TNX-102 SL (19%) versus placebo (0%), and was transient, self-limited, and rated as

mild in all cases. Systemic AEs were low on active, and there were no meaningful changes in weight or blood pressure.

Bedtime TNX-102 SL treatment targets non-restorative sleep and, in FM-type Long COVID, resulted in strong activity in fatigue and sleep as well as in cognitive function and PGIC. Although the pain primary did not separate from placebo, changes from baseline in both groups were large, indicating a substantial placebo response on pain. The effects of TNX-102 SL on fatigue and cognitive symptoms are especially intriguing because similar effects have been observed in studies of TNX-102 SL in FM. TNX-102 SL was well tolerated without clinically significant side effects relating to cognition, weight, blood pressure or sexual function. The results of TNX-102 SL therapy in the PREVAIL study support the hypotheses that (1) common mechanisms underly FM-type Long COVID and FM and (2) addressing the sleep disturbance in FM-type Long COVID has the potential to result in syndromal improvement. These findings suggest that disturbed sleep in FM-type Long COVID is an obstacle to recovery, and targeting sleep has the potential to facilitate recovery.

T17. A RANDOMIZED PLACEBO-CONTROLLED DOUBLE-BLIND PHASE 2 TRIAL OF ADJUNCTIVE KET01 (ORAL PROLONGED-RELEASE KETAMINE) FOR TREATMENT-RESISTANT DEPRESSION

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Abstract Background: Ketamine, originally developed as an anesthetic, has shown utility as a rapidly acting antidepressant. Ketamine is a potent inhibitor of the N-methyl-D-aspartate receptor (NMDAR), but ketamine and its metabolites also bind to other targets, and it has not been conclusively demonstrated that NMDAR inhibition is needed for antidepressant efficacy. Ketamine is associated with dissociative and cardiovascular adverse effects (AE) after intravenous, intranasal, or immediate-release oral administration thus limiting its practical utility. KET01 was developed as an oral prolonged-release formulation of racemic ketamine with a low propensity for dissociation, based on its pharmacokinetic profile.

Methods: Outpatients with treatment-resistant depression (defined as failure to respond to two different courses of antidepressant treatment during the current major depressive episode) were randomized to receive once-daily placebo (PBO, N=40), 120 mg KET01 (N=42), or 240 mg KET01 (N=40), adjunctively to ongoing standard antidepressant treatment for 3 weeks. The first dose was administered under supervision at the trial site, allowing for assessment of acute tolerability and blood draws for pharmacokinetic assessment. The remaining doses were taken at home. The primary endpoint was the mean score change from baseline (BL) in the Montgomery-Åsberg Depression Rating Scale (MADRS) on Day 21 (mixed model for repeated measures).

Results: After administration of 240 mg KET01, an improvement in the MADRS score was seen after 7 hours (change from BL: -7.65; Δ vs PBO: -2.22, n.s.). The separation from PBO reached statistical significance on Day 4 (change from BL: -10.02; Δ vs PBO: -3.66, p=0.020), and Day 7 (change from BL: -12.21; Δ vs PBO: -3.95, p=0.042). The improvement from BL was sustained while on treatment until Day 21 (change from BL: -13.15; Δ vs PBO: -1.82, n.s.), and, additionally, after a 4-week follow-up (change from BL: -12.51; Δ vs PBO: -3.35, n.s.).

KET01 was well tolerated and treatment-emergent AE were reported by 47.5%, 50.0%, and 62.5% in the PBO, 120 mg, and 240 mg KET01 groups, respectively.

No differences in the mean Clinician-Administered Dissociative States Scale (CADSS) scores were observed at any time point. CADSS total score > 4 after BL and > 0 increase from BL was observed in 15%, 12%, and 10% of patients in the 240 mg, 120 mg KET01, and PBO groups, respectively. No clinically relevant changes in heart rate or blood pressure were detected. Elevations in mean plasma gamma-glutamyltransferase and alanine aminotransferase concentrations were observed from week 2 for both KET01 groups and decreased during follow-up.

At 7 hours after the first 240 mg KET01 dose (close to the presumed Tmax of ketamine), observed mean plasma concentrations were 37.7 ng/ml for ketamine, 260.6 ng/ml for norketamine (NK), and 185.3 ng/ml for hydroxynorketamine (HNK). Plasma concentrations of ketamine appeared lower while concentrations of the metabolites NK and HNK appeared higher than reported for intravenous infusions of 0.5 mg/kg of racemic ketamine hydrochloride (1).

Conclusion: This study demonstrated a rapid and clinically relevant reduction of depressive symptoms after treatment with 240 mg/day KET01 with only minimal signs of dissociative and cardiovascular symptoms, suggesting a low degree of NMDAR inhibition. This is in line with challenges to the view that NMDAR inhibition should be necessary for antidepressant efficacy of ketamine-based medications (2).

T18. VORTIOXETINE VS OTHER STANDARD OF CARE ANTIDEPRESSANTS IN PATIENTS WITH MAJOR DEPRESSIVE DISORDER: 12-WEEK INTERIM ANALYSIS FROM PATIENTSLIKEME SURVEY

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Abstract Background: Real-word data for vortioxetine vs other standard of care (SOC) monotherapy antidepressant treatments following a new start or switch in patients with major depressive disorder (MDD) are limited.1,2 PatientsLikeMe (PLM) is an interactive digital health platform that helps patients stay engaged in their treatment journey. The PLM platform can help generate insights about treatment outcomes for patients with MDD in a real-world setting.3

Methods: This ongoing, observational, real-world, prospective, 24-week study enrolled patients aged ≥18 years residing in the US within the PLM community with a confirmed MDD diagnosis and recent start or switch in antidepressant.3 Primary endpoint was improvement in MDD symptoms (Patient Global Impression of Improvement [PGI-I] scores < 2) at week 12 in patients on vortioxetine vs other SOC monotherapy antidepressants. Key secondary endpoints included 5-item Perceived Deficits Questionnaire–Depression (PDQ-D5), 5-item World Health Organization Well-being Index (WHO-5), Quality of Life Enjoyment and Satisfaction Questionnaire–Short Form (Q-LES-Q-SF), and Patient Health Questionnaire-9 (PHQ-9), along with setting up to 3 goals and achievements using the Goal Attainment Scale–

Depression (GAS-D) approach. The Mann-Whitney U test was used for all comparisons, except remission rates, compared using chi-square statistics (significance level $P < 0.05$ for both). Here, we report 12-week interim analysis results.

Results: Among 503 patients, mean age was 47.4 years, 58.4% were female, 62.4% were White, and 67.4% were Not Hispanic/Latino. At week 12, 89% (134/151) of patients in the vortioxetine and 97% (343/352) in the other SOC group completed the survey. At week 12, 4.47% of patients in the vortioxetine and 1.75% in the other SOC group reported improvement in PGI-I scores, but this was not statistically significant (P=0.83). At the same time, vortioxetine patients with a change 3-6 months prior to study start reported significantly better PGI-I scores vs the other SOC group (3.5 vs 3.9; P=0.01). Numerically improved mean scores were observed in the vortioxetine vs other SOC group for PDQ-D5 (7.74 vs 8.49; P=0.09), WHO-5 (11.42 vs 9.62; $P < 0.001$), and Q-LES-Q-SF (49.27 vs 47.61; $P < 0.05$). No statistically significant difference was observed in PHQ-9 scores, but remission rate (PHQ-9 score < 5 at week 12 follow-up) was higher in the vortioxetine (n=12) vs other SOC group (n=8; $\chi 2=8.94$, df=1; $P < 0.01$). In all, 499 patients set at least 1 goal (950 goals), with 45.78% of goals in the physical function and well-being domain. At week 12, the study population was highly engaged in their goal tracking with the average percentage of weeks tracked overall at 74%.

Conclusion: This 12-week interim analysis showed improvements in symptoms of MDD, in some domains, with a new start or switch of vortioxetine vs other SOC treatments. Results from this study may help inform treatment decisions in real-world clinical practice.

T19. AN OPEN LABEL PILOT STUDY OF NON-INVASIVE VAGAL NERVE STIMULATION FOR TREATMENT RESISTANT MAJOR DEPRESSIVE DISORDER

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Abstract Background: Major Depressive Disorder (MDD) is the leading cause of disability worldwide and one of the most economically burdensome conditions in the United States. Thirty nine percent of patients who receive up to four sequential antidepressant trials continue to demonstrate clinically significant symptoms of MDD. New and effective alternatives to the currently available pharmacotherapies are needed for MDD. Surgically implanted vagal nerve stimulation is FDA approved for the treatment of MDD due to its efficacy. Non-invasive vagal nerve stimulation (nVNS) devices are available for the treatment of migraines but have not yet been studied for MDD.

Objectives: To assess the safety profile and preliminary efficacy of nVNS on MDD symptoms in adults who have failed at least one antidepressant trial.

Methods: Adults ages 18 to 75, in a current major depressive episode associated with MDD who failed to respond to one or more adequate trials of antidepressant drugs and did not meet exclusion criteria on screening assessment were enrolled in this investigator initiated open-label trial of nVNS. Participants self-administered nVNS three times daily for up to six months using the gammaCore™ device developed by electoCore. At monthly study visits, participants were assessed for adverse events and changes in MDD symptoms using the MADRS and other

standard scales. Cognitive testing, physical examination and ECG were completed after 3 and 6 months of participation.

Results: Among the six psychiatry outpatients screened, five met study criteria and enrolled, four completed six months of nVNS treatment, and one participant was lost to follow-up after two months of treatment. Each of the five participants had previously failed at least two antidepressant trials and, at baseline visit they reported symptoms on MADRS consistent with moderate or severe major depression. At their last completed study visit, four subjects reported no depression and one reported mild depression. One hundred percent of participants reported a substantial decrease in MDD symptoms in the first two months of nVNS which was relatively sustained during the subsequent months of treatment. Participants' MADRS scores at last study visit decreased by 15 to 36 points compared to baseline. These findings were not statistically significant given the small sample size.

There were no serious adverse events related to nVNS. One participant required surgery that was unrelated to nVNS and was lost to follow-up after month two. The only adverse event reported was one instance of mild neck soreness which resolved after changing the side to which stimulation was administered.

Conclusions: Each participant in this pilot study tolerated nVNS well and reported a substantial decrease in symptoms of MDD. Given these promising preliminary findings of a non-invasive, alternative to pharmacotherapy for MDD, future studies with larger cohorts and randomized and controlled designs are warranted.

T20. UNDERSTANDING PREFERENCES FOR AN ANTIPSYCHOTIC REGIMEN ADMINISTERED ONCE EVERY 2 MONTHS FOR BIPOLAR I DISORDER: A QUALITATIVE, SINGLE-PERSON INTERVIEW STUDY OF PATIENTS, CAREGIVERS, AND PRESCRIBERS CONDUCTED IN THE USA

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Abstract Background: Bipolar-I disorder (BP-I) is a life-long, episodic illness characterized by severe alterations in mood and behavior; pharmacological treatment is recommended to achieve and maintain symptom control. Long-acting injectable (LAI) formulations of antipsychotics can improve treatment adherence and reduce the rate of hospitalization compared with oral treatments. As new LAI formulations with longer dosing intervals become available, there is a need to evaluate how they will impact patient, caregiver, and prescriber preferences for treatment.

Methods: This qualitative study was conducted to explore the preferences of patients, caregivers, and prescribers relating to LAI dosing frequency, and the factors influencing preferences for an LAI administered once every 2 months for the treatment of BP-I. The study recruited 10 adults aged > =18 years diagnosed with BP-I, 5 caregivers, and 5 prescribers. Data were collected in the USA via web-assisted telephone in-depth interviews, using a semi-structured discussion guide, and interview transcripts underwent thematic analysis.

Results: Most patients and caregivers are satisfied with once-monthly LAIs, and value the decreased dosing frequency, "convenience", and that LAIs are not self-administered, compared to oral medication. Patients and caregivers view the main goal of treatment as maintaining adherence to ensure symptom stability, and describe an ideal treatment as one offering decreased dosing frequency and fewer/no side effects. Patients and caregivers are often involved in LAI treatment decisions and also rely on their doctor's advice.

Prescribers report that they spend time discussing treatments, goals, and concerns with patients and caregivers. Prescribers view caregivers as "allies" in patients' healthcare and consider improved quality of life as the primary treatment goal. Prescribers list caregiver involvement, patient characteristics/preferences, adherence history, dosing frequency, and treatment response as important treatment characteristics when selecting an LAI. Some prescribers feel that LAIs may lessen "control" for patients (loss of autonomy) and clinicians (inability to change dose or address side effects).

Patients and caregivers have generally positive views on an LAI with a 2-month dosing interval as it would mean less time spent on appointments and travel. They describe feelings of "freedom" and "serenity", with less responsibility and the possibility of going on vacation. The main concern is the medication wearing off before the next injection; other challenges are remembering the next injection, forgetting the appointment, and the potential for additional side effects.

Prescribers state that a reduced number of visits with an LAI with a 2-month dosing interval may benefit patients, prescribers, and caregivers. Additional benefits that patients may appreciate are fewer injections, and the potential to feel well for longer with a gradual-release treatment. The potential need for supplemental oral antipsychotics is seen as a disadvantage, as is the inability to alter dosing, which is seen with all LAIs. Prescribers view patients stable on oral medication and desiring a reduced dosing frequency as suitable for an LAI with a 2-month dosing interval.

Conclusion: An LAI with a 2-month dosing interval may be generally accepted as a treatment for BP-I due to perceptions of greater freedom and less burden. Effectiveness and duration of efficacy are critical factors for uptake. Consideration of patient and caregiver preferences by prescribers when selecting a treatment could ensure that treatment goals are met.

T21. A PHASE 1 SAFETY, PHARMACOKINETICS (PK) AND QUANTITATIVE ELECTROENCEPHALOGRAPHY (QEEG) PHARMACODYNAMICS STUDY OF SINGLE AND MULTIPLE ASCENDING DOSES OF INTRAVENOUS APIMOSTINEL COMPARED WITH PLACEBO IN HEALTHY VOLUNTEERS

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Abstract: Purpose. NMDA receptors are implicated in mood regulation, memory, and cognition. Apimostinel is a tetrapeptide containing a non-natural that acts as a positive allosteric modulator at a novel site on NMDA receptors to promote receptor activation in the presence of glutamate agonists. Apimostinel stimulates signal transduction in cells expressing human recombinant NMDA receptors over a range of 1-100 nM, and its antidepressant effects

in rodents occurs at CSF concentrations over the same range. In a previous single-dose Phase 2a efficacy study in patients with Major Depressive Disorder, apimostinel, 10 mg IV, elicited rapid antidepressant effects at 24 hours postdose. The purpose of this study was to examine safety and tolerability, PK and EEG pharmacodynamics in healthy volunteers, to assess the rationale for multidose efficacy studies in patients with acute, severe neuropsychiatric disorders.

Methodology: This was a randomized, double-blind, placebo-controlled, single center Phase 1 study. Each of 5 cohorts received drug or placebo 6:2 active:placebo for a total of 40 subjects. Safety was assessed in each cohort: a single dose of 25 mg IV to study plasma and CSF PK, a single dose of 25 mg IV to study qEEG, and 8 daily doses of 1 mg, 5, or 10 mg for 8 consecutive days to assess PK and EEG. The multiple dose cohorts were completed in ascending dose order, with a safety review committee considering safety prior to a decision to approve escalation to the next dose.

Results: Subjects consisted of 55% males, 82.5%% were white, with mean age 35.3 years. The investigational products were generally well-tolerated and prompted no safety concerns. A total of 70 treatment-emergent adverse events (TEAEs) were experienced by 28 (70.0%) subjects, with (50.0% incidence in placebo vs 33.% in single dose active, and 83.3% placebo vs 94.4% in multiple dose active. Two subjects were discontinued for TEAES, 1 for sinus tachycardia on Day 1 and 1 for pyrexia on Day 5. The most common TEAE, headache, was dose-related. Vital signs, clinical laboratory values and ECG parameters were comparable across the study cohorts. One SAE, mood disorder, which was confounded by prior substance abuse, occurred in a subject in the 1 mg apimostinel cohort, hospitalized one day following the last dose of study drug. Plasma Tmax ranged from 0.03-0.15 hours (near the end of infusion, 1-5 min depending on dose). Plasma t1/2 was 1.04-1.64 hr. Plasma Cmax and AUC increased in dose proportional manner. CSF Tmax was 1.52 -2.10 hr and CSF t1/2 was 2.04-2.23 hr. qEEG changes occurred following all dose levels of apimostinel. Alpha power increased dose-dependently from 1-10 mg apimostinel, but increase was blunted at 25 mg.

Specific Findings and Importance: Apimostinel was generally safe and well-tolerated following multiple doses from 1-25 mg IV. Plasma and CSF PK were rapid with Tmax later in the CSF. Apimostinel-stimulated qEEG alpha power was maximal following a dose of 10 mg, with CSF Cmax consistent with concentrations that maximally stimulate NMDA receptors in vitro. Apimostinel-stimulated qEEG alpha power was dose-dependent and consistent with the results of efficacy studies in rodents and the results of the previous human Phase 2a single dose study. These results support previous findings in rodents of CSF concentration associated with the maximum effect of apimostinel on qEEG alpha, and the use of qEEG alpha power as a biomarker of NMDA receptor activation in human subjects.

T22. NEUROPROTECTIVE EFFECT OF MAZINDOL ON NOCTURNAL ACTIVITY IN AN OREXIN-B-SAPORIN-INDUCED NARCOLEPTIC-LIKE MODEL IN SPRAGUE-DAWLEY RATS

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Abstract: The orexin-B–saporin (OX-B-SAP) specifically binds to orexin receptors and lesions orexin neurons and microinjection of OX-B-SAP, into the lateral hypothalamus (LH), produces narcoleptic behavior that is directly correlated with the loss of orexin neurons.
In the present study, the microinjection of the conjugate OXB-SAP (90 ng) in LH increased the sleeping time, especially during the dark phase in 3-week period following lesion in Sprague-Dawley male rats (N=13, 5 weeks old at the time of surgery) housed in a 12/12h light dark cycle until the end of the experiment.

Animals were housed singly in transparent cages which were placed in actimeters allowing to constantly record the locomotor activity (distance travelled) for a 4-weeks period. The distance travelled each day, during dark and light periods and during each 1-h period will be recorded. Normal male rats show a locomotor activity which is 4-5 times higher during the dark phase than during the light phase.

Seven received mazindol (3 mg/kg) orally administered immediately after surgery and every day, at the beginning of the dark phase, for the 21 consecutive days following lesion. Five received vehicle administration from the 14th day to the 21st day post lesion.

The total sleep time was significantly decreased in OXB-SAP rats with mazindol (3 mg/kg, p.o.) in comparison with control OXB-SAP-lesioned rats receiving vehicle ($p < 0.05$). This effect was the most prominent during the dark phase, and especially during the first 3-h period of the dark phase. The increase in the sleeping induced by the OXB-SAP lesion was no more reduced following mazindol withdrawal.

The brain was collected in all rats and the number of orexin neurons in LH was counted by immunohistochemical staining. The number of orexin neurons was decreased by about 70% in OXB-SAP lesioned rats comparatively with Sham-lesioned rats (N=10) but the number of orexin neurons counted was not significantly modified by mazindol.

These results suggest that mazindol reduces the narcoleptic effect of an OXB-SAP-lesioned, an effect related with its stimulant effect, but does not induce neuroprotective effect on the OXB-SAP-induced lesion of orexin neurons.

T23. CAN ADAPTIVE TESTING TECHNOLOGY LEAD TO A BETTER UNDERSTANDING OF THE COURSE OF KETAMINE TREATMENT OUTCOME?

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Abstract: In the last two decades, numerous clinical trials have demonstrated the effectiveness of short-term ketamine for treatment resistant depression. Ketamine has also been observed to produce large effect sizes relative to other treatments for depression. Intravenous ketamine has become an important consideration for clinicians treating patients with treatment resistant depression. To date most reports of ketamine outcome have focused on pre-post efficacy of trials ranging from 1 to 4 weeks in duration, with typical protocols involving twice-weekly infusion. However, computerized adaptive testing methodology offers the opportunity to examine the rapid changes in depression severity that can occur between one infusion and another.

We report on the capacity of Adaptive Testing Technologies CAT-MH™ depression module (CAT-DEP) to capture the infusion-to-infusion variability in depression severity in outpatients treated with ketamine in a study jointly sponsored by Huntsman Mental Health Institute and the University of Utah Department of Psychiatry and Health Rhythms, Inc. We focus on 74 patients with at least 3 repeated CAT-DEP observations. The CAT-DEP is a dimensional measure that produces continuous severity scores of depression, ranging from 0 to 100, based on symptomatology experienced. Using an average of 12 questions, the CAT-DEP maintains a correlation of close to r=0.95 with the entire bank of 389 depression items used to develop the module. CAT-DEP takes an average of 66 seconds to complete, thus minimizing patient burden. Its adaptive testing method has the equally important advantage of presenting a slightly different set of questions to the patient each time it is administered thus decreasing the likelihood of the response fatigue and bias inherent in asking the patient to respond to the identical questions on a very frequent basis.

Patients were typically infused twice weekly on Tuesdays and Thursdays. A CAT-DEP was pushed to their mobile phone on Mondays and Fridays in an effort to capture the short-term changes associated with each infusion. This group of patients provided a mean of 18.2 (SD 7.2) CAT-DEP responses over the course of their initial 12 weeks of ketamine treatment.

We found that CAT-DEP was capable of capturing the sizeable excursions in depression severity related to ketamine infusion. Within each person, we computed (1) the largest magnitude of change between successive CAT-DEP scores and (2) the standard deviation (SD) of the CAT-DEP scores. In our sample, the mean (SD) of the largest successive changes was 31.7 (12.9), indicating that most participants reported substantial changes in depression symptoms across the 12-week treatment period. The average (SD) within-person standard deviation of CAT-DEP scores was 13.5 (5.0), further underscoring the variability of depressive symptom severity. We conclude that computerized adaptive testing holds promise for a deeper understanding of the course of ketamine treatment and could represent a useful tool for dose adjustment and other clinical decisions in the use of this novel treatment.

T24. OPTIMIZING ACUTE STRESS REACTION (ASR) INTERVENTIONS WITH TNX-102 SL (SUBLINGUAL CYCLOBENZAPRINE HCL) – THE OASIS TRIAL: SUSTAINING CIVILIAN PERFORMANCE POST-TRAUMA BY REDUCTION OF ASR AND PREVENTION OF ASD/PTSD

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Abstract Background: U.S. military personnel exposed to life-threatening traumatic events (e.g., combat, injury, witnessing death) can experience acute stress reactions (ASRs) in the war theater, adversely affecting warfighter performance and safety and predisposing to chronic psychopathological outcomes. Symptoms of ASR include intrusions, dissociation, avoidance, arousal (including poor sleep), and negative mood. When an array of these symptoms persists > 72 hours post-trauma, acute stress disorder (ASD) may be diagnosed; when they persist for ≥ a month, posttraumatic stress disorder (PTSD). To reduce the persistence of ASR symptoms and the rate and severity of ASD and PTSD, it may be critical to intervene in the immediate aftermath of trauma.

The present study, the OASIS trial, is being conducted by the University of North Carolina School of Medicine in a network of emergency department (ED) sites. Trauma survivors are enrolled in the ED and receive an intensive multimodal battery of follow-up assessments over a 12-week period. These assessments are modeled after recently completed AUROA study of > 3,800 civilians presenting to ED post motor vehicle collision (MVC).1 TNX-102 SL (sublingual cyclobenzaprine HCl)*, provided by Tonix Pharmaceuticals Inc., is in development for treating fibromyalgia (FM) and PTSD, with prior studies showing not only reduced pain and PTSD symptoms, but improved sleep quality, while having favorable tolerability with increased rates of generally mild, oral sensory AEs. Studies indicate that sleep quality plays a significant role in stress recovery. The present study will evaluate the efficacy and safety of TNX-102 SL in civilians presenting to the ED after an MVC. In the early aftermath of an MVC, the same ASR/ASD/PTSD symptoms occur as in servicemembers exposed to traumatic events. Thus, civilians in a recent MVC are an optimal population to test new treatments for ASR and prophylaxis for ASD and PTSD.

Methods: In this randomized, double-blind placebo-controlled multicenter trial, adults ages 18-55 years who present to the ED within 24 hours of an MVC will be asked to participate in a research study. Key inclusion criteria are posttraumatic stress prediction tool2 risk score of ≥16 and pain severity of ≥4 at baseline. Key exclusion criteria include substantial comorbid injury, pregnant females, chronic opioid use prior to the MVC, active psychosis, suicidal ideation, or need for hospital admission. Participants complete baseline assessments and are randomly assigned to one of two treatment groups: TNX-102 SL (n=90) or placebo (n = 90). Starting on the day of enrollment, participants take TNX-102 SL 5.6 mg (or placebo) at bedtime for 14 days. The primary outcome measure is the ASD Scale, a 14-item self-report inventory of ASD symptom severity. Secondary outcome measures include neurocognitive functioning (e.g., psychomotor vigilance, procedural reaction, response inhibition/control, visual search and change detection, a shooting task, and N-back/working memory task); exploratory outcomes include pain reduction and PTS symptoms.

Results/Discussion: The design of the Phase 2 study and a recruitment update will be presented. TNX-102 SL, a potential first-line treatment for FM and PTSD, is expected to provide similar therapeutic benefits and favorable tolerability for the treatment of ASR/ASD/PTSD, pain, and associated neurocognitive dysfunction. The results may ultimately provide military personnel, veterans, and civilians with a new treatment option that, when administered in the early aftermath of a traumatic event, improves recovery, job performance, and quality of life.

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

T25. DO SECOND GENERATION ANTIPSYCHOTICS PROTECT AGAINST THE EMERGENCE OF (HYPO)MANIA IN DEPRESSED PATIENTS WITH MIXED FEATURES?

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Abstract Background: Currently, 5 medications have been approved for the treatment of bipolar depression: quetiapine, olanzapine/fluoxetine combination, cariprazine, lurasidone, and

lumateperone. No medication has been approved for the treatment of depression with mixed features. For each of the approved medications except quetiapine post-hoc analyses of the bipolar depression trials examined whether the medication was effective in depressed patients with and without mixed features. Each study also examined the emergence of manic symptoms as a possible negative outcome, and each found that the frequency of emergent manic symptoms was more frequent in the patients treated with placebo than the patients treated with medication though in no study was the difference significant. However, the studies were not powered to detect a significant difference in treatment emergent (hypo)manic episodes thereby prompting the current analysis. The goal of the present meta-analysis was to examine whether second generation antipsychotics that have been found effective in treating depression with mixed features protect against the emergence of (hypo)manic episodes in depressed patients with concurrent manic symptoms.

Methods: Six studies of the effectiveness of second generation antipsychotics in the treatment of depressed patients with mixed features were identified. One study did not report information on the emergence of manic symptoms and was not considered further.

Results: The 5 studies included 1,829 depressed patients with mixed features—1,620 with bipolar disorder and 209 with major depressive disorder. In each study, the frequency of treatment emergent manic episodes (TREMEs) was higher in the group treated with placebo, though in no study was this difference significant. Summed across studies the frequency of TREMEs was higher in the patients receiving placebo (4.0% vs. 2.4%, X2=3.66, p=.056). Limiting the analysis to the studies of bipolar disorder, the frequency of TREME's was significantly higher in the patients with bipolar disorder receiving placebo, (3.8% vs. 1.7%, X2=6.46, p=.01).

Conclusions: The presence of mixed features is associated with an increased risk of a switch into a (hypo)manic episode in patients with bipolar depression who are treated with antidepressants. Given the more general risk of a (hypo)manic switch, we wondered if medications proven effective in treating bipolar depression might be protective against such a switch. The results of the present analysis suggest that the second generation antipsychotics that are effective in treating bipolar depression protect against a (hypo)manic switch in patients with mixed features.

T26. EARLY SYMPTOM IMPROVEMENT WITH ADJUNCTIVE CARIPRAZINE IN PATIENTS WITH MAJOR DEPRESSIVE DISORDER: A POST HOC ANALYSIS

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Abstract: Introduction: In patients with major depressive disorder (MDD), the effectiveness of antidepressant therapy (ADT) can be assessed as early as 2 weeks after treatment initiation, with early improvement shown to be a predictor of better outcomes (eg, remission, quality of life, functioning). In clinical trials, although improvement is typically measured as mean change from baseline on a rating scale, patient-level response may further inform clinical decision making. Cariprazine is a dopamine D3-preferring D3/D2 receptor and serotonin 5-HT1A receptor partial agonist that is approved as adjunctive therapy to ADT for the treatment of MDD. Adjunctive cariprazine demonstrated efficacy on the primary outcome (change from baseline in Montgomery–Åsberg Depression Rating Scale [MADRS] total score) in one 6-

week fixed- (NCT03738215) and one 8-week flexible-dose (NCT01469377) randomized, double-blind, placebo-controlled trial in patients with MDD and an inadequate response to ADT alone. We evaluated early symptom improvement using data from the fixed-dose adjunctive cariprazine study in patients with MDD.

Methods: In the primary study, patients with MDD and inadequate response to ADT were randomized to 6 weeks of double-blind treatment with placebo + ADT or cariprazine 1.5 mg/d or 3 mg/d + ADT; patients in the 3 mg/d group were uptitrated from 1.5 mg/d on day 15. Post hoc analyses investigated early symptom improvement using patient-level response defined as the proportion of patients achieving increasing levels of MADRS total score improvement (≥5, ≥10, ≥15, ≥20, ≥25 total score point reduction) at week 2 with missing values imputed using last observation carried forward. Mean changes from baseline to week 2 in MADRS individual item scores and MADRS anhedonia subscale score (sum of MADRS items 1 [apparent sadness], 2 [reported sadness], 6 [concentration difficulties], 7 [lassitude], and 8 [inability to feel]) were analyzed using a mixed-effects model for repeated measures. All analyses were based on the modified intent-to-treat population (randomized patients who took ≥1 dose of study drug and had ≥1 postbaseline MADRS measurement).

Results: Cariprazine + ADT was associated with greater MADRS total score improvement at week 2 across all thresholds tested. Among patients treated with cariprazine 1.5 mg/d + ADT, 3 mg + ADT, or placebo + ADT, respectively, 70%, 68%, and 67% had ≥5 point MADRS total score improvement; 46%, 44% and 34% had ≥10 point improvement; 22%, 19%, and 16% had ≥ 15 point improvement; 12%, 9%, and 5% had ≥20 point improvement; and 5%, 3%, and 4% had ≥25 point improvement. At week 2, change from baseline on some MADRS items was significantly different for least one dose of cariprazine + ADT versus placebo + ADT ($P < .05$): apparent sadness (1.5 mg/d), reported sadness (1.5 and 3 mg/d), lassitude (3 mg/d), and pessimistic thoughts (1.5 mg/d). The least squares mean difference in change from baseline to week 2 on the anhedonia subscale was statistically significant for cariprazine 1.5 mg/d versus placebo (-0.8; P=.0351).

Conclusions: > 40% of cariprazine + ADT-treated patients achieved ≥10-point MADRS total score improvement at week 2, with an approximate 10% difference from placebo suggesting early meaningful improvement for patients treated with cariprazine + ADT. Week 2 improvement versus placebo on multiple MADRS individual items and the anhedonia subscale further suggested an early positive effect for adjunctive cariprazine treatment.

T27. ASSESSING AND MONITORING CLINICAL SEVERITY IN DEPRESSIVE DISORDERS USING AUTOMATED SPEECH ANALYSIS

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Abstract Background: Novel digital technologies, including computational speech analysis, may help provide objective and low-burden markers of symptom severity in depressive disorders, which in turn may facilitate more efficient clinical assessment and monitoring. However, most prior research has been cross-sectional, which limits conclusions about the sensitivity of speech to longitudinal changes in depression. In the current study, we examined associations between speech and clinical severity in a longitudinal observational study of major depressive disorder.

Methods: 134 outpatient participants with a diagnosis of major depressive disorder completed speech assessments and clinical self-report questionnaires at 4 monthly visits. Speech assessments were administered using tasks from the Winterlight assessment app, including picture description (describing the contents of a complex scene), journaling (describing how the participant has been spending their time), positive fluency (listing all positive events the participant expects to experience in the next week in 1 minute), and phonemic fluency (listing all words the participant can think of that begin with a specific letter in 1 minute). Self-report questionnaires assessed the severity of depression (Patient Health Questionnaire-9; PHQ-9), anxiety (Generalized Anxiety Disorder-7; GAD-7), and functional impairment (Sheehan Disability Scale; SDS). Participant speech and language at each visit was examined using 72 features representing core acoustic and linguistic characteristics, which were extracted from signal analysis of speech recordings and natural language process (NLP) of speech transcripts. Associations between speech features and severity of depression, anxiety, and functional impairment were examined with linear mixed-effects models controlling for demographic variables (age, sex, education). Within these models, both between-subject associations (using participants' subject-level mean across visits) and within-subject associations over time (using participants' visit-specific deviations from their subject-level mean) were examined.

Results: Significant associations between speech and clinical scores were observed when examining overall severity between participants (depression: 25 features, anxiety: 18 features; functional impairment: 23 features) and when examining longitudinal within-participant deviations (depression: 19, anxiety: 8, functional impairment: 21), including predominantly linguistic but also acoustic features. Several speech features showed consistent associations for between-subject and within-subject analyses: depression severity was associated with 4 features (fundamental frequency, harmonic-to-noise-ratio, word valence rating, and picture description information units), anxiety was associated with 1 feature (word length), and functional disability was associated with 5 features (minimum semantic distance, word arousal rating, use of prepositional phrases, use of adposition words, picture description information units).

Discussion: Several acoustic and linguistic speech features appear to be robust markers of clinical severity in major depressive disorder, showing associations with clinical severity both between and within participants. These findings indicate the potential utility of digital speech assessment and analysis as an objective and low-burden tool for symptom monitoring in clinical trials.

T28. EFFICACY AND SAFETY OF ICLEPERTIN (BI 425809) IN PATIENTS WITH SCHIZOPHRENIA: CONNEX, A PHASE III RANDOMIZED CONTROLLED TRIAL PROGRAMME

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Abstract Background: Cognitive impairment associated with schizophrenia (CIAS) is a core feature of the disease and a major determinant of poor functional outcomes. Currently, there are no approved pharmacotherapies for the treatment of CIAS. Deficits in glutamatergic signaling play a key role in the neuropathology of schizophrenia, particularly in cognitive symptoms. Iclepertin (BI 425809), a novel inhibitor of glycine transporter-1, enhances N-methyl-D-aspartate receptor signaling in the brain by increasing synaptic levels of its co-agonist glycine. A 12-week, Phase II, proof-of-clinical-concept trial (NCT02832037) that included 509 patients demonstrated that iclepertin was well tolerated and significantly improved cognition in patients with schizophrenia. The Phase III CONNEX program aims to confirm the efficacy, safety, and tolerability of iclepertin in improving CIAS and functioning using a larger cohort of patients with schizophrenia.

Methods: CONNEX consists of three replicate randomized, double-blind, placebo-controlled parallel-group trials in patients with schizophrenia (NCT04846868, NCT04846881, NCT04860830) currently stable on antipsychotic treatment. Each trial aims to recruit ~586 patients, 18–50 years old, treated with 1–2 antipsychotic medications (≥12 weeks on current drug; ≥35 days on current dose prior to treatment), who have functional impairment in day-to-day activities and interact ≥1 hr per week with a designated study partner. Patients with cognitive impairment due to developmental, neurological or other disorders, or receiving cognitive remediation therapy within 12 weeks prior to screening, will be excluded. Participants will be recruited from 41 countries in Asia, Australia, New Zealand, North and South America, and Europe, and randomized 1:1 to receive either oral iclepertin 10 mg (n=293) or placebo (n=293) once-daily over 26 weeks. The primary efficacy endpoint is change from baseline in the MATRICS Consensus Cognitive Battery (MCCB) overall composite T-score. Key secondary efficacy endpoints are change from baseline in Schizophrenia Cognition Rating Scale total score 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 participants were enrolled Aug–Sept 2021), with completion expected in Quarter 1 of 2025. Here we present an overview of the current study status, including any information relating to screening failures and the experience of collecting these data as part of a large multicountry, multicenter study.

Conclusions: To date, most large, industry-sponsored studies testing various compounds to address CIAS have failed to show proof-of-clinical-concept. Demonstration of efficacy of iclepertin in improving cognition 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. Iclepertin may represent the first efficacious medication for cognitive impairment associated with schizophrenia.

Funding: This study is funded by Boehringer Ingelheim (NCT04846868, 1346-0011; NCT04846881, 1346-0012; NCT04860830, 1346-0013).

T29. ACCEPTABILITY, ENGAGEMENT, AND OUTCOMES WITH USE OF A DIGITAL THERAPEUTIC IN PATIENTS LIVING WITH EXPERIENTIAL NEGATIVE SYMPTOMS OF SCHIZOPHRENIA

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Abstract Background: Experiential negative symptoms (ENS) of schizophrenia (avolition, anhedonia, and asociality) are key drivers of disease burden, predicting decreased social functioning and quality of life. Currently, no FDA-approved treatments adequately address ENS. Furthermore, barriers in timely access to psychosocial interventions for ENS limit their impact on improving outcomes. This study evaluated acceptability, engagement, and efficacy of a prescription digital therapeutic in development (CT-155) targeting ENS of schizophrenia.
Methods: This was a multicenter (10 sites), exploratory, 7-week, single-arm study in adults living with ENS of schizophrenia. Eligible patients were ≥18 years old with a diagnosis of schizophrenia and self-reported negative symptoms (score of ≤30 on the Motivation and Pleasure Scale-Self Report) on a stable dose (≥12 weeks) of antipsychotic medication. Patients had on-demand access to the abbreviated beta-version of CT-155. The acceptability and usability of the beta-version of CT-155 were assessed using the Mobile Device Proficiency Questionnaire (MDPQ) at baseline and Mobile Application Ratings Scale (MARS) at Week 7. Engagement with the beta-version of CT-155 was measured throughout the study. ENS were assessed with the Clinical Assessment Interview for Negative Symptoms Motivation and Pleasure Scale (CAINS-MAP). Safety was also assessed.

Results: 43 of 50 (86%) enrolled patients completed the study; most were male (80%) and non-white (70%); mean (standard deviation; SD) age was 48.1 (12.4) years. Baseline median (range) MDPQ score was 30.1 (13.2, 40.0). Across MARS subscale items, the beta-version of CT-155 was rated as acceptable or higher. The highest rating (mean [SD]) score was in the MARS functionality subscale (4.2 [0.81]); the lowest was on the subjective quality score (3.7 [0.82]). Patients engaged on 76% of study days. A significant reduction (p=0.004) in ENS was evident in the 7 weeks from baseline: CAINS-MAP (mean [SD] total score) 20.2 [8.6] to 16.8 [7.8]; n=43. No correlation was observed between baseline CAINS-MAP and MDPQ (r=-0.01, 95% confidence interval [-0.29, 0.28]) or change in CAINS-MAP and MDPQ (r=0.06, [-0.25, 0.35]). There were 3 non-serious adverse events, not related to the beta-version of CT-155.

Conclusions: Patients living with ENS of schizophrenia reported a wide range of digital literacy that was not correlated with baseline ENS or ENS changes observed during the study, suggesting a digital therapeutic approach is feasible for ENS. The beta-version of CT-155 was rated by patients as acceptable across MARS subscales, highlighting their satisfaction with the functionality and information contained in the digital therapeutic. Patients engaged with the beta-version of CT-155 and showed a significant reduction in ENS. The positive results and benign safety profile support continued development and evaluation of CT-155.

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T30. COMPARATIVE ACTIVITY OF MUSCARINIC AGONISTS ML-007 AND XANOMELINE IN PRECLINICAL MODELS OF SCHIZOPHRENIA AND COGNITIVE IMPAIRMENT

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Abstract: Muscarinic agonists represent a potential new class of antipsychotics, with tolerability enabled through receptor subtype selectivity or pairing with peripherally-restricted muscarinic antagonists. However, the specific muscarinic receptor subtypes underlying their antipsychotic and pro-cognitive benefits remain controversial, with M1 and M4 receptors implicated in both psychosis and cognition. Here, we characterize two clinical-stage muscarinic agonists that have shown potential for treating schizophrenia and other disorders: xanomeline and ML-007. GTPgammaS assays demonstrate that ML-007 has stronger intrinsic agonist activity at both M1 and M4 receptors compared to xanomeline. Both xanomeline and ML-007 show robust antipsychotic activity across a range of preclinical models for schizophrenia, including amphetamine-induced hyperlocomotion, PCP-induced hyperlocomotion, and conditioned avoidance response. However, dose-response experiments in M1 and M4 knockout mice reveal that at low doses, the activity of xanomeline is more sensitive to loss of M4 receptors, whereas ML-007 is more sensitive to loss of M1 receptors. Importantly, in a transgenic mouse model of Alzheimer's disease, we find that ML-007, but not xanomeline, improves spatial memory task performance. Taken together, our data suggest that both M1 and M4 receptors contribute to antipsychotic activity in preclinical rodent models of schizophrenia, whereas strong agonism at M1 receptors may be required for treating cognitive impairment.

T31. COMPARISON OF DATA QUALITY BETWEEN HIGH AND LOW RECRUITING SITES IN SCHIZOPHRENIA CLINICAL TRIALS

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Abstract: Introduction: Clinical trial sponsors rely on research sites to enroll adequate study population and reliably assess changes in symptom severity over the course of the trial. We have previously reported a sample in which over 60% of sites participating in schizophrenia clinical trials did not recruit more than 5 subjects (Kott, 2024). In the current analysis we wanted to assess whether low recruiting sites differ in data quality.

Methods: Data were obtained from 19 schizophrenia clinical trials totaling 973 sites. Sites were dichotomized based on the number of randomized subjects into high-recruiting sites (sites with $>$ 5 randomized subjects) and low-recruiting sites (sites with $\leq$ 5 randomized subjects). Data quality concerns represent a family of clinically relevant findings ranging from administration and scoring issues, between and within scale discordances, outlying data variability, and inclusionary concerns. Visits with identified data concerns were summed per site and then compared by site size using Poisson regression with the site size, study and their interaction as predictors and the number of collected visits as exposure.

Results: 80(8.2%) sites did not randomize a single subject, 166 (17.1%) sites randomized a single subject and 616 (63.3%) sites randomized 5 or fewer subjects. Since the interaction term was not significant, it was removed from the model. Data quality findings were significantly more frequent at low-recruiting sites affecting on average 48.8% of visits compared to high-recruiting sites with 37.5% of visits affected (IRR = 1.2 (CI=1.1 - 1.3), $p < 0.001$).

Discussion: In this sample, low-recruiting sites (arbitrarily defined as randomizing $\leq$5 participants) were frequently observed in schizophrenia trials and were associated with significantly more data quality concerns than high recruiting sites. While a single site likely represents a small risk, in aggregate, they can pose a serious challenge. Sponsors should therefore consider strategies to minimize the impact of low-recruiting sites on study outcomes.

Future analyses may address why low recruitment was associated with more frequent data quality issues.

T32. POSITIVE RESULTS ACHIEVED IN A PHASE 2B, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY FOR BNC210, AN ALPHA7 NICOTINIC RECEPTOR NEGATIVE ALLOSTERIC MODULATOR, FOR THE TREATMENT OF PTSD (ATTUNE)

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Abstract: Post-traumatic stress disorder (PTSD) is a serious, debilitating, and chronic condition resulting from exposure to severe trauma such as actual or threatened death, serious injury, or sexual violence. It is characterized by disabling symptoms of intrusive thoughts, nightmares and flashbacks, negative cognitions and mood, avoidance behaviors, hypervigilance, and sleep disturbance. People with PTSD continue to experience adverse effects of their exposure to trauma for years afterward. Thus, the total disease burden (disability plus premature mortality) attributable to PTSD is high. There have been no newly approved drug treatments for PTSD in the past 20 years.

BNC210 is a novel experimental alpha7 nicotinic negative allosteric modulator (NAM) in development for the treatment of psychiatric diseases. BNC210 has a novel mode of action that may be directly relevant to PTSD pathophysiology and which is differentiated from the antidepressants and other therapeutics commonly prescribed for the treatment of PTSD. BNC210 has demonstrated efficacy and evidence of biological activity in several depression preclinical models (O'Connor et al., 2024) and in completed clinical trials in Generalized Anxiety Disorder (GAD) (Wise et al., 2020), Social Anxiety Disorder (SAD) and panic attacks. It is currently also in late-stage clinical development for the acute, "as-needed" treatment of SAD.

In a Phase 2b clinical trial, ATTUNE, 900 mg BNC210 or matched placebo was administered twice daily to 209 PTSD patients (randomized 1:1) for 12 weeks. BNC210 achieved a statistically significant improvement compared to placebo on the primary endpoint of mean change from Baseline to Week 12 in the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) Total Symptom Severity scores (LS Mean difference from placebo of -4.03 and effect size of -0.40; $p < 0.05$). The onset of a statistically significant effect ($p < 0.05$) was observed early (at Week 4, LS Mean difference of -4.11) and was maintained throughout the study, including at Week 8 (-4.74). Importantly, BNC210 also showed statistically significant improvement ($p < 0.05$) from Baseline to Week 12 on depressive symptoms (-3.19) and sleep (-2.19) as measured by the Montgomery-Åsberg Depression Rating Scale (MADRS) and Insomnia Severity Index (ISI), respectively. Trends for improvement ($p < 0.1$) were observed at Weeks 4, 8, and/or 12 in other secondary endpoint measures, including Clinical Global Impressions of Severity (CGI-S), Patient Global Impressions of Severity (PGI-S), and the Sheehan Disability Scale (SDS).

Treatment with 900 mg BNC210 twice daily had a favorable safety and tolerability profile. The most commonly reported treatment-emergent adverse events ($>$ 5% of subjects) were headache, nausea, and fatigue in the BNC210 and placebo treatment groups and asymptomatic hepatic enzyme increases in the BNC210 treatment group.

In conclusion, positive results achieved in the ATTUNE Study support BNC210's potential as a safe and effective treatment for PTSD that will be further tested in future late-stage clinical trials.

T33. THE NATIONAL INSTITUTE ON DRUG ABUSE'S ADDICTION TREATMENT DISCOVERY PROGRAM: PRECLINICAL EVALUATION OF POTENTIAL PHARMACOTHERAPIES FOR SUBSTANCE USE DISORDERS

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Abstract: The Addiction Treatment Discovery Program (ATDP) is a component of the Pharmacotherapies Development Program within the National Institute on Drug Abuse's (NIDA's) Division of Therapeutics and Medical Consequences (DTMC). The aim of the ATDP is to conduct the preclinical evaluation of compounds as potential medications to treat substance use disorders (SUDs), including for stimulants, opioids, cannabinoids, and nicotine. The goal of the ATDP is the discovery of compounds with efficacy in reducing self-administration, preventing reinstatement of drug seeking, and mitigating withdrawal through contracts with academic laboratories and contract research organizations using established preclinical models and standardized protocols. Compounds submitted to the ATDP are evaluated using in vitro and in vivo models based, in part, on their respective mechanism(s) of action. In addition to its discovery efforts, the ATDP offers in silico computational toxicology and in vitro predictive safety testing to submitters for the purpose of lead selection and the de-risking of compounds. Targets and related compounds of interest encompass a wide variety of mechanisms of action (examples include but are not limited to mGluR2 or mGluR3 agonists or PAMs, muscarinic M5 antagonists or NAMs, Ghrelin antagonists or NAMs, GABA-B agonists or PAMs). However, NIDA welcomes and strongly encourages the submission of compounds for which a theoretical rationale can be developed or for which there is supporting preclinical data. NIDA is interested in both evaluating and advancing "late-stage" development compounds for selected targets and collaborating with academic and pharmaceutical partners to evaluate new targets and novel early-stage compounds. Compound submitters retain the rights to their compounds and associated data with strict confidentiality being maintained by the ATDP. The establishment of legal agreements to facilitate collaborations is available as necessary. The ATDP encourages companies and academic researchers to contact us to discuss the submission and evaluation of compounds for potential efficacy in treating SUDs.

T34. ORAL PROLONGED-RELEASE ADJUNCTIVE KETAMINE (KET01): PHASE 2 TRIAL IN TREATMENT-RESISTANT DEPRESSION AND PHASE 1 TRIAL COMPARING TOLERABILITY WITH INTRANASAL ESKETAMINE

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Abstract Background: Ketamine is a rapid-acting antidepressant, and a potent inhibitor of the N-methyl-D-aspartate receptor (NMDAR). However, ketamine and its metabolites also bind to other targets. It has not been conclusively demonstrated that NMDAR inhibition is necessary

for antidepressant efficacy. An intranasal formulation of the (S)-enantiomer esketamine has received regulatory approval for treatment-resistant depression (TRD) in several markets. KET01 is an oral prolonged-release formulation of racemic ketamine with a low propensity for dissociation, due to its pharmacokinetic profile. Compared to other ketamine-based medications frequently used for TRD, administration of KET01 at a similar exposure (area under the curve, AUC) leads to a later occurring and lower concentration peak of ketamine (higher Tmax, lower Cmax), and, importantly, a relatively higher concentration of the metabolites norketamine and hydroxynorketamine.

Methods: In a Phase 2 trial (KET01-02), outpatients (N=122) with TRD were randomized to receive once-daily placebo (PBO), 120 mg KET01, or 240 mg KET01, adjunctively to ongoing antidepressant treatment for 3 weeks. The first dose was administered under supervision and the remaining doses were taken at home. The primary endpoint was the mean score change from baseline (BL) in the Montgomery-Åsberg Depression Rating Scale (MADRS) on Day 21 (mixed model for repeated measures).

In a Phase 1 randomized, placebo-controlled, double-blind, double-dummy, single-center, cross-over trial (KET01-03), healthy volunteers received single antidepressant doses of 240 mg KET01 or 84 mg intranasal esketamine. Acute tolerability was assessed, and blood samples were drawn for pharmacokinetic analysis.

Dissociation was evaluated using the Clinician-Administered Dissociative States Scale (CADSS).

Results: In KET01-02, administration of 240 mg KET01 resulted in an improvement in the MADRS score after 7 hours, and the separation from PBO reached statistical significance on Day 4 and Day 7. The improvement from BL was sustained while on treatment until Day 21, and after a 4-week follow-up.

No differences in mean CADSS scores between the treatment arms were observed at any time point. No clinically relevant changes in heart rate or blood pressure were detected. KET01 was well tolerated and treatment-emergent AEs were reported by 47.5%, 50.0%, and 62.5% in the PBO, 120 mg/day, and 240 mg/day KET01 groups, respectively. Elevations in mean plasma γ-glutamyltransferase and alanine aminotransferase concentrations were observed from week 2 for both KET01 groups and decreased during follow-up.

In KET01-03, twenty-five healthy volunteers received KET01 and intranasal esketamine. The mean maximum change in CADSS score after KET01 treatment was lower by 29.01 (SD=2.35; $p < .00000000001$) than after intranasal esketamine.

Conclusion: The program demonstrates rapid and clinically relevant reduction of depressive symptoms in patients with TRD after treatment with 240 mg/day KET01 with only minimal signs of dissociative symptoms, suggesting a low degree of NMDAR inhibition. The findings challenge the view that NMDAR inhibition is necessary for antidepressant efficacy of ketamine-based medications. The low level of dissociative symptoms during treatment with KET01 is advantageous compared to other currently used ketamine-based depression treatments. KET01 has the potential to be developed as an antidepressant medication to be taken at home.

T35. PRO-COGNITIVE PHARMACODYNAMIC EFFECTS OF ALTO-101: RESULTS FROM BRAIN AND BEHAVIORAL OUTCOMES IN A RANDOMIZED, DOUBLE-BLIND PHASE 1 STUDY

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Abstract Background: Cognitive impairment is a debilitating component of many CNS disorders, such as schizophrenia. Drugs that increase intracellular cyclic adenosine monophosphate (cAMP)/protein kinase A (PKA) signaling have shown promise as pro-cognitive therapeutics in animal models and early-stage clinical trials. ALTO-101 is a selective brain-penetrant inhibitor of phosphodiesterase-4 (PDE4), has been shown to increase cAMP levels in brain regions critical for cognition and may have potential as a novel treatment for cognitive impairment. Here we sought to identify brain/behavior-based pharmacodynamic (PD) biomarkers for ALTO-101 that could indicate the effects of the drug on cognitive processing, as well as elucidate dose-response relationships. Moreover, unlike most phase 1 studies, which are underpowered to detect PD effects (typically 4-8 participants per dose), we conducted a well-powered (N=40) cross-over design study in which each person received drug and placebo. Doing so provides greater confidence in conclusions regarding the human brain mechanisms engaged by the drug.

Methods: 40 healthy adult volunteers (40-64 years old) were enrolled in a randomized, double-blind, placebo-controlled phase 1 study of ALTO-101. Each participant received a single oral dose of placebo, 0.5 mg ALTO-101, and 1.5 mg ALTO-101 in a 3-way counterbalanced crossover fashion, with a 7-day washout between each dose. During the evaluation of the acute phase of the drug effects, participants underwent neurocognitive tests and electroencephalography (EEG), including resting-state EEG (rsEEG) and event-related potentials (ERPs). Analyses focused on prespecified neurocognitive and EEG measures using mixed-effects models to evaluate the PD effects of ALTO-101 vs. placebo.

Results: We identified multiple neurocognitive and EEG measures that differed between the ALTO-101 conditions and placebo. On the ERP outcomes, ALTO-101 led to an increase in the amplitude of the mismatch negativity potential (0.5mg: d = 0.38, p = 0.07; 1.5mg: d=0.53, p=0.02), and an increase in stimulus-driven gamma band phase locking response to auditory stimuli (0.5mg: d = 0.35, p = 0.08; 1.5mg: d=0.68, p=0.003). For rsEEG, ALTO-101 decreased relative theta power (0.5mg: d = 0.51, p = 0.02; 1.5mg: d=0.88, p=0.0003). Behaviorally, ALTO-101 demonstrated improved processing speed (0.5mg: d = 0.32, p = 0.16; 1.5mg: d=0.63, p=0.006).

Conclusions: These findings demonstrate strong PD effects of ALTO-101 in driving key brain processes important for cognition as measured by EEG, along with behavioral evidence of cognitive improvement. Since these measures index schizophrenia-related deficits in cognition and cognitive processing, these data support further development of ALTO-101 for the treatment of cognitive impairment associated with schizophrenia.

T36. TSND-201 (METHYLONE) FOR THE TREATMENT FOR PTSD: FUNCTIONAL AND GLOBAL IMPROVEMENTS FROM THE OPEN- LABEL PORTION OF THE IMPACT-1 STUDY

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Abstract Background: PTSD is a debilitating psychiatric illness affecting approximately 12 million adults in the US each year. Functional impairment is common with PTSD, often resulting in significant impairments in daily life. Current treatment options for PTSD have limited effectiveness. Non-hallucinogenic compounds with rapid and sustained therapeutic benefits may be clinically useful and more accessible to patients, compared to classical psychedelics. Methylone is a non-hallucinogenic, rapid-acting neuroplastogen and the beta-ketone analog of MDMA. Both methylone and MDMA target monoamine transporters, but differences in affinity and a lack of off-target effects (vs. MDMA) produce distinctive pharmacological and subjective effects. Methylone is well-tolerated in healthy volunteers and shows positive clinical effects in a retrospective case series of patients with PTSD and depression. Methylone also has fast-acting, robust, and long-lasting anxiolytic and antidepressant-like activity in preclinical studies. As such, methylone is currently being developed as a potential treatment for PTSD.

Methods: The IMPACT-1 study is a multi-center, two-part clinical trial. Part A has completed and was an open-label evaluation involving 14 participants with PTSD. Eligible participants are adults with severe PTSD (CAPS-5 $\geq$ 35) who had failed at least 1 prior treatment (pharmacotherapy and/or psychotherapy) for PTSD.

Participants were treated with 4 doses of TSND-201 (methylone) given once a week for 4 weeks. Throughout each dosing session, participants were provided non-directive psychological support by a trained mental health practitioner. Following the 4-week treatment period, participants were followed for an additional 6 weeks to evaluate the durability of the therapeutic effect. PTSD symptom improvement was evaluated on the CAPS-5, functioning was assessed via the SDS, and global improvement was measured by the CGI-I. Safety was assessed by monitoring adverse events, vital signs, and C-SSRS.

Results: On the CAPS-5, treatment with TSND-201 resulted in a mean change from baseline of -8.4 points ($p=0.002$) after the first dose; the results were durable with a mean change from baseline of -36.2 points ($p < 0.001$) at the end of study visit (6 weeks after the last dose). At baseline, there was a high level of functional impairment (mean SDS total score: 7.3). After treatment with TSND-201, statistically significant improvements in functioning occurred after the first dose (mean change from baseline: -1.53; $p=0.033$) and were durable through the 6-week follow-up period (-4.26; $p < 0.0001$). Furthermore, underproductive days decreased from 4.7 days per week at baseline to 2.2 days per week at the end of study. On the CGI-I, after the 2nd dose, the majority of patients (69%) were much or very much improved. By the end of the study, all patients were considered much or very much improved.

Conclusion: TSND-201 demonstrated rapid, robust, and durable effects on PTSD symptoms, functional ability, and global improvements. This study supports further development of TSND-201 as a treatment for PTSD. Part B of IMPACT-1; a randomized, placebo-controlled study, is currently ongoing.

T37. CHANGES IN NEUROPLASTICITY RELATED TO NONPHARMACOLOGICAL INTERVENTIONS FOR MAJOR DEPRESSIVE DISORDER: A SYSTEMATIC LITERATURE REVIEW

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Abstract: Introduction: People with major depressive disorder (MDD) have impaired neuroplasticity (eg, altered connectivity between neural networks). Antidepressant treatment and some nonpharmacological interventions, such as cognitive behavioral therapy (CBT), can lead to changes in neuroplasticity that improve MDD symptoms.1 However, there are no recent systematic literature reviews (SLRs) on the effect of nonpharmacological interventions for MDD on neuroplasticity.

Methods: We conducted an SLR of articles with primary results published between January 1, 2013 and December 6, 2023 that included adults with depression or MDD (MDD used to refer to both) treated with nonpharmacological products that are Food and Drug Administration (FDA) cleared and indicated for MDD, or are investigative and need FDA review and clearance for use outside of clinical trials. Studies were included if they had quantifiable findings on changes in neuroplasticity from baseline to post-intervention. Studies were excluded if outcomes were not localized to the brain or participants had mental health diagnoses other than MDD.

Results: Of the 1264 records screened, 116 studies with 5369 participants were included. The most common reason for record exclusion was if studies included participants with diagnoses other than MDD. Most studies were appraised (using the methodology of Hawker et al., 2002) as medium quality (80/116, 69.0%), while 22.4% (26/116) were high quality, and 9.5% (11/116) low quality. Participants had an overall mean age of 41.1 years (range: 24.1–73.0 years). Most studies (74.1%; 86/116) had a female majority, with 59.2% female participants overall. Only 5 studies (4.3%) reported participant race or ethnicity. Electroconvulsive therapy (ECT) was the most common treatment (used by 45.7% of the studies), followed by repetitive transcranial magnetic stimulation (28.4%). Transcutaneous vagus nerve stimulation, CBT, transcranial direct current stimulation, magnetic seizure therapy, functional magnetic resonance imaging neurofeedback, and the Emotional Faces Memory Task were used in $<$ 10% of studies. Of the 57 studies that included a healthy control comparator group, 43 (75.4%) found brain differences at baseline between participants with MDD and the control group. The majority of the studies (107/116; 92.2%) found statistically significant functional or structural changes in the brain following nonpharmacological treatment for MDD. Of the 85 studies that investigated whether there was a relationship between changes in the brain and improvement in MDD symptoms, 60 (70.6%) found that changes in neuroplasticity corresponded with improvement in depression symptoms. The default mode network was the most common neural network, with changes in neuroplasticity detected after nonpharmacological treatment (16 studies). Brain regions that showed neuroplasticity changes in $\geq$ 12 studies included the dorsolateral prefrontal cortex, amygdala, insula, hippocampus, superior frontal gyrus, middle frontal gyrus, angular gyrus, and anterior cingulate cortex.

Conclusions: This SLR shows that nonpharmacological interventions for MDD lead to changes in neuroplasticity, which correspond with improvement in MDD symptoms. It also highlights gaps in our understanding of the mechanisms of action of nonpharmacological interventions; though ECT was well represented, more research is needed for other therapies.

T38. SOLRIAMFETOL IMPROVES COGNITIVE PERFORMANCE IN PRECLINICAL MODELS OF SLEEP APNEA AND IN A RANDOMIZED PLACEBO-CONTROLLED STUDY OF SLEEP APNEA PARTICIPANTS (SHARP)

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Abstract Background: OSA can result in EDS, despite effective Positive Airway Pressure (PAP) treatment, causing cognitive impairment leading to occupational and social dysfunction and lowered quality of life.

Design/Methods: In vitro binding and functional studies were conducted to measure solriamfetol activity. In preclinical studies, mice were exposed to long-term intermittent hypoxia (IH) or sleep fragmentation (SF) protocols that induce declarative memory deficits then given solriamfetol (200mg/kg), modafinil (200mg/kg), or vehicle, and cognitively assessed using the novel object recognition (NOR) task. SHARP (NCT04789174) was a randomized, double-blind, placebo-controlled, crossover trial of participants (n=59) with OSA, EDS, and cognitive impairment. Participants received 2 weeks of treatment: solriamfetol 75mg for 3 days then 150mg/day and placebo and a 1-week washout. Primary endpoint was change from baseline in post-dose Coding Subtest of the Repeatable Battery for the Assessment of Neuropsychological Status (DSST-RBANS) averaged across 2-, 4-, 6-, and 8-hour time points; secondary endpoints included change from baseline on British Columbia-Cognitive Complaints Inventory (BC-CCI).

Results: In vitro experiments showed that solriamfetol inhibits dopamine and norepinephrine transporters (IC50=3.2μM and 14.4μM, respectively) and has agonist activity at TAAR1 (EC=10–16μM) and 5HT1a (EC50=25μM) receptors within the clinically observed therapeutic plasma concentration ranges. In mice, NOR performance was significantly improved with solriamfetol, but not modafinil. In SHARP, DSST-RBANS and BC-CCI scores were improved for solriamfetol versus placebo (6.49 vs. 4.75, p=0.009, Cohen's d=0.36; -4.70 vs -3.11, p=0.002; d =0.43, respectively). Common solriamfetol AEs (≥3%) were nausea (6.9%) and anxiety (3.4%); no new safety signals were observed.

Conclusions: Solriamfetol may be an efficacious and generally safe treatment option for patients with cognitive impairment associated with OSA and EDS.

T39. EFFECT OF LEMBOREXANT ON SLEEP ARCHITECTURE IN ADULT AND ELDERLY PARTICIPANTS WITH MILD TO SEVERE OBSTRUCTIVE SLEEP APNEA

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Abstract Background: Lemborexant (LEM) is a dual orexin receptor antagonist approved to treat adults with insomnia. In such patients, LEM increased total sleep, with prominent increases in rapid eye movement (REM). Since patients with obstructive sleep apnea (OSA)

may report symptoms consistent with an insomnia diagnosis and show decreased REM sleep, sleep architecture was analyzed after treatment with LEM.

Methods: Studies 102 and 113 were double-blind, placebo (PBO)-controlled crossover studies conducted in adult participants with mild OSA (apnea-hypopnea index [AHI] ≥5 to < 15) or moderate (AHI ≥15 to < 30) to severe (AHI ≥30) OSA. Participants were randomized to LEM 10 mg (LEM10) or PBO in two 8-night treatment periods separated by ≥14 days. Least squares mean (LSM) for each sleep stage (minutes) was compared across conditions on days 1 (D1) and 8 (D8). Treatment-emergent adverse events (TEAEs) were recorded.

Results: The analysis set comprised 39 participants with mild OSA and 33 with moderate/severe OSA. On both days, total sleep time (minutes) was significantly higher in the LEM condition in participants with mild OSA (LSM [standard error; SE] D1: LEM10, 434.08 [6.53]; PBO, 385.46 [6.46]; P < 0.0001; D8: LEM10, 415.90 [7.78]; PBO, 386.85 [7.87]; P=0.003) and moderate/severe OSA (LSM [SE] D1: LEM10, 423.10 [7.00]; PBO, 385.48 [7.00]; P < 0.0001; D8: LEM10, 416.96 [8.06]; PBO, 385.57 [8.15]; P=0.001). Compared with PBO, total non-REM sleep was significantly higher only on D1 in participants with mild OSA (LSM [SE] D1: LEM10, 330.57 [5.98]; PBO, 308.55 [5.92]; P=0.001; D8: LEM10, 323.77 [6.44]; PBO, 308.97 [6.52]; P=0.060), but was significantly higher on both days in participants with moderate/severe OSA (LSM [SE] D1: LEM10, 343.23 [7.15]; PBO, 327.45 [7.15]; P=0.006; D8: LEM10, 341.83 [7.60]; PBO, 322.47 [7.68]; P=0.018). Total REM sleep was significantly higher in participants with mild OSA (LSM [SE] D1: LEM10, 103.59 [4.02]; PBO, 76.91 [3.97]; P < 0.0001; D8: LEM10, 92.13 [3.54]; PBO, 77.93 [3.59]; P=0.004) and moderate/severe OSA (LSM [SE] D1: LEM10, 79.87 [4.85]; PBO, 58.03 [4.85]; P < 0.0001; D8: LEM10, 75.13 [5.66]; PBO, 62.69 [5.70]; P=0.006) during the LEM10 condition. REM latency was significantly shorter on both days in participants with mild OSA (LSM [SE] D1: LEM10, 51.96 [5.78]; PBO, 83.36 [5.71]; P < 0.0001; D8: LEM10, 67.52 [8.41]; PBO, 102.34 [8.51]; P=0.005) and on D1 in participants with moderate/severe OSA (LSM [SE] D1: LEM10, 72.13 [9.10]; PBO, 98.90 [9.10]; P=0.029; D8: LEM10, 90.42 [12.85]; PBO, 106.63 [13.00]; P=0.242). LEM was well tolerated; most TEAEs were mild.

Conclusion: In participants with mild to severe OSA and without confirmed insomnia, LEM use was nevertheless associated with higher total sleep, non-REM sleep, and REM sleep versus PBO.

SPONSOR: Eisai, Inc

T40. LUMATEPERONE IN THE TREATMENT OF MAJOR DEPRESSIVE DISORDER AND BIPOLAR DEPRESSION WITH MIXED FEATURES: EFFICACY ACROSS SYMPTOMS

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Abstract Background: Mixed features in patients with major depressive disorder (MDD) or a depressive episode of bipolar disorder is associated with more severe symptoms and poorer treatment response compared with patients without mixed features. Lumateperone (LUMA) is an FDA-approved antipsychotic to treat schizophrenia and depressive episodes associated with bipolar I or bipolar II disorder. In a recent randomized, double-blind, placebo (PBO)-controlled

trial (Study 403; NCT04285515) LUMA 42mg demonstrated efficacy over PBO and a favorable safety profile in patients with a depressive episode that was a part of MDD or bipolar depression with mixed features. This prospectively defined analysis of Study 403 investigated the efficacy of LUMA on individual depressive symptoms as assessed by Montgomery-Åsberg Depression Rating Scale (MADRS) single-item scores.

Methods: Eligible adults (18-75 years) with DSM-5 MDD or bipolar I or bipolar II disorder who were experiencing a major depressive episode (MADRS Total score ≥24, Clinical Global Impression Scale-Severity score ≥4) with mixed features were randomized 1:1 to 6-week LUMA 42mg or PBO. MADRS single-item scores were assessed by visit using a mixed-effects model for repeated measures in the modified intent-to-treat (mITT) population. Safety included adverse events (AEs), Young Mania Rating Scale (YMRS), and suicidality.

Results: In the combined MDD/bipolar depression population with a depressive episode with mixed features, 385 patients received treatment and 383 (PBO, 191; LUMA, 192) were included in the mITT population. The majority (89.4%) of patients completed treatment. LUMA significantly improved MADRS Total score compared with PBO at Day 43 (least squares mean difference vs PBO [LSMD]=−5.7; $P < .0001$). Patients randomized to LUMA showed significantly greater improvements on 9 of the 10 MADRS items compared with the PBO group on Day 43, including apparent sadness (LSMD=−0.9; $P < .0001$), reported sadness (LSMD=−0.8; $P < .0001$), inner tension (LSMD=−0.6; $P < .0001$), reduced sleep (LSMD=−0.9; $P < .0001$), reduced appetite (LSMD=−0.5; $P < .0001$), concentration difficulties (LSMD=−0.4; $P < .01$), lassitude (LSMD=−0.6; $P < .0001$), inability to feel (LSMD=−0.7; $P < .0001$), and pessimistic thoughts (LSMD=−0.4; $P < .001$). Apparent sadness and reduced sleep had the largest improvements with LUMA compared with PBO in change from baseline at Day 43 and the earliest significant reductions from baseline at Day 8 ($P < .05$). An additional 5 items showed significant improvement at Day 15 and persisted throughout the study.

LUMA was well tolerated. Most treatment-emergent AEs (≥99%) were mild or moderate in severity and there was no worsening in YMRS Total score with LUMA. Emergence of suicidal ideation was low and similar between treatment groups.

Conclusion: LUMA 42mg treatment significantly improved a broad range of depression symptoms compared with PBO and was generally well tolerated in depressed patients with mixed features that was a part of MDD or bipolar depression.

T41. LUMATEPERONE TREATMENT FOR MAJOR DEPRESSIVE EPISODES WITH MIXED FEATURES IN MAJOR DEPRESSIVE DISORDER AND BIPOLAR I OR BIPOLAR II DISORDER

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Abstract Background: The DSM-5 and DSM-5-TR define mixed features in major depressive disorder (MDD) or bipolar depression (BPD) as having subsyndromal manic or hypomanic symptoms nearly every day during the majority of days of a major depressive episode (MDE). Mixed features are common in MDD and BPD (25%-35%) and patients with mixed features

have more severe symptoms, more comorbidities, increased suicide risk, and poorer treatment response than patients without mixed features.
Lumateperone is an FDA-approved antipsychotic to treat schizophrenia and depressive episodes associated with bipolar I or bipolar II disorder. This randomized, double-blind, placebo-controlled, multicenter trial (NCT04285515) investigated the efficacy and safety of lumateperone 42mg for the treatment of an MDE in patients with MDD or BPD with mixed features.

Methods: Eligible adults (18-75 years) had DSM-5 diagnosed MDD or bipolar I or II disorder with mixed features and were experiencing an MDE (Montgomery-Asberg Depression Rating Scale [MADRS] Total score ≥24, Clinical Global Impression Scale-Severity [CGI-S] score ≥4). Patients, stratified by MDD or BPD, were randomized 1:1 to 6-weeks treatment with lumateperone 42mg or placebo. The primary and key secondary efficacy endpoints were change from baseline to Day 43 in MADRS Total and CGI-S score, respectively, analyzed using a mixed-effects model for repeated measures. Three populations with mixed features were assessed: the overall combined MDD and BPD population, the individual MDD population, and the individual BPD population. Safety assessments included adverse events (AEs), laboratory parameters, vital signs, and extrapyramidal symptoms.

Results: In this study, 385 patients received treatment (placebo, n=193; lumateperone, n=192) and 344 (89.4%) completed the study. Patients with MDD or BPD and mixed features treated with lumateperone 42mg had significantly greater MADRS Total score improvement compared with placebo as indicated by mean change from baseline to Day 43 (placebo, n=191; lumateperone, n=192; least squares mean difference vs placebo [LSMD]=−5.7; 95% CI, −7.60, −3.84; effect size [ES]=−0.64; $P < .0001$). Improvements with lumateperone were also significant in individual patient populations with MDD with mixed features (placebo, n=92; lumateperone, n=92; LSMD=−5.9; 95%CI, −8.61, −3.29; ES=−0.67; $P < .0001$) or BPD with mixed features (placebo, n=99; lumateperone, n=100; LSMD=−5.7; 95%CI, −8.29, −3.05; ES=−0.64; $P < .0001$). Significant improvements compared with placebo were also observed for CGI-S, the key secondary endpoint, in the combined MDD and BPD population (LSMD=−0.6; 95%CI, −0.81, −0.39; ES=−0.59; $P < .0001$), individual MDD population (LSMD=−0.6; 95%CI, −0.89, −0.27; ES=−0.57; $P < .001$), and individual BPD population (LSMD=−0.6; 95%CI, −0.91, −0.31; ES=−0.61; $P < .0001$). Lumateperone treatment was generally safe and well tolerated and consistent with prior studies. The most common treatment-emergent AEs with lumateperone (≥5% and twice placebo) were somnolence, dizziness, and nausea. No serious AEs were reported with lumateperone.

Conclusion: Lumateperone 42mg demonstrated robust efficacy over placebo in patients with MDD or BPD with mixed features. Lumateperone was generally safe and well tolerated with no new safety concerns. These results suggest lumateperone 42mg is a promising new treatment for MDEs in MDD with mixed features or BPD with mixed features.

T42. EXPLORING CONNECTIONS BETWEEN CHILDHOOD MALTREATMENT AND COGNITIVE PERFORMANCE IN PATIENTS WITH BIPOLAR DISORDER AND HEALTHY CONTROLS: INSIGHTS INTO THE ROLE OF INFLAMMATION

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Abstract: Aims: Early life experiences adversely impact cognition in both healthy adults and patients with mood disorders, with inflammation identified as a potential connecting pathway. The present study aimed to examine 1) the associations between childhood maltreatment and cognitive functioning in patients with bipolar disorder (BD) and healthy controls (HCs), and 2) whether inflammation mediates this link.

Methods: Seventy-nine BD patients (mean age: 40.6±14.8) and 48 HCs (mean age: 43.6±15.2) were recruited from Boston, MA and surrounding areas. The Structured Clinical Interview for DSM-5 was conducted to confirm eligibility. The Hamilton Depression Rating Scale and (HDRS) the Young Mania Rating Scale (YMRS) were administered to measure depressive and manic symptoms, respectively. The Childhood Trauma Questionnaire (CTQ) was utilized to assess childhood maltreatment. Cognitive functioning was assessed by six domains of MATRICS consensus cognitive battery (MCCB) and California Verbal Learning Test (CVLT). All scores were age and sex adjusted using MCCB normative data. Multiple linear regression analyses were performed to determine the associations between childhood maltreatment and cognitive performance. Inflammatory markers (i.e., C-Reactive Protein [CRP], Interleukin [IL]-6 and Tumor Necrosis Factor [TNF]-α) were quantified in blood. A composite inflammation index of CRP, IL-6 and TNF-α was formed to minimize type I error. Mediation analysis was conducted using the PROCESS macro for SAS.

Results: Across the entire sample of BD patients and HCs, higher childhood maltreatment levels were associated with worse performance on global cognition (β=-.46, $p < .001$) and all MCCB domains (speed of processing, attention/vigilance, working memory, visual learning, reasoning/problem solving, social cognition, and verbal learning [unadjusted: βs=-21 to -.39]). No significant interaction was observed between CTQ and diagnosis (p=.42). After controlling for HDRS, YMRS, number of psychotropic medications, education and diagnosis, the associations remained significant for global cognition, speed of processing and working memory ($ps < .05$). Higher childhood maltreatment positively correlated with the inflammation composite (p=.04), controlling for age, sex and HDRS. In the entire sample, the indirect effect of CTQ on global cognition was significant (ab: β=-.04, CI =-.10, -005), holding age and sex constant. There was evidence of a significant total effect of CTQ on global cognition (c: β=-.45, $p < .001$) and direct effect of CTQ on global cognition independent of its effect on inflammation (c′: β=-.41, $p < .001$). Within the BD sample, when controlling for additional potential confounds including HDRS, YMRS, number of medications, education, antidepressants, antipsychotics, and lithium use, associations remained significant between childhood maltreatment, and global cognition (β=-.27, $p < .05$), speed of processing (β=-.28, $p < .05$), and working memory (β=-.29, $p < .05$).

Conclusion: Childhood maltreatment emerged as a risk factor for cognitive impairment, particularly in speed of processing and working memory domains. We found that inflammation partially mediates this link, suggesting the involvement of multiple pathways through which adverse early experiences impact global cognition. Understanding psychobiological mechanisms underlying cognitive deficits will offer insights into mechanistic targets for improving outcomes in BD.

T43. TRANSCRANIAL MAGNETIC STIMULATION IN THE DEPARTMENT OF VETERANS AFFAIRS: IMPACTS OF SLEEP DYSFUNCTION ON THE TREATMENT OF MAJOR DEPRESSIVE DISORDER

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Abstract: Introduction: Treatment resistance (TR) is common in major depressive disorder (MDD).1,2 Transcranial magnetic stimulation (TMS) is an FDA-cleared treatment for the management of TR-MDD, yet a substantial number of patients receiving TMS fail to adequately respond to treatment,3 prompting the need for evaluation of predictors of treatment response. Sleep dysfunction is common in MDD,4 yet the association between sleep and TMS is poorly understood. This study aimed to address this need by examining the associations between baseline sleep dysfunction and sleep improvements throughout TMS treatment with depression outcomes in Veterans receiving TMS for MDD.

Methods: A retrospective observational cohort study was conducted examining Veterans receiving TMS through the U.S. Department of Veterans Affairs "VA TMS Pilot Program" from March 2017 through March 2020. Standard inclusion and exclusion criteria were used for the determination of appropriateness. The PHQ-9 sleep item (P9-I3) was used to assess baseline sleep dysfunction and sleep improvements. The association between baseline sleep dysfunction and end of treatment depression remission rates were analyzed. Sleep improvements were measured, and the associations between improvements in sleep from baseline to the end of week 1, week 3, and week 6 were evaluated as predictors of end of treatment depressive symptoms.

Results: 27 VA sites and 825 Veterans were included. 94.30% reported sleep dysfunction at baseline. Chi-square analysis showed an association between baseline sleep dysfunction and end of treatment depression remission rates, with pairwise comparisons showing significant differences in Veterans experiencing the highest level of sleep dysfunction pre-treatment (P9-I3 = 3) compared to those without sleep dysfunction (P9-I3 = 0; p= .001) and to those with moderate sleep dysfunction (P9-I3 = 2; p=.007); and trended towards significance when compared to mild sleep dysfunction (P9-I3 = 1; p= .153). The relationship between improvements in sleep and depression improvement was then analyzed. Sleep improvement rates were 37.38% at week 1, 51.75% at week 3, and 57.0% at week 6. Chi-square analysis showed an association between sleep improvements and depression remission rates, with those experiencing improvements in sleep having higher rates of depression remission at completion of TMS treatment at all timepoints: week 1, 27.84% vs 18.15% (p= < .001); week 3, 29.32% vs 14.52% (p= < .001); week 6, 30.99% vs. 9.94% (p= < .001). ANOVA analysis found greater reductions in end of treatment PHQ total scores for those with sleep improvements compared to those without sleep improvements, with mean differences: week 1 (M = 2.438, SE = 0.625, 95% CI 1.211 to 3.666); week 3 (M = 3.211, SE = 0.603, 95% CI 2.025 to 4.396); and week 6 (M = 4.825, SE = 0.689, 95% CI 3.471 to 6.180.)

Conclusions: Sleep improvements have a predictive quality on the antidepressant effects of TMS. Veterans with improvements in sleep dysfunction were found to have higher end of treatment depression remission rates and greater reductions in final PHQ total scores than those who did not experience sleep improvements. Additional research is needed to further characterize the relationship between sleep and MDD response to TMS treatment. Future

studies should implement more sophisticated sleep measures and could focus on interventions to improve sleep dysfunction as a potential mechanism for increasing depression remission during TMS treatment for MDD.

T44. EARLY IMPROVEMENT OF SYMPTOMS IN BIPOLAR I DEPRESSION PREDICTS FUNCTIONAL REMISSION AND RECOVERY: A POST HOC ANALYSIS

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Abstract: Introduction: Bipolar I disorder is a complex condition associated with an array of symptoms that contribute to functional impairment. Cariprazine, a dopamine D3-preferring D3/D2 receptor partial agonist and serotonin 5-HT1A receptor partial agonist, has shown efficacy in manic, mixed, and depressive episodes, as well as across a number of other symptom domains associated with bipolar I disorder. The objective of this analysis was to determine if early improvement in key symptom domains such as depression, anxiety, and anhedonia was predictive of functional improvement in patients with bipolar I depression who were treated with cariprazine

Methods: Data from a randomized, double-blind, placebo-controlled clinical trial (NCT01396447) evaluating cariprazine 1.5 mg/d or 3.0 mg/d in patients with bipolar I depression were analyzed. Patients randomized to 3.0 mg/d were up-titrated from 1.5 mg/d on day 15. Early improvement (≥25% reduction at week 2) in Montgomery-Åsberg Depression Rating Scale (MADRS) total score, Hamilton Rating Scale for Depression (HAMD) anxiety/somatization subscale score, and MADRS anhedonia factor score was assessed. Functional remission and recovery were defined as a week 8 Functioning Assessment Short Test (FAST) total score of ≤20 and ≤11, respectively. Predictive statistics and odds ratios associated with early improvement were calculated for each symptom domain.

Results: A total of 313 patients were included in the post hoc analysis; 117 received cariprazine 1.5 mg/d, 95 received cariprazine 3.0 mg/d, and 101 received placebo. A greater proportion of patients who received cariprazine 1.5 mg/d versus placebo met criteria for early improvement on the MADRS total score (53.0% vs 37.6%), HAMD anxiety/somatization subscale score (56.4% vs 43.6%), and MADRS anhedonia factor score (50.4% vs 34.7%). Functional remission was achieved by 50.4% of cariprazine 1.5 mg/d patients and 35.6% of placebo patients, with 27.4%, and 17.8% achieving functional recovery, respectively. Patients treated with cariprazine 1.5 mg/d who met criteria for early improvement via MADRS total score were 5-times more likely than those without early improvement to achieve functional remission at endpoint (OR=4.7) and 6-times more likely to achieve functional recovery (OR=5.9). Similarly, patients treated with cariprazine 1.5 mg/d who met early improvement criteria on the HAMD anxiety/somatization subscale were more likely than those without early improvement to achieve functional remission (OR=3.5) and recovery (OR=4.9). The strongest predictor was early improvement on the MADRS anhedonia factor score, as patients who met early improvement were 6-times more likely than those without early improvement to achieve endpoint functional remission (OR=6.0) and 9-times more likely to achieve endpoint functional

recovery (OR=8.9). Similar patterns were seen in patients receiving cariprazine 3.0 mg/d, although this group did not separate from placebo on FAST measures in the original trials.

Conclusions: In patients with bipolar I depression who were treated with cariprazine 1.5 mg/d, early improvement in depression, anxiety, and anhedonia symptom domains were all predictive of eventual functional remission and recovery, with early improvement in anhedonia being the most robust predictor.

T45. PLACEBO RESPONSE PREDICTION IN MAJOR DEPRESSIVE DISORDER USING MACHINE LEARNING

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Abstract Background: In clinical trials for major depressive disorder (MDD), the placebo response (PR) significantly obscures the accurate assessment of treatment efficacy, often leading to failed trials due to the difficulty in distinguishing true treatment effects [1]. To address this, we introduce a machine learning (ML) model for PR estimation in historical MDD trials and specifically apply it to the control arm of the study NCT04532749. The model identifies key predictors, thereby enhancing the interpretability of PR estimation and reliability of treatment effect estimation, potentially reducing trial failures attributed to PR-related variability.

Methods: We identified 3 training trials (NCT04080752, NCT00095134, NCT03227224) that were similar to NCT04532749 in terms of participant eligibility criteria, study design, and outcome measures. We used the placebo groups in these trials to develop an ML model to map patient-level features to outcomes at 6 weeks measured by the Hamilton Depression Rating Scale (HDRS) score. Patient features were limited to those available at or before baseline: demographics, MDD characteristics family medical history, medication history, vital signs, various mental health assessment questionnaires, and site-level characteristics. We conducted an analysis in which different ML modeling configurations were evaluated using 5-fold and leave-one-trial-out cross-validation. ML models included regularized linear regression, decision trees, random forest, and gradient-boosted ensemble of decision trees. The final model was selected to optimize the Pearson correlation between actual and predicted HDRS scores in cross-validation experiments. The final model was applied to the control arm of the independent test trial NCT04532749.

Results: There were in total 328 placebo patients in the 3 training trials used to develop the model. The final model was a linear regression regularized with the elastic net penalty and achieved a cross-validated correlation of 0.37-0.44 with no significant difference across patient subgroups (age, gender, US vs non-US). When applied to the test trial, a correlation of 0.38 was achieved. The top features identified as the most predictive by the model belong to the following modalities: MDD characteristics, medication history, and mental health questionnaires.

Conclusion: We used multiple trials to develop an ML model to estimate placebo response and reported the results on an unseen test trial, which aligns with the TRIPOD [2] guidelines for development of clinical predictive models. The model achieved comparable performance

in the training trials and the test trial. We plan to incorporate additional trials and evaluate the impact of trial study design differences on PR. Placebo modeling scores could be useful as covariates in placebo-controlled studies to help increase precision in treatment effect estimation in future trials.

T46. ILOPERIDONE TREATMENT ASSOCIATED INCREASE IN SERUM URATE AND INTERACTION WITH SLC2A9 VARIANT RS7442295

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Abstract: Serum urate concentrations represent a complex genetic trait influenced by genetic variation as well as environmental factors. Serum uric acid levels correlate with blood pressure, metabolic syndrome, diabetes, gout, and cardiovascular disease. Hyperuricemia, can lead to monosodium urate crystal deposition and thereby cause gout, the most common type of inflammatory arthritis among adults. Recent GWAS have found common genetic variants of SLC2A9 to be associated with increased serum urate level and gout. The SLC2A9 gene encodes a high-capacity urate transporter in humans which is mainly expressed in kidneys, liver and intestine. Loss of function variants were previously identified in hypouricemia.
Bipolar I disorder is characterized by episodes of manic and hypomanic activity, and it has one of the highest rates of serious impairment among mood disorders. Iloperidone is a second-generation antipsychotic approved by the FDA that has anti-manic effects. Here we report genetic association of rs7442295 with urate levels at baseline and in interaction with iloperidone In a placebo-controlled trial of patients with bipolar mania, treatment with iloperidone 24mg/day resulted in a small but statistically significant increase of serum urate levels of approximately 27.2 μmol/L (0.457 mg/dL) compared to 0.1 μmol/L (0.002 mg/dL) in placebo group. This observation led to an investigation to see if genetic information could be used to predict which patients may be most susceptible to increases in serum urate following iloperidone treatment.

WGS was conducted using whole blood samples obtained from the study subjects. A pronounced increase of 40.1 μmol/L (0.674 mg/dL) was seen in iloperidone-treated patients homozygous for the for the rs7442295 (G) allele at the SLC2A9 gene, compared to a decrease of -16.86 μmol/L in the corresponding GG placebo group. Similar results were observed for iloperidone in a second study in schizophrenia patients supporting generalization of the results across patient populations. The results show iloperidone-associated increases in serum urate are greatest in patients who were homozygous (GG) for the rs7442295 (G) allele at the SLC2A9 gene. Among male patients with the GG genotype, serum urate concentrations frequently shifted to above the upper limit of normal for iloperidone-treated patients in comparison to placebo group.

The mechanism and clinical significance of this iloperidone-induced increase in serum urate levels is likely due to a decrease in clearance of urate through interaction with the SLC2A9 urate transporter protein.

T47. KEY CHARACTERISTICS OF THE LONG-ACTING INJECTABLE ATYPICAL ANTIPSYCHOTIC ARIPIPRAZOLE LAUROXIL FOR THE TREATMENT OF ADULTS WITH SCHIZOPHRENIA

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Abstract: Evidence-based practice involves consideration of best available data, clinical judgment, and patients' values and preferences. Among available long-acting injectable (LAI) atypical antipsychotics for schizophrenia, aripiprazole lauroxil (AL) offers a range of dosing options intended to meet the medical and quality-of-care needs of individual patients. In this presentation, key characteristics of AL are reviewed based on published data from studies examining efficacy, safety/tolerability, and pharmacokinetic profiles. AL was developed using an innovative prodrug technology that enables predictable dissolution over time after intramuscular injection and results in a pharmacokinetic profile characterized by a long half-life with little variation between peak and trough aripiprazole concentrations across the dosing interval. This pharmacokinetic profile supports a range of dose strengths and injection intervals (once every month, 6 weeks, or 2 months) so that clinicians can recommend a regimen that best meets a patient's needs. The AL prodrug technology was further refined to allow creation of a nanocrystal dispersion formulation that facilitates AL treatment initiation in a single day. In phase 3 trials, 2 different monthly regimens of AL were efficacious vs placebo, and the efficacy of the AL every-2-months regimen was consistent with that of the monthly AL regimens. In randomized controlled trials and long-term safety studies, AL was safe and generally well tolerated at initiation, during acute treatment, and during maintenance treatment. Pharmacokinetic, efficacy, and safety characteristics support the use of AL across multiple approved dose strengths and dosing intervals, including treatment initiation in 1 day without further oral supplementation or loading doses, permitting versatility across treatment settings.

T48. EVALUATING FUNCTIONAL OUTCOMES IN MAJOR DEPRESSIVE DISORDER: A PATIENT INTERVIEW STUDY

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Abstract Background: Many patients with major depressive disorder (MDD) experience functional deficits. Even for patients who achieve remission, those who do not attain normal functioning have a greater risk of relapsing than those who do, highlighting the importance of functional recovery. To better understand the effects of MDD on patient functioning, we developed a conceptual model based on a literature review and enhanced it based on qualitative patient interviews to make it more patient-centric.

Methods: A literature review was performed to identify clinical outcomes assessments and develop a literature-based conceptual model of functional outcomes in MDD. Following institutional review board approval, qualitative interviews were conducted with participants from 3 US clinical sites. An interview guide was used to elicit and understand functional impairments experienced by patients, using spontaneous and probing approaches. Interview results were analyzed and used to revise the literature-based conceptual model.

Results: Following the literature review, 80 abstracts informed clinical outcomes assessment identification and 34 articles supported the development of a conceptual model of functional outcomes in MDD. The literature-based model comprised 6 domains: cognitive (eg, lack of attention/difficulty concentrating), physical (eg, chest tightness), sexual dysfunction (eg, decreased libido), work (eg, autonomy), sleep (ie, poor sleep quality), and social (eg, family relationships). A total of 20 adults with MDD participated in the interviews. On average, participants were 38.6 years old, female (60.0%), and had an MDD diagnosis for 4.9 years. Most participants (70.0%) indicated that their first signs/symptoms of depression appeared before the age of 18 years. The following functional outcomes were identified during interviews: emotional, cognitive, social, physical, work/school, sexual dysfunction, activities of daily living, and sleep. Difficulty falling asleep, apathy, and negative impact on satisfaction with sex were reported to be the most bothersome functional outcomes on average. After analysis of interview results, the revised conceptual model included the following additional or revised domains: emotional functioning (eg, hopelessness), work/school functioning (eg, decreased productivity/presenteeism), and functioning related to activities of daily living (eg, negative impact on personal hygiene).

Conclusion: Overall, these results highlight the broad impact that MDD has on patient functioning, directly from a patient perspective. Future studies evaluating functional outcomes in MDD should consider measuring these concepts. This study was supported by AbbVie.

T49. LONG-TERM SAFETY AND EFFICACY OF OLANZAPINE/SAMIDORPHAN: RESULTS OF A 4-YEAR OPEN-LABEL STUDY

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Abstract Background: This study evaluated the long-term safety, tolerability, and durability of effect of olanzapine/samidorphan (OLZ/SAM).

Methods: This phase 3, multicenter, open-label extension study assessed the long-term safety and efficacy of up to 4 years of OLZ/SAM in patients who completed the following OLZ/SAM trials: 52-week open-label studies NCT02873208 and NCT02669758, which were rollover extensions of phase 3 pivotal randomized controlled trials in adults with schizophrenia (SZ), and NCT03187769 in young adults with recent-onset SZ, schizophreniform disorder, or bipolar I disorder (BD-I). Depending on geography and enrollment date, patients in the current long-term study had the opportunity to receive up to 2 to 4 years of treatment. Safety assessments included the incidence of adverse events (AEs) and changes from baseline in body weight and waist circumference. Changes in lipid (high-density lipoprotein [HDL], low-density

lipoprotein [LDL], and total cholesterol and triglycerides) and glycemic (glucose and glycosylated hemoglobin [HbA1c]) parameters were also evaluated. Antipsychotic efficacy was assessed with the Clinical Global Impressions–Severity (CGI-S) scale.

Results: Of 524 patients enrolled in the study, 523 received ≥1 dose of OLZ/SAM. 188 (35.9%) patients completed between 2 to 4 years of treatment. The mean (SD) duration of exposure was 652.4 (454.8) days. Among 451 patients who were eligible to receive at least 2 years of treatment, 242 (53.7%) received ≥2 years of treatment. Among 335 patients who were eligible to receive 4 years of treatment, 109 (32.5%) received 4 years of treatment. In the treated population, patients were mostly male (61.6%) and White (72.7%), with a mean (SD) age of 35.1 (12.2) years. Overall, 60.0% of patients reported at least one AE; the most common were weight increased (9.8%), headache (7.1%), anxiety (6.1%), insomnia (5.9%), somnolence (5.9%), nausea (5.7%), and weight decreased (5.7%). For patients who contributed data to the 2-year assessment (n=238), mean (SD) change from baseline in body weight was 0.84 (6.84) kg and waist circumference was -0.56 (6.24) cm. For patients who contributed data to the 4-year assessment (n=108), the mean (SD) change from baseline in body weight was 2.65 (8.12) kg and waist circumference was 1.37 (8.65) cm. Lipid and glycemic parameters were generally stable over the treatment period. Patients' symptoms remained stable—for patients contributing data at 2 years, mean (SD) change from baseline in CGI-S was -0.18 (0.67) and for those at 4 years was −0.24 (0.65).

Discussion: In this 4-year open-label extension study, treatment with OLZ/SAM resulted in a safety profile consistent with previous short-term studies and was associated with small changes in body weight and minimal changes in waist circumference and lipid and glycemic parameters. Similarly, OLZ/SAM maintained symptom control during long-term treatment. Based on these results, OLZ/SAM maintained long-term antipsychotic efficacy while mitigating the weight gain and metabolic dysfunction associated with olanzapine.

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T50. A RETROSPECTIVE STUDY OF REAL-WORLD CLINICAL EFFECTIVENESS OF ESKETAMINE NASAL SPRAY THERAPY AMONG PATIENTS WITH TREATMENT RESISTANT DEPRESSION

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Abstract: Introduction: As many as thirty percent of adults with major depressive disorder (MDD) meet criteria for treatment resistant depression (TRD), generally defined as a failure to respond to at least two antidepressant (AD) trials of adequate dose and duration. 1 Esketamine nasal spray was approved by the FDA for treatment of TRD in 2019, but there is still limited clinical data on patients receiving esketamine in real-world settings. A retrospective observational analysis of depression outcomes for real-world patients with TRD receiving esketamine was conducted using Osmind's electronic health record-derived de-identified database.

Methods: The ESK all-comers cohort included patients with MDD who received at least one esketamine treatment. The ESK-TRD cohort was a subset of those patients for whom use of at

least two unique ADs within two years of esketamine treatment could be confirmed. Patients in the primary outcomes analysis completed a baseline PHQ-9 within 30 days prior to initiation of treatment and a PHQ-9 after treatment (within 30 days of an esketamine treatment). Mixed effects models evaluated change in PHQ-9 scores as a function of the number of esketamine treatments and baseline covariates. The primary outcomes analysis was completed in the ESK TRD cohort and repeated in the larger ESK all-comers cohort.

Results: Within the ESK all-comers sample (N=664), ESK-TRD patients (N=361) had a mean age of 45, were 64% Female, and 95% White. On average, baseline PHQ-9 was moderately severe (M=17, SD=6), and patients had tried 3 different antidepressants (M=3, SD=1) and 2 unique antidepressant classes (M=2, SD=1) prior to esketamine initiation. The most common co-occurring psychiatric diagnoses were anxiety disorders (74%), followed by trauma- and stressor-related disorders (29%). In the ESK-TRD cohort 71% completed induction, defined as at least 8 treatments within 42 days of esketamine initiation. In the outcomes analysis, esketamine treatment was associated with reduced PHQ-9 scores in both the ESK-TRD (N=158) and the ESK all-comers cohorts (N=294). Statistically significant reductions from baseline PHQ-9 were observed after as few as 1 treatment, with estimated reductions exceeding 4 points after 5-8 treatments (b=-4.2/-4.9 for ESK-TRD and ESK-all-comers respectively) and larger clinically significant reductions after additional treatment (b=-5.1/-5.9 respectively after 13-16 treatments).

Conclusion: Significant reductions in depression symptoms were observed during esketamine therapy, with continued improvements after 8-12 esketamine treatments. These results suggest that esketamine is an effective treatment for TRD in real-world settings at rates consistent with prior studies2 and that patients who remain in esketamine therapy after the 8-treatment induction continue to experience benefits.

T51. A VA INTERVENTIONAL PSYCHIATRY CONSULTATION MODEL FOR PROCESSING, EXPERT EVALUATION, AND DISPOSITION OF INTERVENTIONAL REFERRALS

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Abstract: The model for the Edward Hines, Jr. VA Interventional Psychiatry Consultation (IPC) program was first conceptualized as a quality improvement (QI) initiative, receiving a Hines Innovation Award in January 2021. The model was created to provide a process for optimally triaging the significant number of referrals anticipated with the start of our intravenous (IV) ketamine for depression service, which has a finite capacity. This was one of the first such programs within VA to integrate multiple distinct clinical intervention services at that time.

This presentation, approved as a non-research QI report by the Hines Determination Committee, provides a descriptive summary of our IPC process. Clinical criteria and/or

logistical reasons that patients were discontinued from further ketamine consideration are summarized and the number of Veterans falling into broad disposition groups presented. Disposition groups include continuation of ketamine-specific consultation and ultimate treatment, referral for further difficult-to-treat depression (DTD) consultation with in-depth assessment and recommendations, referral for transcranial magnetic stimulation (TMS), electroconvulsive therapy (ECT), other mental health treatment services, as well as withdrawal of referral by patient or referring clinician.

The Hines IPC team is currently comprised of seven psychiatrists, one psychologist, and two mental health pharmacists representing significant expertise in ketamine, transcranial magnetic stimulation (TMS), electroconvulsive therapy (ECT), advanced psychopharmacology, difficult-to-treat depressions (DTD), anxiety disorders, and evidence-based psychotherapies. The IPC team has developed and refined a set of recommended clinical parameters and pragmatic triage considerations for ketamine evaluation, informed by national guidelines and consultation with depression and ketamine clinicians nationally.

The IPC process begins with triage review of IPC consultation requests by the IPC medical director or designee, referring-physician consultation, and clinical record review. Cases moving forward are assigned to an IPC team member to perform a clinical evaluation. Consultation findings are presented and discussed at weekly IPC team meetings and recommendations made regarding next steps; these may include continuation onto full ketamine consultation, or discontinuation of ketamine consideration and potential recommendations for other IPC treatments.

From September 2021 through December 2023, the Hines IPC program received 65 patient referrals, all with the request for consideration of ketamine treatment. Clinicians and patients had all been informed that consideration would be given to all currently available interventions, based upon clinical determination of the team. Ultimately, thirteen Veterans (20%) received ketamine treatment for their depression.

This IPC model presents future research opportunities to test the effectiveness of such a specialized, evidence-based clinical triage model for novel resource-intensive/limited capacity treatments such as ketamine, and potentially even psychedelics, in terms of impact upon resource allocation, cost-effectiveness, and sustained outcomes.

T52. TREATMENT PATTERNS AND HEALTHCARE RESOURCE UTILIZATION FOLLOWING INITIATION OF ARIPIPRAZOLE LAUROXIL USING A 1-DAY INITIATION REGIMEN

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Abstract Background: The long-acting injectable aripiprazole lauroxil (AL) initiated using a one-time injection of a NanoCrystal Dispersion formulation of AL (ALNCD) and a 30 mg oral dose of aripiprazole significantly improved symptoms of schizophrenia in a phase 3 study.
Objective: The current analysis examined treatment patterns and healthcare resource utilization (HCRU) among patients with schizophrenia initiating AL using ALNCD in the real-world setting.

Methods: This retrospective analysis used administrative claims data from January 1, 2018, to December 31, 2022. Adult patients with schizophrenia with continuous enrollment ≥6 months before (baseline) and after (follow-up) AL initiation using ALNCD were eligible. Treatment patterns were evaluated during and after initiation. Inpatient admissions, emergency department (ED) visits, and outpatient visits were compared between baseline and follow-up periods.

Results: Included patients (N=1152) had a mean age of 38.4 years; 36% were female. Most patients received AL 1064 mg (39%) or 882 mg (37%); 90.3% initiated with ALNCD and their first AL injection on the same day, and 78% received a second AL dose. Proportions of patients with all-cause, mental health (MH)-related, and schizophrenia-related inpatient admissions and ED visits significantly decreased between baseline and follow-up (all $P < 0.001$); the proportions of patients with all-cause, MH-related, or schizophrenia-related outpatient visits did not decrease.

Conclusion: Findings from this first real-world study suggest that initiating AL using ALNCD may result in clinically meaningful reductions in patient burden and healthcare costs, as evidenced by significant declines in HCRU.

T53. THE CLINICAL GLOBAL IMPRESSION OF SEVERITY (CGI-S): BRIDGING THE RESEARCH-PRACTICE GAP

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Abstract: Background and Purpose: Clinicians treating depression regularly assess but rarely systematically record overall depression severity at each visit. This report examines whether the mandated routine use and electronic health record (EHR) recording of the Clinical Global Impression of Severity (CGI-S)—a common outcome metric in randomized controlled trials—might be sufficient to reliably inform administrative or program level decisions in a large representative sample of patients with depression. If so, this simple effort would help bridge findings from controlled trial and real-world practice.

Methods: This study leveraged de-identified EHR data from the NeuroBlu Database, a longitudinal behavioral health real-world database. Included patients had an MDD diagnosis, were at least 18 years old, were prescribed ≥1 antidepressant medication (ADM) for ≥6 weeks, had a smoothened CGI-S score of ≥4 (exponential smoothing) at some point during the medication trial period and had ≥14 days covered by CGI-S measurements during the prescription period. Responsive, non-responsive, and incompletely treated patient groups were identified based on CGI-S outcomes of two ADM trials. CGI-S scores (3 or less) or changes of at least 2 points identified the responsive group. Those who did not respond to one ADM and never had a second trial were incompletely treated. Responsive and non-responsive groups were compared using univariate analysis in terms of clinical, demographic, and treatment characteristics. The survival probability of hospitalization or emergency department visit was calculated using the Kaplan-Meier method and stratified by responsiveness status. Cox proportional hazards models estimated the hazard ratio (HR) of hospitalization between responsive and non-responsive patients. A logistic lasso regression model predicting responsiveness status with demographic variables, stressors, and other characteristics was

developed. A random forest model was constructed to provide another method to identify predictors of responsiveness and to compare with results of the logistic regression.

Results: The final analytic cohort included 24,265 patients (23.1% responsive; 19.1% non-responsive; 57.7% incompletely treated). The survival probability of no hospitalization within one year was consistently higher (85.0%; 95% confidence interval [CI]: 84.0%, 86.0%) in responsive than non-responsive patients (79.8%; 95% CI: 78.6%, 81.0%). The HR of hospitalization in non-responsive patients to responsive patients was 1.28 (95% CI: 1.18, 1.39; p=0.001). The logistic lasso regression model achieved an area under the ROC (AUROC) curve of 71.1% (sensitivity = 68.5%; specificity = 60.7%). In comparison, the random forest model achieved an AUROC of 74.0% (sensitivity = 61.1%; specificity = 73.6%). Several ADMs were identified as being associated with significantly increased odds of response, whereas high baseline CGI-S, older age, pre-index hospitalization, and use of augmentation agents were associated with a lower likelihood of response. The first ADM used contributed the most to discrimination of responsive from non-responsive patients, followed by age and baseline CGI-S.

Conclusions: A routinely recorded simple global estimate of disease severity for depression by clinicians without specific training can meaningfully bridge controlled trial and real-world research and inform administrative decisions.

T54. DOES THE KETOGENIC DIET IMPROVE OUTCOMES IN SEVERE AND PERSISTENT MENTAL ILLNESS AND NEUROCOGNITIVE DISORDERS? A SYSTEMATIC REVIEW

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Abstract: Introduction: The established safety and efficacy of the ketogenic diet in the treatment of epilepsy and other neurological disorders support its potential as a treatment option for individuals with psychiatric and neurocognitive disorders. We sought to identify and analyze results from all primary research investigating the impact of the ketogenic diet on clinical outcomes for individuals with severe and persistent mental illness and/or neurocognitive disorders.

Methods: We searched English-language articles in Medline, Embase, PsycINFO, Cochrane Database of Systematic Reviews, Cochrane Central, Cochrane Methodology Register, CAB Abstracts, and Web of Science from database inception to August 18, 2023. Studies were included that reported on psychiatric or cognitive outcomes in individuals with a major mood disorder, schizophrenia spectrum, or cognitive disorder, who were treated with a ketogenic diet or ketone supplement. A narrative synthesis of the findings from the included studies was organized by target population.

Results: A total of 3,038 articles were identified of which 67 met inclusion criteria for full analysis: 52 were in individuals with a cognitive disorder, 8 in mood disorders (6 in bipolar disorder, 2 in depression), 5 in schizophrenia spectrum disorders, and 2 in mixed populations. An analysis of included reports identified significant improvements in cognitive performance

in individuals with cognitive disorders, with some reports showing improvements in positive and negative symptoms in schizophrenia and mood disorders. Reports capture treatment duration ranging from 6 weeks to 12 years. Most of the articles included in the review were case reports and case series, with few published controlled studies.

Discussion: This systematic review highlights promising findings from studies of the ketogenic diet in improving cognitive and mood outcomes in populations with severe mental illness and neurocognitive disorders. High-quality primary research (e.g. randomized controlled trials) is needed to replicate these effects in controlled settings to better establish the clinical efficacy of the ketogenic diet in these populations.

T55. KETAMINE'S INFLUENCE ON MAGNETOENCEPHALOGRAPHY PATTERNS DURING A WORKING MEMORY TASK IN INDIVIDUALS WITH TREATMENT-RESISTANT DEPRESSION

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Abstract Background: Cognitive deficits, including issues with working memory, attention, and concentration, are common in individuals with unipolar and bipolar treatment-resistant depression (TRD). There is a lack of effective pharmacological interventions for cognitive dysfunction in TRD. Ketamine, a glutamatergic modulator, has shown promise for its rapid-acting antidepressant effects. Preliminary evidence suggests ketamine could improve cognition in TRD patients through synaptogenic effects on the prefrontal cortex. Magnetoencephalography (MEG) studies demonstrate that ketamine increases gamma power in parts of the occipital, temporal, and frontal cortices. Additionally, pregenual anterior cingulate cortex activity during a working-memory task was correlated with the response to ketamine in TRD patients using MEG. This study aims to investigate the effect of ketamine on n-back performance (reaction time and accuracy on the task) and gamma power (30-58 Hz) in patients with unipolar and bipolar TRD.

Methods: This post-hoc analysis combined two cross-over double-blind, randomized, placebo-controlled trials performed at the National Institute of Mental Health. Twenty-one subjects (14 female, mean age 42.35, SD = 11.10), 14 with bipolar disorder, and 7 with major depressive disorder, received a single intravenous infusion of subanesthetic ketamine (0.5 mg/kg) or saline placebo approximately two weeks apart. Patients with bipolar disorder were on ongoing treatment with either lithium or valproate, while patients with major depressive disorder were unmedicated. Subjects performed an n-back task during MEG scanning at baseline (1-3 days before the first infusion) and 6-9 hours following each infusion. Depression was assessed 60 minutes before and 230 minutes after each infusion using the Montgomery-Åsberg Depression Rating Scale (MADRS). A mixed model regression was used to compare the effects of the drug on n-back performance after each infusion. All models included a random intercept per person and a fixed drug effect. Study, age, gender, and MADRS were also included as covariates. Gamma power was projected during the maintenance period of the task (-500 to 0 ms peristimulus time) for each subject and memory load (0-, 1-, and 2-back) using the multiple sparse priors algorithm in SPM12 (https://www.fil.ion.ucl.ac.uk/spm/). A two-way repeated measures analysis of variance examined the effect of infusion (ketamine vs. placebo) and memory load on source-localized gamma power.

Results: Ketamine led to a significant improvement in MADRS scores ($p < 0.01$). Behaviorally, there were no statistically significant differences when comparing ketamine and placebo reaction time [(0-back: $p = 0.66$), (1-back: $p = 0.053$), (2-back $p = 0.26$)] or accuracy [(0-back: $p = 0.61$), (1-back: $p = 0.76$), (2-back: $p = 0.46$)] 6-9 hours post-infusions. While there was no effect of memory load on source-localized gamma power, ketamine increased gamma power in the parieto-occipital junction ($t = 2.61$, $p < 0.01$) and decreased gamma power in the posterior superior temporal sulcus ($t = 2.5$, $p < 0.01$) and the inferior frontal gyrus ($t = 2.51$ $p < 0.01$) compared to placebo.

Conclusion: A single infusion of ketamine, despite improving depression, was not associated with improvements in n-back performance compared to placebo. However, ketamine led to gamma power changes in regions associated with attention, concentration, and working memory. Further studies are needed to investigate the cognitive impact of ketamine in TRD with larger sample sizes, different cognitive tests, other aspects of cognition, assessments at different time points, and repeated ketamine infusions.

T56. A BIOMARKER-BASED ENRICHMENT STRATEGY FOR NEUROPSYCHIATRIC DRUG DEVELOPMENT: EXAMPLES FROM TWO ONGOING PHASE 2B STUDIES

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Abstract: Psychiatric drugs in development and in clinical care suffer from high variability in treatment response and small effect sizes in traditional clinically-defined patient populations. This variability is likely due to biological and clinical heterogeneity in psychiatric disorders such as major depressive disorder (MDD), wherein some patients respond well to treatment but a majority do not. Clinical trials that utilize all-comer designs are unable to distinguish these populations. Precision psychiatry leverages individual patient characteristics, such as behavioral profiles or brain activity patterns, to identify individuals more likely to benefit from specific drugs or mechanisms. This requires (1) identification and validation of candidate predictive biomarkers and (2) implementation of a biomarker-based enrichment strategy to test drug efficacy in biomarker-identified patients. Here, we present our enrichment strategy in two ongoing Phase 2b studies in MDD (ALTO-100-201, NCT05712187; ALTO-300-201, NCT05922878) investigating candidate antidepressants with distinct and novel mechanisms of action.

Predictive biomarkers for each compound were identified and replicated in independent prospective test sets in prior Phase 2a trials (with > 200 patients in each program). ALTO-100's biomarker is derived from cognitive test performance while ALTO-300's biomarker is based on resting-state electroencephalogram (EEG). ALTO-100 is being studied as both monotherapy and adjunctive treatment of MDD, with ALTO-300 only used as adjunctive treatment.

Our ongoing placebo-controlled studies use a primary endpoint of change in Montgomery-Asberg Depression Rating Scale in biomarker-defined patients following treatment. We collect a suite of biomarkers (neurocognitive battery, EEG, wearables) but select patients during screening based on the relevant biomarker for that study. Patients are then randomized 1:1 to drug versus placebo, stratified by biomarker status, and treated for six weeks, with all patients

allowed to receive open-label drug afterwards. Our engineering team receives biomarker data in near real-time and conducts automated quality control (QC) checks, with biomarker status determined and used for randomization of clinically eligible patients. Crucially, sites, participants, and sponsor clinical staff are blinded to patient biomarker status, and both patients with and without the key biomarker profile are enrolled in the study to manage outcome expectations and quantify impact of enrichment. Powering for primary outcome is done based on the biomarker-defined population.

ALTO-100-201 and 300-201 studies are actively enrolling participants and aim to randomize approximately 266 and 200 participants, respectively, with about 30 nationwide sites each, including in-person and decentralized sites. Outcomes and allocation data are blinded until ultimate study readout. Strikingly, at the time of abstract submission < 8% of selection biomarker data has been excluded due to not meeting QC standards. This is significant considering that data collection involves more than 50 sites with limited experience on biomarker assessments, suggesting widespread feasibility of our biomarker-based enrichment strategy.

In conclusion, we describe an innovative approach in precision psychiatry clinical trial methodology, focusing on biomarker-based enrichment while preserving blinding of biomarker type and status, and utilizing real-time QC and biomarker determination. The encouraging biomarker QC pass rates from two ongoing trials suggest this approach can be used at scale both in future Phase 3 programs as well as in ultimate implementation in clinical care.

T57. HIPPOCAMPAL METAPLASTIC MECHANISMS ACTIVATED BY KETAMINE METABOLITE (2R,6R)-HYDROXYNORKETAMINE PROMOTE LONG-LASTING ANTIDEPRESSANT-RELEVANT EFFECTS

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Abstract: The pharmacologically active (R,S)-ketamine (KET) metabolite (2R,6R)-hydroxynorketamine (HNK) maintains the rapid and prolonged preclinical antidepressant-like effects of KET without adverse effects and has completed human phase I clinical trials. While several hypotheses have been proposed to explain how KET and its metabolites initiate their antidepressant-relevant effects, it is unclear how these therapies promote persistent antidepressant effects following their elimination. Metaplasticity is a concept that describes the ability of previous stimuli to persistently regulate the threshold for future plasticity events and may mediate sustained antidepressant action of KET/HNK. Studies suggest that KET/HNK and KET-like rapid-acting antidepressants activate metaplastic mechanisms to persistently induce therapeutic effects by lowering the threshold for beneficial changes in synaptic plasticity. To study the initiation and maintenance of in vitro KET/HNK metaplastic effects, we incubated hippocampal slices collected from male and female mice with KET/HNK for 60 minutes followed by an artificial cerebrospinal fluid washout for 35 minutes or 3 hours. To study the sustained effects of HNK ex vivo, mice were treated with HNK and sacrificed for electrophysiology experiments 24 hours later. Primary outcomes assessed were input/output (I/O) excitatory postsynaptic potential slope, paired-pulse facilitation (PPF), and long-term potentiation (LTP) at the Schaffer collateral-CA1 synapse. Incubation with KET resulted in no detectable alterations in responses 35 min after 1, 5, or 20 μM KET wash-out. However, HNK enhanced presynaptic-mediated synaptic transmission 35 min after 2, 10, or 50 μM HNK

washout in a concentration-dependent manner as indicated by enhanced basal I/O responses and reduced PPF. Impaired LTP magnitude was also observed at 10 and 50 μM HNK. The effects of HNK were blocked by preincubation with 10 μM adenylyl cyclase inhibitor SQ22536 or 10 μM cell-permeable protein kinase A inhibitor H89, suggesting the requirement of adenylyl cyclase-cyclic AMP-protein kinase A activity in the induction of HNK's rapid effects. Preincubation with the NMDAR antagonist D-APV (50 μM) did not prevent HNK's effects. Similar to the 35 min time point, no alterations in any responses were observed 3 h after 1, 5, or 20 μM KET wash-out. On the contrary, LTP magnitude was quantitatively greater, and basal transmission/PPF were unaffected, 3 h after 10 μM HNK washout, suggesting HNK persistently activated metaplastic mechanisms. Metaplastic mechanisms activated by in vitro HNK exposure were recapitulated in ex vivo recordings in which 10 and 50 mg/kg, but not 2 mg/kg, HNK treatment led to a dose-dependent enhancement of LTP without significant alterations in basal synaptic transmission or PPF. Our in vitro findings suggest that rapid HNK effects are initiated by a presynaptic mechanism that enhances glutamatergic transmission whereas our ex vivo results suggest sustained HNK antidepressant-relevant effects are maintained by a postsynaptic metaplastic mechanism. These findings provide insight into KET/HNK's rapid and sustained mechanism of action, suggesting that targeting metaplastic mechanisms may be an effective approach for developing novel antidepressants. Further, as metaplastic mechanisms are persistently activated following the elimination of the therapeutic, there are numerous therapeutic advantages of engaging metaplastic signaling cascades including reduced dosing frequency and drug-related adverse responses.

T58. KARXT (XANOMELINE AND TROSPIUM) FOR THE TREATMENT OF SCHIZOPHRENIA: NUMBER NEEDED TO TREAT, NUMBER NEEDED TO HARM, AND LIKELIHOOD TO BE HELPED OR HARMED

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Abstract Background: KarXT (xanomeline and trospium chloride) is an investigational agent in clinical development for the treatment of schizophrenia. This post hoc analysis investigated the efficacy and tolerability of KarXT in adult patients with an acute exacerbation of schizophrenia using the evidence-based medicine metrics of number needed to treat (NNT), number needed to harm (NNH), and likelihood to be helped or harmed (LHH).

Methods: Data sources were three completed Phase 2/3, 5-week, randomized, double-blind, placebo-controlled studies (NCT03697252, NCT04659161, NCT04738123). Efficacy outcomes included response as measured by ≥ 20%, 30%, 40%, or 50% reduction from baseline on the total Positive and Negative Syndrome Scale (PANSS) score, a Clinical Global Impressions-Severity (CGI-S) score of ≤ 2 or 3 points, or a decrease from baseline in CGI-S of ≥ 1, 2, or 3 points. Tolerability outcomes included rates of adverse events (AEs), discontinuation because of an AE, dose reduction because of an AE, and changes in metabolic variables, prolactin, and ECG QTc interval. LHH was calculated contrasting acute efficacy vs. the above tolerability outcomes. Indirect comparisons with other agents used to treat schizophrenia are made using data from previously published and similarly designed analyses.

Results: From the pooled data across the 3 studies, endpoint NNT estimates vs. placebo were as robust as 5 (95% CI 4-7) for the outcome of ≥ 20% reduction from baseline on the total PANSS score, and remained < 10 at endpoint for most other efficacy outcomes, including for the outcome of ≥ 30% reduction from baseline on the total PANSS score (NNT 5 [4-8]), ≥

40% reduction from baseline on the total PANSS score (NNT 8 [6-16]), CGI-S of ≤ 3 (NNT 8 [5-14]), CGI-S decrease from baseline ≥ 1 point (NNT 5 [4-7]), and CGI-S decrease from baseline ≥ 2 points (NNT 7 [5-12]). NNH estimates vs. placebo were < 10 for the AEs of nausea (7 [6-10]) and vomiting (9 [7-13]), however the NNH for patients discontinuing from the study because of an AE of nausea, dyspepsia, or vomiting was 49 (28-182). Dose reduction because of an AE of nausea, dyspepsia, or vomiting yielded a NNT of 170 (ns). All other AEs had NNH estimates ≥ 10 or the rate was higher with placebo than with KarXT resulting in a "negative" NNH, such as for the outcome of weight gain of ≥ 7% from baseline at LOCF endpoint, with a NNH 0f -17 (-10 to -72). When contrasting KarXT with available first-line oral second-generation antipsychotics for schizophrenia, KarXT is the only agent that shows no difference from placebo in terms of weight gain ≥ 7% and has the most favorable NNH estimate for somnolence and/or sedation. For KarXT, when calculating LHH for different harms vs. response, in all instances LHH > 1, such that response would be encountered more often than any single harm. LHH for response vs. discontinuation because of an AE is 21.8, and for response vs. discontinuation because of nausea, dyspepsia, or vomiting, the LHH is 9.8.

Conclusion: KarXT demonstrated an effect size comparable to, or better than, other first-line agents that are FDA-approved for the treatment of schizophrenia. No head-to-head trials have been completed to date, but in this analysis KarXT has the least likelihood to be associated with weight gain or somnolence among these other agents. In clinical trials to date, KarXT is associated with gastrointestinal adverse effects with a relatively high incidence, but with a relatively low likelihood to be associated with a need for dose-lowering or discontinuation.

T59. THE COMPLEX INTERPLAY OF SEIZURE DISORDER, DEPRESSION, AND MEDICATION: A CASE REPORT

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Abstract: Specific Purpose: Psychiatrists often see patients with comorbid seizure disorders. Understanding the pharmacological side effects of the neuroleptic treatments, particularly the rare side effects, is critical for optimizing pharmacology treatments and optimizing patient function.

Content: The patient is a 21 year old single, male with a history of a seizure disorder and major depression, with one prior hospitalization for an overdose of buspirone and alcohol in 2022, with family history for seizure disorders, no known family history for psychiatric medical conditions, raised by his parents until age 16, and grew up with his mother following parent's divorce, who presented to the emergency department after suicide attempt, severe depression with psychomotor retardation, possible mutism, job loss several months prior to admission for unknown reasons at a local drugstore, and failure to return to college following onset of seizure disorder two years ago. The patient had no prior psychiatric symptoms prior to onset of seizure disorder his freshman year in college. He was diagnosed with mood disorder due to medical condition of seizure disorder. When given an antidepressant, he did have paranoid thoughts and antidepressant was discontinued for and antipsychotic with resolution of paranoid thoughts.

In addition, the patient had minimal speech output on admission with one word responses, slow processing, and shallow affect. Due to concern for cognition dysfunction, Montreal Cognitive

assessment was performed with a score of 18/30, with deficits in trail making, copying the cube, drawing the hands on the clock, naming the camel, hand tap at letter A, naming 11 words that start with letter F, abstraction, delayed recall 1/5, day of the week. Patient's family states that he was no longer able to perform the series of event related to changing a tire when formerly able to make most car repairs himself. His mother noticed a change in his behavior starting zonisamide six months ago. After consultation with neurology, negative MRI, he was converted from zonisamide to lamotrigine, and neurocognitive deficits resolved as evidenced by patient was able to attain employment, and resume functional life at home, at work, and in relationships.

Methodology: Montreal cognitive assessment before medication transition. Repeat evaluation 6 months post discharge.

Results: The patient had significant return of cognitive function following discontinuation of zonisamide, which was demonstrated in his ability to gain employment, and his hope for independent living in the near future.

Importance: The patient's symptoms might have been attributed to cognition changes related to his seizure disorder. It is important for the medical community to expand our understanding of the rare side effects of medications to promote appropriate monitoring for these medications. These efforts will help to ensure accurate diagnosis, and to coordinate improvements in pharmacological treatment selections with our colleagues, and most importantly, improve function outcomes for patients.

T60. ULOTARONT DELAYS GASTRIC EMPTYING TIME IN SCHIZOPHRENIA PATIENTS WITH METABOLIC SYNDROME (NCT05402111)

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Abstract Background: Metabolic syndrome, which can be induced or exacerbated by the current class of antipsychotic drugs, is highly prevalent in schizophrenia patients and presents challenges to lifetime disease management [1]. Ulotaront is an investigational trace amine-associated receptor 1 (TAAR1) agonist with 5-HT1A agonist activity in clinical development for schizophrenia. In line with other TAAR1 agonists, ulotaront improves glycemic control and reduces body weight in rodent models via peripheral effects on glucose homeostasis as well as central regulation of energy balance [2]. Given that TAAR1 agonists improve oral glucose tolerance in rodents by delaying gastric emptying (a mechanism implicated in the beneficial effects of GLP-1 receptor agonist), our aim was to assess the effect of ulotaront on gastric emptying in patients with schizophrenia with metabolic syndrome at high risk to develop diabetes.

Methods: Twenty-seven patients with schizophrenia and metabolic syndrome were randomized to receive in open-label fashion either a single dose of ulotaront (150 mg) or their prior antipsychotic in a 2-sequence crossover design. Patients were required to maintain a stable dose and regimen for one of 4 antipsychotics as treatment for schizophrenia at the time of screening (risperidone, olanzapine, quetiapine, or aripiprazole). Patients fulfilled at least 3 of 5 metabolic syndrome criteria and demonstrated glycemic-derived insulin resistance by either HbA1c values between 5.7% and 6.4% or fasting HOMA-IR values equal or above 2.22.

Prior to the single dose of ulotaront, patients underwent a washout period (of 3 to 16 days) of their prior antipsychotic drug. Following an overnight fast, patients received a single dose of either ulotaront or the prior antipsychotic medication and underwent scintographic measure of solid gastric emptying. This entailed receiving a 99mTc-labeled meal (320kcal, 30% fat meal) and successive γ camera abdominal scans (anterior and posterior) every 60 minutes over a 4-hour period. Primary endpoints were gastric emptying half-time, T1/2 (GE T1/2) and gastric retention (%GR) at 4h. Secondary endpoints were %GR at 1h and 2h.

Results: Following a single-dose of 150 mg ulotaront, gastric emptying was delayed (T1/2 = 145 ± 17 min; median ± SE) compared to patients receiving a single dose of their prior antipsychotic drug (125 ± 4 min, p-value 0.0028). The median percent gastric retention post-dose (1h, 2h, 4h) was greater following ulotaront (83%, 66%, 17%) compared to prior antipsychotic (76%, 51%, 7%, respectively).

Discussion: Ulotaront significantly delayed gastric emptying following a single dose. In this first study of its kind, we enrolled patients with schizophrenia with metabolic syndrome, and who were at high risk for diabetes. The within-subject crossover design allowed the comparison of the activity of ulotaront in each patient to the activity of their prior antipsychotic medication. Further studies of ulotaront in this patient population (NCT05463770, NCT05542264) are in progress and will help to elucidate ulotaront's potential for benefit on glycemic control and body weight.

T61. PREDICTING CONVERSION TO INSULIN SENSITIVITY WITH METFORMIN IN TREATMENT RESISTANT BIPOLAR DEPRESSION -- A NOVEL CLINICAL TOOL

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Abstract Background: Insulin resistance (IR) can contribute to treatment-resistance in bipolar depression. The randomized controlled clinical trial TRIO-BD demonstrated that IR reversal by metformin may improve outcomes in treatment-resistant bipolar depression (TRBD). Using TRIO-BD data, we developed a predictive tool using body mass index (BMI) and homeostatic model assessment -insulin resistance (HOMA-IR) to help clinicians identify TRBD patients that might reverse IR with metformin.

Methods: A logistics regression model was used to test the predictive performance of baseline BMI and HOMA-IR; area under the receiver operating curve (AUC), sensitivity, and specificity were generated and examined. In view of the high benefit to low risk of metformin in reversing IR, high sensitivity was favored over specificity in developing the model.

Results: The model's AUC was 0.79. Sensitivity was 91 % (95% CI: 57% to 99%) and specificity 56% (95%CI = 36% to 73%) at a cut-off probability of conversion of 0.17. For each unit increase in BMI or HOMA-IR, respectively, there was a 15% (OR = 0.85, 95% CI [0.71 – 0.99]) or 43 % (OR = 0.57, CI [0.18 – 1.36]) decrease in the odds of conversion to insulin sensitive.

Conclusions: This prototype tool was developed using easily to obtain clinical measures, BMI and HOMA-IR, and predicted IR reversal with metformin with high sensitivity. Model

exploration suggests that early intervention with metformin, when a patient has a relatively lower BMI and HOMA-IR, would be more likely to reverse IR in TRBD. Development of such tools, based on clinical trial data, could help practicing clinicians integrate novel treatment interventions into practice.

T62. PET/CT STUDY OF DOPAMINE TRANSPORTER (DAT) BINDING WITH THE NOVEL TRIPLE REUPTAKE INHIBITOR TOLUDESVENLAFAXINE IN RATS AND HUMANS

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Abstract: Purpose: Toludesvenlafaxine is a recently developed antidepressant that belongs to the triple reuptake inhibitor class. Despite the in vitro evidence that toludesvenlafaxine inhibits the reuptake of serotonin (5-HT), norepinephrine (NE) and dopamine (DA), there is no in vivo evidence that toludesvenlafaxine binds to DAT and increases DA level, a mechanism thought to contribute to its favorable clinical performance.

Methods: Positron emission tomography/computed tomography (PET/CT) was used to examine the DAT binding capacity in healthy rats and human subjects and microdialysis was used to examine the striatal DA level in rats. [18F]FECNT and [11C]CFT were used as PET/CT radioactive tracer for rat and human studies, respectively.

Results: In rats, 9 mg/kg of toludesvenlafaxine hydrochloride (i.v.) followed by an infusion of 3 mg/kg via minipump led to the binding rate to striatum DAT at 3.7% – 32.41% and to hypothalamus DAT at 5.91% – 17.52% during the 45 min scanning period. 32 mg/kg oral administration with toludesvenlafaxine hydrochloride significantly increased the striatal DA level with the AUC0-180min increased by 63.9%. In healthy volunteers, 160 mg daily toludesvenlafaxine hydrochloride sustained-release tablets for 4 days led to an average occupancy rates of DAT at 8.04% ± 7.75% and 8.09% ± 7.00%, respectively, in basal ganglion 6 h and 10 h postdose.

Conclusion: These results represent the first to confirm the binding of toludesvenlafaxine to DAT in both rats and humans using PET/CT, and its elevation of brain DA level, which may help understand the unique pharmacological and functional effects of triple reuptake inhibitors such as toludesvenlafaxine.

T63. FLUOXETINE AND SERTRALINE INHIBIT HEIGHT GROWTH DURING PUBERTY

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Abstract: Objectives: This study aimed to characterize change in height and weight in fluoxetine- vs sertraline-treated youth undergoing pubertal growth, and to examine the medications' effect on markers of growth hormone signaling.

Methods: Medically heathy girls aged 8 to 15 years and boys aged 9 to 15 years were enrolled, prior to or within 1 month of starting fluoxetine or sertraline. Inclusion criteria included being in stages 2 through 4 of sexual maturation and having no serious medical conditions. Height, weight, and BMI (kg/m2) measurements and a fasting blood sample were collected at baseline, and 2 and 6 months later. Insulin growth factor-1 (IGF1) and insulin growth factor binding protein-3 (IGFBP3) were measured. Data from unmedicated healthy controls were used for comparison. Linear mixed effect regression analysis evaluated the effect of the medications on change in age-sex-specific anthropometric measurements z-scores, after adjusting for sex, sexual maturation rating, and corresponding baseline age-sex-specific anthropometric z-scores.
Results: A total of 66 medicated participants (age: 12.7 ± 1.5 years; fluoxetine, n = 39; female, n = 48) and 36 unmedicated participants (age: 12.6 ± 1.3 years; female, n = 24) contributed to the analysis. After adjusting for relevant covariates, there was a significant SSRI dose-by-time interaction effect predicting height z-score ($\beta = -0.181$; $p < 0.04$) and a marginally significant medication type-by-dose-by-time 3-way interaction effect ($p = 0.063$), whereby a higher sertraline dose was associated with a significant failure to grow in height. Compared to being unmedicated, fluoxetine 40mg or sertraline 100mg daily led to an estimated 45% smaller increase in height over 6 months ($p < 0.04$). The dose-by-time interaction effect was significantly associated with BMI z-score ($p < 0.03$), as was the SSRI type-by-dose-by-time interaction effect ($p < 0.04$), whereby sertraline predicted a larger increase in BMI z-score. Importantly, the SSRI dose was inversely associated with IGF1 but not with IGFPB3 concentrations ($\beta = -62.5$, $p < .02$; and $\beta = -200.3$, $p > .20$, respectively).
Conclusions: The use of SSRIs, particularly sertraline, is associated with failure to grow in height, likely mediated by a suppression of growth hormone signaling. Future studies should examine whether adult height and body composition are impacted.

T64. PAPR: PSILOCYBIN-ASSISTED THERAPY + MINDFULNESS-BASED STRESS REDUCTION (MBSR) FOR FRONT-LINE HEALTHCARE PROVIDER COVID-RELATED BURNOUT AND DEPRESSION

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Abstract: This is a presentation of outcome data from a randomized clinical trial examining the effects of group psilocybin-assisted psychotherapy (PAP) and an 8 week Mindfulness Based Stress Reduction (MBSR) curriculum on frontline healthcare providers experiencing burnout and depression related to the COVID-19 pandemic. This is an open-label pilot study enrolling 24 total participants (MDs and RNs) randomized to either MBSR alone (12) or MBSR + PAP (12) run at the Huntsman Mental Health Institute which will be completed this spring (NCT05557643). Primary outcome measures include safety, feasibility, and change in depressive symptoms as measured by the QIDS-SR-16 (at 2 weeks and 6 months post intervention). Secondary outcome measures include change in symptoms of burnout (as measured by the Maslach Burnout Inventory for Medical Professionals), change in symptoms of post traumatic stress (PCL-5), change in symptoms of demoralization (Demoralization-II scale), and measures of quality of life (McGill QOL Inventory). Exploratory outcome measures include assessments of change in state and trait mindfulness (Nondual Awareness Dimensional Assessment- trait, Toronto Mindfulness Scale, Brief Savoring Inventory) as well as relationship between experiential assessments (Mystical Experience Questionnaire, Challenging Experience Questionnaire, Nondual Awareness Dimensional Assessment) and change in depressive symptoms at 2 weeks post intervention. Additional exploratory outcome

measures include the utilization of Storyline Health, a smartphone-based AI platform that gathers video based behavioral data to build models to predict treatment response.
This study is novel both in terms of the combination of a mindfulness training curriculum and a psilocybin-assisted therapy intervention as well as the utilization of a full group format for the psilocybin intervention, which includes group preparation, group dosing sessions, and group integration for 4-5 participants at a time. At present we have completed 2 out of 3 cohorts for this study and will have completed the study intervention for all participants by early March.

Burnout is a recognized psychological syndrome with three dimensions: a) emotional exhaustion, b) depersonalization, and c) reduced personal accomplishment. Healthcare provider burnout- a recognized crisis in the U.S. healthcare system for many years- amplified considerably with the SARS-CoV-2 pandemic where chronic, system-dependent stressors related to work dissatisfaction, lack of personal meaning, increasing administrative burden, and marginalization of providers have been coupled with sudden, dramatic increases in clinical demand, limited resources and resource rationing, assumption of increased personal risk, and increasing difficulties in balancing family life and multiple roles and responsibilities. Healthcare provider burnout has significant downstream effects on patient care due to its association with impaired job performance, decrease in empathy, and increases in medical errors. Provider burnout is clearly linked to poor mental health outcomes among providers, increased problematic substance and alcohol use, as well as safety concerns with patient care. To date, there have been no firmly established meaningful interventions for this important psychological syndrome, however there is evidence to suggest that mindfulness-based interventions may lead to reductions in symptoms of burnout. There are compelling reasons to hypothesize that psilocybin-assisted psychotherapy (PAP) may offer a uniquely effective way of augmenting the benefits of mindfulness interventions as well as catalyzing significant improvements in symptoms of burnout.

T65. A PRELIMINARY INVESTIGATION OF TRANSCRANIAL FOCUSED ULTRASOUND FOR THE TREATMENT OF TREMOR

Chloe Deveney[*1], Kevin Enemuo[1], Katelyn Hoffman[1], Jean Surya[1], Jonathan Haroon[1], Kennedy Mahdavi[1], Kaya Jordan[1], Sergio Becerra[1], Taylor Kuhn[2], Alexander Bystritsky[2], Sheldon Jordan[3]*

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Abstract Background: Essential tremor (ET), a potentially debilitating neurological condition, is characterized by rhythmic shaking of the hands. Current treatments for ET include medication (beta-blockers) as well as deep brain stimulation (DBS) and high-intensity focused ultrasound (HIFU). Medication is only successful in approximately half of the patient population. Additionally, DBS and HIFU involve greater risks due to their invasive nature and use of ablation. Therefore, low-intensity focused ultrasound (LIFU) may provide an in-clinic treatment route for patients who do not respond to medication and seek non-invasive treatment options.
Methods: In this open-label study, IRB-approved clinical trial exploring the safety and feasibility of LIFU treatment for ET (NCT #05475340), patients between the ages of 18-90 who were diagnosed with essential tremor were enrolled to complete the protocol. Currently, 12 patients have completed this protocol receiving eight, ten-minute sessions of LIFU targeted

at the ventral intermediate nucleus (Vim) of the thalamus. At the time of poster presentation, we will report on the primary outcomes of safety, efficacy, and feasibility of LIFU for the treatment of essential tremor. We will also report on secondary outcomes that seek to access the potential benefits of treatment of ET with LIFU including the Global Rating of Change (GRC) and the Essential Tremor Rating Scale (TETRAS).

Results: Primary outcome measures show that no adverse effects were reported in the patients enrolled in the study. In evaluating secondary outcome measures, eight of the first ten patients enrolled reported a GRC at or above two indicating a clinically significant improvement. On the TETRAS scale, the performance sub-scale showed a clinically meaningful improvement in all 10 patients. At the time of poster presentation, we intend to report on both primary and secondary outcomes of additional patients enrolled.

Conclusion: Preliminary findings from the first ten patients enrolled in the protocol demonstrate the safety and feasibility of LIFU for the treatment of ET with no adverse events for primary outcome measures. Secondary outcome measures suggest the potential efficacy of the use of LIFU for the treatment of essential tremor.

T66. TREATING EMOTIONAL AND COGNITIVE DISORDERS LINKED TO TRAUMATIC BRAIN DAMAGE WITH TRANSCRANIAL INFRARED LASER STIMULATION: ADDITIONAL FINDINGS

Katelyn Hoffman[*1], Chloe Deveney[1], Kevin Enemuo[1], Jonathan Haroon[1], Kennedy Mahdavi[1], Sergio Becerra[1], Lider Chan[2], Sheldon Jordan[3]*

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Abstract Background: Preliminary analysis of an open-label trial using transcranial near-infrared (NIR) light therapy to treat traumatic brain injury (TBI) revealed beneficial results on mood inventories and cognitive tests. Research has demonstrated that TBI is associated with an increased chance of developing mood disorders, tauopathies, and other dementias. NIR targets the repair of tissue beneath the skull by utilizing lasers with red-to-near-infrared wavelengths that can pass through. NIR light treatment has been used in prior research that has demonstrated cognitive advantages; however, these studies have only used EEG to target the frontal cortex. Building on previous results, this study localizes the treatment target to anatomically exact coordinates on the skull that match localized ASL signal dropout on each participant's fMRI. We predicted that individuals with TBIs will have clinically significant improvements in their mood and cognitive function following treatment with focused NIR light therapy.

Methods: Patients who were diagnosed with TBI and exhibit symptoms of mood disorders received treatment to the bilateral frontal lobes using the Cytonsys CytonPro 5000 system with a wavelength of 1064 nm. Participants completed a thorough battery of neuropsychological tests at baseline and after the final treatment session. These tests evaluated neurocognitive function across several domains, including executive functioning, attention, and concentration, as well as mood using the Beck Anxiety (BAI) and Depression Inventory (BDI).

Results: This abstract is an update to a case series on the first ten patients, indicates that six out of 10 patients had a clinically significant improvement on the BDI and seven out of 10 patients had a significantly increased BAI. Furthermore, in an attention and concentration task (RAVLT trial A1), seven out of ten patients showed improvement, and on an executive

functioning task (DKEFS Color-Word Interference Condition 3), six out of 10 patients showed improvement. Since this publication, 13 additional participants have been enrolled and their data will be included in the finalization of the poster presentation. Any updated statistical analyses will be included.

Conclusions: The safety of NIR light therapy as a therapeutic intervention for the treatment of TBI is supported as every patient included in this study protocol withstood the study procedures without experiencing any adverse events or side effects. These results point to the potential therapeutic benefits of transcranial NIR light treatment for patients who present with emotional and cognitive problems.

T67. COMPARATIVE EFFECTIVENESS OF INTRAVENOUS KETAMINE AND INTRANASAL ESKETAMINE FOR TREATMENT RESISTANT DEPRESSION IN ADULTS

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Abstract Background: Intravenous ketamine and intranasal esketamine are two interventions that have shown promise with alleviating symptoms in patients with treatment-resistant depression. There is little data comparing both treatments. We report on the effectiveness of each treatment at a specialized interventional psychiatry center.

Methods: A retrospective chart review was conducted with patients from a Treatment-Resistant Depression (TRD) program who either received an acute course of six intravenous ketamine treatments between February 2017 and March 2023 or eight intranasal esketamine treatments between November 2020 and May 2023. Clinical response and improvement were assessed using Beck Depression Inventory (BDI) and Clinical Global Impression Severity (CGI-S) scale.

Results: One hundred and thirteen ketamine patients and thirty-five esketamine were reviewed. Ketamine response rate (50% reduction in BDI) was 25.7%, and remission rate (BDI < 10) was 17.1%. Initial BDI: M=27.4 (SD=10.5); end of acute course: M= 18.0 (SD=10.3). Esketamine response rate was 24.7% and remission rate was 18.5%. Initial BDI: M= 30.9 (SD= 12.3); end of acute course: M=21.0 (SD=14.8). No statistical difference was found (p=0.6239). CGI-S response rate (> 2 point overall decrease) for ketamine was 55% and remission rate (final CGI-S < 2) was 38%. CGI-S response rate for esketamine was 82% and remission rate was 48%.

Conclusions: In this TRD center the reduction of depressive symptoms, response and remission rates in an acute course were similar between ketamine and esketamine. Interestingly, clinical observations assessed higher response rates than self-report scales. The findings of this study are important because as intranasal esketamine and intravenous ketamine continue to become a staple in treating depression, we will need as much data as possible looking at how effective they both are and how they compare to each other.

T68. ADHESION PROTEINS IN PRECLINICAL AND PRODROMAL AD: A PROTEOMIC STUDY

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Abstract Background: Mild cognitive impairment is considered a precursor to dementia, especially Alzheimer's Disease (AD). Although the preclinical and prodromal stages of AD are associated with Aβ and Tau-related pathologies in the brain, they still represent a golden window to develop therapies to prevent further progression. Therefore, this study was designed to compare cerebrospinal fluid (CSF) proteomic profiles of individuals with normal cognition, preclinical AD, prodromal AD, and non-AD MCI. Specifically, proteins that are associated with CSF amyloid beta1–42 (Aβ42), Tau, phosphorylated tau (pTau), and are related to cardiometabolic, vascular/endothelial, and neuronal injury.

Methods: We performed targeted proteomics on CSF and plasma samples from 354 participants recruited for the BSHARP study. We Used an Olink® panel of 276 proteins, followed by an advanced bioinformatic pipeline for data reduction, protein-protein interaction networks, and module development. Resultant Hub proteins that were associated with various clinical phenotypes and biological traits such as levels of CSF AD biomarkers (Aβ42, Tau, and pTau) and the Aβ42/Tau Ratio (TAR) were identified. We then used the STRING database to identify critical proteins within each protein module and conducted an analysis on the clinical/biomarker phenotypes of (normal control, preclinical AD, prodromal AD, and Non-AD MCI). We also performed a pathway enrichment analysis using Gene Ontology (GO) Biological Process to understand their role in AD.

Results: The 276 proteins clustered into five modules that were linked to AD phenotypes. All 5 modules had significant associations with levels of CSF AD biomarkers: Aβ42, Tau, and pTau. (all p-value < 0.05) We next identified critical proteins that are differentially expressed for each AD phenotype: 1 critical protein associated with MCI diagnosis TNFRSF12A, 1 critical protein associated with disease progression CCL3, and 7 critical proteins associated with Cognitive function and TAR status (HGF, ICAM1, VCAM1, NRP1, NRP2, SCARB2, PLAU). (all < 0.05) Furthermore, we found a significant difference in the CSF/Plasma ratio for the proteins associated with Cognitive Status and TAR in the CSF. Pathway enrichment analysis revealed that pathways related to cell adhesion and endothelial dysfunction (all p-value < 0.05) to be involved in the pathogenesis of AD.

Conclusion: Our study revealed a CSF proteomic signature that might be involved in the progression of AD during the preclinical phase of AD. Future studies investigating the molecular function of the adhesion molecules identified in the CNS and periphery might provide insight into novel biomarkers and treatment targets for AD.

T69. IN A WORLD OF RISING DELTAS, REVIEW OF CLINICAL IMPLICATION OF DELTA 8, 9 AND 10 THC IN PSYCHIATRY

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Abstract: Along with the legalization of marijuana throughout the U.S., there is an increase in use of delta products as well. While these delta-THCs are widely available and advertised, little information about the effects and possible risks are broadcast to the public. Marijuana is federally classified as a Schedule 1 substance; however, the Delta drugs are not regulated.

According to the Farm Bill from 2018, hemp products with < 0.3% THC can legally be bought, sold, and grown in most states in the U.S., creating a loophole for marketing of these products. For the user this means that there is no assurance of content of the purchased product, and they bear the risk of potentially containing harmful byproducts.

Delta-9-THC is one of the primary psychoactive cannabinoids of marijuana. Delta-9 is hemp derived and binds to the same cannabinoid receptors as marijuana. It can induce the same psychoactive effects which are euphoria, feeling "stoned", anxiety or paranoia as well as aggression.

Delta-8-THC is commonly called "marijuana lite" or "diet weed". Marijuana contains Delta-8 THC only in a small percentage. The sold Delta 8 product is typically made by synthetically converting CBD or Delta 9 THC into Delta 8. Delta 8 binds to the same receptors as Delta 9; Little research is available on Delta 8, but available studies are showing side effects that are comparable to marijuana ranging from paranoia, difficulties with concentration, memory, perception of time to sedation and euphoria. Concerning are reports of accidental severe intoxication, resulting in more than 2000 calls to poison control centers between January 2021 and February 2022. Several states have started to ban the recreational sales of delta-8-THC.

Delta-10-THC, however, is often reported to cause more euphoria and energy rather than sedation. Little research is available regarding its benefits and side effects, but the novelty of this substance makes it especially attractive to users.

The delta-drugs are available in various forms: edibles, vaped concentrates as well as smoking bud or flower or in topical ointments. About 50% of consumers of delta-drugs also reported in surveys to use marijuana as well.

It is important for psychiatrist to know and understand these substances in order to be able to assess the clinical presentation correctly and to provide the effective clinical care for acute and ongoing stabilization.

This presentation is a systematic review of literature looking at the available data for Delta 8,9,10 for psychiatric and medical use. Utilized sources were PubMed, Ovid, Medline, Psych Info, EMBASE.

T70. A PHASE IB/II MULTICENTER, RANDOMIZED, DOUBLE BLIND, PLACEBO CONTROLLED, ASCENDING DOSE FINDING STUDY OF BXCL501 IN AGITATION ASSOCIATED WITH DEMENTIA

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Abstract Background: BXCL501, a sublingual film formulation of dexmedetomidine, a highly selective α2 adrenoceptor agonist, is currently approved in adults for the acute treatment of agitation associated with schizophrenia or bipolar disorder (120 µg and 180 µg doses). The objective of this study was to determine the appropriate dose for studying BXCL501 in elderly patients with dementia.

Methods: This was a Phase 1b/2, multicenter, randomized, double-blind, placebo-controlled, ascending dose study assessing efficacy, PK, safety, and tolerability of BXCL501 for treatment of acute agitation associated with dementia. Subjects were randomized to active treatment with BXCL501 (30, 40, 60 µg) or placebo. The main efficacy measures were PANSS Excited

Component (PEC) and Pittsburgh Agitation Scale (PAS) scores. Adverse events, laboratory tests, and vital signs were monitored and recorded.

The study recruited male and female patients 65 years and older who had met DSM-5 criteria for neurocognitive disorder or dementia and who had history of acute agitation. Randomization criteria included a total PAS score of ≥8. Patients with agitation caused by acute intoxication were excluded.

Results: A total of 96 patients were included. Most subjects had moderate agitation at baseline based on the PEC score. At 2 hours post dose (primary efficacy endpoint), a significant improvement from baseline in PEC total score was observed in the 60 µg group compared with placebo (least squares mean difference from placebo: 4.2, P = 0.0011). The response rates (≥40% reduction in PEC score from baseline) were 70% in the 60 µg group and 7% with placebo (P=0.0004). Significant and clinically meaningful improvements from baseline in PEC total scores were also observed at 1, 4, and 8 hours post-dose. In the 40 µg group, which was tested separately vs placebo, significant improvements from baseline in PEC total score were observed at 1, 2, and 4 hours (least squares mean difference from placebo at 2 hours: 5.2, P=0.0002). The response rate in this group was 39% vs 9% for placebo (P=0.0351). No significant differences from placebo were observed in the 30 µg group. The PEC data were also supported by PAS and other efficacy outcome measures.

BXCL501 doses of 30, 40, and 60 µg were well tolerated in this patient population. None of the observed TEAEs were severe and no subjects discontinued the study due to an AE. The most frequently reported TEAE in the BXCL501 30, 40, and 60 µg treatment groups was somnolence (56.3%, 34.8%, and 60.0%, respectively); the incidence was 5.4% with placebo. All cases of somnolence were considered to be mild in severity, with the exception of one moderate case in the 60 µg group. Hypotension was reported in 2 subjects each in 40 µg and 60 µg groups, and in no subjects treated with placebo. One patient each in the 30 µg and 60 µg groups experienced orthostatic hypotension and one patient in the 60 µg group experienced mild bradycardia. No cases of syncope or falls were reported in any of the groups.

Conclusions: There are currently no FDA-approved treatments for acute management of agitation in elderly patients with dementia. In this study, BXCL501 60 µg and 40 µg significantly reduced the symptoms of agitation at 2 hours after administration in this patient population, as measured by PEC. At those doses, the treatments were relatively well tolerated. Based on this study, these two doses were chosen for the Phase 3 program.

T71. LB-102, A NOVEL BENZAMIDE FOR THE TREATMENT OF SCHIZOPHRENIA: SAFETY AND DOPAMINE RECEPTOR OCCUPANCY DATA FROM TWO CLINICAL STUDIES

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Abstract: Background: There is substantial evidence that the dopaminergic system is hyper-responsive in schizophrenia and the current approved antipsychotic drugs block DA D2 receptors at clinically effective doses. LB-102 (N-methyl amisulpride) is a novel dopamine D2/3/5HT7 antagonist currently being developed as a treatment for schizophrenia. LB-102 has

been studied in a pair of clinical trials evaluating both its safety and its ability to engage dopamine receptors. A Phase 2 clinical study evaluating the efficacy and safety of LB-102 in schizophrenia patients is underway and results are expected in the second half of 2025.

Methods: LB-102-001 was a phase 1 clinical study (NCT04187560) in 64 healthy volunteers [1]. This was a double-blind, placebo-controlled, study in which subjects were randomized 3:1 to receive either single or multiple ascending doses of LB-102 or placebo. Subjects in the single ascending dose portion of the study were dosed from 10 mg/day up to 200 mg/day. Subjects in the multiple ascending dose portion of the study were dosed with oral LB-102 BID from 50 mg/day up to 200 mg/day for a week.

LB-102-002 (NCT04588129) was a positron emission tomography (PET) study using

11C raclopride as a radiotracer to measure dopamine receptor occupancy (RO): for dopamine inhibitors in the treatment of schizophrenia dopamine RO in the 60% ~ 80% range is typically desired to maximize improvements in symptoms of schizophrenia [2], with the risk of extrapyramidal symptoms (EPS) increasing as dopamine RO surpasses 80% [3]. Sixteen healthy volunteers in the study were dosed with either single oral doses of LB-102, from 50 mg to 100 mg, or with 4 daily doses of LB-102 QD, at 50 mg/day and 100 mg/day, to measure RO under steady-state conditions. PET scans measured dopamine RO over the course of 90 minutes starting at baseline and at 2.5, 7.5, 23.5, or 47.5 h post-dose. PK samples were drawn from subjects contemporaneously to measure LB-102 plasma concentration.

Results: For LB-102-001 plasma PK parameters measured in this study showed that Tmax was 3 h post dose and that LB-102 had a half-life of ~13 hours. Unexpectedly, comparison of the AUC of a single 50 mg dose of LB-102 to published data [4] on the same dose of amisulpride from an earlier clinical study showed that plasma exposure of LB-102 was 2.5X > that for amisulpride. LB-102 was safe and well-tolerated up to 150 mg/day with prolactin was elevated at all doses and was independent of dose, consistent with amisulpride. There were four reports of acute dystonia, all at doses ≥ 150 mg/day. In LB-102-002 steady-state QD dosing of 50 mg LB-102, striatal dopamine occupancy (RO) reached the optimal range of 60-80% [3.5], over the course of the course of 24 hours. Importantly, data from this study suggested that LB-102 could be dosed QD as opposed to BID as it typically the case with amisulpride. Contrary to usual RO vs plasma concentrations, maximum dopamine RO significantly lagged maximum plasma concentration (as expected based on prior modeling). LB-102 was safe and well-tolerated at all doses.

Conclusions: LB-102 was safe and well-tolerated up to 150 mg/day and showed dopamine RO in the desired 60 to 80% rage under steady-state conditions at 50 mg/day. Unlike most SCZ treatments, dopamine RO of LB-102 was consistent 24 h post dose; consistent dopamine RO may be one of the contributing factors to the greater efficacy of long-acting injections in treating SCZ. A large Phase 2 clinical study, LB-102-003 (NCT06179108), is currently enrolling 350 schizophrenia patients at 25 sites in the USA. This is a double-blind, placebo-controlled (patients are randomized 3:3:3:1 placebo:50 mg:75 mg:100 mg LB-102 QD) with change in PANSS from baseline at 4 weeks as the primary endpoint.

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T72. A RANDOMIZED PLACEBO-CONTROLLED PHASE 2 TRIAL OF NAVACAPRANT, A NOVEL AND SELECTIVE KAPPA OPIOID RECEPTOR ANTAGONIST, IN MAJOR DEPRESSIVE DISORDER

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Abstract Background: Major depressive disorder (MDD) affects over 21 million U.S. adults and is a leading cause of disability, morbidity, and mortality. A significant unmet need remains for patients with MDD as many do not respond to existing first-line pharmacotherapies and experience side effects. In addition, anhedonia, a core symptom of depression affecting 70% of patients, is not adequately treated with existing therapies. Kappa opioid receptors (KORs) are novel targets that are abundantly expressed in brain circuits regulating mood, cognition, reward, and behavior. KOR antagonists are believed to restore the regulation of multiple neurotransmitters including dopamine in pathways that play a role in regulating mood, reward, and cognition. Navacaprant (NMRA-140, BTRX-335140) is a novel, potent, highly selective KOR antagonist with no agonist activity at kappa, mu, or delta opioid receptors that is in development to treat the symptoms of MDD.

Methods: Participants (18-65 y) were randomized 1:1 to 8 weeks of once-daily oral navacaprant (80 mg) or placebo (PBO) in this randomized, double-blind, placebo-controlled study. The primary endpoint was changed from baseline (CFB) to Wk 8 in the 17-item Hamilton Depression Rating Scale (HAMD-17). Secondary endpoints included CFB in Snaith-Hamilton Pleasure Scale (SHAPS) and HAMD-17 response (≥50% decrease from baseline [BL]) and remission (score ≤7) rates at Wks 4 and 8. The primary efficacy analysis used mixed-models-repeated-measures (MMRM). Since ≥10% of patients had missing data, a prespecified last-observation-carried-forward (LOCF) analysis was also used for the primary/secondary endpoints. A prespecified analysis also evaluated the efficacy of navacaprant in patients with moderate-to-severe MDD.

Results: 204 patients from 31 US sites were randomized (102 in each group). For the MMRM analysis of HAMD-17 CFB (n=171), navacaprant was superior to PBO at Wk 4 (least squares mean difference, LSMD [SE] -2.7 [0.90], P=0.003) but not Wk 8 (-1.7 [1.08], P=0.121; primary endpoint). Due to ≥10% missing data, LOCF analyses were performed. A statistically significant improvement in the HAMD-17 was detected at Wks 4 and 8 (-2.9 [0.88], P=0.002

and -2.2 [0.98], P=0.024). For SHAPS CFB, navacaprant was superior to PBO at Wks 4 and 8 (-2.8 [0.96], P=0.004 and -3.4 [1.10], P=0.002). In patients with moderate -to-severe MDD (BL HAMD-17 ≥22; n=100), navacaprant was superior to PBO for HAMD-17 CFB at Wks 4 and 8 (-3.0 [1.20], P=0.015 and 2.8 [1.33], P=0.037). For SHAPS CFB in this subgroup, a trend favoring navacaprant was seen at Wk 4 (LSMD [SE] -2.4 [1.31], P=0.071) and a significant difference was seen at Wk 8 (-4.8 [1.35], P=0.001). Significant benefit of navacaprant was also observed for HAMD-17 response and remission rates in this subgroup. Response rate differences were 21.4% (95% CI 6.1–36.8%, P=0.010) at Wk 4 and 25.9% (8.1–43.7%, P=0.007) at Wk 8, and remission rate differences were 14.9% (3.9–25.8%, P=0.014) at Wk 4 and 20.3% (7.3–33.2%, P=0.005) at Wk 8. TEAE incidence was lower with navacaprant (35.3%) vs PBO (44.1%).

Conclusions: Navacaprant was associated with statistically significant reductions in depressive symptoms including anhedonia in participants with moderate-to-severe MDD and a favorable safety profile. The clinical relevance of the efficacy findings is underscored by the superior response and remission rates observed with navacaprant. These data support the further development of navacaprant as monotherapy in MDD.

T73. ENHANCING ACCESS TO CARE AS WELL AS PATIENT EDUCATION FOR BIPOLAR DISORDER WITH GROUP MEDICAL VISITS / SHARED MEDICAL APPOINTMENTS

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Abstract: Group Medical Visits (GMVs), also known as Shared Medical Appointments, is a newer model of care that usually involves two clinicians providing individual patient care within a group consisting of patients with a similar disorder, together with group education and discussion of illness self-management skills. We adapted a model created by Remick and colleagues for mood and anxiety disorders to a specific model for bipolar disorder, utilizing a staff psychiatrist and resident psychiatrist treatment team. Here, we report on patient evaluation of the model that we launched several years ago. Our presentation will detail the format of GMVs, how to run GMVs, and its outcomes.

Methods: The Bipolar Group Medical Visits (GMVs) program includes approximately 50 patients who obtain psychiatric medical care exclusively within this model. The 39 individuals who attended a GMV in the past two years were invited to participate in this study. Patients completed a questionnaire with 25 quantitative items and 3 qualitative items covering patient satisfaction (using the Client Satisfaction Questionnaire), clinical value of GMVs model, challenges/benefits for program users, and the current state of their bipolar treatment.

Results: 24/39 (61.5%) patients responded, reporting high satisfaction on the Client Satisfaction Questionnaire (an average score of 30.29 out of 32). Patients reported (1) feeling supported by other group members (70.8%), (2) receiving additional value from receiving care in the group (83%), (3) easier access to care due to the group (70.8%), and (4) learning new strategies/information from other group members (70.8%). The most common challenge reported was the time and length of the group appointment (2 and 5 mentions, respectively).

Conclusions: Patients rated Group Medical Visits as a valuable method of receiving care, having unique benefits compared to the traditional one-on-one format, and provided avenues to explore for improving the program. Such pilot data, as well as our earlier reported favorable evaluation of GMVs as an educational modality by residents, support additional expansion and evaluation of GMVs. Widespread adoption of GMVs offers the possibility of substantial improvement in access to care.

T74. CLINICAL OUTCOMES IN THE BIOMARKERS OF KETAMINE (BIO-K) STUDY OF OPEN-LABEL IV KETAMINE FOR REFRACTORY DEPRESSION

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Abstract: Objective: We conducted an open-label clinical trial ("Bio-K") using IV ketamine for treatment-resistant depression to identify biomarkers linked to remission. Here, we report the clinical efficacy and side effect outcomes of Bio-K.

Methods: Across 4 US sites, 75 patients ages 18 – 65 with treatment-refractory unipolar or bipolar depression received 3 IV ketamine infusions over an 11-day period. Key exclusion criteria were psychotic symptoms, significant substance abuse, unstable medical conditions, and any use of cannabis. Pre-existing antidepressant medication was maintained. Primary outcome was remission as measured by Montgomery-Asberg Depression Rating Scale (MADRS), with secondary outcome of 50% reduction in Beck Suicide Scale score. Safety monitoring and varying durations of infusions were also key parameters.

Results: Using remission as MADRS score $<$ 10, after 3 infusions 52% achieved remission, with 67% achieving response. Of those achieving response after a single infusion, 66% (22 of 33) reached remission after 3 infusions, while 40% (16 of 40) non-responders after the first infusion went on to achieve remission after 3 infusions. Only 20% of non-responders after 2 infusions achieved remission. Most (81%) participants had significant suicidal ideation at baseline; of these, two-thirds (67%) experienced at least a 50% reduction in suicidality. Side effects were minimal. Uniquely, we had three different types of infusion categories, with individuals receiving: (1) slow (100-minute) infusions only or (2) regular (40-minute) infusions only or (3) a mix of infusion durations. These three infusion groups showed comparable safety and efficacy. Exploration of clinical factors revealed no link between BMI, age, or gender to remission.

Conclusions: The consistency of outcomes across 4 clinical sites and across multiple instruments, suggests high acute efficacy and safety of IV ketamine for serious depressive episodes. Duration of infusion did not alter outcomes. Meaningfully, 40% of non-responders after a single infusion did reach remission subsequently, while only 20% of non-responders after 2 infusions achieved remission, suggesting early response is suggestive for eventual remission. Our data on varying ketamine infusion duration adds novel insights into the clinical administration of this new treatment for refractory and severe patients. Our limitations included a lack of a control group, necessitating caution about conclusions of efficacy, balanced by the

utility of reporting “real-world” outcomes across multiple clinical sites. We could also not separately analyze results for bipolar disorder due to small numbers. Together, the Bio-K clinical results are promising and provide significant sample sizes for forthcoming biological markers analyses.

T75. USE AND EXPERIENCE OF EUROPEAN HEALTHCARE PROFESSIONALS WITH ARIPIPRAZOLE ONCE-MONTHLY 400 MG TWO-INJECTION START INITIATION REGIMEN IN ADULT PATIENTS WITH SCHIZOPHRENIA

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Abstract Aripiprazole once monthly 400mg (AOM400) is a commonly used long-acting injectable (LAI) for the maintenance treatment of adult patients with schizophrenia. The AOM400 two-injection start initiation regimen (AOM400-TIS) is available as an alternative to the one-injection start plus 14-days oral supplementation initiation regimen. This survey investigated the views and experiences of European healthcare professionals (HCPs) with AOM400-TIS.

HCPs in Italy, Germany and the United Kingdom (UK) who had prescribed and/or administered the AOM400-TIS regimen to ≥3 patients with schizophrenia were invited to participate in an online survey. The survey aimed to gain insight into HCPs' perspectives and attitudes towards prescribing and/or administering AOM400-TIS according to the European label in clinical practice, including reasons for its use and potential benefits, as well as common barriers and/or concerns. Descriptive analysis was performed on data collected between February 1–March 7, 2024.

The analysis included 89 HCPs, 34% from the UK, 34% from Italy and 33% from Germany; 63% were psychiatrists, 29% psychiatric nurses, 7% community nurses and 1% general practitioners/primary care physicians. 62% worked primarily in a specialist mental health clinic, 34% in inpatient hospital settings, 24% in outpatient hospital settings, 7% in general practice and 6% other. The median number of years in practice was 21.0 (range: 3.0-53.0). HCPs estimated that the median proportion of patients in their caseload diagnosed with schizophrenia was 30% (IQR: 20.0-60.0), and of these patients, 30% were treated with LAIs (IQR: 20.0-50.0). 44% of HCPs were primarily responsible for prescribing AOM400-TIS, 28% for administering it, and 28% were responsible for both. Most HCPs (44%) estimated that they had started prescribing and/or administering AOM400-TIS more than 24 months ago. HCPs estimated that 42% of patients typically spent 14-28 days on oral aripiprazole prior to initiation with AOM400-TIS, with HCPs rating the severity of symptoms of patients initiated with AOM400-TIS as moderate (67% of HCPs), severe (44% of HCPs), and mild (15% of HCPs). 80% of HCPs reported typically prescribing the AOM400-TIS regimen in an outpatient setting and 52% in an inpatient setting (multiple selections were possible).

The three most common reasons for initiating patients with AOM400-TIS after transitioning from oral aripiprazole were poor adherence (85%), relapse(s) (60%), and patient preference

(47%), and the three most commonly reported goals for prescribing AOM400-TIS were to improve adherence (72%), prevent relapses (70%), and improve quality of life (62%). Common barriers to the use of AOM400-TIS were patient reluctance to receive two injections (66%), concerns about tolerability (30%), and safety of administering a high dose in a single day (30%). Prior treatment adherence (56%) and efficacy (47%) were the most cited factors influencing prescribing of AOM400-TIS. Overall, HCPs "agreed" or "strongly agreed" that AOM400-TIS was easy to administer (80%) and that it had a similar safety/tolerability profile to the one-injection start initiation regimen (69%), while the majority were satisfied with patient outcomes with AOM400-TIS (83%).

Overall, HCPs in Italy, Germany and the UK with experience of using AOM400-TIS reported that it is easy to administer, well tolerated and improves treatment outcomes, while barriers to its use include patient reluctance and perceived safety concerns.

T76. RESPONSE TO KARXT IN SHORT-TERM PLACEBO-CONTROLLED TRIALS IN SCHIZOPHRENIA

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Abstract Background: KarXT (xanomeline and trospium chloride) is an investigational M1 /M4 preferring central muscarinic receptor agonist that was found to reduce psychosis symptoms in three acute trials. Findings from the EMERGENT program (randomized, double-blind, placebo-controlled, 5-week inpatient trials in people with schizophrenia experiencing acute psychosis) showed that KarXT significantly reduced Positive and Negative Syndrome Scale (PANSS) scores compared to placebo in acute schizophrenia. However, there likely is variability in treatment response. Here we characterize differences in percent improvement in psychosis symptoms during a 5-week trial, as well as factors that may distinguish responders and non-responders.

Methods: Data from EMERGENT-1 (NCT03697252), EMERGENT-2 (NCT04659161), and EMERGENT-3 (NCT04738123) were pooled across participants randomized to KarXT (N=314) or placebo (N=326) with both a baseline and at least one postbaseline PANSS score. PANSS scores were floor-adjusted, converted to percent change from baseline, and imputed with the last observation carried forward to the end of the study (Day 35). As described in the statistical analysis plan, participants who showed a ≥30% reduction in PANSS total score were identified as "responders". The Cochran-Mantel-Haenszel test was used to determine whether the KarXT and placebo groups differed by responder status at each study visit. Two-tailed t-tests were used to perform follow-up comparisons between Day 35 responders and non-responders based on age, body mass index (BMI), and baseline PANSS total score, while chi-squared tests were used to compare race and sex.

Results: 91.7% of participants on KarXT (compared to 78.2% of participants on placebo) showed a reduction in PANSS total score by the end of treatment. Rate differences in ≥30% responder status between KarXT and placebo were observed at study Day 14 (.068; p=.0144), Day 21 (.105; p=.006), Day 28 (.179; $p < .0001$), and Day 35 (.205; $p < .0001$). At the end of treatment, 41.4% of participants on KarXT compared to 20.9% of participants on placebo showed ≥30% reduction in PANSS total score. In the KarXT group, no factors at baseline (including age, sex, race, BMI, or baseline PANSS score) differentiated Day 35 responders and non-responders (all p's $> .24$). In the placebo group, baseline PANSS scores were lower in

responders compared to non-responders at Day 35 (t=2.54; p=.01) but did not statistically differ on other baseline factors (all p's > .11).

Conclusion: In short-term placebo-controlled trials in schizophrenia, a 30% or greater reduction in symptoms was observed in nearly twice as many people assigned to KarXT (41.4%) compared to placebo (20.9%). This result is comparable to established antipsychotics such as aripiprozole and risperdone, which have shown similar response rates in short-term placebo-controlled trials, although no head-to-head trials have been completed to date. No clinical or demographic factors measured at baseline distinguished KarXT responders from non-responders. Together these findings demonstrate that KarXT may provide a robust and clinically meaningful benefit to people with acute schizophrenia, regardless of their demographic or clinical history.

T77. FUNCTIONAL AND SEXUAL DISABILITY, AND QUALITY OF LIFE AFTER ONE DOSE OF MM120 (LYSERGIDE D-TARTRATE) IN ADULTS WITH GENERALIZED ANXIETY DISORDER

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Abstract Background: Generalized Anxiety Disorder (GAD) is one of the most common psychiatric disorders and is associated with a reduced quality of life (QoL), psychosocial functioning, and work productivity. It is a chronic disorder that is characterized by excessive worry and apprehension accompanied by somatic symptoms, including fatigue, muscle tension, irritability, and sleep disturbances. Current treatments frequently fail to alleviate symptoms that affect patients' QoL, and in many cases have been determined to cause sexual dysfunction (SD). We evaluated the efficacy of a single administration of MM120 (lysergide D-tartrate) on functional disability (FD), SD, and QoL in participants with GAD.

Methods: In this multicenter, randomized, double-blind, placebo-controlled study, 198 participants aged 18 to 74 years with GAD and moderate to severe anxiety as indicated by a Hamilton Anxiety Rating Scale (HAM-A) score ≥20 were randomized evenly across study arms to receive a single administration of MM120 at doses of 25µg (n=39), 50µg (n=40), 100µg (n=40), or 200µg (n=40) or placebo (n=39). The effect of MM120 on FD as measured by the Sheehan Disability Scale (SDS), QoL as measured by EQ-5D-5L, and the Pittsburgh Sleep Quality Index (PSQI), and sexual function as measured by the Arizona Sexual Experiences Questionnaire (ASEX) were assessed throughout the trial (weeks 1, 2, 4, 8 and 12).

Results: The MM120 100µg and 200µg doses demonstrated consistent improvements in FD. These improvements were evident as early as 1 week post dose and were sustained through week 12. The MM120 100µg dose, which was found to have the optimal level of clinical activity on the HAM-A, showed a placebo-adjusted improvement of 7.17 (-14.6 MM120 vs -7.4 placebo) and 6.86 (-15.1 MM120 vs -8.2 placebo) points at weeks 1 and 12, respectively, post dose. Similar improvements in the SDS score were observed with MM120 200µg. On the EQ-5D-5L, MM120 100µg demonstrated placebo-adjusted improvements in utility index scores of 0.111, 0.081, and 0.116 points at weeks 4, 8, and 12 post dose. On the visual analog scale (VAS) of the EQ, a measure of the participant's self-rated health, MM120 100µg

demonstrated placebo-adjusted improvements of 4.02, 5.41, and 6.04 points at weeks 4, 8 and 12 post dose. On the PSQI, there was an improvement at weeks 4, 8 and 12 across all groups including placebo. Results from the ASEX demonstrated that at week 12, there was a considerable decrease in the proportion of male participants who had SD with MM120 100µg (29.2% at baseline vs 10% at week 12) and 200µg (41.7% at baseline vs 0 at week 12) versus placebo (15.4% at baseline vs 12.5% at week 12). Similar decreases from baseline were observed in the proportion of female participants who had SD at week 12 in the MM120 100µg (75% at baseline vs 46.2% at week 12) and 200µg (57.1% at baseline vs 33.3% at week 12) groups versus placebo (50% at baseline vs 33.3% at week 12).

Conclusion: Overall, MM120 demonstrated rapid and durable improvements in anxiety, and demonstrated clinically meaningful improvements in FD, SD, and QoL, which represents a significant distinction from existing standard of care treatments.

Funding: Mind Medicine (MindMed), Inc supported this study.

Trial registration: NCT05407064 A Dose-Finding Study of MM-120 (LSD D-Tartrate) for the Treatment of Anxiety Symptoms.

T78. MEASUREMENT OF POSITIVE AND NEGATIVE SYMPTOMS THROUGH SPEECH ANALYSIS FROM PANSS INTERVIEW RECORDINGS IN PATIENTS WITH SCHIZOPHRENIA

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Abstract Background: Speech is a clinically meaningful indicator of schizophrenia symptom severity. Measures such as poverty of speech, pause characteristics, emotional sentiment, lexical richness, tangentiality, and loose associations have been shown to be indicative of symptom severity. Quantifying these measures through digital health technologies has applications in patient recruitment, trial enrichment, and measurement of treatment progression. However, collecting these measures has historically required dedicated speech collection platforms, which introduce burden to patients and clinicians. In this study, we determine whether archival PANSS interview recordings collected for quality assurance purposes allow for quantification of clinically meaningful speech measures in patients with schizophrenia.

Methods: As part of a 5-week Phase 2 clinical trial of KarXT in 182 patients with schizophrenia, PANSS administrations were audio recorded as part of routine practice. The recordings were subsequently processed for speech measures of schizophrenia. Notably, the processing was done locally by Signant Health, the eCOA vendor, using software licensed from Brooklyn Health built atop OpenWillis, an opensource library for digital phenotyping (www.github.com/bklynhlth/openwillis). The processing resulted in de-identified speech measures sharable externally for further analysis. The analysis included ordinary least squares multiple regressions to assess the relationship between each speech measure as the independent variable and PANSS positive and negative subscale scores as the dependent variable, with age, biological sex, and race as covariates.

Results: The list of measures extracted can be found in the OpenWillis documentation. Across timepoints, speech measures were significantly associated with PANSS scores. Positive symptom severity was associated with increased amount of speech ($\beta = 19.7$, $p < 0.001$), shorter pauses ($\beta = -10.0$, $p = 0.005$), decreased use of nouns ($\beta = -0.6$, $p < 0.001$), increased use of pronouns ($\beta = 0.59$, $p < 0.001$), and decreased lexical richness ($\beta = -19.3$, $p < 0.001$). Negative symptom severity was associated with decreased speech ($\beta = -10.1$, $p = 0.005$), increased pause lengths ($\beta = 11.2$, $p < 0.001$), and greater negative sentiment ($\beta = 24.9$, $p = 0.029$).

Conclusions: In line with existing literature, we observed significant relationships between digital health measures and PANSS scores, providing further evidence for the clinical validity of these measures in assessing symptom severity. Importantly, we also demonstrated the feasibility of using archival clinical interview recordings to process meaningful speech measures with no additional burden to clinicians or patients. We believe analysis of PANSS recordings allowed for one of the largest data samples for processing of speech measures of schizophrenia reported in the literature. Though this analysis was retrospective, processing of speech measures from clinical interview recordings can be conducted in near-real-time as clinical interviews are conducted during regular operations of a clinical trial. Access to these measures allows for informed decision-making during recruitment and screening along with their inclusion in more comprehensive models of disease severity that could serve as digital endpoints.

T79. PREVALENCE AND CORRELATES OF COGNITIVE IMPAIRMENT IN DEPRESSION: FINDINGS FROM THE TEXAS RESILIENCE AGAINST DEPRESSION STUDY

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Abstract Background: Cognitive dysfunction is common in those with major depressive disorder (MDD) and is associated with worse clinical and functional outcomes. And yet, prevalence of objective cognitive impairment in depression is poorly understood, with estimates ranging between 30-60%. Prior studies have been limited by smaller samples or have used a fixed criteria for cognitive impairment without taking into consideration premorbid functioning – an important consideration and more sensitive approach for the identification of cognitive impairment.

Methods: This analysis used data from the Texas Resilience Against Depression (T-RAD) study, a large observational study of individuals who have a past or current depression. The current study included patients with a current primary diagnosis of depression and who completed the National Institute of Health Toolbox – Cognition Battery (NIHTB-CB), a well-validated measure of cognitive functioning. Patients were classified as having cognitive impairment if they performed approximately one standard deviation below their premorbid functioning on two or more tests (Holdnack et al., 2017). Participants also completed several clinical, functioning, and impairment measures.

Results: Analyses included 378 patients aged 18+, of which 48% met criteria for cognitive impairment. Prevalence of cognitive impairment was similar across all age groups and was

similar in those with mild symptoms of depression (45%) and those with moderate-to-severe symptoms (50%). Groups did not differ in demographic characteristics or in depression severity (all $p > 0.067$). After adjusting for multiple comparisons, patients with cognitive impairment reported greater anhedonia on the Dimensional Anhedonia Rating Scale and worse quality of life on the WHO Quality of Life BREF. Moreover, patients with cognitive impairment were more likely to be unemployed and report worse impairment in activities than those without cognitive impairment.

Conclusions: These findings suggest that objectively determined cognitive impairment is present in approximately half of all individuals with depression, regardless of current clinical severity. These impairments are present across the adult lifespan and are associated with worse quality of life and greater functional impairment. Given that cognitive impairment in depression is associated with poorer treatment outcomes, these findings suggest that cognitive impairment may be an important factor in explaining poorer outcomes given its prevalence in the77epresssed population.

T80. α-TUBULIN POST-TRANSLATIONAL MODIFICATIONS AS POTENTIAL TRANSLATIONAL BIOMARKERS IN MAJOR DEPRESSIVE DISORDER

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Abstract Background: Neuronal microtubules (MTs) are cytoskeletal protein elements, which are comprised of the tightly regulated polymerization of α- and β-tubulin dimers, both of which are subject to post-translational modifications (PTMs). Neurons possess two compartmentalized pools of MTs, less and more dynamic, and α-tubulin PTMs such as tyrosination and acetylation are associates with the dynamic status. Increased levels of MT dynamics are required for structural neuronal plasticity phenomena. α-Tubulin acetylation at Lys40, tyrosination and detyrosination at the C-terminus generate Acet-Tub, Tyr-Tub and Glu-Tub respectively, which are hallmarks of less or more dynamic MTs. Specifically, increases in the Acet/total **α**-tubulin ratio and decreases in the Tyr/Glu-Tub ratio indicate a shift towards less dynamic MTs. Dysregulation of **α-**tubulin PTMs may be associated with neuropsychiatric disorders characterized by synaptic pathology, including major depressive disorder (MDD).

Methods: α-Tubulin PTM ratios (Acet/Tot-Tub; Tyr/Glu-Tub) were measured using infrared western blot (IFWB) in plasma of subjects diagnosed with moderate (N=37) or severe MDD (N=35) and compared with healthy controls (N=40). A comparison of post-mortem hippocampal brain tissue α-tubulin PTM ratios of MDD subjects (N=12) and healthy controls (N=8) was performed using IFWB.

Results: Tyr/Glu-Tub was significantly decreased in the plasma of moderate and severe female MDD subjects compared with healthy controls ($p < 0.01$), but not in males. When combined, Tyr/Glu-Tub was significantly lower in the plasma of moderate and severe MDD subjects compared with healthy controls ($p < 0.01$). Tyr/Glu-Tub was significantly negatively correlated with HAM-D score clinical depression score ($r=-0.1068$, $p < 0.05$). Although Acet-Tub/Total-Tub was not significantly altered between control and MDD groups, subjects with severe MDD showed a trend towards lower plasma Acet-Tub/Total-Tub compared with moderate patients for both male ($p=0.05$) and combined cohorts ($p=0.07$). In a post-mortem brain tissue comparison of MDD vs healthy control subjects, there was a trend of increased Acet-Tub/Total Tub and decreased Tyr/Glu-Tub in the hippocampus.

Conclusions: Previous studies indicate decreased brain microtubule dynamics in animal models of depression which can be rescued by antidepressant treatment (Barbiero et al., 2022). Recent data show decreased plasma Acet-Tub in healthy volunteers treated acutely with the antidepressant dose of ketamine (Colic et al., 2019). The decrease in plasma and post-mortem tissue Tyr/Glu-Tub in MDD subjects indicates that they have less dynamic microtubules. Less dynamic MTs are associated with reduced synaptic plasticity and behavioral and cognitive impairments. The increase in post-mortem Acet-Tub supports decreased MT dynamics although there is a trend of a decrease in plasma Acet-Tub. Together, the data suggest a potentially dysfunctional MT state, even if not clearly defined, and the association with MTs adopting a less dynamic state in MDD **α-**tubulin. **α-**Tubulin PTMs represent a potential plasma biomarker of disease progression in neuropsychiatric disease and MTs may serve as a novel therapeutic target.

Barbiero I, et al. Therapeutic potential of pregnenolone and pregnenolone methyl ether on depressive and CDKL5 deficiency disorders: Focus on microtubule targeting. J Neuroendocrinol. 2022 Feb;34(2):e13033.

Colic L, et al. Neuronal glutamatergic changes and peripheral markers of cytoskeleton dynamics change synchronically 24 h after sub-anaesthetic dose of ketamine in healthy subjects. Behav Brain Res. 2019 Feb 1;359:312-319.

T81. THE SEATTLE TRAUMA NIGHTMARE INDEX: A NOVEL, QUANTITATIVE SELF-REPORT FOR TRAUMA NIGHTMARES AND SLEEP DISRUPTIONS

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Abstract: Sleep disruption is a key feature of posttraumatic stress disorder (PTSD), including symptoms such as persistent nightmares, repeated awakenings, and REM without atonia. While sleep disruption after trauma is often associated with poorer outcomes, treatment of sleep disturbances can be associated with improvement of both nighttime and daytime symptoms, making sensitive assessment of trauma-related sleep disruption relevant to both diagnosis/prognosis and the assessment of treatment response. Finally, increasing evidence suggests that there is significant heterogeneity in both the underlying pathobiology of PTSD and the response of PTSD symptoms to the noradrenergic antagonist prazosin. This raises the possibility that there may be specific characteristics of trauma-related sleep disruption that vary among individuals, and which may hold predictive value for treatment response.

The Seattle Trauma Nightmare Index (STNI) was developed as a low-burden quantitative self-report questionnaire measuring trauma nightmares and sleep-related hyperarousal. The STNI in particular captures characteristics of trauma-related sleep disruption observed in previous work to be either highly responsive to treatment with prazosin, or to be associated in post hoc analyses with an increased likelihood of response to prazosin.

Here, we provide an initial psychometric validation of the STNI. Based on self-report measures collected from a survey of healthcare workers (N=534), we compare the STNI to other self-report measures including (PCL-5 [PTSD]; ISI [insomnia]; GAD-7 [anxiety]; PHQ-9 [depression]). The original 11-item version of the STNI was found to be strongly associated with insomnia (r=.56), depression (r=.63), and anxiety (r=.65) with its strongest correlate being

PTSD (r=.76). The STNI identified individuals whose PCL-5 response suggested a probable PTSD diagnosis with a sensitivity of 0.80 and a specificity of 0.82, and was internally consistent (α=0.89; ω=0.91).

The STNI was further examined using exploratory factor analysis, which, after item reduction to a 9-item instrument, yielded three factors: traumatic dream intensity, sleep-related hyperarousal, and excessive movement during sleep. This factor structure was cross validated using confirmatory factor analysis, where, based on measures of goodness-of-fit, it was found to be well-fitting (RMSEA: .038; CFI: .999; GFI: .997; Chi-square: .103).

These results support the psychometric validity of the STNI, and its potential use to assess trauma-related sleep disruption. Next steps will include validation in a Veteran population and using the CAPS-5 to diagnose PTSD, a prospective test of the relationship of STNI total and factor scores to individuals' overall response of PTSD to treatment with prazosin, and exploration of the relationship of the STNI to quantitative measures of sleep disruption including actigraphy and polysomnography, physiological measures of the autonomic regulation, and biomarkers of noradrenergic signaling.

T82. EVALUATION OF PSYCHOSOCIAL AND BIOLOGICAL MARKERS OF VULNERABILITY FOR DEPRESSIVE SYMPTOMS DURING PREGNANCY: PRELIMINARY FINDINGS FROM THE STUDY PRESENT

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Abstract Background: The perinatal period represents a window of vulnerability for the development of psychiatric disorders due to the significant physiological changes that occur in women's bodies, affecting especially their metabolism, immune system and hormonal profile [1]; however, some women appear to be more vulnerable than others. Importantly, a history of psychiatric disorders or childhood trauma are major risk factors for perinatal depressive symptoms [2].

Method: From hospitals and family counselling centres of Bergamo's territory (northern Italy) a total of 75 pregnant women were recruited and evaluated for clinical, psychosocial and obstetric variables through a battery of questionnaires. Based on psychological assessments, 25 women were classified as depressed, whereas, among non-depressed, 25 were at-risk for depression in pregnancy due to previously experienced psychiatric problems or childhood trauma, while 25 were classified as controls. Plasma and serum samples were collected at the 25th and 32nd gestation weeks and used to measure a panel of pro- and anti-inflammatory cytokines, as well as hormones, such as cortisol, oestradiol, progesterone and thyroid hormones, with the Luminex Multiplex Immunoassay.

Results: Based on preliminary collected data, anxiety levels, perceived stress, history of past spontaneous abortion resulted significantly different among groups. Biological analyses are still ongoing; however, preliminary results suggest an increase in some pro-inflammatory cytokines, including IFNγ, IL2, IL-1β, TNFα, IL17A, IL21, and reduced levels of anti-inflammatory IL-10, in depressed and at-risk women, compared with controls, respectively.

Conclusion: Depression in pregnancy heavily impairs the health of both affected women and their babies, hence early identification and preventive measures are of utmost importance. Psychosocial and obstetric factors can help stratify these women. However, it is necessary to identify underlying biological alterations that could represent reliable biomarkers of vulnerability, and, in this regard, the immune and the hormonal systems are putative targets to study.

T83. SHOULD PSYCHOSIS BE TREATED WITH TPA LIKE A STROKE? EVIDENCE FOR PATHOLOGICAL COAGULOPATHY IN PSYCHOSIS

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Abstract Background: Many published studies report that antipsychotic therapy is associated with a state of hypercoagulability. However, fewer studies have examined whether increased coagulability exists in unmedicated schizophrenia (SZ) or other psychoses. Some studies have reported a full remission of psychotic symptoms with warfarin, a well-known anti-coagulant, raising the possibility that psychosis may be associated with coagulopathy. Here, we summarize the available literature on biomarkers of coagulopathy in unmedicated patients with SZ and other psychoses.

Methods: A PubMed search using the keywords "psychosis" OR "schizophrenia" AND ("coagulation" OR "tissue plasminogen activator" OR "thromboembolism") for studies published between 2012 and 2023 yielded 290 results. Studies were included for final analysis if they were (1) controlled studies; (2) reported on individuals with a clinical diagnosis of schizophrenia or psychoses related to psychiatric illness; (3) in the English language. Studies were excluded from review if they (1) were review articles; (2) case reports; (3) animal studies; (4) focused on antipsychotics as a factor in coagulopathy.

Results: Seven studies met study criteria and were included for qualitative synthesis in this review. Five studies included patients with SZ and related psychoses, while two studies also included patients with major depression and bipolar disorders. Numerous plasma proteins involved in regulating coagulation were identified as being low in patients with SZ, including thrombolytic agents such as tissue-type plasminogen activator (tPA), plasmin, protein S, and plasminogen, although one study found that tPA was reduced in chronic SZ but elevated in first-episode SZ (FES) patients. Contributing to a hypercoagulable state, FES patients had elevated levels of plasminogen activator inhibitor-1 (PAI-1) and soluble P-selectin (sP-sel), as well as a higher PAI-1/tPA ratio. The risk of deep vein thrombosis and pulmonary embolism was found to be relatively increased in not only individuals with SZ but those with depressive and bipolar disorders; both SZ and bipolar disorder were found to have alterations in serums proteins involved in the coagulation cascade. SZ patients had a high prevalence of markers of low tPA/plasmin, including hyperinsulinemia, hypertriglyceridemia, hyperhomocysteinemia, free-protein S deficiency, and antiphospholipid antibodies, all of which decrease or increase tPA activity or PAI-1, respectively. However, in patients with schizoaffective disorder, plasma levels of PAI-1 were found to be significantly lower than in patients with SZ. tPA was also found to be reduced in schizoaffective disorder, but not significantly so. Patients with psychosis spectrum disorders presenting with acute psychosis had increased markers of thrombogenesis, including plasma levels of D-dimers, factor VIII, and sP-sel, which were significantly increased prior to antipsychotic treatment and remained elevated one year after medication initiation.

Discussion: Taken altogether, these findings suggest that the association between hypercoagulability and psychosis spectrum disorders may not be purely iatrogenic in nature but a persistent feature of the disease. Further studies are warranted to confirm this hypothesis.

T84. PHYSICAL ACTIVITY IN INDIVIDUALS WITH SCHIZOPHRENIA

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Abstract Background: It is well documented that individuals living with schizophrenia have altered motor behavior compared to healthy controls. In general, individuals living with schizophrenia tend to spend less time in active behaviors and may exhibit unstructured, or disorganized movement when they are active. Evidence suggests that low activity in schizophrenia is associated with negative syndrome scores, and unstructured movement patterns are associated with positive syndrome scores. However, due to a lack of objective, low burden assessment modalities, insight into the physical activity profiles of people with schizophrenia have largely been limited by short investigations (e.g., 1 hour) in semi-confined environments such as in-patient treatment facilities. Digital health technologies (DHTs), such as wearable accelerometers now allow movement and behavior to be studied in free-living environments for long periods of time, as individuals go about their daily lives.
Purpose: The purpose of this pilot study was to better understand the physical activity profile of individuals with schizophrenia as they go about their daily lives. Specifically, we investigated whether activity volume was associated with disorganized movement patterns.
Methods: Three hundred and sixty-two individuals with schizophrenia wore a DHT on their wrist for 7-consecutive days. Activity volume was calculated as the average number of steps taken per day. To determine degree of disorganized behavior, activity fragmentation was calculated. Activity fragmentation was defined as the active-to-sedentary transition probability, calculated as the reciprocal of the mean stepping bout duration.
Results: Participants took an average of 8133 steps per day (SD = 4865). In terms of activity fragmentation, participants had an average active-to-sedentary transition probability of 0.57 (SD = 0.25). Activity volume was negatively correlated with activity fragmentation ($r = -0.37$, $p < .001$).
Conclusion: Although there was large between person variability, participants accumulated more steps per day than the general population, however they also exhibited a high degree of activity fragmentation. Those that took more steps per day tended to accumulate those steps in more structured walking bouts of longer duration compared to those that took fewer steps per day, however this was a weak association. These data suggest that total activity volume and activity fragmentation capture distinct characteristics of real-world physical activity in schizophrenia. Future randomized control trials should leverage the advancement of digital health technologies to better understand the physical activity profiles of individuals living with schizophrenia. Specifically, the association of both volume and pattern of activity should be investigated in relation to established clinical outcomes and their responsiveness to change.

T85. ACTION PLANS TO PROMOTE DIVERSITY, EQUITY, AND INCLUSION IN ASCP

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Abstract: The lack of diversity among biomedical researchers represents a significant equity challenge in our profession, with consequential impact on our ability to solve important health challenges affecting population groups historically excluded. The American Society of Clinical Psychopharmacology (ASCP) acknowledges this lack of representation and has an expressed commitment to supporting inclusivity of underrepresented groups.

To address such challenges, the ASCP established its Inclusivity Committee in 2018, aiming at increasing diversity among ASCP members including age, culture, ethnicity, gender, gender identity, race, and sexual orientation. Efforts of the Inclusivity Committee, and their integration into the ASCP strategic plan resulted in the following strategies: 1) collect and review demographic data from ASCP meeting attendees and members; 2)brainstorm and implement diversity initiatives; 3) promote transparency through the dissemination of ASCP membership demographics; 4) organize annual inclusivity/diversity sessions at the ASCP Annual Meeting; 5) develop guidelines for Early Career Board Member slots, and 6) promote leadership opportunities for individuals from diverse backgrounds.

The Inclusivity Committee's initiatives led to the establishment of several priorities. Preliminary updates on the strategic priorities indicate progress in several areas, such as increased diversity within leadership positions, the support for increased diversity of presenters and topic content, and the implementation of inclusivity sessions at the annual meeting.

The establishment and efforts of the ASCP Inclusivity Committee represent important steps toward addressing the critical need for diversity in the biomedical research field. The strategic plan of the ASCP Inclusivity Committee is promising in promoting inclusivity and equity within the ASCP. However, continuous evaluation and adaptation of these strategies are necessary to identify gaps, measure their impact effectively, and address new challenges as they arise. Future directions include enhancing the transparency of demographic data and further integrating diversity and inclusivity efforts into the society's core functions and strategic objectives.

T86. SEX DIFFERENCES IN THE ASSOCIATION BETWEEN IRRITABILITY AND SUICIDAL IDEATION

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Abstract Background: Irritability has been linked to higher severity of suicidal ideation (SI). However, whether this association between irritability and SI differs on the basis of sex remains unknown. Here, we evaluated whether the association between irritability and SI is different in males and females.

Method: Data for this report are obtained from an ongoing neuroimaging study of irritability (NCT05046184). Data from individuals (N=57) with ratings of irritability (Concise Associated Symptom Tracking Irritability domain; CAST-IRR; and Affective Reactivity Index; ARI) and suicidal ideation (suicidal thoughts factor of Concise Health Risk Tracking scale; CHRT and

10th item of Montgomery Asberg Depression Rating Scale; MADRS) were included. Spearman correlation coefficients (rspearman) were computed to estimate association among these measures.

Results: Study sample comprised of 16 males and 41 female individuals. Mean (SD) of CHRT, 10th item of MADRS, CAST-IRR, and ARI were 0.88 (1.63), 0.75 (1.18), 10.06 (5.81), and 3.06 (3.26), in males and 1.51 (2.69), 1.51 (1.73), 9.95 (5.16), and 2.97 (3.37), in females, respectively. Higher severity of suicidal ideation as measured with CHRT was associated with higher levels of irritability in males (rspearman of 0.72 with CAST-IRR and 0.58 with ARI) and in females (rspearman of 0.44 with CAST-IRR and 0.39 with ARI). Similar associations were noted when SI was measured with the 10th item of MADRS (males: rspearman of 0.71 with CAST-IRR and 0.55 with ARI; females: rspearman of 0.51 with CAST-IRR and 0.35 with ARI).

Conclusion: Association between irritability and SI may be stronger among males as compared to females. Larger scale studies replicating these findings are needed.

T87. ASSOCIATION OF PAIN WITH SYMPTOMS OF IRRITABILITY AND ANHEDONIA IN INDIVIDUALS WITH MAJOR DEPRESSIVE DISORDER AND HEALTHY CONTROLS

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Abstract Background: Chronic pain conditions are the leading causes of disability and are often present in individuals with psychiatric disorders including major depressive disorder. Work from our group has previously shown that irritability mediates that association between symptoms of pain and overall depression in individuals with major depressive disorder (MDD). Here, we evaluate whether this association is specific to MDD or also present in non-depressed healthy control individuals.

Method: Data for this report is obtained from an ongoing neuroimaging study of irritability (NCT05046184). Data from individuals (N=56) with ratings of pain (Pain Frequency Intensity and Burden; PFIBS), irritability (Concise Associated Symptom Tracking Irritability domain; CAST-IRR; and Affective Reactivity Index; ARI) and anhedonia (Snaith Hamilton Please Scale; SHAPs; and Temporal Experiences of Please scale; TEPS) were included. Spearman correlation coefficients (rspearman) were computed to estimate association among these measures.

Results: Study sample comprised of 17 healthy controls (5 Males/12 Females) and 39 individuals with MDD (9 Males/30 Females). Mean (SD) of PFIBS, CAST-IRR, ARI, SHAPS and TEPS were 2.94 (6.50), 4.00 (4.20), 0.29 (0.59), 51.35 (6.08), and 91.76 (15.23) in healthy controls and 8.81 (6.97), 12.21 (3.45), 4.22 (3.40), 36.32 (7.80), and 66.19 (15.96), respectively. Higher severity of pain was associated with higher levels of irritability (rspearman of 0.33 with CAST-IRR and 0.55 with ARI) and anhedonia (rspearman of -0.55 with SHAPS and -0.49 with TEPS) in healthy controls (all $p < 0.05$ except for CAST-IRR). Magnitude of associations were smaller in individuals with MDD where higher severity of pain was associated with higher levels of irritability (rspearman of 0.27 with CAST-IRR and 0.17 with ARI) and anhedonia (rspearman of -0.20 with SHAPS and -0.06 with TEPS).

Conclusion: Pain may be an often unrecognized symptom that is associated with higher levels of irritability and anhedonia. Effective management of pain may reduce the burden of these symptoms.

T88. EXAMINING THE ASSOCIATION BETWEEN ALTITUDE OF RESIDENCE AND THE PATTERNS OF CIGARETTE AND ALCOHOL USE IN THE UNITED STATES

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Abstract Background: Excessive alcohol use and cigarette smoking are two significant public health concerns affecting 16 and 28 million Americans, respectively, that annually cause 658,000 deaths. Additionally, the CDC estimates a combined yearly economic burden of $849 billion. These statistics point to an urgent need for novel pharmacotherapies targeting both alcohol use and smoking cessation, ideally with rational development guided by improved mechanistic understanding. The prevalence of cigarette smoking varies regionally across the U.S., with prior research indicating that regional rates of smoking-related diseases demonstrate a negative association with altitude. Geographic variation has also been reported with alcohol consumption, but it is unknown whether altitude is a predictor of excessive alcohol use. We aimed to determine the relationship between altitude and the prevalence of cigarette smoking and excessive drinking by U.S. county (N=3,106). Contrary to our previous work reporting a positive association between altitude and opioids, cocaine, methamphetamine, depression, and suicide, we hypothesized that smoking and excessive drinking prevalence among U.S. adults would be negatively associated with altitude.

Methods: County-level cigarette smoking and excessive alcohol use rates were obtained from the 2023 County Health Ranking National Database (CHRND), which includes data from the 2020 CDC Behavioral Risk Factor Surveillance System (BRFSS). Mean county altitude data were obtained from the NASA Shuttle Radar Topography Mission (SRTM) altitude dataset. A multivariate linear regression was performed to examine the relationship between mean county-level altitude and excessive drinking rates in 3,106 counties in the U.S. Potential covariates were individually tested for correlation with excessive drinking rates, and significant associations were included in the final model. Similar analyses were then conducted using the cigarette smoking rate in 3,106 counties as the outcome of interest. The applicable federal, state, and local alcohol and cigarette taxes were accounted for.

Results: The multivariate linear regression for cigarette use indicated that county-level smoking rates are significantly decreased at higher altitudes ($p < 0.001$). The final model, including altitude, accounted for 89.5% of the variance in U.S. county smoking prevalence, and for each 1,000-foot increase in altitude above sea level, smoking rates decreased by 0.143%. In addition, our analyses of county-level alcohol data found that excessive drinking is significantly reduced at higher altitudes ($p < 0.001$), with rates decreasing by 0.276% with each 1,000-foot increase in altitude above Sea Level.

Conclusions: The results presented suggest that rates of cigarette smoking and excessive drinking are negatively associated with altitude in the U.S. The present findings stand in

notable contrast to our previous reports regarding opioid, cocaine, and methamphetamine usage -- as well as rates of depression and suicide -- all of which increase with altitude. The variability in population-level data suggests an effect of altitude that is translated to the pharmacokinetics, pharmacodynamics, and/or mechanistic pathways involved in the absorption, processing, and brain effects of substances of misuse. Future preclinical and human subjects research is required to understand how altitude alters physiology and thus alternately serves as a protective factor -- or poses a risk -- for the acquisition and maintenance of addictions. Such work would then inform the development of novel drugs aimed at reducing the substantial burdens of substance use disorders.

T89. TSND-201 (METHYLONE) FOR THE TREATMENT OF PTSD, MDD, AND OTHER CNS DISORDERS

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[1]Transcend Therapeutics

Abstract Background: TSND-201 is currently in development to treat post-traumatic stress disorder (PTSD). PTSD is a debilitating psychiatric illness that has a lifetime prevalence of 6.4-7.8%. Currently available treatments for PTSD show limited effectiveness. Non-hallucinogenic compounds with rapid and long-lasting therapeutic effects may be clinically useful and more accessible to patients compared with classical psychedelics. Since PTSD, anxiety, and depression share high rates of comorbidity and overlapping neural substrates, TSND-201 may have potential to also treat other CNS disorders.

TSND-201 is a rapid-acting neuroplastogen and the beta-ketone analog of MDMA. Neuroplasticity is an underlying mechanism of rapid-acting pharmacotherapies, and neuroplasticity-related gene expression is rapidly induced by TSND-201 in key brain areas associated with PTSD and depression. TSND-201 is a highly-selective monoamine reuptake inhibitor and releaser with distinct pharmacological effects compared with MDMA. It shows no activity at the 5HT2A receptor and has no hallucinogenic effects in humans or animal models. In preclinical models of PTSD, MDD, and anxiety, methylone has demonstrated rapid, robust, and long-lasting effects. An open-label study in 14 patients with PTSD has recently completed.

Methods: The IMPACT-1 study is a multi-center, two-part clinical trial. Part A was an open-label evaluation of 14 participants with PTSD. The study included patients with severe PTSD (CAPS-5 $\geq$ 35) who failed at least 1 prior treatment (pharmacotherapy and/or psychotherapy). Participants received 4 doses of TSND-201 given once a week for 4 weeks with non-directive psychological support during the dosing session. Participants were followed for an additional 6 weeks to evaluate the durability of the therapeutic effect. Evaluations included PTSD symptom improvement (CAPS-5), functioning (SDS), global improvement (CGI-I) and safety (adverse events, vital signs, and C-SSRS). Effects of TSND-201 on sleep disturbance (CAPS-5, MADRS, PSQI) and depression symptoms were also evaluated (MADRS).

Results: After the first dose, TSND-201 treatment resulted in a mean change from baseline of -8.4 points on the CAPS-5. The results were durable with a mean change from baseline of -36.2 points at the end of study, 6-weeks after the last dose. Significant improvements in functioning occurred after the first dose (mean change from baseline: -1.53) and were also

durable through the 6-week follow-up period (-4.26). Underproductive days decreased from 4.7 days per week at baseline to 2.2 days per week at the end of study. On the CGI-I, after the 2nd dose, most patients (69%) were much or very much improved. By the end of the study, all patients were considered much or very much improved. Sleep scores improved significantly, including a -4.0 point change on the PSQI and similar improvements on PSQI subscales (e.g., sleep latency, disturbance, quality). TSND-201 reduced depression symptoms (MADRS mean change from baseline after one dose: - 8.2 points). At the end of study, the mean change from baseline was -21.4 pts. TSND-201 was generally safe and well-tolerated.

Conclusions: TSND-201 showed rapid, robust and durable effects on PTSD symptoms, functional ability, global improvements, sleep and depression symptoms. This study supports further development of TSND-201 as a treatment for PTSD. Part B of IMPACT-1; a randomized, placebo-controlled study, is currently ongoing.

T90. INVESTIGATING THE IMPACT OF PSYCHOSTIMULANTS AND COMORBID DISORDERS ON MISCONDUCTS AMONG INDIVIDUALS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN THE PRISON: A PRELIMINARY STUDY

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Abstract Background: Research has shown that ADHD is highly prevalent in the prison population with approximately 25% of incarcerated adults meeting the diagnostic criteria for ADHD. Additionally, ADHD is associated with frequent comorbid psychiatric conditions including substance use, mood, anxiety, and personality disorders, which further complicate the recognition and treatment of ADHD. Previous research indicates that incarcerated individuals with ADHD display a greater number of misconducts compared to inmates without ADHD. Although research demonstrates the effectiveness of psychostimulants for treating ADHD, individuals in prison populations with ADHD are often misdiagnosed and undertreated. Therefore, the purpose of this study is to investigate the influence of psychostimulants and comorbid disorders on misconducts among inmates with ADHD.

Methods: The total sample (N=50) consisted of individuals incarcerated at the Central North Correctional Centre (CNCC) in Canada from 2006-2017. The inmates in this sample diagnosed with ADHD (n=35) were given either lisdexamphetamine or methylphenidate from 2012-2017. The number of misconducts exhibited by the total sample was compared between pre-stimulant years (2006-2011) and post-stimulant years (2012-2017).

Results: Results show that in the post-stimulant years, inmates (M = 0.157, SD = 0.527) committed significantly less misconducts ($t(269) = 1.658$, $p = 0.049$) compared to the pre-stimulant years (M = 0.267, SD = 0.566). Additionally, it was shown that individuals with a cannabis use disorder (M = 0.403, SD = 0.744) committed significantly more misconducts ($t(269) = 3.55$, $p < 0.001$) than inmates without a cannabis use disorder (M = 1.407, SD = 0.438). Interestingly, there was no significant difference in the number of misconducts between individuals with and without a diagnosis of alcohol use disorder, cocaine use disorder, opioid use disorder, and chronic pain.

Discussion: Despite the substantial efficacy of psychopharmacological agents in treating ADHD, the use of controlled stimulants in prison settings remains controversial due to the

concerns of abuse and issues of safety. Previous studies have revealed that there is a lack of access to effective diagnostic screening and first-line pharmacological stimulant therapy for incarcerated individuals with ADHD. Results from this preliminary study suggest that lisdexamphetamine and methylphenidate may be beneficial treatments for incarcerated individuals diagnosed with ADHD. In fact, it is suggested that stimulant treatment could potentially reduce the number of disciplinary infractions and recidivism rates, while alleviating hyperactive and attentional symptoms. Finally, these results indicate that inmates with alcohol use disorder, cocaine use disorder, opioid use disorder, or chronic pain do not commit significantly more misconducts than those without these disorders. Thus, these findings suggest that the controlled and monitored administration of specific psychostimulants to inmates with ADHD may be an important treatment approach to improve ADHD symptoms and limit the number of misconducts even in the presence of comorbid disorders. Although recent studies have begun to investigate the impact of psychostimulants on inmates with ADHD, there remains a lack of research and awareness surrounding ADHD and the high prevalence of comorbid disorders within the prison setting. Therefore, there is a need for research exploring the effects of pharmacological treatment in inmates with ADHD.

T91. OXYBUTYNIN IS EFFECTIVE ON METHADONE- INDUCED HYPERHIDROSIS TREATMENT: A CASE REPORT

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Abstract: Methadone is a synthetic opioid with the longest history of use for opioid use disorder treatment, having been used since 1947. Methadone maintenance treatment (MMT) is a long-term and slow-onset substitution therapy, which needs complete medication adherence to achieve optimal outcomes. Hyperhidrosis is a common adverse effect experienced by patients using methadone as opioid replacement therapy; research has suggested the rate may be as high as 45%. Sweat glands are enervated by the sympathetic nervous system, activated via muscarinic receptors, and it is not surprising that an anti-muscarinic would antagonize perspiration through its peripheral action on exocrine glands. Oxybutynin is an anticholinergic medication able to antagonize the M1, M2, and M3 subtypes of the muscarinic acetylcholine receptor. It is generally used to relieve urinary and bladder difficulties. In the second half of the last decade, specific treatment with oxybutynin began to be reported for treatment of hyperhidrosis. This condition could be one of the barriers to methadone maintenance treatment adherence. On the other hand, reducing or discontinuing methadone might result in withdrawal symptoms and relapse. Hence, optimizing the treatment and improvement of compliance require addressing and taking care of side and adverse effects of methadone.

Case Description: The patient was a 27-year-old single male with no prior medical or psychiatric history who was maintained on methadone 180 mg daily, when he was no longer reported his withdrawal symptoms and craving for opioid use. Before starting methadone maintenance treatment, the patient was misusing Percocet for the past 6 years, which was introduced by his friends. He also admitted to smoking 1 joint of Marijuana and occasional misusing half a tablet of Xanax 2 mg to self-treat his anxiety. All urine tests were positive for Methadone, also for Cannabis and Benzodiazepine consistently on every 2-week basis. Serum methadone level was measured 3 hours after methadone administration to determine adequate plasma concentrations of methadone and it was 1200 ng/ml (normal range of 100-400 ng/ml).

The patient did not show or endorse any other symptoms of opioid withdrawal, including nausea, vomiting, body ache, dilated pupils, insomnia, etc. Review of systems and physical exam findings were unremarkable for any symptoms of thyroid disease, diabetes, autonomic disorders, infection, or malignancy which were compatible with blood work lab results.

The patient had no medical conditions and did not take any medication other than methadone. While the patient had self-reporting of social anxiety and depression, he was screened and evaluated carefully and was diagnosed with substance-induced mood disorder including depression and anxiety. These conditions were managed successfully by prescribing Escitalopram 20 mg daily and he did not endorse anxiety when sweating occurred. The patient reported excessive sweating in both axillae, face and on both palms, which only began after receiving methadone and interfered with his occupational, relationship and other social activities. The patient denied having this symptom during the time of missing the methadone dose for a day due to his floating work schedule. He was educated and recommended treating w ith Oxybutynin to reduce his hyperhidrosis. All indications, risks and benefits of medication were explained, and he expressed his strong desire to start on this medication. He had an informed consent discussion before onset of medication. After obtaining consent, he was placed on Oxybutynin 5 mg twice daily, which resulted in the complete cessation of the hyperhidrosis within a few days of starting the medication.

Conclusion and Discussion: There are a few cases treated for opioid-induced sweating described in previous studies. Mercadnate reported that morphine-induced sweating was treated adequately with hyoscine butylbromide. Biperiden, is an anticholinergic medication which has been used to treat methadone-induced diaphoresis and sweating in 3 cases, while Al-Adwani described the successful management of opioid-induced hyperhidrosis by an antihis tamine, desloratidine, and most recent case who was treated successfully with Oxybutynin 5 mg QID for methadone-induced hyperhidrosis reported in 2017. Sweating remains a rare occurrence in clinical practice and under-recognition of this side effect may lead to patient discomfort as well as failure in treatment compliance. Hence, a careful history inquiring about additional symptoms, review of systems for underlying medical comorbidities, medication history and frequent urine toxicology screening can be useful to rule out other possible causes of hyperhidrosis. This study supports the prior case report finding about treatment of methadone- induced hyperhidrosis with oxybutynin. The present case proposes that oxybutynin 5 mg oral tablet twice daily) can be very effective and merits consideration in patients with methadone-induced hyperhidrosis and help methadone clinic and health care providers to diagnose and treat one of the less recognized adverse effects of methadone.

T92. EFFECT OF ROPANICANT (SUVN-911), AN α4β2 RECEPTOR ANTAGONIST IN ANIMAL MODELS OF DEPRESSION

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Abstract: Depression is a mood disorder that affects about 280 million people worldwide. It is estimated that 1 in 5 adolescents or adults suffer from depression. The cholinergic theory of depression suggests that there is an imbalance between the adrenergic and cholinergic systems

in depressed patients. Ropanicant (SUVN-911) is a novel nicotinic acetylcholine α4β2 receptor antagonist. The primary purpose of the research was to investigate the efficacy of ropanicant in animal models of depression and anhedonia. A mechanistic approach was explored to find the possible reason for the efficacy that was observed in the animal models of depression. For this purpose, 5-hydroxytryptamine (5-HT) and brain-derived neurotrophic factor (BDNF) levels were estimated. The secondary purpose was to assess the advantages of ropanicant over conventional antidepressants, namely with respect to the onset of action and sexual dysfunction. From the forced swim test, it was observed that ropanicant reduced the duration of immobility. The decrease in the duration of immobility was devoid of any adverse effects on locomotor activity assessed using an open field test. Ropanicant enhanced the sucrose intake in rats that were subjected to chronic mild stress, indicating its effect on anhedonia. Ropanicant increased 5-HT and BDNF levels in rats subjected to chronic mild stress. To assess the onset of action, ropanicant was administered to submissive rats in a dominant-submissive assay. Ropanicant showed an onset of action within a week of administration in this assay. Unlike conventional antidepressants, ropanicant does not have an adverse effect on learning or memory. This was assessed using the object recognition task. When subjected to a sexual dysfunction assay in rats, ropanicant was found to be devoid of sexual side effects, which are common with conventional antidepressants. Ropanicant is currently being evaluated for major depressive disorders in clinical trials (NCT06126497).

T93. NONINTERVENTIONAL, RETROSPECTIVE, PROSPECTIVE, LONGITUDINAL COHORT STUDY TO ASSESS ANTIDEPRESSANT TREATMENT PATTERNS AND OUTCOMES IN INDIVIDUALS WITH MAJOR DEPRESSIVE DISORDER

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Abstract Background: Certain barriers (patient, provider, and system) can prevent timely diagnosis and optimal treatment of major depressive disorder (MDD) in primary care, where patient populations are diverse and day-to-day challenges can affect follow-up care and adherence.1 Real-world data on antidepressant (AD) treatment in clinical practice covering effectiveness, tolerability, and associated medical or psychiatric comorbidities are limited for all ADs, including the multimodal AD vortioxetine.2 This study aims to examine and compare the demographics, treatment patterns, and outcomes of actual patients with MDD being treated with vortioxetine and other ADs.

Methods: Phase 1 of this noninterventional, retrospective, prospective, longitudinal US-based study included 10,931 individuals aged ≥18 years from the general population after follow-up at a 3-year interval.1 Phase 2, currently underway, aims to enroll up to 1000 participants with previously diagnosed MDD into 2 matched cohorts (n=500 treated with vortioxetine and n=500 with other ADs). A web-based instrument, the Ad-Infer EVAL system,3,4 will be used for both phases.1 The Ad-Infer EVAL system is a hybrid artificial intelligence expert system designed for use with the general population, and it has been trained on DSM-5 psychiatric classification.1,3 Data for phase 2 will be collected at baseline, 3 months, and 6 months. Demographic, medical, psychiatric, and other relevant data will be collected at baseline. At all timepoints, the system will collect medication history (eg, AD treatment patterns, medications

for comorbid conditions, over-the-counter medications, and supplements), clinical characteristics (including symptoms of depression), other medical and psychiatric comorbid conditions, and other relevant data (eg, SF-12 and WHO-5 scores, number of consultations in the previous year). At 3 and 6 months, the assessment will include clinical outcomes (ie, depressive status, response and remission rates, side effects, tolerability, cognitive impairment, and function when treated with an AD by medication class).

Results: In phase 1, the 12-month prevalence of MDD was 9.5% (95% CI, 9.0%-10.0%) at the initial interview and 12.1% (95% CI, 11.5%-12.7%) at follow-up.1,5 In the month prior to the interview, 52.2% of the participants with MDD were treated with an AD; SSRIs were the most frequently used (34.7%).1 At follow-up, 43.4% of participants treated with an AD at the initial interview achieved a full remission; the highest remission rate was observed with norepinephrine-dopamine reuptake inhibitors (61.7%) and the lowest with serotonin and norepinephrine reuptake inhibitors (35%). Study enrollment for phase 2 is projected to end in January 2024; study completion is targeted for June 2024.

Limitations: Participants will be instructed to report psychiatric and medical conditions previously diagnosed by a physician or other health specialist, but these conditions and any undiagnosed medical conditions will not be verified. Additionally, the assessments will be performed at specific timepoints that may not align with each participant's duration of depression and treatment.

Conclusions: Using the Ad-Infer EVAL system, this study will provide real-world data on the patient experience with MDD, including the characterization of people with MDD from the general population, their burden of illness, and treatment outcomes with vortioxetine compared with other ADs.

T94. CT-155: EARLY STAGE EVIDENCE IN THE DEVELOPMENT OF A PRESCRIPTION DIGITAL THERAPEUTIC TO TREAT EXPERIENTIAL NEGATIVE SYMPTOMS OF SCHIZOPHRENIA

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Abstract Introduction: Negative symptoms are prominent in people with schizophrenia. Experiential negative symptoms (ENS) are a subdomain of negative symptoms that include avolition, asociality and anhedonia, and contribute substantially to the emotional and socioeconomic burden of schizophrenia. There are currently no FDA-approved pharmacotherapies for ENS, and access to available psychosocial therapies is limited. Prescription digital therapeutics (PDTs) are digital therapeutics (DTx) that have demonstrated rigorous evidence for efficacy and safety according to FDA regulatory controls and require a prescription for use. CT-155 is a PDT under investigation to target ENS via smartphone delivery and is co-developed and guided by patient feedback. Given widespread smartphone ownership, CT-155 could deliver scalable, evidence-based care alongside standard treatments and address access barriers to traditional therapy. Two exploratory studies were designed to evaluate the establishment and overall strength of the digital working alliance (DWA), a potentially important factor akin to the therapeutic alliance that may influence outcomes,

between patients living with ENS of schizophrenia and CT-155. These studies also explored the feasibility and acceptability of treatment with CT-155 to address ENS in this population.
Methods: Two independent, single-arm, multicenter exploratory studies of abbreviated versions of CT-155 (CT-155 beta) in adults with schizophrenia and ENS on stable antipsychotics for ≥12 weeks were conducted. Treatment periods for both Study 1 and Study 2 included a 3-week orientation with lessons to build a DWA (Weeks 1–3), while Study 2 (NCT05486312) also included a subsequent abbreviated adaptive goal-setting (AGS) phase (Weeks 4–7). Engagement was assessed throughout both studies by measuring the number of lessons completed. The DWA strength between participants and CT-155 beta was measured in Study 1 and Study 2 using the mobile Agnew Relationship Measure (mARM) questionnaire. ENS were assessed at baseline in both studies and at Week 7 in Study 2 using the Clinical Assessment Interview for Negative Symptoms Motivation and Pleasure Scale (CAINS-MAP).

Results: Studies 1 and 2 enrolled 49 and 50 participants, respectively; 46 (94%) and 43 (86%) completed. Most were male (71% and 80%), non-white (57% and 70%), never attended college (63% and 64%), and had an income < $25,000 (94% in both). Participants completed a median of 16/21 (76.2%) lessons over the 3-week period in Study 1 and 18/21 (85.7%) lessons over the equivalent period in Study 2. Across both studies, a positive DWA was established during the orientation phase (Week 3 mean [standard deviation; SD] mARM: Study 1, 5.16 [0.77]; Study 2, 5.36 [1.06]) and was maintained after the AGS phase at Week 7 in Study 2 (mean [SD] mARM: 5.48 [0.97]). DWA was unaffected by negative symptom severity in Study 1 and Study 2. In Study 2, ENS improved after 7 weeks (mean [SD] CAINS-MAP scores: baseline, 20.2 [8.6]; Week 7, 16.8 [7.8]; p=0.004; n=43). No adverse events (AEs) were reported in Study 1; 3 non-serious, non-treatment-related AEs were reported in Study 2.

Conclusion: People living with schizophrenia engaged with beta versions of CT-155 to support their treatment during the DWA establishment and AGS phases. ENS improvement after 7 weeks suggests that this PDT under investigation could become a new scalable treatment modality for people with schizophrenia, addressing a major unmet need. These favorable results support advancing CT-155 into late-phase clinical development (CONVOKE: CT05838625/CT-155-R-001).

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T95. A PHASE 2 RANDOMIZED PROOF-OF-CONCEPT TRIAL OF NBI-1065846 (TAK-041) IN ADULTS WITH ANHEDONIA ASSOCIATED WITH MAJOR DEPRESSIVE DISORDER: RESULTS OF THE TERPSIS STUDY

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Abstract Background: Anhedonia (the inability to feel pleasure) is a symptom of several neuropsychiatric disorders, affecting up to 72% of individuals with major depressive disorder (MDD) and 80% of individuals with schizophrenia.1,2 As a core symptom of MDD, anhedonia may predict poor treatment response to antidepressants and increased suicide risk.1 Lateral habenula (LHb) hyperexcitability may contribute to the dysregulated reward circuitry underlying anhedonia in MDD.3,4 Targeting G-protein coupled receptor (GPCR) 139 (GPR139), an orphan GPCR enriched in the medial habenula5, may potentially improve anhedonia by reducing aberrant LHb activity.
NBI 1065846 (TAK-041) is an investigational GPR139 agonist that improved anhedonia, anxiety, and depression in rodent behavioural models, and increased ventral striatal activity during reward anticipation in adults with schizophrenia. Here we report efficacy and safety results from TERPSIS, a phase 2 study of NBI-1065846 in adults with MDD and anhedonia (NCT05165394).

Methods: This double-blind, proof-of-concept study was conducted in adults with MDD who were receiving or had received stable antidepressant medication for their most recent depressive episode but still had anhedonia (Snaith Hamilton Pleasure Scale ≥30 at screening and baseline [BL]). Participants were stratified by illness severity (Hamilton Depression Rating Scale [HAMD-17] scores) and allocated 1:1 to receive once-weekly placebo or NBI 1065846 at a loading dosage of 160 mg, followed by 80 mg on Weeks 2–8.

The primary endpoint was the change from BL (CFB) to Day 57 in Dimensional Anhedonia Rating Scale (DARS). Secondary endpoints were the CFB to Day 57 in Montgomery Asberg Depression Rating Scale (MADRS) in participants with a HAMD-17 score ≥19 and in Clinical Global Impression – Severity (CGI-S). Safety endpoints included treatment emergent adverse events (TEAEs) and the Columbia Suicide Severity Rating Scale (C-SSRS).

Results: Of 93 randomized participants, 88 (94.6%) completed the study treatment and 83 (89.2%) completed the study. BL demographics and characteristics were broadly similar between treatment groups. No significant improvement in DARS was observed with NBI-1065846 vs placebo at Day 57 (p = 0.8663, 1-sided), with a least-squares mean (standard error of the mean) [1 sided 90% confidence interval] difference of –3.9 (3.5) [–8.4, infinity]. MADRS and CGI S scores with NBI 1065846 were not statistically different from placebo at Day 57.

Most TEAEs were mild or moderate in severity, occurring at a slightly lower frequency with NBI 1065846 than with placebo. TEAEs occurring in ≥3 participants were headache, insomnia, COVID 19, diarrhea and fatigue. C-SSRS suicidal ideation increased from BL to post-BL in 10 participants (NBI 1065846, n=3). One participant assigned to placebo with a history (GREATER THAN 1 year before screening) of suicide attempts had a serious TEAE of suicide attempt and discontinued study treatment.

Discussion: The TERPSIS study did not meet its primary or secondary endpoints. NBI 1065846 was generally well tolerated, with fewer TEAEs observed than with placebo. Being predictive of clinical outcome in MDD, anhedonia remains an important unmet therapeutic need.

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