2025 ASCP ANNUAL MEETING

ABSTRACT BOOK

Navigating the Evolution of Clinical Psychiatry: When is Newer Better

Scottsdale, Arizona

May 27 - May 30, 2025
Fairmont Scottsdale Princess

Tuesday, May 27, 2025

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

*USING GROUP MEDICAL VISITS / SHARED MEDICAL APPOINTMENTS TO IMPROVE ACCESS TO CARE FOR BIPOLAR DISORDER AND OTHER PSYCHIATRIC DISORDERS: EVALUATION OF A NOVEL SERVICE DELIVERY MODEL

Sagar Parikh, University of Michigan

Overall Abstract: Group Medical Visits (GMV) (a.k.a. Shared Medical Appointments) is a model of care that typically involves two clinicians providing individual patient care within a group of patients with a similar disorder. Across medicine, shared appointments are used for routine care of chronic conditions (particularly diabetes) and for patient education, with studies finding improved access, outcomes and patient satisfaction. Patients receive peer input and doctors provide basic advice more efficiently. Use of GMV in psychiatry, however, has been sparse. In addition to providing medical management, psychoeducation, and peer support, psychiatric GMVs can also provide training opportunities. This panels showcases 3 psychiatric GMV which illustrate its potential.

Dr. Gorrepati from University of Texas, Austin will present on a Shared Medical Appointment program for bipolar disorder launched in October 2023, with approximately 30 individuals enrolled so far. Individuals begin with an individual assessment, participate in a 6-session Life Goals Psychoeducation program, and then may continue to receive care in the Shared Medical Appointment model. Three psychiatric residents, 3 clinical pharmacy residents, and 2 psychiatric pharmacists facilitate our group. Clients who are currently participating in our Life Goals psychoeducation group are offered an opportunity to receive their medical care through our shared medical appointment. This initial group experience may sensitize clients to receiving care in a group setting. By April 1st, 2025, we will gather patient satisfaction survey data and report on the results at the symposium.

Dr. Penner-Goeke from the University of Manitoba reports on a pilot GMV program to evaluate the feasibility and acceptability of biweekly virtual GMVs for anxiety and depression compared to standard care, summarizing recruitment rates, retention, participant satisfaction, and initial effectiveness on clinical outcomes. The GMV enrolled 48 patients between October 2017 and January 2019, 41 of whom consented to participate. Of those, 10 did not attend, 8 attended but did not complete, and 23 completed. Significant and meaningful reductions in PHQ-9 and GAD-7 scores from baseline to last visit attended occurred among those who attended at least 1 visit (decrease of 5.26 and 5.13 points, respectively). Subsequently, a virtual GMV was launched in September 2023 and the first round was completed in March 2024.

Dr. Parikh provides data from two separate surveys on a longstanding GMV for bipolar disorder conducted by a staff psychiatrist and psychiatric resident. The Michigan GMV includes bipolar I and bipolar II patients obtaining psychiatric medical care exclusively within this model. One psychiatrist and one resident hold 90-minute sessions with a maximum of 5 participants, with attendance based on clinical need. The first survey found residents identifying GMV as having high value for teaching: (1) interview skills (87.5%), (2) diagnostic skills (50%), and (3) treatment skills (62.5%). Additionally, residents perceived the GMV as having high clinical value for the patients, with none finding it inferior to individual visits. A second survey of patients found high satisfaction on the Client Satisfaction Questionnaire (Average score:30.29 out of 32) as well as 83 % reporting

additional value from receiving care in the group, 71% feeling supported by other group members, 71% claiming easier access to care, and 71% learning new strategies/information from peers.
Together, these diverse Group Medical Visit programs demonstrate great promise for enhancing psychiatric care while improving access, with the panel providing additional advice to attendees on how to launch a GMV.
Learning Objective 1: Explain the format and delivery of Group Medical Visits (GMV) / Shared Medical Appointments as a Service Delivery model
Learning Objective 2: Describe and provide evaluations of three different Group Medical Visit programs in terms of educational value for training psychiatry resident, patient satisfaction, and utility in improving access to care.
Literary References: 1. Ramdas K, Darzi A. Adopting Innovations in Care Delivery - The Case of Shared Medical Appointments. N Engl J Med. 2017 Mar 23;376(12):1105–7.
2. Parikh SV, Taubman DS, Severe J, Thompson S. Enhancing Resident Education and Expanding Care with Group Medical Visits/Shared Medical Appointments. Acad Psychiatry. Published online September 4, 2024. doi:10.1007/s40596-024-02034-1

PROVIDING SPECIALIZED CARE FOR BIPOLAR DISORDERS THROUGH SHARED MEDICAL APPOINTMENTS

Vijay Gorrepati, The University of Texas at Austin

Individual Abstract: The Bipolar Disorder Center at UT Health Austin provides specialized care for people with a bipolar disorder in central Texas. An estimated 14,000 people in this region meet criteria for a bipolar disorder diagnosis. Access is a critical issue in providing evidence-based and coordinated care to this clinical population, as general psychiatry clinics and primary care providers struggle to meet the overall demand for mental health services. Shared medical appointments may be a novel approach to provide specialized psychiatric care, expand access and improve recovery-oriented outcomes.
Shared medical appointments are a form of medical care in which groups of individuals with similar diagnosis meet with a multidisciplinary team (typical 2 or more providers) for their medical treatment. Systematic reviews and meta-analyses have explored the efficacy of this modality for chronic diseases in primary care and in the peripartum setting. In addition to standard medical care, clients receive psychoeducation on their illness as well as peer support from other members in the group. In this symposium, we describe our experience starting shared medical appointments for bipolar disorder at our specialty clinic.
In October 2023 we began enrolling interested clients in our shared medical appointments. Thus far approximately 30 people with bipolar disorder have participated in a shared medical appointment. We have also had 3 psychiatric residents, 3 clinical pharmacy residents, and 2 psychiatric pharmacists facilitate our group. Clients who are currently participating in our Life Goals psychoeducation group are offered an opportunity to receive their medical care through our shared medical appointment. This initial group experience may sensitize clients to receiving care in a group setting. By April 1st, 2025, we will gather patient satisfaction survey data and report on the results at the symposium.
Literature References: Cunningham SD, Sutherland RA, Yee CW, Thomas JL, Monin JK, Ickovics JR, et al. Group medical care: a systematic review of health service performance. Int J Environ Res Public Health. 2021;18(23):12726.
Housden L, Wong ST, Dawes M. Effectiveness of group medical visits for improving diabetes care: a systematic review and metaanalysis. CMAJ. 2013;185(13):E635-644.
Remick RA, Araki Y, Bruce R, Gorman C, Allen J, Remick AK, et al. The Mood Disorders Association of British Columbia Psychiatric Urgent Care Program: a preliminary evaluation

of a suggested alternative model of outpatient psychiatric care. Can J Psychiatry. 2014;59(4):220–7.

GROUP MEDICAL VISITS FOR PSYCHIATRIC CARE: PILOTS IN POST-CRISIS AND OUTPATIENT CARE

Kirsten Penner-Goeke, University of Manitoba

Individual Abstract: Objective: To implement and evaluate GMV models in psychiatric care.
Methods: A GMV was implemented in a post-crisis psychiatric follow-up clinic for individuals with mood and anxiety disorders referred from emergency and crisis centres. Attendance was flexible, with target length of stay being 12 weeks. Baseline, attendance and follow-up data were collected from consenting individuals. PHQ-9 and GAD-7 were done at all sessions. Implementation barriers were recorded. A subsequent virtual GMV was implemented in an outpatient psychiatric clinic that accepted referrals from primary care providers and non-psychiatric specialists for patients with depression and anxiety disorders. We are currently starting recruitment for a pilot randomized controlled trial to asses the feasibility and acceptability of virtual GMVs for outpatient follow-up of patient with depression and anxiety disorders.
Results: The post-crisis GMV enrolled 48 patients between October 2017 and January 2019, 41 of whom consented to participate. Of those, 10 did not attend, 8 attended but did not complete, and 23 completed. Significant and meaningful reductions in PHQ-9 and GAD-7 scores from baseline to last visit attended occurred among those who attended at least 1 visit (decrease of 5.26 and 5.13 points, respectively). Significant implementation barriers led to program discontinuation. The subsequent virtual GMV launched in September 2023 and the first round was completed in March 2024. Our pilot randomized controlled trial of a similar GMV is currently in the recruitment phase.
Conclusions: GMVs have promise for psychiatric care delivery, with the potential to bridge gaps in access and improve population outcomes. Implementation support and adequate infrastructure is essential to their success and sustainability. Randomized study designs in this area are important in order to control for confounding variables.
Literature References: Remick RA, Araki Y, Bruce R, et al. The Mood Disorders Association of British Columbia Psychiatric Urgent Care Program: A Preliminary Evaluation of a Suggested Alternative Model of Outpatient Psychiatric Care. Can J Psychiatry. 2014;59(4):220-227.
Palay J, Bolton JM, Sareen J, Hensel JM. Increasing access to specialist care with group medical visits: summary of a pilot in a post-crisis psychiatric clinic. Front Health Serv. 2023; 3:1127725.

USING GROUP MEDICAL VISITS / SHARED MEDICAL APPOINTMENTS TO IMPROVE RESIDENT EDUCATION AND ENHANCE ACCESS AND QUALITY OF CARE FOR BIPOLAR DISORDER

Sagar Parikh, University of Michigan

Individual Abstract: Group Medical Visits (GMV) (a.k.a. Shared Medical Appointments) is a newer model of care that typically involves two clinicians providing individual patient care within a group of patients with a similar disorder, including group psychoeducation and illness self-management skills. This model also provides unique training opportunities. The Michigan GMV program has been in existence for five years and includes bipolar I and bipolar II patients obtaining psychiatric medical care exclusively within this model. One psychiatrist and one resident hold 90-minute sessions with a maximum of 5 participants. Attendance is based on clinical need. In order to evaluate the value of the Bipolar GMV, two

surveys were conducted, one for psychiatric residents, and one for patients. Residents participated in GMVs in PGY-3 or PGY-4 year. Residents completed a questionnaire with 34 quantitative items and 2 qualitative items covering learner satisfaction, educational value of GMVs model, challenges/benefits for both provider and patient, practical tips, and interest in further training. Resident survey response was 8/21 (38.1%), with all indicating high satisfaction. Respondents also reported high value in teaching: (1) interview skills (87.5%), (2) diagnostic skills (50%), and (3) treatment skills (62.5%). Additionally, residents perceived the GMVs as having high clinical value for the patients, with none finding it inferior to individual visits. Residents noted the unique nature of the clinical encounter in their training and supported additional GMVs programs. Most (62.5%) wish to provide GMVs for clinical care in the future. A second survey was done of patients, with 39 patients who had attended GMV in the past two years invited to complete a questionnaire covering patient satisfaction, clinical value of GMV model, benefits/challenges for users, and their current bipolar treatment. Twenty-four out of 39 (61.5%) patients responded. Respondents were ages 26 upward, with 44% above 65 years, 91% Caucasian and 57% male. Seventy-five percent had attended 4+ sessions in the past year. Respondents reported high satisfaction on the Client Satisfaction Questionnaire (Average score:30.29 out of 32). The most common challenge reported was the time and length of the group appointment (4 and 2 mentions, respectively). Quantitative results included: (1) 83 % reported additional value from receiving care in the group, (2) 71% felt supported by other group members, (3) 71% claimed easier access to care with the group, and (4) 71% learned new strategies/information from other group members. In conclusion, psychiatric residents rated Group Medical Visits as an excellent skill-building exercise and unique overall educational experience with high interest in future adoption of GMVs to provide clinical care. Similarly, patients respondents reported GMVs exceptionally satisfying as a clinical service with unique benefits compared to individual care, with GMVs improving access to care.

Literature References: Remick RA, Araki Y, Bruce R, et al. The mood disorders association of British Columbia psychiatric urgent care program: a preliminary evaluation of a suggested alternative model of outpatient psychiatric care. Can J Psychiatry. 2014;59(4):220-227. doi:10.1177/070674371405900407

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*^ADVANCING CARE IN GERIATRIC PSYCHIATRY: UPDATES IN DIAGNOSIS, TREATMENT, AND CLINICAL PRACTICE

Lydia Ann, University of California, Irvine

Overall Abstract: Advancing Care in Geriatric Psychiatry: Updates in Diagnosis, Treatment, and Clinical Practice

As the global population continues to age, the need for appropriate, evidence-based diagnosis and treatment of psychiatric disorders in geriatric patients is more pressing than ever. This session highlights recent advancements in geriatric psychiatry, focusing on updates in the diagnosis and treatment of neurocognitive disorders, delirium, depression, and schizophrenia. Special attention will be given to the pharmacokinetic and pharmacodynamic changes that occur in the aging population, providing essential insights for optimizing pharmacotherapy. The session will commence with an in-depth exploration of the latest advancements in the diagnosis and treatment of neurocognitive disorders. This includes an introduction to cutting-edge tools such as the Self-Administered Gerocognitive Examination, which offers promising

potential for the early detection of mild cognitive impairment. Additionally, the session will highlight the expanding role of advanced functional imaging techniques with novel disease biomarkers. Recent FDA approvals for disease modifying treatment for Alzheimer's disease including lecanemab and donanemab as well as brexpiprazole for managing agitation associated with Alzheimer's, will also be thoroughly discussed, emphasizing their implications and limitations in clinical practice.

Recognizing the unique susceptibility of the geriatric population to delirium, the session will address this critical concern with a detailed review of current best practices in delirium management, including the evolving use of dexmedetomidine as a therapeutic agent.

Transitioning to geriatric depression, the discussion will delve into significant research findings, such as the TRANSFORM-3 trial, which demonstrated the efficacy of esketamine, as well as the potential role of intravenous ketamine for geriatric patients. Furthermore, the session will examine the roles of emerging pharmacological agents, including gepirone and bupropion-dextromethorphan, exploring their potential applications and impact on treatment paradigms for geriatric depression.

Lastly, the session will turn its focus to the treatment of schizophrenia within the geriatric population, particularly addressing the challenges faced by geriatric patients at higher risk for extrapyramidal symptoms and other side effects. Newer medications such as lumateperone and xanomeline-trospium and the potential of these agents in the geriatric population. This comprehensive review aims to equip attendees with an enriched understanding of these updates and their integration into clinical practice.

Learning Objective 1: Participants will demonstrate the ability to evaluate and apply recent advancements in the diagnosis and treatment of neurocognitive disorders, including recently FDA-approved treatments and early detection tools.

Learning Objective 2: Participants will review updates in managing geriatric depression, including esketamine, intravenous ketamine, and emerging medications like gepirone and bupropion-dextromethorphan.

Literary References: 1) Oughli, H. A., Gebara, M. A., Ciarleglio, A., Lavretsky, H., Brown, P. J., Flint, A. J., ... and Lenze, E. J. (2023). Intravenous ketamine for late-life treatment-resistant depression: a pilot study of 1tolerability, safety, clinical benefits, and effect on cognition. The American Journal of Geriatric Psychiatry, 31(3), 210-221.

2) Belder, Christopher R S et al." Preparing for disease-modifying therapies in Alzheimer's disease." The Lancet Neurology, Volume 22, Issue 9, 782 - 783. 2023

ADVANCING CARE IN GERIATRIC PSYCHIATRY: UPDATES IN DIAGNOSIS, TREATMENT, AND CLINICAL PRACTICE

Hanadi Ajam Oughli, UCLA, Semel Institute

Individual Abstract: As the global population continues to age, the need for appropriate, evidence-based diagnosis and treatment of psychiatric disorders in geriatric patients is more pressing than ever. This session highlights recent advancements in geriatric psychiatry, focusing on updates in the diagnosis and treatment of neurocognitive disorders, delirium, depression, and schizophrenia. Special attention will be given to the pharmacokinetic and pharmacodynamic changes that occur in the aging population, providing essential insights for optimizing pharmacotherapy.

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biomarkers. Recent FDA approvals for disease modifying treatment for Alzheimer's disease including lecanemab and donanemab as well as brexpiprazole for managing agitation associated with Alzheimer's, will also be thoroughly discussed, emphasizing their implications and limitations in clinical practice.

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Mendez MF, Melrose RA, Feil DG, Holiday KA, Hunt M, Jazi AN, Lamba SL, Mahler ME, Okobi DE, Von Walter HF. A Transdisciplinary Program for Care of Veterans With Neurocognitive Disorders. Fed Pract. 2023;40(Suppl 2):1-6. doi: 10.12788/fp.0343. Epub 2022 Dec 14. PMID: 36950504; PMCID: PMC10026702.

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Lee D, Slomkowski M, Hefting N, Chen D, Larsen KG, Kohegyi E, Hobart M, Cummings JL, Grossberg GT. Brexpiprazole for the Treatment of Agitation in Alzheimer Dementia: A Randomized Clinical Trial. JAMA Neurol. 2023 Dec 1;80(12):1307-1316. doi: 10.1001/jamaneurol.2023.3810. PMID: 37930669; PMCID: PMC10628834.

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Hall J. Schizophrenia – new treatments soon. The British Journal of Psychiatry. Published online 2024:1-2. doi:10.1192/bjp.2024.195

ADVANCING CARE IN GERIATRIC PSYCHIATRY: UPDATES IN DIAGNOSIS, TREATMENT, AND CLINICAL PRACTICE

Daniel Okobi, Advent Health

Individual Abstract: As the global population continues to age, the need for appropriate, evidence-based diagnosis and treatment of psychiatric disorders in geriatric patients is more pressing than ever. This session highlights recent advancements in geriatric psychiatry, focusing on updates in the diagnosis and treatment of neurocognitive disorders, delirium, depression, and schizophrenia. Special attention will be given to the pharmacokinetic and pharmacodynamic changes that occur in the aging population, providing essential insights for optimizing pharmacotherapy.

The session will commence with an in-depth exploration of the latest advancements in the diagnosis and treatment of neurocognitive disorders. This includes an introduction to cutting-edge tools such as the Self-Administered Gerocognitive Examination, which offers promising potential for the early detection of mild cognitive impairment. Additionally, the session will highlight the expanding role of advanced functional imaging techniques with novel disease biomarkers. Recent FDA approvals for disease modifying treatment for Alzheimer's disease including lecanemab and donanemab as well as brexpiprazole for managing agitation associated with Alzheimer's, will also be thoroughly discussed, emphasizing their implications and limitations in clinical practice.

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Oughli HA, Gebara MA, Ciarleglio A, Lavretsky H, Brown PJ, Flint AJ, Farber NB, Karp JF, Mulsant BH, Reynolds CF, Roose SP, Yang L, Butters MA, Lenze EJ. Intravenous ketamine for late-life treatment-resistant depression: a pilot study of tolerability, safety, clinical benefits, and effect on cognition. The American Journal of Geriatric Psychiatry. 2023;31(3), 210-221.

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Belder CRS, Schott JM, Fox NC. Preparing for disease-modifying therapies in Alzheimer's disease. Lancet Neurology. 2023;22(9):782-3.

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Katy Lunny, University of California, Irvine

Individual Abstract: As the global population continues to age, the need for appropriate, evidence-based diagnosis and treatment of psychiatric disorders in geriatric patients is more pressing than ever. This session highlights recent advancements in geriatric psychiatry, focusing on updates in the diagnosis and treatment of neurocognitive disorders, delirium, depression, and schizophrenia. Special attention will be given to the pharmacokinetic and pharmacodynamic changes that occur in the aging population, providing essential insights for optimizing pharmacotherapy.

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ADVANCING CARE IN GERIATRIC PSYCHIATRY: UPDATES IN DIAGNOSIS, TREATMENT, AND CLINICAL PRACTICE

Farah Khorassani, UCI

Individual Abstract: As the global population continues to age, the need for appropriate, evidence-based diagnosis and treatment of psychiatric disorders in geriatric patients is more pressing than ever. This session highlights recent advancements in geriatric psychiatry, focusing on updates in the diagnosis and treatment of neurocognitive disorders, delirium, depression, and schizophrenia. Special attention will be given to the pharmacokinetic and pharmacodynamic changes that occur in the aging population, providing essential insights for optimizing pharmacotherapy.

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Lastly, the session will turn its focus to the treatment of schizophrenia within the geriatric population, particularly addressing the challenges faced by geriatric patients at higher risk for extrapyramidal symptoms and other side effects. Newer medications such as lumateperone and xanomeline-trospium and the potential of these agents in the geriatric population. This comprehensive review aims to equip attendees with an enriched understanding of these updates and their integration into clinical practice.

Literature References: Subramanian S, Oughli HA, Gebara MA, Palanca BJA, Lenze EJ. Treatment-Resistant Late-Life Depression: A Review of Clinical Features, Neuropsychology, Neurobiology, and Treatment. Psychiatr Clin North Am. 2023 Jun;46(2):371-389. doi: 10.1016/j.psc.2023.02.008. Epub 2023 Mar 27. PMID: 37149351.

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*^~RECENT ADVANCES IN KETAMINE AND ESKETAMINE: RESEARCH AND CLINICAL PRACTICE

Joshua Rosenblat, University of Toronto

Overall Abstract: Over the past 25 years, ketamine has been extensively researched for a variety of clinical applications in psychiatry, most notably for treatment resistant depression (TRD) and suicidal thoughts. Research into ketamine has led to the development of

esketamine nasal spray that is FDA approved for two indications: (1) TRD in adults and (2) depressive symptoms in adults with major depressive disorder (MDD) with acute suicidal ideation or behavior. Racemic ketamine continues to be used off label for TRD and other indications and is an active area of research globally. This panel will present highly relevant developments and new data on ketamine's clinical and neurobiological effects. The session is meant for both clinicians providing patient care and scientists focused on research and development of novel interventions.

During this panel, internationally recognized ketamine experts will present new data and exciting developments with ongoing clinical trials.

Joshua Rosenblat (Chair) will provide a brief background on ketamine, focused on recent developments and clinical utility.

Rebecca Price (Speaker) will present original data exploring plasticity mechanisms across psychological, cognitive, and neural domains following ketamine treatment for depression.

Elizabeth Ballard (Speaker) will present new data on suicide-related biomarkers of response to ketamine with important clinical implications and insights for neurobiological mechanisms of ketamine's effects on suicidality.

Gerard Sanacora (Speaker) will present new 5-year data from the Esketamine REMS database over the first 58 months of post-approval data in the United States analyzing a total of 1,486,213 outpatient treatment sessions completed by 58,483 enrolled patients. This data will provide the most comprehensive real-world investigation related to the longer-term safety and use patterns associated with IN esketamine in the US.

Samuel Wilkinson (Speaker) will discuss the controversial topic on if there is a clinically meaningful difference between intravenous racemic ketamine and intranasal esketamine. He will present original data and the study design for the world's largest trial comparing ketamine and esketamine (EQUIVALENCE trial, funded by the Patient Centered Outcomes Research Institute (NCT06713616)).

Sara Di Luch (Speaker) will discuss the association between acute dissociation and antidepressant efficacy. Many providers and patients believe that a psychedelic or dissociative experience is necessary for clinical benefits. We will review evidence to date and present new data suggesting that acute dissociation is not predictive of clinical benefits.

Joshua Rosenblat (Discussant) will provide expert commentary bringing together what was discussed during the session with additional comments on key future directions for the field.

This session will also exemplify the diversity of perspectives that is celebrated at ASCP with gender representation (in speakers and data presented), diverse training backgrounds and career stages (trainee, psychiatrists, psychologists, scientists), different institutions (University of Toronto, Yale University, National Institute of Mental Health, University of Pittsburgh) and cover both clinically focused and neurobiologically focused research presenting a wide breadth of new data from these diverse perspectives.

Learning Objective 1: Critically evaluate the role of ketamine and esketamine in the treatment of depression and related disorders

Learning Objective 2: Explore recent research developments in our understanding of the clinical and neurobiological effects of ketamine in humans.

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EXPLORING PLASTICITY MECHANISMS ACROSS PSYCHOLOGICAL, COGNITIVE, AND NEURAL DOMAINS FOLLOWING KETAMINE TREATMENT FOR DEPRESSION

Rebecca Price, University of Pittsburgh

Individual Abstract: Exploring Plasticity Mechanisms across Psychological, Cognitive, and Neural Domains following Ketamine Treatment for Depression
Background: Ketamine is known for its rapid antidepressant effect, which is hypothesized to be rooted in rapid enhancement of neuroplasticity mechanisms. However, the majority of experimental work to delineate mechanisms has been performed in animal models exhibiting depressive-like behaviors and phenotypes. Ketamine's impact across a range of putative 'plasticity' markers in human patients remains relatively unexplored. These potential markers are measurable across multiple levels of analysis, and include: affective information processing patterns (e.g., attentional bias towards sad content); cognitive flexibility in goal-directed decision making (e.g., 'model-based' planning); psychological/conscious experiences (e.g., experiences of awe, vastness, connectedness, etc.); and neuroimaging markers of functional and structural connectivity. In a series of studies using both randomized and open-label designs in depressed patients, we harnessed a single dose of ketamine to assess mechanistic shifts in a range of integrative 'plasticity' markers and their relation to antidepressant efficacy.
Methods: In two open-label, single-dose studies in depressed patients, a novel dual probe video task was used to index attentional bias toward sad film clips before and after intravenous ketamine (0.5mg/kg over 40min). In a randomized controlled trial (RCT) comparing ketamine to saline infusion, the 'AWE-S' self-report scale was used to test for a mediating role of self-reported experiences of ‘awe’ during ketamine infusion, and structural and functional MRI markers were examined pre- and post-infusion in relation to depression improvements. In both the RCT and the open-label studies, the 'two-step task' was used to provide a performance-based index of cognitive flexibility and goal-directed behavior.
Results: Rapid antidepressant effects of ketamine were evident in clinical outcomes across all datasets. Participants in both of the open-label studies exhibited a robust reduction in attentional bias toward sad film content from pre- to 24-hrs post-ketamine infusion, and changes in attentional bias were correlated with improved symptoms from pre- to post-infusion. Participants in the RCT reported robust, ketamine-specific acute infusion day experiences of 'awe,' which strongly mediated both rapid and more enduring antidepressant effects of ketamine. Patients in the RCT also exhibited rapid, ketamine-specific shifts in both structural and functional neuroimaging markers of neuroplasticity within prefrontal and affective circuits, which were tied to the degree of depression improvement across individuals. In contrast, neither the RCT nor the open-label studies contributed any evidence for a rapid effect of ketamine on goal-directed behavior, as measured in the two-step task.
Conclusions: Findings across multiple levels of analysis indicate that ketamine reliably and rapidly impacts several specific markers of cognitive, behavioral, and neural plasticity, including attentional bias, structural and functional connectivity, and induces an acute cognitive shift towards self-reported 'awe-like' experiences; and yet, does not impact 'model-based planning,' a specific form of cognitive flexibility that has been previously associated with clinical phenotypes (most notably, compulsivity). Findings offer novel translational

insights into the precise mechanisms involved in ketamine's rapid antidepressant action among human patients, informing an integrative model of ketamine's rapid, plasticity-enhancing effects.

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REAL-WORLD SAFETY OF ESKETAMINE NASAL SPRAY: A COMPREHENSIVE ANALYSIS OF DATA FROM THE FIRST 58 MONTHS AFTER APPROVAL

Gerard Sanacora, Yale University

Individual Abstract: The repurposing of ketamine for the treatment of psychiatric disorders has led to concerns about longer-term safety associated with repeated dosing. The US FDA approval of intranasal (IN) esketamine for the indications of treatment resistant major depressive disorder and major depressive disorder associated with suicidal ideation granted alongside a comprehensive risk evaluation and mitigation strategy (REMS). To comprehensively examine the real-world safety of (IN) esketamine we reviewed the REMS database over the first 58 months of post-approval data in the United States. Safety data from patient monitoring forms submitted to the esketamine Risk Evaluation and Mitigation Strategy program in addition to reports submitted to the Janssen United States Global Medical Safety database between (March 5, 2019, to January 5, 2024). A total of 1,486,213 outpatient treatment sessions were completed by 58,483 enrolled patients who had ≥1 esketamine treatment session. Data on patient characteristics, usage and dosage patterns, adverse events of interest (actively solicited sedation, dissociation, and increased blood pressure), and serious adverse events following esketamine administration will be discussed along with the identified incidence of suicidal behavior. This data will provide the most comprehensive real-world investigation related to the longer-term safety and use patterns associated with IN esketamine in the US.

Literature References: Morrison R, Singh J, Daly E, et al. Effect of Esketamine Nasal Spray on Cognition in Patients with Treatment-Resistant Depression: Results From Four Phase 3 Studies Int J Neuropsychopharmacol. 2024 Nov 1;27(11):pyae046.
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SUICIDE-RELATED BIOMARKERS OF RESPONSE TO KETAMINE

Elizabeth Ballard, National Institute of Mental Health

Individual Abstract: While racemic ketamine has been linked to reductions in suicidal thoughts, its impact as an intervention for suicide risk has yet to be established. In this presentation, I will review recent findings on suicide-related biomarkers of response to ketamine. First, I will present findings on the effect of ketamine on suicide risk factors such as psychological pain and traumatic stress, which can be used as treatment targets for suicide risk. Then, I will highlight new findings on implicit markers of suicide risk using electrophysiological techniques such as magnetoencephalography (MEG), implicating the anterior insula and salience network in suicide risk. Lastly, I will provide data on the impact of ketamine on nocturnal alpha, beta and delta oscillations during polysomnography,

underscoring the critical need to understand whether ketamine improves suicide risk and depression through sleep-related factors. Implications for future research on suicide and ketamine will be discussed.
Literature References: Ballard ED, Neely L, Waldman L, Greenstein D, Zarate CA. Clinical indicators of the suicide crisis and response to ketamine. J Affect Disord, In Press.
Ballard ED, Greenstein D, Reiss PT, Crainiceanu C, Cui E, Duncan WC, Hejazi N, Zarate CA. Functional changes in sleep-related arousal after ketamine administration in individuals with treatment-resistant depression. Translational Psychiatry. 2024:14:238.

ESKETAMINE AND KETAMINE - IS THERE A MEANINGFUL DIFFERENCE?

Samuel Wilkinson, Yale School of Medicine

Individual Abstract: Strong opinions exist as to whether a meaningful clinical difference exists between ketamine and esketamine. This presentation will review literature on this topic and present the protocol for a large, multi-site comparative effectiveness trial investigating ketamine v. esketamine for treatment-resistant depression. The EQUIVALENCE trial is conducted under an IND and is designed as a non-inferiority trial that will enroll and randomize 400 patients over 6 sites to a treatment course of intranasal esketamine or intravenous ketamine (8 treatments given twice weekly for 4 weeks). Esketamine dosing will be 56 or 84mg, according to the package insert; ketamine dosing will start at 0.5mg/kg and may increase per clinician judgment up to the FDA limit for clinical trials. The primary outcome is change in self-reported depression severity, as measured by the Quick Inventory of Depression Symptomatology (QIDS) from baseline to 1 month. The EQUIVALENCE trial is funded by the Patient Centered Outcomes Research Institute (NCT06713616).
Literature References: Evaluation of the Trajectory of Depression Severity With Ketamine and Esketamine Treatment in a Clinical Setting. Nikayin S, Rhee TG, Cunningham ME, de Fontnouvelle CA, Ostroff RB, Sanacora G, Wilkinson ST. JAMA Psychiatry. 2022 Jul 1;79(7):736-738.
Efficacy and safety of racemic ketamine and esketamine for depression: a systematic review and meta-analysis. Bahji A, Zarate CA, Vazquez GH. Expert Opin Drug Saf. 2022 Jun;21(6):853-866.

EVALUATING THE ASSOCIATION BETWEEN ANTIDEPRESSANT EFFICACY AND DISSOCIATION WITH KETAMINE

Sara Di Luch, University Health Network

Individual Abstract Introduction: Intravenous (IV) ketamine has demonstrated rapid and robust antidepressant effects at sub-anesthetic doses for treatment-resistant depression. Ketamine induces variable dissociative effects, creating a wide spectrum of “psychedelic experience” intensity between patients. However, whether this mind-altering experience is required for clinical benefits in mood disorders remains largely understudied.
Methods: We conducted a linear regression on adults (n = 14) with treatment-resistant bipolar depression (TRBD) who received four acute ketamine infusions in an ongoing single-arm, open-label study (NCT05339074) to examine the correlation between the intensity of dissociation and antidepressant efficacy. Antidepressant efficacy was evaluated as a change in depression severity between baseline and after four infusions using the Montgomery-Åsberg Depression Rating Scale (MADRS). Dissociation was assessed after the first infusion using the Clinician-Administered Dissociative States Scale (CADSS).

Results: Depression severity decreased over time, with a mean MADRS score reduction of 10.9 points (± 8.7) from a baseline mean of 24.4 (± 5.7). The mean CADSS score following the first infusion was 22.6 (± 13.1). Linear regression analysis showed no significant correlation between peak CADSS scores and change in MADRS scores ($R^2 = 0.01$), indicating that the intensity of dissociative effects did not predict antidepressant response.

Conclusion: As one of the first studies to evaluate ketamine's dissociative symptoms in TRBD, these findings can significantly challenge existing paradigms surrounding ketamine and related psychedelic therapies, suggesting that ketamine's clinical benefits may not depend on a meaningful psychedelic experience. Further research can lead to the engineering of ketamine-like treatments that minimize psychoactive side effects for improved tolerability.

Literature References Ballard, E.D., Zarate, C.A. The role of dissociation in ketamine's antidepressant effects. Nat Commun 11, 6431 (2020). https://doi.org/10.1038/s41467-020-20190-4

Mathai DS, Nayak SM, Yaden DB, Garcia-Romeu A (2023) Reconsidering "dissociation" as a predictor of antidepressant efficacy for esketamine. Psychopharmacology (Berl) 240:827–836.

*EXPANDING THE REACH OF CLINICAL TRIALS: INCLUDING PATIENTS WITH SUICIDAL THOUGHTS AND BEHAVIOR

Manish Jha, University of Texas Southwestern Medical Center

Overall Abstract: Approximately one-third to one-half of people with mental health conditions have thought about suicide and up to one-half report having made a suicide attempt. Unfortunately, only about one-third of people who die by suicide are in some kind of treatment at the time of their death and those who are medicated are typically undermedicated. Given the extent of this experience with suicide, it is important for people with suicidal ideation and past behavior to be included in clinical trials to fortify the quality and impact of medications and treatments. There are many researchers who engage in clinical trials and research concerning a people with variety of mental health conditions such as depression and psychosis and include people with suicidal ideation and/or behavior yet there is a reluctance to include people with such experience in pharmacological trials. This panel will present how people with suicidal ideation and/or behavior can be included in clinical trials so that we can expand our reach to people with suicidal ideation and/or behavior. Examples of how this is done in clinical trials that focus on people with treatment resistant depression rather than suicidal ideation and/or behavior itself will be provided. Perspective from regulators such as the FDA will also be included. The goal is to foster the inclusion of people who have experienced suicidal ideation and/or behavior in clinical trials and to provide the tools necessary to make this a robust and informative process. The impact will be to foster the development of medications and treatments that are directed to the people who can benefit most from them.

Learning Objective 1: Discuss the unmet need for novel treatment development targeting suicidal ideation and/or behaviors.

Learning Objective 2: Identify opportunities for designing and conducting inclusive studies that enroll individuals with suicidal ideation or behaviors

Literary References: Nock MK, Kleiman EM, Abraham M, Bentley KH, Brent DA, Buonopane RJ, Castro-Ramirez F, Cha CB, Dempsey W, Draper J, Glenn CR, Harkavy-Friedman J, Hollander MR, Huffman JC, Lee HIS, Millner AJ, Mou D, Onnela JP, Picard

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Wilkinson ST, Bryan CJ, Alphs LD, Canuso CM, Ostacher MJ, Price RB, Bloch MH, Zarate CA, Rhee TG. Making Progress in Clinical Trials for Suicide Prevention: A Review. JAMA Psychiatry. 2025 Feb 12. doi: 10.1001/jamapsychiatry.2024.4810.

SUBTYPING SUICIDALITY: BREAKTHROUGHS AND CHALLENGES IN ASSESSING THE NEUROBIOLOGY OF SYMPTOM HETEROGENEITY IN ADULTS WITH UNIPOLAR DEPRESSION

Katharine Dunlop, University of Toronto

Individual Abstract: Major depressive disorder (MDD) is a heterogeneous condition that is diagnosed when a patient presents with five or more of nine possible symptoms, such as low mood, anhedonia, and suicidality. Motivated by this complexity, there is renewed interest in efforts to delineate biologically-based MDD subtypes, which could open avenues for understanding pathophysiological mechanisms, identifying subtype-specific biomarkers, and informing treatment selection decisions. Unfortunately, many clinical trials exclude individuals with active suicidal ideation, making it challenging to understand symptom heterogeneity and the clinical utility of subtyping models in this subpopulation. The purpose of this talk is to discuss how suicidality impacts in subtyping approaches in MDD.
Resting-state fMRI scans and symptom severity from 328 adults with MDD were used to train a regularized canonical correlations analysis explaining dimensions of co-occurring symptoms and resting-state functional connectivity (RSFC). These dimensions were used to identify distinct patient clusters. 46% of the sample reported active ideation, with or without suicidal intent on the Hamilton Rating Scale for Depression, Item 3 GREATER THAN 1. Our analysis identified three robust and stable symptom-RSFC dimensions, which clustered participants into four MDD subtypes with distinct symptoms, atypical RSFC and response to repetitive transcranial magnetic stimulation (rTMS). Subtype 1, characterized by mood and somatic symptoms, exhibited the lowest rates of suicidality and greatest responses to rTMS. Subtype 3, characterized by increased anhedonia, exhibited the greatest rates of suicidality and lowest response rates to rTMS. This subtype also exhibited significantly greater RSFC between the dorsolateral prefrontal cortex and nodes of the cingulo-opercular and salience networks related to nondepressed controls. We next projected new participant RSFC data, with a restricted range of suicidality and were treated with escitalopram, into this model. In this sample, 14 of 130 of participants reported active suicidal ideation, and participants assigned to subtype 3 also exhibited the poorest responses to escitalopram.
The results support the robustness and clinical utility of biologically-based subtyping approaches in a diverse MDD sample. These findings underscore the importance of biologically-based subtyping in MDD, particularly in understanding the complex interplay between symptoms, brain connectivity, and treatment responses. By identifying distinct subtypes with unique symptom profiles and differential responses to therapies like rTMS and escitalopram, this research paves the way for more personalized, effective treatment strategies. Moreover, the inclusion of suicidality in MDD subtyping models highlights the need for further exploration into this often-overlooked aspect of the disorder. The results also acknowledge limitations related to characterizing suicidality in subtyping approaches using secondary data analyses, including few scales quantifying suicidality, and limited item response range. These advancements not only enhance our understanding of the

neurobiological underpinnings of MDD but also bring us closer to developing targeted interventions that address the diverse needs of individuals with this debilitating condition.
Literature References: Dunlop K, Grosenick L, Downar J et al. Dimensional and categorical solutions to parsing depression heterogeneity in a large single-site sample. Biological Psychiatry. 2024;50(1):230-45.
Tozzi L, Zhang X, Pines A et al. Personalized brain circuit scores identify clinically distinct biotypes in depression and anxiety. Nature Medicine. 2024;30:2076-87.

MANAGING SUICIDALITY IN CLINICAL TRIALS FOR PROLONGED GRIEF: AN EXAMPLE OF TWO STUDIES

Natalia Skritskaya, Columbia University

Individual Abstract: This presentation will reflect on inclusion of participants with suicidal ideation in clinical trials for prolonged grief, a condition of persistent pervasive impairing grief. It will include data from an NIMH funded multi-site study (n=395) of the efficacy of citalopram vs. pill placebo, when administered with and without Prolonged Grief Therapy (PGT). Out of 395 bereaved participants randomized to the overall study, over half reported at least some suicidal ideation at baseline. Participants included 58 suicide-bereaved individuals as part of an AFSP funded sub-project. Individuals were included in the overall study unless the participant was considered to be at an imminent risk for suicide. Approach to management of suicidality in this study will be reviewed as well as study results including changes in suicidal thinking and behavior during treatment. Additionally, we will describe plans for inclusion and suicidality management in a current treatment development study of adapting PGT for suicide-bereaved families, comparing and contrasting procedures used in an efficacy RCT compared to a treatment development project.
Literature References: Shear, M K, Reynolds, C, Simon, N, Zisook, S, et al. "Optimizing treatment of complicated grief: A randomized clinical trial." JAMA psychiatry 73.7 (2016): 685-694.
Zisook, S, Shear, M K, Reynolds, C, Simon, N, Mauro, C, Skritskaya, N, et al. "Treatment of complicated grief in survivors of suicide loss: a HEAL report." The Journal of clinical psychiatry 79.2 (2018): 21274.

REGULATORY PERSPECTIVES ON SUICIDAL IDEATIONS AND BEHAVIORS IN CLINICAL TRIALS

Zimri Yaseen, FDA/CDER/OND/ON/DP

Individual Abstract: Suicide is an important public health issue and, although treatments effective for major psychiatric disorders are likely to reduce suicide risk overall among patients with those disorders, a significant unmet medical need remains for treatments effective in reducing the risk of suicide and the burden of suicidal thoughts and behaviors. In this talk, regulatory perspectives are offered regarding the assessment of suicidal thoughts and behaviors in clinical trials from both safety and efficacy perspectives. The focus is on trials intended to support drug development, but the concepts are expected to be broadly applicable to clinical trials more generally. This talk will discuss categorization of suicidal ideation and behavior (SIB), the spectrum of target and study populations, how study population can impact the approach to evaluating SIB as a safety outcome, and various ways in which SIB might be approached as an efficacy outcome.
Study population can be considered as falling on a spectrum of salience of SIB as a concern, ranging from populations where SIB is the primary treatment target to populations that may have some increase in risk of prevalent or incident SIB but for which SIB is not considered a

key aspect of the condition being studied. SIB should always be recorded as an adverse event when it is new or increased from baseline; however, the threshold for considering it a serious adverse event may be lowered as it becomes less expected for the study population. Suicidal ideation and behavior are clearly clinically important, but how they relate to a clinical endpoint – one that represents a direct measure of how a person feels functions or survives – is less clear. A variety of approaches to this issue may be viable, but all require engagement with FDA to be used to support a claim of effectiveness in a regulatory context. We invite and encourage such engagement as there is a great need to develop valid and reliable SIB-related endpoints. Doing so will advance our public health mission by supporting and facilitating the development of new and effective treatments.

Literature References: Food and Drug Administration, Center for Drug Evaluation and Research (CDER). Guidance for Industry: Suicidal Ideation and Behavior: Prospective Assessment of Occurrence in Clinical Trials
DRAFT GUIDANCE. 2012; available at: https://www.fda.gov/media/79482/download
Meltzer, H. Y., Alphs, L., Green, A. I., Altamura, A. C., Anand, R., Bertoldi, A., ... and InterSePT Study Group. Clozapine treatment for suicidality in schizophrenia: international suicide prevention trial (InterSePT). Archives of general psychiatry. 2003; 60(1), 82-91

INCLUDING PEOPLE WITH SUICIDAL THOUGHTS AND BEHAVIORS IN CLINICAL TRIALS OF MOOD DISORDERS

Andrew Nierenberg, Massachusetts General Hospital

Individual Abstract: Clinical trials of interventions for major depressive disorder and bipolar disorder generally exclude participants who have suicidal ideation or behavior or who are at high risk of dying by suicide, with a few exceptions (e.g., ketamine). Reasons for these exclusions include regulatory, ethical, liability, and safety concerns. The main problem is limited generalizability, given that about 47% of people with MDD and 80% will experience suicidal ideation or behaviors over their lifetime. Another problem is by excluding these people from clinical trials we have limited data about how best to treat them. But all is not lost. There have been successful clinical trials, ranging from randomized, placebo control trials to large pragmatic trials that include people at risk. This presentation will cover a discussion of an NIMH framework to mitigate risk, how this was implemented in the STAR*D study, and how suicide risk has been implemented in pragmatic trials.

Literature References: Nierenberg, A.A., Trivedi, M.H., Ritz, L., Burroughs, D., Greist, J., Sackeim, H., Kornstein, S., Schwartz, T., Stegman, D., Fava, M. and Wisniewski, S.R. Suicide risk management for the sequenced treatment alternatives to relieve depression study: applied NIMH guidelines. Journal of Psychiatric Research. 2004;38, 83-589.
Köhler-Forsberg, O., Madsen, T., Behrendt-Møller, I., Sylvia, L., Bowden, C.L., Gao, K., Bobo, W.V., Trivedi, M.H., Calabrese, J.R., Thase, M. and Shelton, R.C. Trajectories of suicidal ideation over 6 months among 482 outpatients with bipolar disorder. Journal of Affective Disorders. 2017:223, 146-152.

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

***REIMAGINING LITHIUM – FROM BEDSIDE TO BENCH**
Paul Keck, Lindner Center of HOPE/University of Cincinnati

Overall Abstract: From bedside to bench, the clinical benefits of lithium spurred basic science research that sheds new light on neurogenesis and synaptic plasticity, opening new avenues for drug development. The clinical benefits and therapeutic promise of lithium will be reviewed in diverse settings including bipolar disorder, suicidality, depression, and dementia. While the benefits of lithium have been attributed to multiple mechanisms, new data suggest a central role for GSK3β inhibition. In one study, human induced pluripotent stem cells (hiPSCs) were derived from people with bipolar disorder (BD) who were lithium responsive (N=7), non-responsive (N=3), or people unaffected by BD (N=6). Proteomics were analyzed in neurons treated and untreated with lithium, and genes of candidate proteins were queried against a gene expression database for BD. Collapsin-response mediated protein 2 (CRMP2) was identified as a primary mediator of lithium effects. Lithium and GSK3βinhibitor CHIR99021 (each p LESS THAN 0.0001, Tukey test), reduced CRMP2 phosphorylation at site T514. Baseline CRMP2-p-T514 was higher in hiPSC-derived neurons from lithium responders vs. non-responders (p LESS THAN 0.0001, t-test). Dendritic spine density was 25% lower in CRMP2 knockout mice vs. wild-type mice (WT, p LESS THAN 0.001, t-test), while lithium increased dendritic spine density 36% in WT mice (p LESS THAN 0.001). Higher CRMP2-p-T514 (p=0.01) and lower dendritic spine density (p=0.003) were present in post-mortem human brain among those who were not on lithium at the time of death (N=5) vs. unaffected individuals (N=16). Methamphetamine elevated CRMP2-p-T514 vs. saline in hippocampal neurons (n=3 mice brains/group, p LESS THAN 0.05, unpaired t-test), while CRMP2 knock-in mice (N=17) with CRMP2 that could not be phosphorylated at T514 showed less methamphetamine-induced locomotion than WT mice (N=10, p LESS THAN 0.05, repeated measures ANOVA), mimicking the effects of lithium. The lithium response pathway involves a reduction in GSK3β phosphorylation of CRMP2 that is associated with an increased dendritic spine density.
Learning Objective 1: Appreciate the clinical evidence supporting lithium's unique clinical benefits, including its neuroprotective properties, and the hypothesis that potent GSK3β inhibition underlies these effects
Learning Objective 2: Understand the science which indicates that potent GSK3ββ inhibition induces activation of a collapsin response mediator protein 2 (CRMP2) to support synaptic plasticity, and how this paradigm supports the development of investigational drugs to harness the benefits or lithium while avoiding renal dysfunction
Literary References: [1] Meyer JM, Stahl SM: The Lithium Handbook - Stahl's Handbooks. New York, NY, Cambridge University Press; 2023.
[2] Zhao WN, Tobe BTD, Udeshi ND, Xuan LL, Pernia CD, Zolg DP, Roberts AJ, Mani D, Blumenthal SR, Kurtser I, Patnaik D, Gaisina I, Bishop J, Sheridan SD, Lalonde J, Carr SA, Snyder EY, Haggarty SJ. Discovery of suppressors of CRMP2 phosphorylation reveals compounds that mimic the behavioral effects of lithium on amphetamine-induced hyperlocomotion. Transl Psychiatry. 2020;10:76.

REIMAGINING LITHIUM – FROM BEDSIDE TO BENCH

Paul Keck, Lindner Center of HOPE/University of Cincinnati

Individual Abstract: While the benefits of lithium have been attributed to several mechanisms, new data suggest a central role for GSK3β inhibition.

In one study, human induced pluripotent stem cells (hiPSCs) were derived from people with bipolar disorder (BD) who were lithium responsive (N=7), non-responsive (N=3), or people unaffected by BD (N=6). Proteomics were analyzed in neurons treated and untreated with lithium, and genes of candidate proteins were queried against a gene expression database for BD. Collapsin-response mediator protein-2 (CRMP2) was identified as a primary mediator of lithium effects. Lithium and GSK3β inhibitor CHIR99021 each reduced CRMP2 phosphorylation at site T514 (p LESS THAN 0.0001, Tukey's HSD post-hoc test). Baseline CRMP2-p-T514 was higher in hiPSC-derived neurons from lithium responders vs. non-responders (p LESS THAN 0.0001, t test). Dendritic spine density was 25% lower in CRMP2 knockout mice vs. wild-type mice (WT, p LESS THAN 0.001, t test), while lithium increased dendritic spine density 36% in WT mice (p LESS THAN 0.001). Higher CRMP2-p-T514 (p=0.01) and lower dendritic spine density (p=0.003) were present in post-mortem human brains among those who were not on lithium at the time of death (N=5) vs. unaffected individuals (N=16). Methamphetamine elevated CRMP2-p-T514 vs. saline in hippocampal neurons (n=3 mice brains/group, p LESS THAN 0.05, unpaired t-test), while CRMP2 knock-in mice (N=17) with CRMP2 that could not be phosphorylated at T514 showed less methamphetamine-induced locomotion than WT mice, (N=10, p LESS THAN 0.05, repeated measures ANOVA), mimicking the effects of lithium.

The lithium response pathway in BD involves a reduction in GSK3β phosphorylation of CRMP2 that is associated with an increased dendritic spine density.

Literature References: [1] Fountoulakis KN, Tohen M, Zarate CA. Lithium treatment of bipolar disorder in adults: a systematic review of randomized trials and meta-analyses. European neuropsychopharmacology: the journal of the European College of Neuropsychopharmacology. 2022;54:100-115.

[2] Tobe BTD, Crain AM, Winquist AM, Calabrese B, et al. Probing the lithium-response pathway in hiPSCs implicates the phosphoregulatory set-point for a cytoskeletal modulator in bipolar pathogenesis. Proc Natl Acad Sci U S A. 2017;114:E4462-E4471.

REIMAGINING LITHIUM – FROM BEDSIDE TO BENCH

Gary Sachs, Massachusetts General Hospital and Harvard Medical School

Individual Abstract: The clinical benefits of lithium and possibly other GSK3β inhibitors extend beyond psychiatry. In vitro evidence points to lithium's neurotrophic and neuroprotective effects via inhibition of GSK3β and induction of signaling mediated by BDNF. In one study, transgenic mice overexpressing mutant human tau were treated with lithium chloride (LiCL) which resulted in significant GSK-3 inhibition and significantly lower levels of phosphorylation at several epitopes of tau known to be hyperphosphorylated in Alzheimer's disease. LiCL also significantly reduced levels of aggregated, insoluble tau in the cortex of LiCl-treated male mice (n = 5) relative to controls (n = 5), as revealed by CP27. Tau phosphorylated at Ser-202 and Ser-396/404 was also diminished by the treatment. In the brainstem, Sarkosyl-insoluble tau was decreased (p LESS THAN 0.01) in either male or female mice (vehicle, n = 5; LiCl, n = 6). Pathology in the gray matter of spinal cord from mice was analyzed with antibody MC1 and Gallyas silver stain. A positive correlation was seen between insoluble tau levels and MC1-immunopositive cell staining (12-month-old mice, LiCl: R = 0.7, P = 0.005, n = 11; PBS: R = 0.5, p = 0.05, n = 12; 8-month-old mice,

LiCl: R = 0.97, P = 0.003, n = 6; PBS, R = 0.88, p = 0.03, n = 6). There was no difference between the percentage immunostaining for MC1 and treatment in either group.
Treatment of neurological disorders such as tauopathies may benefit from the use of kinase inhibitors.
Literature References: [1] Noble W, Planel E, Zehr C, et al. Inhibition of glycogen synthase kinase-3 by lithium correlates with reduced tauopathy and degeneration in vivo. Proc Natl Acad Sci U S A. 2005;102(19):6990-5.
[2] Chiu CT, Chuang DM. Neuroprotective action of lithium in disorders of the central nervous system. PMCID. 2011;PMCID: PMC3172812.

REIMAGINING LITHIUM – FROM BEDSIDE TO BENCH
Pablo Lapuerta, 4M Therapeutics
Individual Abstract: There is agreement among treatment guidelines that lithium is the gold standard mood stabilizer for patients with a history of mania due to its broad efficacy and its unique impact on the risk of completed suicide. Lamentably, lithium utilization remains low worldwide in part due to clinician fear of adverse effects, especially concerns around lithium's risk for renal dysfunction. There is, however, hope on the horizon, and the treatment paradigm may in the future be altered by harnessing a core essential mechanism of lithium: inhibition of the kinase GSK3β.
This symposium will thus present the modern view of lithium, exploring the clinical evidence for its distinct benefits on mood, cognition and suicidality, the current mechanism underlying lithium related renal dysfunction, and how GSK3β inhibition plays a central role in lithium's therapeutic profile. Recent research has identified that the crucial downstream effect of potent GSK3β inhibition is to activate collapsin response mediator protein 2 (CRMP2), a protein with a key role in synaptic plasticity. This symposium will review how this new understanding of GSK3β and synaptic plasticity is supporting the development of new investigational GSK3β inhibitors with the potential to become effective and safer alternatives to lithium and other medications for bipolar disorder.
Literature References: Fountoulakis KN, Tohen M, Zarate CA, et al. Lithium treatment of bipolar disorder in adults: a systematic review of randomized trials and meta-analyses. Eur Neuropsychopharmacol. 2022;54:100-115.
Meyer JM, Stahl SM, et al. The Lithium Handbook - Stahl's Handbooks. New York, NY: Cambridge University Press; 2023.

***ALCOHOL AND COCAINE USE DISORDERS: NEW FINDINGS IN TELEHEALTH AND NOVEL TREATMENT APPROACHES**
Lori Davis, Veterans Affairs Medical Center

Overall Abstract: This panel brings together three diverse topics with cutting edge results that offer promise in the treatment of alcohol and cocaine use disorders. Dr. Verrico will present the rationale and early drug development results of a selective glucocorticoid receptor antagonist, PT150, in the treatment of alcohol use disorder. Dr. Hendricks will present the preliminary results of a randomized controlled trial of psilocybin combined with cognitive behavioral therapy in individuals with cocaine use disorder, most of whom had concurrent alcohol use disorder. Dr. Davis will present a retrospective analysis of archival Veteran Health Administration (VHA) electronic medical records of 441,678 veterans diagnosed with alcohol use disorder (AUD) showing the patterns of telehealth services, AUD medication use, and health resource utilization during a 4-year period (2 years before and after the onset of the COVID-19 pandemic in 2020). Although gender and racial disparities exist, there was strong association between the receipt of telehealth mental health services, as well as

prescriptions for AUD medications, and a reduction in high intensity service utilization and suicidality. The distinguished Dr. Ivan Montoya will serve as our discussant to highlight the importance of advancing the telehealth delivery of treatment and novel medications in combination with psychotherapy in the treatment of substance use disorders.
Learning Objective 1: The participant will be more informed on new targets for the treatment of alcohol and cocaine use disorders, specifically a selective glucocorticoid receptor antagonist and psilocybin.
Learning Objective 2: The participant will become more informed on the patterns of telehealth mental health services and medications for the treatment of alcohol use disorder (AUD) in a large cohort of Veterans over a four-year period, and that the receipt of telehealth services and AUD medications are associated with a reduction in high intensity services such as emergency department and inpatient treatment, as well as reduced suicidality after the COVID-19 pandemic began in 2020.
Literary References: 1. Morice C, Baker DG, Patel MM, et al. A randomized trial of safety and pharmacodynamic interactions between a selective glucocorticoid receptor antagonist, PT150, and ethanol in healthy volunteers. Sci Rep. 2021;11(1):9876. Published 2021 May 10. Doi:10.1038/s41598-021-88609-6
2. Perumalswami PV, Kilpatrick S, Frost MC, et al. The impact of COVID-19 on trends in alcohol use disorder treatment in Veterans Health Administration. Addiction. 2023;118(6):1062-1071. Doi:10.1111/add.16156

INTERACTIONS BETWEEN ETHANOL AND PT150, A SELECTIVE GLUCOCORTICOID RECEPTOR ANTAGONIST, IN HEALTHY VOLUNTEERS
Ynhi Thomas, Baylor College of Medicine & Michael E. DeBakey VA Medical Center

Individual Abstract Background: PT150, a novel competitive glucocorticoid receptor (GR) antagonist, has shown safety in animal models, healthy volunteers, and individuals with depression. Its potential as a treatment for alcohol use disorder necessitates safety and tolerability studies, including investigations into pharmacodynamic and pharmacokinetic interactions with ethanol.
Study 1 Objectives and Methods: The first study was a single-site, Phase I pilot trial conducted to evaluate the pharmacodynamic interactions between PT150 and ethanol. Community-recruited, healthy, alcohol-experienced participants aged 21–64 years were enrolled. PT150 (900 mg/day) was administered orally for five days. Participants underwent beverage challenges on Day 1 (prior to PT150 exposure) and Day 5 (after PT150 exposure), receiving both alcohol (1.03 mL/kg of 16% ethanol) and placebo (1% ethanol) beverages in random order. Primary outcomes included breath alcohol levels, blood pressure, heart rate, electrocardiograms (ECGs), and adverse events.
Study 1 Results: There were no statistically significant differences in vital signs or estimated breath alcohol concentrations between PT150 non-exposed and exposed conditions during the ethanol challenge. No clinically significant ECG abnormalities or serious adverse events were observed, demonstrating that PT150 was safe and well tolerated during co-administration with ethanol.
Study 2 Objectives and Methods: The second study was a non-randomized, single-site drug-drug interaction trial conducted to assess PT150's pharmacokinetics (PK) when co-administered with ethanol. Healthy, alcohol-experienced participants aged 21–64 years served as their own controls. Blood samples were collected before and after 1.03 mL/kg ethanol administration on Day 1 (baseline, prior to PT150 exposure), after the 5th of five daily doses of PT150 (900 mg/day), and after a 6th dose co-administered with ethanol on Day 6. PK outcomes included peak plasma concentration (Cmax), time to reach peak plasma

concentration (tmax), terminal elimination half-life (t½), and area under the concentration-time curve (AUC).
Study 2 Results: Co-administration of ethanol did not significantly impact PT150's PK parameters, and PT150 did not alter ethanol PK. No clinically significant ECG abnormalities or serious adverse events occurred.
Conclusions: Across both studies, PT150 was safe and well tolerated when administered with ethanol, with no significant pharmacodynamic or pharmacokinetic interactions observed. These findings provide the foundation for further investigation of PT150 as a potential treatment for alcohol use disorder.
Literature References: Reynolds AR, Saunders MA, Brewton HW, Winchester SR, Elgumati IS, and Prendergast MA. Acute oral administration of the novel, competitive and selective glucocorticoid receptor antagonist ORG 34517 reduces the severity of ethanol withdrawal and related hypothalamic-pituitary-adrenal axis activation. Drug Alcohol Depend. 2015;154: 100-4.
Radevski ME, Prendergast MA, Bardo MT, and Akins CK. PT150 blocks the rewarding properties of ethanol and attenuates ethanol-induced reduction of egg laying in Coturnix quail. Psychopharmacology (Berl). 2023;240(2): 295-301.

PSILOCYBIN-FACILITATED TREATMENT FOR COCAINE USE DISORDER

Peter Hendricks, The University of Alabama at Birmingham

Individual Abstract Background: Annual cocaine-related deaths are estimated at 28,000 in the US, an almost 75% increase since 2019. Most interventions for cocaine use disorder (CUD) result in modest success rates, and there are no approved pharmacotherapies for CUD. Prior research suggests that psilocybin may have broad anti-addictive properties, with recent clinical trials suggesting safety and efficacy of psilocybin in the treatment of alcohol use disorder and tobacco user disorder.
Methods: This clinical trial randomized 40 individuals with CUD to receive either 25 mg/70 kg psilocybin (n = 20) or 100 mg diphenhydramine (n = 20). Both groups received an 8-session manualized cognitive behavioral therapy (CBT) intervention for CUD. Drug administration sessions occurred after the 4th CBT session. Biochemically verified percentage of abstinent days (primary) and sustained abstinence rates (secondary) through 180 days after end-of-treatment were compared between groups using intent-to-treat analysis.
Results: No unexpected or serious adverse events were attributed to psilocybin or diphenhydramine. Percentage of abstinent days and sustained abstinence rates were significantly higher among those randomized to psilocybin, with large effect sizes.
Conclusions: One psilocybin session, compared to diphenhydramine, with manualized CBT, significantly and substantially increased long-term cocaine abstinence. These results indicate the promise of psilocybin in the treatment of CUD.
Literature References: Bogenschutz MP et al. Percentage of heaving drinking days following psilocybin-assisted psychotherapy vs placebo in the treatment of adult patients with alcohol use disorder: A randomized clinical trial. JAMA Psychiatry. 2022; 79 (10): 953-962.
Johnson MW et al. Long-term follow-up of psilocybin-facilitated smoking cessation. Am J Drug Alcohol Abuse. 2017; 43 (1): 55-60.

TELEHEALTH SERVICES AND PRESCRIPTIONS FOR MEDICATIONS IN THE TREATMENT OF ALCOHOL USE DISORDERS ARE ASSOCIATED WITH A REDUCTION IN HIGH INTENSITY HEALTH RESOURCE UTILIZATION AND SUICIDALITY IN VETERANS

Lori Davis, Veterans Affairs Medical Center

Individual Abstract Background: Although COVID-19 had a negative impact on mental health outcomes including those related to heavy alcohol use, the pandemic accelerated the adoption of telehealth delivery of mental health services in many health care systems.
Methods: A retrospective analysis of archival Veteran Health Administration (VHA) electronic medical records of 441,678 veterans diagnosed with alcohol use disorder (AUD) was conducted to determine the patterns of telehealth services and health resource utilization during a 4-year period, i.e. 2 years before and after the onset of the COVID-19 pandemic in 2020.
Results: There was negligible utilization of telehealth group and individual psychotherapy services in the pre-COVID period in VHA in veterans with diagnosis of AUD. However, there was a substantial and sustained increase in the use of telehealth services post-COVID. Group psychotherapy was predominantly driven by telehealth rather in-person group psychotherapy during the 2 years post-COVID observation period. In-person psychotherapy plunged during the immediate post-COVID period and then rebounded for in-person individual psychotherapy but not for in-person group psychotherapy. The prescription fills for AUD medications (oral and extended-release naltrexone, disulfiram, topiramate, and acamprosate) experienced a slight decline immediately following the onset of COVID-19, however, subsequently surpassed baseline levels in the post-COVID period. In those diagnosed with AUD in the prior 6 months and prescribed a medication for AUD during the 4-year period, the use of any psychotherapy, telehealth psychotherapy or medications for AUD in the prior 30 days were all associated with significantly fewer emergency department visits, lower suicidality, and fewer mental health admissions. Further analysis revealed significant racial and gender disparities, with white veterans receiving a greater number of AUD medication prescriptions than black veterans, and women receiving more AUD-related prescriptions than men. Compared to men, women are more likely to utilize AUD telehealth services and medications for AUD. In conclusion, telehealth counseling for AUD witnessed a post-COVID-19 surge that has been sustained in VHA. More importantly, telehealth psychotherapy services and/or prescriptions for AUD medications may be positive influencers in lowering suicidality and preventing high intensity services such as emergency department and inpatient admissions. Gender and racial disparities exist, and further exploration of these findings are warranted.
Literature References: 1. Grebla R, Liu J, O'Sullivan AK, et al. Treatment Journey and Healthcare Resource Use Among Patients With Alcohol Use Disorder Who Initiated Extended-Release Naltrexone: An Analysis of Veterans Affairs Data. Subst Use. 2024;18:29768357241280713. Published 2024 Sep 26. doi:10.1177/29768357241280713
2. Perumalswami PV, Kilpatrick S, Frost MC, et al. The impact of COVID-19 on trends in alcohol use disorder treatment in Veterans Health Administration. Addiction. 2023;118(6):1062-1071. doi:10.1111/add.16156

***TARGETING MAJOR DEPRESSIVE DISORDER SUBTYPES FOR TREATMENT DEVELOPMENT. SELECTING OPTIMAL ASSETS FROM THE PIPELINE**

George Papakostas, Massachusetts General Hospital

Overall Abstract: Depression is the leading cause of disability in the world and is associated with high rates of suicidal behavior. More than a third of patients suffering from MDD do not experience adequate treatment response with currently available first-line therapy, highlighting the need for additional therapies with new mechanisms of action. In addition, many approved therapies have a significant side effect burden, including sexual dysfunction and weight gain, which cause patients to discontinue their therapy. These medications often fail to address the full range of MDD symptoms. These factors contribute to treatment resistance and treatment discontinuation. More effective and easily tolerated therapeutic interventions are needed to address the immense individual and societal burdens of MDD. In particular, developing treatments for specific sub-populations of patients remains a major unmet need. I the current workshop, speakers will select assets from the existing pipeline and present arguments why these are best suited for clinical development in three sub-populations: pediatric populations, anxious depression and depression with prominent irritability.

Learning Objective 1: To understand unique opportunities for treatment development in pediatric populations

Learning Objective 2: To understand unique opportunities for treatment development in anxious depression and depression with prominent irritability.

Literary References: Jha MK, Minhajuddin A, South C, Rush AJ, Trivedi MH. Irritability and Its Clinical Utility in Major Depressive Disorder: Prediction of Individual-Level Acute-Phase Outcomes Using Early Changes in Irritability and Depression Severity. Am J Psychiatry. 2019 May 1;176(5):358-366.

Guidetti C, De Martin S, Serra G, Apicella M, Pani L, Pappagallo M, Mattarei A, Folli F, Manfredi P, Fava M. Effect of Time From Onset of Major Depressive Disorder on the Therapeutic Response to Esmethadone (REL-1017). J Clin Psychiatry. 2024 May 13;85(2):22m14735.

PIPELINE FOR MAJOR DEPRESSIVE DISORDER: CANDIDATE COMPOUNDS FOR DRUG DEVELOPMENT IN DEPRESSION WITH HIGH LEVELS OF IRRITABILITY

Manish Jha, University of Texas Southwestern Medical Center

Individual Abstract: Irritability, anger, and aggressiveness are transdiagnostic and interrelated constructs that remain poorly understood. While these are reported commonly by patients across a range of psychiatric disorders, there are no specific treatments that target these symptoms and behaviors. Hence, medications approved for other indications are commonly repurposed for their management. However, this approach has significant limitations, resulting in persistent symptomatic burden, functional impairments and higher rates of suicide-related morbidity and mortality. This presentation will include a review of candidate compounds in therapeutic pipeline, such as second generation antipsychotics, orexin receptor antagonists and esketamine, and present data on improvement in irritability with ketamine.

These data will include those from secondary analysis of a double-blind randomized controlled trial of ketamine versus midazolam that recruited 24 patients with suicidal ideation/behaviors. Overall depression severity was measured with the 16-item Quick Inventory of Depressive Symptomatology Self-Report (QIDS-SR) and the 10-item clinician-

rated Montgomery Asberg Depression Rating Scale (MADRS). Irritability was measured with the 5-item irritability domain of Concise Associated Symptom Tracking scale (CAST-IRR) while suicidality was measured with the 3-item suicidality factor of Concise Health Risk Tracking Scale (CHRT Suicidal Thoughts). Assessments were conducted at baseline, 24 hours, 48 hours, 72 hours and 7 days. Repeated measures analyses of variance evaluated changes in these symptoms over time. Correlations analyses were used to evaluate if changes in irritability were associated with changes in suicidal ideations.
There was a statistically significant difference in changes in irritability with ketamine versus midazolam (F=5.8, df=1,21, p=0.025). Participants randomized to irritability experienced greater reduction in irritability as compared to those randomized to placebo within 24 hours of infusion and this difference persisted till 7 days. Notably, there was no significant difference in changes in QIDS-SR (F=1.16, df=1,20, p=0.30) and MADRS (F=2.0, df=1,21, p=0.17) scores between ketamine and midazolam suggesting the effect on ketamine was independent of changes in overall depression severity. Further there was a very strong correlation between baseline-to-7-day changes in irritability and suicidal ideations (Pearson's correlation coefficient r=0.66, p LESS THAN 0.001).
In conclusion, preliminary data suggest that use of IV ketamine may be associated with marked reduction in irritability. Studies with longer-term follow-up are needed to evaluate durability of these improvements.
Literature References: Jha MK, Minhajuddin A, South C, Rush AJ, Trivedi MH. Irritability and Its Clinical Utility in Major Depressive Disorder: Prediction of Individual-Level Acute-Phase Outcomes Using Early Changes in Irritability and Depression Severity. Am J Psychiatry. 2019 May 1;176(5):358-366.
Jha MK, Williamson DJ, Magharehabed G, Turkoz I, Daly EJ, Trivedi MH. Intranasal esketamine effectively treats treatment-resistant depression in adults regardless of baseline irritability. J Affect Disord. 2023 Jan 15;321:153-160.

NOVEL THERAPIES FOR PEDIATRIC DEPRESSION: EXPLORING THE PIPELINE FOR BEST-FITTING CANDIDATES.
Clotilde Guidetti, Massachusetts General Hospital, and Harvard Medical School

Individual Abstract: Major depressive disorder (MDD) has point prevalence rates of approximately 2% in childhood and between 5% and 8% in adolescence. Pediatric MDD is often associated with problems in interpersonal relationships, school performance, and delays in social, emotional, and cognitive development.
The treatment of pediatric depression is challenging due to the limited efficacy and tolerability of current treatments, as well as the complex, heterogeneous nature of the condition. Currently, approved antidepressants for the pediatric population are limited to fluoxetine (ages 8-18 years) and escitalopram (ages 12-17 years). These treatments have been reported to be less effective in pediatric patients compared to adult patients (Feeney et al., 2022). Effective and safe treatments for pediatric depression remain an unmet medical need. This presentation will review the current MDD treatment pipeline and discuss select novel therapies that could be the best fit for treating pediatric depression.
Literature References: 1) Guidetti C, Serra G, Pani L, Pappagallo M, Maglio G, Martin S, Mattarei A, Folli F, Manfredi PL, Fava M. Subanalysis of Subjective Cognitive Measures From a Phase 2, Double-Blind, Randomized Trial of REL-1017 in Patients With Major Depressive Disorder. Prim Care Companion CNS Disord. 2023 Feb 14;25(1):22m03267
2)Feeney A, Hock RS, Fava M, Hernández Ortiz JM, Iovieno N, Papakostas GI. Antidepressants in children and adolescents with major depressive disorder and the influence

of placebo response: A meta-analysis. J Affect Disord. 2022 May 15;305:55-64. Doi: 10.1016/j.jad.2022.02.074. Epub 2022 Mar 3. PMID: 35247482.

SELECTING PROMISING TREATMENT LEADS FOR INSOMNIA IN MAJOR DEPRESSIVE DISORDER

Venkat Bhat, University of Toronto

Individual Abstract: Depression is the leading cause of disability worldwide and is associated with high suicide rates. Insomnia is a common symptom of Major Depressive Disorder (MDD), adversely affecting treatment outcomes and quality of life. Over a third of MDD patients do not respond to first-line therapies, underscoring the need for new treatments with distinct mechanisms. Standard treatments often fail to adequately address insomnia in MDD, complicating disease management. More effective and well-tolerated options are crucial for reducing the impact of MDD. This talk will review the current management of insomnia in MDD and explore new pharmacological options in the treatment pipeline, concentrating on agents that may provide improved efficacy and tolerability compared to traditional approaches for depression-related insomnia.

Literature References: De Crescenzo F, D'Alò GL, Ostinelli EG, et al. Comparative effects of pharmacological interventions for the acute and long-term management of insomnia disorder in adults: a systematic review and network meta-analysis. Lancet. 2022;400(10344):170-184.
Kishi T, Koebis M, Sugawara M, et al. Orexin receptor antagonists in the treatment of insomnia associated with psychiatric disorders: a systematic review. Transl Psychiatry. 2024;14(374).

***OPTIMIZING AND DEVELOPING TRANSCRANIAL MAGNETIC STIMULATION IN THE VETERANS AFFAIRS HEALTHCARE SYSTEM: RESEARCH UPDATES FROM THE NATIONAL TMS PROGRAM**

Alexandra Aaronson, Edward Hines VA Hospital

Overall Abstract: This symposium will showcase how researchers within the Veterans Affairs Healthcare System (VA) are advancing the field of Transcranial Magnetic Stimulation (TMS) for both established and novel applications in treating mental health disorders in Veterans. As an early adopter of TMS for depression, now available at over 35 VA sites nationwide, the VA provides a unique research platform where national TMS data, and access to the Veteran population, support insights into treatment mechanisms, outcomes, and potential new uses for neuromodulation. Dr. Alexandra Aaronson will begin by sharing her work exploring the mechanisms underlying suicidality among Veterans with Traumatic Brain injury (TBI) via retrospective chart review and MRI studies. Her major findings include establishing impulsivity as a mediator in the relationship between TBI and suicidal ideation, and finding that the triad of impulsivity, suicidality and TBI appear to be related to diminished functionality of the VMPFC. These findings provided the framework to create a novel frontal-pole intermittent theta burst (iTBS) treatment for Veterans with TBI, impulsivity and suicidality, which she is presently testing. Dr. Zachary Zuschlag will share results of a retrospective cohort study analyzing the impacts of sleep dysfunction on TMS treatment for MDD using the national VA TMS database, where he found a strong correlation between improvements in sleep and depression remission rates among Veterans treated with TMS. He will also discuss proposed future work in this area. Dr. Yosef Berlow will discuss a nonlinear mixed-effects modeling approach developed to analyze the antidepressant effects of TMS over the treatment course among Veterans in the national VA TMS database, with

findings indicating that the greatest improvements occur early in treatment. This modeling approach may help us understand the pattern of TMS response, how to predict treatment outcomes, and optimize TMS treatment. Finally, Dr. Andrew Kozel will conclude our session with a discussion of an analysis of the national VA TMS database to better understand the impact of various concomitant medications on clinical outcome of TMS for the treatment of depression and PTSD symptoms. Outcomes were not significantly affected by medication co-administration. Dr. Kozel will explore what this means, and how we should move forward as a field, in light of this finding. Together, these presentations underscore the VA's leading role in expanding TMS research, exploring predictors of response, and tailoring treatment protocols to the unique needs of Veterans.

Learning Objective 1: To understand how clinical TMS outcomes are affected by concomitant psychotropic medication administration.

Learning Objective 2: To understand the role of impulsivity in the relationship between traumatic brain injury and suicidality, and why TMS stimulation of the VMPFC might ameliorate these connected conditions.

Literary References: Madore MR, Kozel FA, Williams LM, Green LC, George MS, Holtzheimer PE, Yesavage JA, Philip NS. Prefrontal transcranial magnetic stimulation for depression in US military veterans - A naturalistic cohort study in the veterans health administration. J Affect Disord. 2022; Jan 15;297:671-678.

Berlow, Y.A., Zandvakili, A., Brennan, M.C. et al. Modeling the antidepressant treatment response to transcranial magnetic stimulation using an exponential decay function. Sci Rep. 2023;13, 7138.

RETHINKING SUICIDALITY IN VETERANS WITH TRAUMATIC BRAIN INJURY: ESTABLISHING A TREATMENT TARGET AND DEVELOPING A NOVEL FRONTAL-POLE ITBS PROTOCOL

Alexandra Aaronson, Edward Hines VA Hospital

Individual Abstract Background: For the past 20 years, suicide has been the second leading cause of death in the military, with a rate approximately 1.5 times higher than that of civilians [1]. Past large-scale studies have established that traumatic brain injury (TBI) is a major risk factor for suicide among Veterans [2]. Current evidence-based treatments to reduce suicidal ideation largely do not account for the contributions of TBI.

Between 30-60% of all individuals who sustain a TBI will struggle with impulsivity [3], and there are no well-established treatments for it. Impulsivity is yet another established risk factor for suicidality. It is theorized that post-TBI impulsivity may be so common because the ventromedial prefrontal cortex (VMPFC), the part of the brain responsible for top-down control of the emotive limbic system, is nearly almost always injured in TBI, due to its location, abutting the frontal bone of the cranium and the cranial base. Our team aimed to 1) Explore the relationship between TBI and suicidality, and whether impulsivity might mediate this relationship 2) determine if there are differences in VMPFC volume between veterans with TBI and impulsivity versus veteran controls and 3) Create a novel intermittent theta burst (iTBS) treatment protocol based on these findings.

Methods: For the examination of TBI/impulsivity/suicidality relationships – The team completed a cross-sectional retrospective chart review study including 164 Veterans enrolled in previous research. 69 Veterans had no TBI history, 95 had a TBI history (mild N=44, moderate N=13, severe N=12 and unclear severity N=26). To examine relationships, chi-squared tests, t-tests and logistic regression models were used.

For the MRI volumetric study – The team included the MRIs of 10 Veterans enrolled in previous research, 5 Veterans who had a history of TBI and impulsive behavior, and 5

Veteran controls. All MRI images were pre-processed through FSL and then run through Freesurfer cortical parcellation, using the Desikan-Killiany Atlas. Our defined region of interest was the right VMPFC.
Results:TBI/impulsivity/suicidality – Unadjusted analyses indicated that veterans with TBI were more likely to report suicidal ideation; however, in analyses controlling for mediators, this relationship was no longer significant. Among veterans with TBI, suicidal ideation was related most strongly to high impulsivity (odds ratio=15.35, 95% CI=2.43–96.79), followed by depression (odds ratio=5.73, 95% CI=2.53–12.99) and posttraumatic stress disorder (odds ratio=2.57, 95% CI=1.03–6.42).
MRI volumetrics – The mean volume of the r VMPFC for the TBI group was 4200 mm3 and the mean volume for the control group was 4491 mm3, a difference of 291 mm3. The Cohen's d effect size for this difference is 0.7, moderate.
Conclusions: These findings collectively suggest that impulsivity most strongly mediates the relationship between TBI and suicidality, and may mechanistically be related to suicidality among Veterans with TBI. The difference in VMPFC size among veterans with impulsivity and TBI and Veteran controls further supports this finding, and supports the VMPFC as being a target of interest in future neuromodulation trials.
In this panel session, I will discuss the implications of these research study findings and how they informed the development of a novel iTBS treatment protocol, wherein we will provide excitatory stimulation to the r VMPFC to Veterans with a history of TBI, impulsivity and suicidal ideation to hopefully strengthen damaged connections in this area, in effort to treat these potentially lethal conditions. This study is ongoing.
This work has been supported by VA RR and D ORD Grants IK2RX004298 and 1IK1RX003082
Literature References: 1. Bachynski, K.E., et al., Mental health risk factors for suicides in the US Army, 2007--8. Inj Prev. 2012; 18(6): p. 405-12.
2. Madsen, T., et al., Association Between Traumatic Brain Injury and Risk of Suicide. Jama. 2018; 320(6): p. 580-588.
3. Mosti, C. and E.F. Coccaro, Mild Traumatic Brain Injury and Aggression, Impulsivity, and History of Other- and Self-Directed Aggression. J Neuropsychiatry Clin Neurosci. 2018; p. appineuropsych17070141.
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SLEEP DYSFUNCTION, MAJOR DEPRESSION, AND TRANSCRANIAL MAGNETIC STIMULATION: RESULTS FROM THE NATIONAL VA TMS CLINICAL PILOT PROGRAM

Zachary Zuschlag, James A. Haley Veterans Hospital

Individual Abstract Introduction: Major depressive disorder (MDD) is a condition frequently encountered in Veterans receiving care through the U.S. Department of Veterans Affairs (VA), and treatment resistance (TR) is common. Sleep dysfunction occurs in as many as 90% of patients with MDD and has been associated with poor outcomes. The association between sleep and depression treatment outcomes may be particularly important in TR-MDD due to the high frequency of sleep dysfunction observed in this population.
Transcranial magnetic stimulation (TMS) is an FDA-cleared treatment for TR-MDD, yet a substantial number of patients receiving TMS fail to respond to treatment, prompting the need for evaluation of predictors of response. As sleep dysfunction is common in MDD, and the association between sleep and TMS is poorly understood, this study aimed to address a

gap in the literature 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 VA TMS Clinical Pilot Program from March 2017 through March 2020. Standard inclusion and exclusion criteria were used to determine 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: 825 Veterans treated across 27 VAMC sites 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. McNemar chi-square analysis demonstrated 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= LESS THAN .001); week 3, 29.32% vs 14.52% (p= LESS THAN .001); week 6, 30.99% vs. 9.94% (p= LESS THAN .001). Univariate analysis of variance 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. The proposed symposium session will discuss the results of this study and highlight current and proposed future work in the area of TMS treatment for MDD with concurrent sleep dysfunction.
Literature References: 1) Madore MR, Kozel FA, Williams LM, Green LC, George MS, Holtzheimer PE, Yesavage JA, Philip NS. Prefrontal transcranial magnetic stimulation for depression in US military veterans - A naturalistic cohort study in the veterans health administration. J Affect Disord. 2022 Jan 15;297:671-678. doi: 10.1016/j.jad.2021.10.025. Epub 2021 Oct 20. PMID: 34687780; PMCID: PMC8667345.
2) Norred MA, Zuschlag ZD, Madore MR, Philip NS, Kozel FA. Sleep as a predictor of improved response to transcranial magnetic stimulation for depression (SPIRiTeD). J Affect Disord. 2024 Oct 1;362:9-13. doi: 10.1016/j.jad.2024.06.077. Epub 2024 Jun 27. PMID: 38944289.

MODELING THE TMS ANTIDEPRESSANT RESPONSE IN VETERANS

Yosef Berlow, Alpert Medical School, Brown University

Individual Abstract Background: Transcranial magnetic stimulation (TMS) is an effective treatment for pharmacoresistant depression that has been implemented nationally at more than 35 VA facilities. In a previous study of 97 Veterans, we demonstrated that TMS treatment response often follows a nonlinear pattern, with large improvements in depression symptoms occurring early in the treatment course, followed by continued smaller improvements that approach a plateau. We demonstrated that this nonlinear pattern can be modeled using an exponential decay function. This current study aimed to replicate and validate this modeling approach in a large sample of Veterans (n=1529) who received TMS for depression.

Methods: Longitudinal symptom ratings from 1529 Veterans who received TMS as part of the VA National TMS Program were included in this study. Depression ratings were measured using the Patient Health Questionnaire 9 item (PHQ-9) at baseline and weekly during TMS treatment. We constructed a nonlinear mixed effects (NLME) model based on an exponential decay function to model the reduction in depressive symptoms over the course of TMS treatment. This nonlinear model was then compared to a corresponding linear mixed effects (LME) model using the Akaike information criterion (AIC), Bayesian information criterion (BIC), and likelihood ratio test (LRT).

Results: The mixed effects models incorporated 8945 longitudinal depression ratings from 1529 Veterans undergoing TMS. The reduction in depression symptom ratings during TMS was well modeled with the exponential decay function, with the NMLE model yielding significant estimates for all parameters (all p LESS THAN 0.0001). Depression scores decreased an average of 7.5 points, with a time constant of 2.1 weeks, approaching a plateau of 10.6 points. When compared to the corresponding linear model (LME), the NLME model based on the exponential decay function was found to be a better fit, with lower AIC and BIC values and a significant likelihood ratio (LRT 758.8, p LESS THAN 0.0001).

Conclusions: This study confirms that the antidepressant response to TMS demonstrates a nonlinear pattern of symptom improvement that follows an exponential decay function. These findings successfully replicate our previous work in a large national cohort of Veterans and demonstrate that the greatest improvements in depressive symptom reduction occur early in the TMS treatment course. This approach provides a mathematical framework of the relationship between early symptom changes and TMS treatment outcomes. This symposium session will discuss the implications of this model for understanding TMS response, predicting treatment outcomes, and guiding clinical treatment decisions.

Literature References: Berlow YA, Zandvakili A, Brennan MC, Williams LM, Price LH, Philip NS. Modeling the antidepressant treatment response to transcranial magnetic stimulation using an exponential decay function. Sci Rep. 2023 May 2;13(1):7138.
Madore MR, Kozel FA, Williams LM, Green LC, George MS, Holtzheimer PE, Yesavage JA, Philip NS. Prefrontal transcranial magnetic stimulation for depression in US military veterans - A naturalistic cohort study in the veterans health administration. J Affect Disord. 2022 Jan 15;297:671-678.

IMPACT OF MEDICATIONS ON CLINICAL OUTCOME OF TRANSCRANIAL MAGNETIC STIMULATION TREATMENT OF DEPRESSION AND PTSD IN THE VA CLINICAL TMS PROGRAM

F. Andrew Kozel, Florida State University

Individual AbstractBackground: Whether medications have a negative or positive effect on the outcome of Transcranial Magnetic Stimulation (TMS) for the treatment of depression or Posttraumatic Stress Disorder (PTSD) is controversial (Hernandez et al. 2020). The Veterans Administration (VA) national database of clinical TMS provides a unique opportunity to investigate the impact of medications in a large, multi-site naturalistic sample.
Methods: The database is comprised of Veterans whose depression is being treated clinically with TMS using various standard treatment parameters (Madore et al. 2022). Many Veterans suffer from PTSD in addition to depression. Clinical change with TMS was assessed with pre and post treatment Patient Health Questionnaire (PHQ-9) and PTSD Checklist for DSM-5 (PCL-5) scores. Concomitant medications were determined from the VA medical record and grouped as: Atypical Antipsychotic; Stimulant DA; Benzodiazepine; Gaba Hypnotic; Tricyclic Antidepressant; Atypical Antidepressant; Bupropion; Anti-anxiety 5HT1A agonist; Typical Antipsychotic; SSRI; Alpha 2-adrenergic receptor agonist; SNRI; Anti-convulsant; MAOI inhibitor; Gabapentin or derivative; Lamotrigine; Lithium; Melatonin; and Trazodone. Student t-tests determined significant (p LESS THAN 0.05) differences in percent change in PHQ-9 and PLC-5 from baseline to end of treatment for sample taking a class of medication versus those not taking that class.
Results: The sample included 430 Veterans treated with TMS for depression who had required information. The percent change in PHQ-9 change was not significantly different (p GREATER THAN 0.05) for those receiving versus not receiving for any class of medications including benzodiazepines and anticonvulsants. Several classes including Postsynaptic alpha-adrenoreceptor blockade, Dopamine Agonists, Stimulant – non-DA, Straterra, Topiramate did not have adequate numbers to assess difference. Analysis is ongoing for PTSD symptoms.
Conclusions: Contrary to some reports and in agreement with others, the presence versus absence of certain classes of medication did not significantly impact clinical outcome of TMS for depression. The session will address the nuances in the data.
Literature References: Hernandez MJ, Reljic T, Van Trees K, Phillips S, Hashimie J, Bajor L, Yehl J, McKenzie BC, Burke C, Kumar A, Sanchez DL, Catalano G, Kozel FA. Impact of Comorbid PTSD on outcome of repetitive Transcranial Magnetic Stimulation (rTMS) for Veterans with Depression. J Clin Psychiatry. 2020 Jul 7;81(4). PMID: 32659874
Madore MR, Kozel FA, Williams LM, Green LC, George MS, Holtzheimer PE, Yesavage JA, Philip NS. Prefrontal Transcranial Magnetic Stimulation for Depression in US Military Veterans – A Naturalistic Cohort Study in the Veterans Health Administration. Journal of Affective Disorders. 2022 Jan 15;297:671-678. doi: 10.1016/j.jad.2021.10.025. Epub 2021 Oct 20. PMID: 34687780

2:00 p.m. - 4:00 p.m.
Pharmaceutical Pipeline Session

ORAL, ONCE-DAILY LB-102 (N-METHYL AMISULPRIDE): RECENT POSITIVE RESULTS FROM A PHASE 2 STUDY IN PATIENTS WITH ACUTE SCHIZOPHRENIA

Anna Eramo[1], Leslie Callahan[1], Niccolo Bassani[2], Baker P. Lee[1], Zachary Prensky[1], Andrew R Vaino[1], John Kane[3]*
[1]LB Pharmaceuticals Inc., [2]Worldwide Clinical Trials, Nottingham, UK, [3]The Donald and Barbara Zucker School of Medicine at Hofstra/Northwell

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

Abstract: Schizophrenia is a chronic and debilitating mental illness that affects ~1% of the population. The course of schizophrenia is highly variable, with periods of psychosis and stabilization of varying duration and intensity. Sustained remission of both positive and negative symptoms occurs in a minority of patients even with prolonged therapy. Compliance with long-term medication is a significant problem due to dissatisfaction with side effects or self-discontinuation of medication, contributing to relapse among schizophrenia patients. Patients with schizophrenia suffer a profoundly reduced quality of life, have a 3.5-times higher mortality rate, and are 10 times more likely to commit suicide than the general population. Half of all suicides occur within the first 2 years of disease onset, pointing to the urgency for behavioral and pharmaceutical intervention.

LB-102 (N-methyl amisulpride), a potential first-in-class benzamide antipsychotic was designed based on the safe and effective benzamide amisulpride with a goal of increasing its permeability across the blood-brain barrier, potentially decreasing plasma concentration needed to achieve efficacy (which could decrease the magnitude and frequency of adverse events typically observed with amisulpride). In vitro studies confirmed that LB-102 has similar activity and selectivity toward the D2, D3, and 5HT7 receptors as amisulpride. In vivo studies demonstrated LB-102 had a PK profile in rats and mice similar to amisulpride, and had similar/superior efficacy to amisulpride in animal schizophrenia models.

In a Phase 1 randomized, double-blind, placebo-controlled study designed to evaluate the safety and PK of LB-102 in healthy volunteers, LB-102 was well-tolerated; all TEAEs mild or moderate, and there were no SAEs. The maximum tolerated dose in health volunteers was 150 mg/day. This study achieved its objectives of identifying the safety, tolerability, and PK of single and multiple oral doses of LB-102 in healthy volunteers.

A Phase 1 open-label, positron emission tomography study was conducted to evaluate the dopamine receptor occupancy (RO) of orally dosed LB-102 in healthy volunteers. This study highlighted that LB-102 afforded dopamine RO in the desired range to treat schizophrenia under steady-state conditions, as doses as low as 50 mg/day with no SAEs.

A Phase 2 US-based, double-blind, placebo-controlled, 28-day inpatient trial of LB-102 (NCT06179108, NOVA1) was recently completed. Adults (18–55 yr) with schizophrenia (DSM-V) were randomized (3:3:3:1) to oral once-daily placebo, LB-102 50 mg, LB-102 75 mg, or LB-102 100 mg. The primary endpoint of this study was the change from baseline to week 4 in PANSS total score. Secondary endpoints included change from baseline in CGI-S score and PANSS responder rates. Safety was assessed through TEAEs and other assessments. LB-102 met the primary endpoint, with mean change from baseline to week 4 in PANSS total score of placebo, -9.3; 50 mg, -14.3; 75 mg, -14.0; and 100 mg, -16.1. Each treatment arm demonstrated a statistically significant (Hochberg multiplicity correction for 50 and 75 mg) reduction in PANSS score vs. placebo (50 mg: -5.0, p=0.0009, effect

size=0.61; 75 mg: -4.7, p=0.0022, effect size=0.41; 100mg: -6.8, p=0.0017, effect size=0.83).
The phase 2 NOVA1 clinical trial provided robust evidence demonstrating the efficacy and safety of LB-102 in adults with acute schizophrenia, informing the continued clinical development of LB-102.

TSND-201 (METHYLONE) AS A TREATMENT FOR PTSD: RAPID, ROBUST AND LONG-LASTING ACTIVITY IN PHASE 2

Jennifer Warner-Schmidt[*1], Amanda Jones[1], Martin Stogniew[1], Blake Mandell[1], Benjamin Kelmendi[2]*
[1]Transcend Therapeutics, [2]Yale School of Medicine

Jennifer Warner-Schmidt, 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%. Compounds with rapid and long-lasting therapeutic benefit may offer significant advantages over currently available treatments (e.g. SSRIs) that show limited effectiveness. 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. Dysregulated monoamine neurotransmission and deficits in structural and functional neuroplasticity have been observed in PTSD. TSND-201 is a highly selective serotonin, norepinephrine, and dopamine releaser and rapid-acting neuroplastogen. TSND-201 increases neuroplasticity-related gene expression in brain areas associated with PTSD and depression and stimulates neurite outgrowth. Rapid and long-lasting changes in neuroplasticity may help to explain how a drug with a short half-life (~6h in humans) maintains long-lasting beneficial effects. Unlike classic psychedelics, TSND-201 shows no agonist/antagonist activity at the 5HT2A receptor and no hallucinogenic effects in humans or animal models. In preclinical models of PTSD, depression, and anxiety, methylone has demonstrated rapid, robust, and long-lasting antidepressant-like and anxiolytic activity. In clinical studies, TSND-201 has been well-tolerated. Here we present results from IMPACT-1, a multi-center two-part phase 2 clinical trial in participants with PTSD.
Methods: IMPACT-1 Part A was an open-label evaluation of 14 participants, completed in late 2023, and IMPACT-1 Part B is a randomized, placebo-controlled study in approximately 64 participants with PTSD. The study included patients with severe PTSD (CAPS-5 ≥ 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: Results from the open-label portion of the study demonstrated rapid and durable effects on PTSD symptoms. On the CAPS-5, the mean change from baseline after the first dose was -8.4 points and -36.2 points at the end of study (6-weeks after the last dose). Significant improvements in functioning, CGI-I, and sleep were also observed. In patients with comorbid depression, TSND-201 significantly reduced depression symptoms. On the MADRS, the mean change from baseline after the first dose was -8.2 points and -21.4 pts at the end of study. TSND-201 was generally safe and well-tolerated. The results from the placebo-controlled portion of the study are expected in Q2 2025 and will be presented.

Conclusions: TSND-201 has shown 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 and supports potential use for other CNS disorders.

DEVELOPMENT OF GATE-251, AN ORALLY BIOAVAILABLE POSITIVE ALLOSTERIC MODULATOR OF THE NMDA RECEPTOR, TO TREAT MAJOR DEPRESSIVE DISORDER IN SUBJECTS WITH COMORBID INSOMNIA AND ANXIETY

*Anantha Shekhar**[1], Ronald Burch[2], John Donello[2]*
[1]University of Pittsburgh, [2]Gate Neurosciences, Inc

Anantha Shekhar, University of Pittsburgh

Abstract: GATE-251 (zelquistinel) is a positive allosteric modulator of the N-methyl-D-aspartate (NMDA) receptor being developed for the treatment of major depressive disorder (MDD). To date, a single ascending dose study and a multiple ascending dose study have defined the pharmacokinetics in plasma and cerebrospinal fluid, and studied the dose-dependence of qEEG alpha power, a biomarker of target activation. An initial phase 2a dose-ranging study has also been completed and a phase 2b study is ongoing in MDD subjects.
Safety. GATE-251 has been generally well-tolerated. A total of 493 subjects have received GATE-251. Of these, 133 healthy subjects received 1-10 doses of GATE-251, at doses up to 100 mg orally, and 360 subjects with MDD received 1-14 doses of GATE-251, ranging from 0.25–25 mg per dose. Among 120 healthy subjects, TEAES of GREATER THAN 2% incidence, have been headache, 5.8%, constipation, 3.3%, somnolence, 2.5%, and insomnia, 2.5%. Headache and constipation were of greater incidence in subjects who received GATE-251 compared to placebo (0% of subjects). Post-lumbar puncture syndrome was also prominent in healthy subjects, with incidence of 7.5% of subjects who received GATE-251 and 6.7% of subjects who received placebo. Among subjects who received GATE-251, the most common treatment-emergent adverse events have been headache and abnormal dreams, both with incidence somewhat greater than in subjects who received placebo.
Pharmacokinetics. Following oral administration (tablet) GATE-251 is rapidly absorbed, with plasma Tmax of 0.5-1.0 hr and terminal t1/2 of 3-4 hr. Tmax in CSF is reached in 4 hr, with absorption from the plasma compartment into the CSF compartment of 20-25%.
Phamacodynamics. qEEG in healthy subjects and subjects with MDD found that alpha power increased in a dose-dependent fashion from 0.1 – 10 mg oral dose within 1 hr. Alpha power increased less at 25 mg compared to 10 mg and was not apparent at 50 mg.
Efficacy in phase 2a dose-ranging study. Following once-weekly oral doses (tablet), reduction in MADRS scores occurred in dose-dependent fashion with little difference compared to placebo noted follow 1 mg doses, some statistically significant time points following 3 mg doses, and maximum efficacy following 10 mg doses, consistent with the dose-response observed for increased qEEG alpha power.
Currently, GATE-251 is being investigated in a double-blind, placebo-controlled, parallel group study of 10 mg tablet administered orally one time each week for 6 weeks. The primary efficacy endpoint is change in the Hamilton Depression Rating Scale-17 (HDRS-17) compared to placebo at the end of Week 6. The main secondary endpoint is change in Clinical Global Impression-Severity compared to placebo at the end of Week 6. In this study screening and baseline HDRS-17 must be GREATER THAN 22, any subject taking another antidepressant at screening must be washed out for at least 14 days prior to randomization and dosing, subjects may not have treatment-resistant MDD, subjects may not have comorbid

psychiatric diagnoses, except that subjects must have baseline scores GREATER THAN 15 in the Hamilton Anxiety Rating Scale and the Insomnia Severity Index.
Conclusions. To date, GATE-251 has been generally well-tolerated in healthy subjects and subjects with MDD. GATE-251 has been shown to enhance qEEG alpha power within 1 hr of dosing following oral administration in a dose-dependent fashion. Reduction of HDRS-17 score has demonstrated a similar dose-response to the qEEG alpha biomarker of NMDA receptor activation.

ROBUST ANTIDEPRESSANT EFFICACY OF THE NOVEL 5-HT2A RECEPTOR AGONIST GM-2505 IN A DOUBLE BLIND, RANDOMIZED, CONTROLLED PHASE 2A TRIAL IN PATIENTS WITH MDD

Gerard Marek[*1], Daniel Umbricht[2], Edward Christian[1], Jason Winters[1], Shane Raines[3], William Leong[1], Laszlo Kiss[1], Zoe Hughes[1], Robert Berman[4], Jorge Quiroz[1], Andrew Kruegel[1], Jonathan Sporn[1]*

[1]Gilgamesh Pharmaceuticals, Inc., [2]Xperimed GmbH, [3]2b Analytics, [4]Yale University School of Medicine

Gerard Marek, Gilgamesh Pharmaceuticals, Inc.

Abstract: GM-2505 is a novel 5-hydroxytryptamine2A (5-HT2A) receptor agonist and serotonin (5-HT) releaser with a short half-life and duration of psychotropic effects. It is currently being investigated for the treatment of major depressive disorder (MDD) and other neuropsychiatric disorders. Described here are the results of a randomized, double-blind, active-controlled Phase 2a trial of GM-2505 in 40 male and female patients with recurrent MDD. All participants were antidepressant-free for at least 6 weeks prior to screening and remained off antidepressant medication throughout the trial. All patients were administered two intravenous doses of GM-2505 with a 2-week interval between dosing. In Arm 1, half of the patients initially received a low dose on Day 1 as active control, which produced measurable, but minimal, psychotropic effects in healthy volunteers (HVs). In Arm 2, the other half received a moderate dose on Day 1, which exerted robust psychedelic effects in HVs. On Day 15, all patients received a high dose, which induced maximal psychedelic effects in HVs. The patients were monitored for safety and antidepressant responses through Day 29, with a priori timepoints for comparing MADRS change from baseline scores at Day 14 and Day 29. This allowed for initial examination of dose-response for efficacy, safety, PK, and PD. Statistically significant decreases in MADRS scores were observed in both study arms and decreases were always greater for Arm 2, which received two robustly psychedelic doses. At Day 14, there was an effect size of ~1.0 for a between-subjects comparison of the least square mean change from baseline in MADRS scores for Arm 2 treated with the moderate dose compared to Arm 1 treated with the active control low dose. At Day 29, two weeks following the high dose, MADRS scores further significantly decreased in both arms based on a within-subject comparison of Day 29 to Day 14 and the MADRS change from baseline in Arm 2 was significantly greater than in Arm 1 based on a between-subjects comparison. Further, there were robust categorical MADRS response and remission rates indicating that both the moderate and high doses were efficacious. The superior response in Arm 2 also suggests that a regimen of two robustly psychedelic doses, administered two weeks apart, produces greater efficacy than a single robust psychedelic dose. There were no serious adverse events (SAEs) and the treatment emergent adverse events (TEAE) profile was similar to that in HVs. There were no patients with suicidal ideation and a plan/intent. GM-2505 induced expected transient increases in systolic and diastolic blood pressure and pulse rate. In conclusion, GM-2505 is a promising, best-in-class 5-HT2A receptor agonist with the

potential to safely and effectively treat patients with MDD, offering a novel and transformative approach to depression treatment.

ONCE-DAILY NBI-1117568, A HIGHLY SELECTIVE ORTHOSTERIC M4 MUSCARINIC RECEPTOR AGONIST, DEMONSTRATES MEANINGFUL IMPROVEMENTS IN PANSS TOTAL SCORE AND IS WELL TOLERATED IN ADULTS WITH SCHIZOPHRENIA: PHASE 2 STUDY RESULTS

Abigail Nash[*1], Elia E. Acevedo-Diaz[2], Kurt Olson[1], Satjit Brar[1], Ashley Whitcomb[1], Eiry Roberts[1], Samir Siddhanti[1], Jaskaran Singh[1]*
[1]Neurocrine Biosciences, Inc., [2]CenExel CBH

Abigail Nash, Neurocrine Biosciences, Inc.

Abstract Background: Current therapies for the treatment of schizophrenia have limited efficacy and/or poor tolerability. Novel mechanisms that might improve efficacy and safety are urgently needed. Muscarinic receptor agonists represent a novel approach for treating schizophrenia. A phase 2 dose-finding study (NCT05545111) was conducted to assess the efficacy, safety, and tolerability of NBI-1117568, a highly selective orthosteric M4 muscarinic receptor agonist, in adults with schizophrenia.
Methods: Adults (18-55 years) with schizophrenia experiencing acute exacerbation or symptom relapse requiring hospitalization and a Positive and Negative Syndrome Scale (PANSS) total score ≥80 were randomized (2:1) to NBI-1117568 or placebo (PBO). Other antipsychotics were not allowed during the study. The adaptive dose-escalation design comprised double-blind placebo-controlled treatment (6 weeks) and safety follow-up (2 weeks). Based on results of 2 independent, unblinded, interim safety analyses, the final treatment arms were as follows: PBO, 20 mg QD, 40 mg QD, 60 mg QD, and 30 mg BID. Changes from baseline (BL) were analyzed for PANSS total score and Clinical Global Impression Scale-Severity (CGI-S), with results presented as least-squares mean (LSM) changes by treatment arm (±standard error [SE]) and the LSM difference (LSMD) between treatment arms.
Results: Demographics and BL characteristics were generally similar across treatment arms: placebo (n=70); 20 mg QD (n=40); 40 mg QD (n=39); 60 mg QD (n=34); 30 mg BID (n=27). Significant improvements in PANSS total score were observed with NBI-1117568 20 mg QD by Week 3 (-13.4 [±2.1] vs -7.7 [±1.5] for PBO, LSMD -5.7 [±2.6], P=0.0141) and at all post-BL visits to Week 6 (primary endpoint: -18.2 [±2.7] vs -10.8 [±1.9], LSMD -7.5 [±3.2], P=0.0113, Cohen's d effect size=0.61). A significant improvement in CGI-S was also observed at Week 6 with NBI-1117568 20 mg QD (-1.2 [±0.2] vs -0.5 [±0.1] for PBO, LSMD -0.7 [±0.2], P=0.0003). For other doses (40 mg QD, 60 mg QD, 30 mg BID), mean decreases from BL at Week 6 in PANSS total and CGI-S scores were greater with NBI-1117568 versus PBO, but not statistically significant. The percentage of participants reporting ≥1 treatment-emergent adverse event (TEAE) was similar between NBI-1117568 (56.4% [all doses]) and PBO (58.6%), as was the percentage who discontinued study drug due to a TEAE (5.0% vs 4.3%). TEAEs reported in ≥5% of all NBI-1117568–treated participants were somnolence (10.7% vs 2.9% for PBO), dizziness (9.3% vs 1.4%), headache (8.6% vs 20.0%), nausea (5.7% vs 2.9%), and constipation (5.0% vs 2.9%). Transient increases in heart rate (HR) were observed with NBI-1117568, which attenuated over the course of treatment (HR mean change from BL: +10.3 bpm [Week 1], +6.2 bpm [Week 6]). No weight gain was associated with NBI-1117568 relative to PBO.
Conclusions: Adults with schizophrenia experiencing acute exacerbation or relapse of symptoms had significant PANSS and CGI-S improvements after 6 weeks of treatment with

NBI-1117568 20 mg QD. NBI-1117568 was well tolerated with low incidences of peripheral cholinergic-related TEAEs (e.g., nausea) and TEAEs common with other antipsychotic medications (e.g., constipation). NBI-1117568 was associated with transient increases in HR that attenuated over the course of treatment, and it was not associated with weight gain relative to PBO. These results support further investigation of NBI-1117568 as a novel therapeutic approach for schizophrenia.

EVALUATING AUGMENTATION OF ANTI-SUICIDAL EFFECTS OF INTRAVENOUS KETAMINE BY LOW ORAL DOSES OF OPIOID RECEPTOR PARTIAL AGONISM

Jason Tucciarone[*1], Igor D. Bandeira[1], Ian H. Kratter[1], Jarrod Ehrie[1], Christine Blasey[1], Boris D. Heifets[1], Alan F. Schatzberg[1]*
[1]Stanford University School of Medicine

Jason Tucciarone, Stanford University School of Medicine

Abstract Background: Ketamine has demonstrated rapid-onset antidepressant and anti-suicidal properties. Most mechanistic studies attribute the therapeutic properties of ketamine to NMDA receptor antagonism. Our group previously demonstrated that mu opioid receptor antagonism attenuates intravenous ketamine's acute antidepressant effects. Others have found that ultra-low oral doses of a partial mu receptor agonist have potent antidepressant and anti-suicidal properties. To reduce the burden and risk of repeated ketamine dosing needed to maintain therapeutic efficacy, we explored whether low dose opioid receptor agonism with buprenorphine could extend the anti-suicidal and antidepressant properties of a single administration of intravenous ketamine.
Methods: In an ongoing, double-blinded trial to be completed by mid-March 2025, 42 participants to date (average age 37.5 +/- 10.9 years, 75% female) diagnosed with treatment resistant depression have received open-label IV ketamine infusion (0.5mg/kg), followed by randomization two days later to receive either dose-escalated buprenorphine (0.2-0.8 mg QOD) or placebo for 4 weeks, followed by a post taper follow up for 2 weeks. Study entry criteria include a major depressive episode lasting ≥ 8 weeks, a history of at least one treatment failure in the current episode, a Beck Scale for Suicidal Ideation (BSSI) score ≥ 6 and a minimum score of 3 on the Columbia-Suicide Severity Rating Scale (CSSRS). The primary measure outcome was change in the BSSI. Pre-defined secondary outcomes include changes from baseline on the Montgomery–Åsberg Depression Rating Scale (MADRS), Hamilton Depression Rating Scale (HAMD-21). The time course was analyzed via mixed-effects ANOVA and Bonferroni correction.
Results: Of the 42 participants infused thus far with a single dose of IV ketamine, 33 participants have completed the day 45-day time course. On day 3 post infusion, 52.1% of participants achieved ≥ 50% reduction of BSSI; response and remission rates were 35/17.5% on the HAM-D-21 and 37.5/25% on the MADRS respectively. With recruitment ongoing, the intervention allocation remains blinded, but preliminary results for the entire study are provided here. At day 45, BSSI decreased from 15.81 to 7.15 ($F_{4,139} = 28.40$, $p < 0.0001$); mean HAM-D-21 decreased from 24.88 to 16.94 ($F_{4,128} = 20.98$, $p < 0.0001$), and mean MADRS decreased from 33.98 to 22.45 ($F_{3,117} = 18.56$, $p < 0.0001$). At day 45, 21% of participants continued to remit using HAMD, with 27% continuing to remit using MADRS criteria. As of this submission recruitment is ongoing and blinded to buprenorphine treatment but completion will be before the ASCP meeting.
Conclusion: A single dose IV ketamine infusion substantially reduced depression and suicidality at day 3, with somewhat greater effect observed for suicidality than depression.

The overall therapeutic benefits were largely maintained out to day 45, beyond what has been typically reported in the literature. While this outcome could be consistent with our hypothesis that low dose mu opioid agonism in the buprenorphine arm will prolong the therapeutic benefits of ketamine greater than placebo, we can only speculate until study completion and unblinding. The study will be completed prior to the ASCP meeting, and unblinded results will be presented at ASCP.

TARGETING THE KCNQ (A.K.A., KV7) POTASSIUM CHANNEL AS A NOVEL TREATMENT FOR DEPRESSION AND ANHEDONIA: INITIAL RESULTS FROM A RANDOMIZED, CONTROLLED TRIAL OF XEN1101 VS. PLACEBO IN ADULTS WITH MAJOR DEPRESSIVE DISORDER

*James Murrough**[1], Rachel Freemont[1], Jessica Ables[1], Philipp Neukam[1], Usha Govindarajulu[1], Helena Chang[1], Sara Hameed[1], Marcella Corwin[1], Mackenzie Hargrove[1], Laurel Morris[1], Sanjay Mathew[2]*

[1]Icahn School of Medicine at Mount Sinai, [2]Baylor College of Medicine

James Murrough, Icahn School of Medicine at Mount Sinai

Abstract Background: Basic research suggests that enhancing signaling at KCNQ (a.k.a., Kv7) type potassium channels in the brain may represent a promising new strategy for drug discovery for depression and related conditions. Our group previously conducted a randomized, controlled trial (RCT) of the KCNQ2/3-preferring positive allosteric modulator (PAM) ezogabine in adults with major depressive disorder (MDD) and elevated levels of anhedonia. In that study, individuals randomized to ezogabine showed improvements in depression and anhedonia compared to placebo. Herein, we report the first clinical results from a new RCT comparing the novel selective Kv7 PAM XEN1101 to placebo in adults with MDD.

Methods: Adults with MDD in a current major depressive episode with elevated levels of anhedonia who met all eligibility criteria were randomized 1:1 under double-blind conditions to XEN1101 20 mg or matching placebo daily for eight weeks. Change over time in response to reward during functional magnetic resonance imaging compared between XEN1101 and placebo represents the primary outcome. Change over time compared between XEN1101 and placebo on depression severity measured every two weeks by the Montgomery-Åsberg Depression Rating Scale (MADRS) and anhedonia measured by the Snaith-Hamilton Pleasure Scale (SHAPS) represent the key secondary outcomes. A two-sided alpha level was set at 0.10 for each specified test.

Results: Of 60 participants, 29 were randomly assigned to XEN1101 and 31 to placebo. [Efficacy and safety results to be added]

THE ENTACTOGEN, EMP-01, REPRESENTS A NOVEL APPROACH TO THE TREATMENT OF SOCIAL ANXIETY DISORDER WITH ITS PHARMACOLOGICAL SELECTIVITY AND DISTINCT SUBJECTIVE EFFECTS SUPPORTIVE OF SAFETY AND THERAPEUTIC UTILITY

Sarah McEwen[1], Sarah McEwen[2], Carrie Bowen[2], Jonathon Holt[2], Holden Janssens[2], Glenn Short[2], Kevin Craig[2], Srinivas Rao[2]*

[1]atai Life Sciences, [2]EmpathBio Inc.

Sarah McEwen, Atai Life Sciences

Abstract Background: Social anxiety disorder (SAD) is among the most common psychiatric disorders, with an estimated lifetime prevalence of 12.1% and has one of the lowest remission rates in psychiatry (~35%) (Keller, 2006; Ruscio et al., 2008). Untreated SAD can be associated with debilitating avoidant behaviors due to fear-based beliefs and leads to chronic health problems and co-morbid psychiatric disorders (Vriends et al., 2014). Entactogens, including racemic MDMA, have been shown to be effective in treating SAD in autistic adults, post-traumatic stress disorder (PTSD), anxiety, and by facilitating improvements in affect, empathy, introspection, openness to new ideas and prosocial behaviors, while reducing social anxiety and increasing emotional disclosure and trust (Bedi et al., 2010; Danforth et al., 2018; Fluyau et al., 2024; Hysek et al. 2014; Mithoefer et al., 2011). EMP-01, the R-enantiomer of MDMA, is an entactogen with subjective effects indicative of therapeutic utility in SAD and has a favorable safety profile.
Methods: The pharmacology of EMP-01 was characterized using in vitro assays of receptor and transporter interactions and functional activity. SAD translational in vivo, disease-relevant effects of EMP-01 were determined in the mouse fear extinction assay. Following full characterization of the nonclinical safety and tolerability of EMP-01, a first-in-human (FiH) Phase 1 single-ascending dose study characterized the safety, tolerability, pharmacokinetic (PK), and PD effects of EMP-01 in healthy adult volunteers.
Results: EMP-01 selectively activates known targets of entactogen potential with selectivity toward beneficial serotonergic activity and low activity at catecholaminergic targets (receptors and reuptake transporters). In mice, EMP-01 facilitated fear extinction, an SAD-relevant translational assay. EMP-01 presented no significant concerns in rat and dog absorption, distribution, metabolism, and excretion (ADME), safety pharmacology and toxicology studies, with the potential for a good therapeutic window across species. In the FiH study with EMP-01, 32 adults received a single dose of EMP-01 at a dose level of 75mg, 125mg, 175mg, 225mg or placebo. EMP-01 was found to be safe and well-tolerated at all dose levels up to 225 mg, with no serious adverse events (SAEs). There were no early study or drug discontinuations. No clinically significant abnormalities were found in vital signs, laboratory parameters, or ECG in any cohort. Treatment emergent AEs (TEAEs) were mild or moderate and generally dose-dependent; the most common were nausea and headache. EMP-01 was associated with dose-related increases in emotional breakthrough experiences, greater introspective awareness, increased self-compassion scores, and it produced subjective experiences and altered states that were more like those of classic serotonergic psychedelics.
Conclusions: There is substantial nonclinical and clinical data to support the development of an entactogen to treat SAD. The entactogen EMP-01 was found to be safe and well-tolerated in healthy adults. EMP-01 has a distinct pharmacology leading to differentiated subjective effects and a favorable safety profile and is being developed as a novel treatment for SAD. A Phase 2a, randomized, placebo-controlled trial of EMP-01 with SAD patients is currently underway.
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SUSTAINED MOOD IMPROVEMENT WITH LAUGHING GAS EXPOSURE (SMILE): A RANDOMIZED, PLACEBO-CONTROLLED PILOT TRIAL OF NITROUS OXIDE FOR TREATMENT-RESISTANT DEPRESSION

Karim Ladha[1], Jiwon Lee[2], Gabriella Mattina[2], Janneth Pazmino-Canizares[2], Duminda Wijeysundera[1], Fatemeh Nezhad[2], Vanessa Tassone[2], Fathima Adamsahib[2], Wendy Lou[1], Sidney Kennedy[1], Venkat Bhat[1]*
[1]University of Toronto, [2]St. Michael's Hospital

Venkat Bhat, University of Toronto

Abstract Background: Nitrous oxide may possess antidepressant effects; however, limited data exist on repeated administrations and active placebo-controlled studies in treatment-resistant depression (TRD). We aimed to test the feasibility of a randomized controlled trial (RCT) examining a 4-week course of nitrous oxide or active placebo, midazolam.
Methods: In this randomized, active placebo-controlled pilot trial, 40 participants with TRD were assigned either a 1-hour inhalation of 50% nitrous oxide plus intravenous saline (n=20) or a 1-hour inhalation of 50% oxygen plus intravenous midazolam (0.02 mg/kg, up to 2mg; n=20) once-weekly, for 4 weeks. Feasibility was assessed by examining rates of recruitment, withdrawal, adherence, missing data, and adverse events. The primary clinical efficacy measure was the change in depression severity, assessed by the Montgomery-Åsberg Depression Rating Scale (MADRS) score, from baseline to day 42.
Results: The recruitment rate was 22.3% (95% confidence interval [CI]: 16.9-29.0). Withdrawal rates were 10% (95% CI: 2.8-30.1) in both groups and adherence rates were 100.0% (95% CI: 82.4-100) in the nitrous oxide group and 94.4% (95% CI: 74.2-99.0) in the placebo group. There were no missing primary clinical outcome data in either group (0.0%, 95% CI: 0.0-17.6). MADRS score changed by -20.5% (95% CI: -39.6 to -1.3) in the nitrous oxide group and -9.0% (95% CI: -22.6 to 4.6) in the placebo group. Nearly all adverse events were mild to moderate and transient.
Conclusion: The findings support the feasibility and the necessity of conducting a full-scale trial comparing nitrous oxide and midazolam in patients with TRD.

SAFETY AND EFFICACY OF GH001 IN TREATMENT-RESISTANT DEPRESSION: RESULTS FROM A PHASE 2B, DOUBLE-BLIND, RANDOMIZED, CONTROLLED TRIAL

Michael E. Thase[*1], Bernhard T. Baune[2], Narcís Cardoner[3], Rosa Maria Dueñas Herrero[4], Luboš Janů[5], John R. Kelly[6], Shane McInerney[7], Alexander Nawka[8], Tomáš Páleníček[9], Andreas Reif[10], Víctor Pérez Sola[11], Madhukar H. Trivedi[12], Velichka Valcheva[13], Eduard Vieta[14], Wiesław J. Cubała[15]*

[1]University of Pennsylvania and Corporal Michael J. Crescenz VAMC, [2]University of Muenster, [3]Hospital Santa Creu i Sant Pau, Institut de Recerca Sant Pau, Universitat Autònoma de Barcelona, [4]Parc Sanitari Sant Joan de Deu Hospital de Dia de Numancia, [5]A-Shine SRO, [6]Tallaght University Hospital, [7]University of Galway, [8]Institut Neuropsychiatrické Péče, [9]Psyon SRO., [10]Goethe University Frankfurt, [11]Pompeu Fabra University, [12]University of Texas Southwestern Medical Center, [13]GH Research, [14]University of Barcelona, [15]Medical University of Gdańsk

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

Abstract Background: Treatment-resistant depression (TRD) affects approximately 30% of patients treated for major depressive disorder (MDD) and is associated with higher rates of comorbidity, hospitalization, mortality, suicide, and poorer quality of life compared to MDD patients who are more responsive to treatment. Current therapies for TRD are limited and there is a great unmet need for treatments that offer rapid and sustained effects. Mebufotenin acts as a non-selective serotonin (5-HT) agonist with highest affinity for the 5-HT1A receptor subtype. Early phase trials in patients with TRD suggest that GH001, which is a synthetic form of mebufotenin for pulmonary inhalation, may have the potential to induce ultra-rapid improvement in depressive symptoms. The aim of this placebo-controlled trial was to investigate the safety and efficacy of GH001 in patients with TRD.
Methods: This Phase 2b multicenter trial planned to assess the efficacy and safety of GH001 in 80 patients with TRD. The trial consisted of two parts: Part 1, fully described here, was a randomized, double-blind (DB), placebo-controlled trial with follow up to 7 days post-dose. Patients were randomized in a 1:1 ratio to receive GH001 or placebo. Part 2 is an ongoing 6-month open-label extension (OLE), where up to five GH001 retreatments may be administered, depending on the patient's clinical status. In Part 1, patients were randomized to receive an individualized dosing regimen (IDR) of up to three escalating doses of GH001 (6, 12, and 18 mg) or placebo on a single day. There was a 1-hour interval between doses. Administration of subsequent doses was based on the patient's subjectively reported psychoactive effects and the safety and tolerability of the previous dose. As in previously conducted GH001 trials, this trial was conducted under the supervision of physicians, nurses, and other qualified healthcare professionals, but without any planned psychotherapeutic intervention before, during, or after dosing. The primary endpoint of Part 1 of this trial was mean change in Montgomery–Åsberg Depression Rating Scale (MADRS) from baseline to Day 8, assessed by a rater without knowledge of the treatment condition.
Results: A total of 81 patients with TRD were enrolled in Part 1 with 40 patients randomized to receive GH001 IDR and 41 patients to receive placebo IDR. Change in MADRS total score from baseline to Day 8 was significantly greater with GH001 than with placebo (difference of least square means=-15.5; SE=1.7); likewise, statistically significant reductions were observed in the GH001 group at 2 hours postdose and on Day 2. Remission (MADRS total score ≤10) was achieved in 57.5% of patients treated with GH001 on Day 8 compared with 0% in the placebo group (P LESS THAN 0.0001). Inhalation of GH001 was well tolerated and no serious adverse events were reported. All treatment-emergent adverse events

were mild or moderate with no severe adverse events. Preliminary results from 54 patients who have completed the ongoing OLE indicate that GH001 can maintain long-term remission from TRD with 77.8% of patients (n=42) in remission at 6 months. This is achieved with relatively infrequent treatment visits and rapid reduction in MADRS after each GH001 re-treatment. No serious adverse events have been reported in the OLE to date.
Conclusion: In this randomized trial, GH001 demonstrated significant improvements in depressive symptoms with an acceptable safety profile, supporting the potential of GH001 as a novel, rapid-acting treatment for TRD.

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

^RECENT RESULTS FROM NIMH-FUNDED CLINICAL TRIALS OF RAPID ANTIDEPRESSANTS TO REDUCE SUICIDE RISK
Samuel Wilkinson, Yale School of Medicine

Overall Abstract: In 2020, the NIMH issued a request for applications (RFA) for trials for rapid-acting interventions for severe suicide risk (RFA-MH-20-345). The proposed workshop will present the results of three of the trials that this RFA funded. Dr. Kitay (Emory) will present the results of the CBT-ENDURE study, which enrolled patients with major depression and significant suicidal ideation and randomly assigned them to esketamine + cognitive behavioral therapy (CBT) + treatment as usual (TAU) or esketamine + TAU (overall PI: Samuel Wilkinson). Dr. Anand will present results of a study of placebo-controlled study of ketamine in adolescent with recent history of suicide attempt. Dr. Price will present results from a placebo-controlled study of ketamine +/- cognitive training to induce rapid and sustained improvement in suicidal ideation. Dr. Wilkinson will discuss contemporary issues in the design and management of trials that enroll patients at elevated risk of suicide, including key learning points from the NIMH-supported RFA.
Learning Objective 1: To learn the contemporary issues in clinical trial design for subjects at elevated risk of suicide
Learning Objective 2: To learn the outcomes of recent NIMH-funded trials of rapid-acting antidepressants for severe suicide risk
Literary References: 1. Kitay BK, Murphy E, et al., Cognitive behavioral therapy following esketamine for major depression and suicidal ideation for relapse prevention: The CBT-ENDURE randomized clinical trial study protocol. Psychiatry Res. 2023.
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EFFECTIVENESS AND IMPLEMENTATION OF A BRIEF, RAPID-ACTING, SYNERGISTIC, BIO-BEHAVIORAL TREATMENT AMONG HOSPITALIZED INPATIENTS FOLLOWING A SUICIDE ATTEMPT
Rebecca Price, University of Pittsburgh

Individual Abstract: Over a decade ago, we first reported that intravenous (IV) ketamine showed large, rapid effects on suicidal ideation and implicit suicidal cognition (i.e., implicit associations between “self” and “escape”) among depressed patients, and suggested that such rapid effects might have real-world clinical utility in the face of a suicidal crisis. Yet, in spite of substantial interest in ketamine from the research, clinician, and patient communities alike, fundamental questions about ketamine’s actual clinical utility and effectiveness in real-world clinical settings remain virtually untested. In controlled research settings, ketamine rapidly

reduces suicidal thoughts as early as 2-24 hours after a single infusion, both in depressed patients and in transdiagnostic patients selected for high suicide risk. Yet, a significant barrier to clinical adoption of this treatment approach is the lack of evidence for durability of these effects, raising concerns about illusory recovery and subsequent rebound of suicide risk, and introducing significant barriers to patient access and uptake in real-world clinical settings. In a pilot feasibility and safety trial we previously conducted among 16 transdiagnostic inpatients who were recruited during the acute inpatient stay following a suicide attempt, a single, open-label ketamine infusion was delivered, and we observed rapid decreases across multiple measures of depression and suicidal symptoms (p's LESS THAN 0.001) with large to very large effect sizes (Cohen's d's: 1.7–8.8) observed at acute timepoints (24 h; 5 days). In addition, these rapid gains were uniformly maintained out to 6 months post-infusion, with no evidence that new safety concerns or iatrogenic effects emerged.

In an ongoing randomized controlled trial (RCT; n=200) that has now entered the longer-term follow-up period, we are testing the real-world effectiveness of a recently developed synergistic treatment approach, involving a single infusion of IV ketamine followed by a very brief, fully automated, digital cognitive training intervention ("Automated Self-Association Training"; ASAT), using a deployment-focused study design. We recruited a highly heterogeneous sample of recent suicide attempters on a tertiary-care Consultation-Liaison (CL) psychiatry service and delivered all study interventions as an adjunct to treatment-as-usual (which involves medical stabilization, followed by psychiatric inpatient hospitalization and subsequent outpatient referral). Participants were randomized to four groups (in a 2 x 2 design): ketamine followed by 4 days of the digital ASAT intervention; ketamine followed by a sham variant of ASAT (i.e., a computer task not targeting suicide-relevant cognition); or one of two no-infusion arms: ASAT-alone; or sham-ASAT alone. Patients are being followed longitudinally for 1 year, enabling a test of both rapid and enduring effects of this novel intervention combination on depression symptoms and suicidal thoughts and behaviors during a high-risk period for recurrent suicidality. In this presentation, we will present the short-term efficacy, feasibility, implementation metrics (e.g., patient and provider acceptability, usability, satisfaction), and safety data from the acute intervention phase of the study, and provide an update on progress towards completion of data collection for the final, 1-year follow-up outcomes. If our ongoing RCT upholds and extends the pilot study findings, it could suggest ketamine, paired with our novel digital therapy, might be readily integrated into the settings where high-risk patients already receive healthcare, with the potential to become an important and novel tool in the treatment of acute suicidal crises.

Literature References: Price RB, Spotts C, Panny B, Griffo A, Degutis M, Cruz N, Bell E, Do-Nguyen K, Wallace ML, Mathew SJ, Howland RH. A novel, brief, fully automated intervention to extend the antidepressant effect of a single ketamine infusion: A randomized clinical trial. Am J Psychiatry. 2022; 179:959-968.

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KETAMINE TREATMENT IN YOUTH FOR FAST REDUCTION OF SUICIDALITY AND ENGAGEMENT IN PSYCHOTHERAPY: AN ONGOING RANDOMIZED PLACEBO CONTROLLED TRIAL

Amit Anand, Harvard Medical School

Individual Abstract Background: Over the last ten years, there has been a significant rise in suicide attempts among individuals aged 14 to 30, with suicide now ranking as the second leading cause of death among adolescents. Research has demonstrated that ketamine can produce rapid anti-suicidal effects, though its safety and effectiveness in younger populations remain underexplored. Meanwhile, the Collaborative Assessment and Management of Suicidality (CAMS), a clinical intervention specifically designed to address suicidality, has been shown to reduce suicidal ideation, alleviate general distress, and positively influence suicidal behaviors. Although CAMS is one of the few evidence-based treatments that quickly and effectively addresses suicidal risk, it has not yet been studied in combination with ketamine.

Objectives: This study aims to determine whether an acute infusion of ketamine, compared to a placebo, can swiftly reduce severe suicidality in young people and enhance the effectiveness of CAMS in mitigating suicidality both immediately after treatment and at a three-month follow-up. Additionally, the study will examine whether participants who receive ketamine infusions experience lower levels of suicidality as measured by the Scale for Suicidal Ideation (SSI). It will also assess whether these individuals have fewer suicide attempts, reduced emergency department visits for suicidal thoughts, and fewer psychiatric readmissions over the following three months.

Methods: This randomized controlled trial, funded by the National Institute of Mental Health, is currently enrolling participants aged 14 to 30 yrs. who have been admitted to an inpatient psychiatric unit due to severe suicidal ideation or following a suicide attempt. Participants are randomly assigned to receive either a ketamine infusion (0.5 mg/kg over 40 minutes) or a placebo (normal saline), with a maximum dose of 50 mg for adolescents and 57.5 mg for adults. During their inpatient stay, participants may receive up to six infusions (administered every other day from Monday through Friday, excluding holidays) until they achieve an SSI score below 4, exhibit more than a 50% reduction from their baseline score, and are clinically assessed as no longer experiencing suicidality, or until they are discharged from the unit. Simultaneously, participants will engage in weekly CAMS sessions starting during their inpatient stay and continuing post-discharge for up to 12 sessions or until they meet CAMS' criteria for resolving suicidality for three consecutive sessions. Follow-up assessments will be conducted monthly for three months to monitor suicidal ideation, attempts, and readmissions.

Results: Recruitment is ongoing at Massachusetts General Hospital and Cleveland Clinic. At this time N = 32 subjects have been enrolled (Median Age 18.22 yrs. [16.03, 22.21]; 23 F, 4 M, 3 transgender, and 2 non-binary; Race: White: 24; African American: 6; Multiracial: 2; and N = 28 non-Hispanic). Detailed methods, statistical analyses, as well as insights into the challenges and advantages of conducting such a high-risk trial will be presented.

DISCUSSION: This study hypothesizes that ketamine infusions will lead to rapid reductions in suicidality compared to placebo recipients. Furthermore, it is expected that ketamine will enhance patient engagement with CAMS therapy, resulting in fewer required sessions to resolve high-risk suicidality after discharge. Finally, it is anticipated that those receiving ketamine will show greater reductions in suicidality scores, fewer suicide attempts, and lower rates of psychiatric readmissions compared to those receiving placebo during the three-month follow-up period. Funding: R01MH125214 (TF and AA)

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COGNITIVE BEHAVIORAL THERAPY FOLLOWING ESKETAMINE FOR MAJOR DEPRESSION AND SUICIDAL IDEATION FOR RELAPSE PREVENTION (ENDURE-CBT)

Matthew Macaluso, The University of Alabama at Birmingham

Individual Abstract Purpose: Cognitive behavioral therapy (CBT) is a highly effective approach to relapse prevention in major depression, particularly suicide prevention in high-risk populations. We report findings from the CBT-ENDURE trial, where the effect of adjunctive CBT on outcomes was examined in depressed and suicidal patients receiving intranasal esketamine.
Background: In 2020, intranasal esketamine, which was already approved for treatment resistant major depression (TRD), received a supplemental indication for major depressive disorder with suicidal ideation (MDSI). The MDSI indication was based on clinical trials that enrolled hospitalized patients. Despite the TRD and MDSI indications, the total duration of esketamine treatments in real world clinical practice is not well understood. For TRD, the package insert suggests maintenance treatment "be individualized to the least frequent dosing to maintain remission/response." For the MDSI indication, the package insert states that "treatment beyond 4 weeks has not been systematically evaluated." Further complicating the question of how long to treat with esketamine is the high risk of suicide following psychiatric hospital discharge. Similarly, there are high relapse rates associated with the discontinuation of intranasal esketamine.
Methods: Cognitive Behavioral Therapy Following Esketamine for Major Depression and SUicidal Ideation for RElapse Prevention (ENDURE). Patients with depression who were admitted to psychiatric hospitals or outpatients with clinically significant suicidal ideation were enrolled in the study. All patients received intranasal esketamine (twice weekly for four weeks) and were randomly assigned (1:1 ratio) to receive a 16-week course of CBT plus treatment as usual (CBT group) or treatment as usual only (TAU only group). Patients were followed for up to 26 weeks.
Results: The preliminary results for the CBT-ENDURE study will be presented at the 2025 ASCP Annual Meeting.
Disclosure: The study is supported by a funding announcement from NIMH to conduct safety and feasibility trials for patients at high risk for suicide (RFA-MH-20-345).
Literature References: 1) Kitay BM, Murphy E, Macaluso M, Corlett PR, Hershenberg R, Joormann J, Martinez-Kaigi V, Nikayin S, Rhee TG, Sanacora G, Shelton RC, Thase ME, Wilkinson ST. Cognitive behavioral therapy following esketamine for major depression and suicidal ideation for relapse prevention: The CBT-ENDURE randomized clinical trial study protocol. Psychiatry Res. 2023 Dec;330:115585. doi: 10.1016/j.psychres.2023.115585. Epub 2023 Oct 30. PMID: 37935086.
2) Canuso CM, Ionescu DF, Li X, Qiu X, Lane R, Turkoz I, Nash AI, Lopena TJ, Fu DJ. Esketamine Nasal Spray for the Rapid Reduction of Depressive Symptoms in Major

Depressive Disorder With Acute Suicidal Ideation or Behavior. J Clin Psychopharmacol. 2021 Sep-Oct 01;41(5):516-524. doi: 10.1097/JCP.0000000000001465. PMID: 34412104; PMCID: PMC8407443.

MAKING PROGRESS IN CLINICAL TRIALS FOR SUICIDE PREVENTION - DESIGN AND CONDUCT CONSIDERATIONS

Samuel Wilkinson, Yale School of Medicine

Individual Abstract Background: Suicide is a public health crisis. Despite renewed efforts to confront this problem, suicide rates continue to rise in the United States. While suicide prevention approaches encompass a broad array of strategies, treatment development is lagging. Within this realm, clinical trials are the gold standard for evaluating safety and efficacy of new treatments.
Observations: The majority of clinical trials conducted among patients with mental illness have excluded patients at risk of suicide. Historical reasons for this include regulatory challenges, liability concerns, ethical questions, discomfort working directly with high-risk patients, and the belief that research is too risky for individuals at elevated risk for suicide.
Conclusions and Relevance: Based on significant experience conducting trials that have targeted at-risk populations, several considerations are provided for investigators in the design of such trials. These include thoughtful selection of study outcome, use of time-to-event design and analysis (which may best simultaneously satisfy ethical concerns and scientific aims), a focus on enrolling an enriched sample (i.e., from among patients recently discharged from the hospital), and provision of usual care in the comparator arm. Caution should be exercised to avoid excessive or unreasonable safety requirements, which may lead subjects to minimize self-report of suicidal ideation or lead participants to drop out of trials, leading to a situation where, paradoxically, they have less monitoring and less access to care. Where possible, regulatory bodies (institutional review boards [IRBs]; data, safety, and monitoring boards [DSMBs]) should consult with or include as members those with direct clinical experience with this high-risk population.
An important ethical principle for IRB members and other regulators to consider is that suicide-related events are expected in this clinical population.
Literature References: Iltis AS, McCall WV, Deria R. Suicidality, Depression, and the FDA: Health Inequities and the Ethical Conduct of Research. The Journal of clinical psychiatry. 2020;81(2).
Iltis AS, McCall WV, Deria R. Suicidality, depression, and the FDA: health inequities and the ethical conduct of research. The Journal of clinical psychiatry. 2020;81(2).

***#^+NAVIGATING RESEARCH CAREER TRAJECTORIES: AN INTERACTIVE WORKSHOP AND TOOLKIT FOR BUILDING TEAMS, NURTURING RELATIONSHIPS, AND ETHICAL AND INCLUSIVE CLINICAL RESEARCH PRACTICE FOR THE LONG HAUL**

Renee Martin-Willett, The University of Colorado Boulder

Overall Abstract Background: Early and mid-career scientists face significant barriers in establishing independent research programs, which have been exacerbated by the COVID-19 pandemic. These include intensified competition for funding, restricted budgets, and increased turnover.
Objective: To equip early and mid-career scientists with skills in recruitment, financial management, self-advocacy, contract negotiation, mentorship, and collaboration, addressing challenges particularly for underrepresented groups in the biomedical workforce.

Methods: The interactive workshop features panelists from various career stages. It begins with a 5-minute introduction and includes 3-5 role-play scenarios on recruitment, contract negotiation, team building, research infrastructure, mentorship, and collaboration. Attendees will role-play as early or mid-career scientists, engaging with panelists and peers to discuss and apply scenarios to their professional lives.
Outcome: Attendees will gain access to an online toolkit with resources discussed during the workshop (e.g., mentorship training materials, human resources guidelines, budgeting tools). They will also have an opportunity to collaboratively discuss their own challenges and successes with peers and expert panelists.
Conclusion: The workshop aims to provide early and mid-career scientists with the necessary skills to overcome challenges in establishing and maintaining independent research programs, especially in a post-COVID environment.
Learning Objective 1: Gain awareness of resources to support the establishment of independent research programs in areas such as recruitment, financial management, self-advocacy, contract negotiation, mentorship, and collaboration
Learning Objective 2: Benefit from experiences and expertise of peers and expert panel members towards creatively problem solving individual career challenges
Literary References: Piano, M., Diemer, K., Hall, M. et al. A rapid review of challenges and opportunities related to diversity and inclusion as experienced by early and mid-career academics in the medicine, dentistry and health sciences fields. BMC Med Educ 23, 288 (2023). https://doi.org/10.1186/s12909-023-04252-x
Johnson RW, Weivoda MM. Current Challenges for Early Career Researchers in Academic Research Careers: COVID-19 and Beyond. JBMR Plus. 2021 Aug 19;5(10):e10540. doi: 10.1002/jbm4.10540. PMID: 34514285; PMCID: PMC8420267.

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Anita Clayton, University of Virginia

Individual Abstract Background: Early and mid-career scientists face significant barriers in establishing independent research programs, which have been exacerbated by the COVID-19 pandemic. These include intensified competition for funding, restricted budgets, and increased turnover.
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Lealani Mae "Leah" Acosta, Vanderbilt University Medical Center

Individual Abstract Background: Early and mid-career scientists face significant barriers in establishing independent research programs, which have been exacerbated by the COVID-19 pandemic. These include intensified competition for funding, restricted budgets, and increased turnover.
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Angela Bryan, The University of Colorado Boulder

Individual Abstract Background: Early and mid-career scientists face significant barriers in establishing independent research programs, which have been exacerbated by the COVID-19 pandemic. These include intensified competition for funding, restricted budgets, and increased turnover.

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*EVOLVING PHARMACOTHERAPY TARGETS IN MOOD DISORDERS: WHEN THE OLD MEETS THE NEW, THE TRIED, AND THE TRUE

Carlos Zarate, National Institute of Mental Health

Overall Abstract: Depression—both major depressive disorder (MDD) and bipolar depression—is a significant and growing public health issue and a leading cause of disability worldwide. While antidepressant medications are a mainstay of depression treatment, many individuals with mood disorders do not respond to currently available antidepressants. This workshop will bring together a panel of experts to discuss the existing pharmacopoeia for depression, taking into account both well-established treatments and novel, rapid-acting agents. Targets for developing new agents will also be discussed.
Dr. Nierenberg will begin by discussing the therapeutic role played by some of the oldest drugs available to psychiatry, particularly in the context of the newest drugs available. Lithium valproate, tricyclic antidepressants, MAOIs, and first-generation antipsychotics will be discussed. He will also discuss the importance of comparative effectiveness trials and the challenges—both financial and logistical—that surround conducting them.
Dr. Zarate will then discuss how the rapid and sustained antidepressant effects exerted by subanesthetic-dose racemic ketamine prompted investigation into other glutamatergic modulators for depression. His presentation will discuss the interplay between the glutamatergic, GABA-ergic, and opioid-ergic systems in the mechanisms underlying rapid-acting antidepressant effects. New molecular drug targets identified in conjunction with NMDA receptor antagonism— including opioid receptor signaling and modulation of inflammatory processes—will be discussed. Dr. Zarate will also present preliminary findings from a Phase 1 study of the ketamine metabolite (2R,6R)-hydroxynorketamine (HNK) and clinical trial results for TS-161, an mGluR2/3 modulator.
Dr. Clayton will then discuss emerging GABA-ergic agents for the treatment of depression. GABA-A receptors are the main inhibitory neurotransmitter in the CNS. Dr. Clayton will focus on zuranolone; when administered orally for 2 weeks, 30-50mg/day of the GABA-A

positive allosteric modulator (PAM) zuranolone is an approved treatment for postpartum depression. Some similarities in addressing unmet needs in treating depression (short course of treatment, rapid action, sustained effect) may be seen with a 5-HT2 agonist. In this context, Dr. Clayton will discuss RE-104, a psilocybin-type rapid-acting single injection leading to a 3-4 hour mystical experience, which is under investigation for the treatment of PPD.
Finally, Dr. Mathew will discuss kappa opioid receptors (KORs) as novel targets for anhedonia. KORs are abundantly expressed in brain circuits regulating reward, motivation, stress, and anxiety. Two KOR antagonists are in the late stages of clinical development for MDD: aticaprant and navacaprant. A recent Phase 2 randomized, double-blind, placebo-controlled of adjunctive aticaprant found statistically significant improvements that were more pronounced in patients with higher anhedonia symptoms at baseline. In addition, an initial randomized, double-blind, placebo-controlled Phase 2a trial of Navacaprant (NMRA-140) as monotherapy found statistically significant improvements in depressive symptoms, including anhedonia, in the moderate-to-severe subgroup. Both agents were found to be safe and well tolerated.
Learning Objective 1: Understand the existing pharmacopoeia for depression, taking into account both well-established treatments and novel, rapid-acting agents.
Learning Objective 2: Understand the novel mechanisms of action that may present new molecular drug targets for developing novel therapeutics for depression
Literary References: Elias, E, Zhang, AY, Manners, MT. Novel pharmacological approaches to the treatment of depression. Life 2022;12(2): 196
Marwaha S, Palmer E, Suppes T, et al. Novel and emerging treatments for major depression. Lancet 2023;401:141-153

WHEN RETRO IS "IN": THE PLACE OF LITHIUM, VPA, TRICYCLICS, AND MAOIS IN THE 2025 PHARMACOPOEIA

Andrew Nierenberg, Massachusetts General Hospital

Individual Abstract: The FDA approves new drugs for psychiatric disorders based on placebo-controlled RCTs but without requiring comparison with older existing drugs. Without these comparisons, the relative benefits and risks of the new drugs cannot be known directly. Instead, clinicians use practical reasoning (phronesis) to estimate the comparisons (and clinicians are constrained by prior authorization denials and the cost of the newer drugs), while researchers try to use network meta-analyses to simulate comparisons (and these are imperfect at best). Comparative effectiveness (pragmatic) trials can address questions about how the newer drugs compare to the older ones, but these tend to be expensive, take years to complete, and are not a priority of NIMH (the Patient Centered Outcomes Research Institute does fund comparative effectiveness trials, but these are highly competitive with all areas of medicine). This presentation will address the challenges of how to think about the role of some of the oldest drugs available to psychiatry in the context of the newest drugs available. Specifically, lithium valproate, tricyclic antidepressants, MAOIs, and first-generation antipsychotics will be discussed.
Literature References: 1. Malhi GS, Bell E, Jadidi M, Gitlin M, Bauer M. Countering the declining use of lithium therapy: a call to arms. International Journal of Bipolar Disorders. 2023;26;11(1):30.
2. Giménez-Palomo A, Chamdal AK, Gottlieb N, Lotfaliany M, Jokinen T, Bastawy EM, Adlington K, Benachar N, Dodd S, Pacchiarotti I, Vieta E. Efficacy and tolerability of monoamine oxidase inhibitors for the treatment of depressive episodes in mood disorders: A systematic review and network meta-analysis. Acta Psychiatrica Scandinavica. 2024 Jul 12.

MODULATING THE GLUTAMATERGIC, GABA-ERGIC, AND OPIOID-ERGIC SYSTEMS TO ACHIEVE RAPID ANTIDEPRESSANT EFFECTS

Carlos Zarate, National Institute of Mental Health

Individual Abstract: Many individuals with mood disorders such as major depressive disorder (MDD) and bipolar depression do not respond to currently available antidepressants, underscoring the urgent need to develop novel therapeutics. Both clinical and preclinical studies have implicated glutamatergic system dysfunction in the pathophysiology of mood disorders. In particular, the rapid and sustained antidepressant effects exerted by subanesthetic-dose racemic (R,S)-ketamine has prompted investigation into other glutamatergic modulators for depression, both as monotherapy and adjunctively. Several glutamate receptor-modulating agents have been tested in proof-of-concept studies for mood disorders. Many of these agents are still in the preliminary stages of development and, to date, most have demonstrated relatively modest effects compared with (R,S)-ketamine and esketamine.

Interestingly, novel agents that selectively antagonize NMDA receptors have often failed in Phase 2 clinical trials, in direct contrast to the success of ketamine. This general lack of efficacy may be due to ketamine's ability to target a variety of biological systems in addition to ionotropic glutamatergic modulation. In this context, new evidence supports the role of both the endogenous opioid system and GABA-ergic modulation in rapid-acting antidepressant efficacy.

This presentation will discuss the interplay between the glutamatergic, GABA-ergic, and opioid-ergic systems in the mechanisms underlying rapid-acting antidepressant effects. Collectively, these systems underpin the mechanism of action of agents from several different categories, including broad glutamatergic modulators, glycine site modulators, subunit (NR2B)-specific NMDA receptor antagonists, metabotropic glutamate receptor (mGluR) modulators, and allosteric modulators of GABA signaling. Of these novel agents, the most promising, and the ones for which the most evidence exists, appear to be those with polypharmacological characteristics that are also capable of targeting ionotropic glutamate receptors.

This presentation will also discuss proposed novel mechanisms underlying the antidepressant effects of (R,S)-ketamine that may present new molecular drug targets in conjunction with NMDA receptor antagonism. Finally, preliminary findings from a Phase 1 study of the ketamine metabolite (2R,6R)-hydroxynorketamine (HNK) and clinical trial results for TS-161, an mGluR2/3 modulator will also be presented.

Literature References: Hess, EM, Riggs, LM, Michaelides, M, and Gould, TD Mechanisms of ketamine and its metabolites as antidepressants. Biochem Pharmacol, 2022;197:114892. Williams, NR, Heifets, BD, Blasey, C, et al. Attenuation of antidepressant effects of ketamine by opioid receptor antagonism. Am J Psychiatry 2018; 175: 1205-1215.

SELECTIVE KAPPA OPIOID RECEPTOR ANTAGONISTS AS NOVEL THERAPEUTIC TARGETS FOR MAJOR DEPRESSIVE DISORDER AND ANHEDONIA

Sanjay J. Mathew, Baylor College of Medicine

Individual Abstract: Major depressive disorder (MDD) is a leading cause of disability, morbidity, and mortality. Despite available treatments, a significant unmet need remains, as many patients do not adequately respond to first-line pharmacotherapies and often experience side effects. Current antidepressants also do not adequately treat anhedonia, a core clinical feature of MDD that affects approximately 70% of patients and is associated with more

severe depressive symptoms and functional impairment. New targeted therapies are needed to treat MDD, including symptoms of anhedonia, while also improving tolerability over current antidepressants. Kappa opioid receptors (KORs) are novel targets for anhedonia that are abundantly expressed in brain circuits regulating reward, motivation, stress, and anxiety. KOR activation is a strong negative modulator of multiple neurotransmitters, including dopamine, and results in dysphoria. Conversely, KOR antagonists are believed to restore the regulation of multiple neurotransmitters including dopamine in reward processing pathways, which play an important role regulating mood, cognition, reward, and behavior. This presentation will discuss the clinical development to date for two KOR antagonists which are in late-stage clinical development for MDD. Aticaprant is in development as adjunctive therapy. Aticaprant was initially examined in the NIMH FAST-MAS consortium (Krystal AD et al 2020) which provided proof-of-mechanism suggested by changes in mean fMRI ventral striatal activation in anticipation of rewards in the monetary incentive delay task and improvement in anhedonia symptoms. A subsequent phase II randomized, double-blind, placebo-controlled adjunctive trial (Schmidt et al 2024) reported statistically significant improvements which were more pronounced in patients who reported higher anhedonia symptoms at baseline. Navacaprant (NMRA-140) is a novel, potent, and highly selective KOR antagonist with no agonist activity at mu, kappa, or delta opioid receptors and is being tested as a monotherapy. An initial randomized, double-blind, placebo-controlled phase 2a trial found statistically significant improvements in depressive symptoms including anhedonia in the moderate-to-severe subgroup. Both compounds had acceptable safety and tolerability with low rates of discontinuation due to adverse events, supporting further development in phase III programs.

Literature References: Krystal AD et al. A randomized proof-of-mechanism trial applying thefast-fail approach to evaluating k-opioid antagonism as a treatment for anhedonia. Nat Med 2020; 26(5): 760-768.

Schmidt ME et al. Efficacy and safety of aticaprant, a kappa receptor antagonist, adjunctive to oral SSRI/SNRI antidepressant in major depressive disorder. Neuropsychopharm 2024; 49(9):1437-1447.

*BIPOLAR DISORDER VERSUS BORDERLINE PERSONALITY DISORDER: A CLINICAL CONUNDRUM

Joseph Goldberg, Icahn School of Medicine at Mount Sinai

Overall Abstract: There has long been conceptual and nosologic controversy about points of phenomenologic overlap and divergence between bipolar and borderline personality disorders. Both conditions involve elements of affective instability, impulsivity, risk-taking, depression, heightened suicide risk, and psychosocial impairment; they differ in their trait versus state manifestations, syndromal characteristics, prominence of rage or anger versus euphoria, potential for self-injury (e.g., suicidal versus nonsuicidal), features related to suicidal ideation, time course to symptom evolution and resolution, propensity to psychosis (e.g., macro- versus micro-), environmental triggers (e.g., circadian dysrhythmias in bipolar disorder, interpersonal provocations in borderline personality disorder), psychological dimensions (e.g., splitting, projection, feelings of numbness, impact of past trauma, and identity diffusion in borderline personality disorder) and predominant treatment modalities (primary pharmacotherapy versus primary psychotherapy). Bipolar disorder and borderline personality disorder can be difficult to differentiate from one another; or they can co-occur (about 1 in 5 individuals with borderline personality disorder may develop mania or hypomania). Clinicians and investigators alike often struggle to determine which is the more appropriate diagnosis when considering appropriate pharmacotherapies, psychotherapies, or

both. Clinical trialists often fear that negative pharmacotherapy studies may sometimes actually constitute failed trials because diagnostic ambiguity can lead to borderline personality disorder patients erroneously becoming enrolled in trials for bipolar disorder; or vice-versa.
This workshop will provide an overview of salient issues surrounding the construct validity and discriminant validity of these distinguishable clinical entities, as well as the strengths and weaknesses of diagnostic screening measures as deployed in varying clinical settings. Insofar as the targets of both pharmacotherapy and structured psychotherapy may differ substantially between these conditions, confidence in their rigorous clinical differentiation bears strongly on clinician, investigator, patient, and family expectations about treatment outcomes. We shall consider the extent to which overattention to subcomponent features of either condition – such as affective lability, prominent irritability, suicidality, or poor response to antidepressants – may encourage imprecise classifications or failed trials because of absence of salient non-mood target symptoms (such as high energy, overactivity, or sleeplessness without fatigue). Audience participation in this workshop will include straw-polling and discussion about attendees' experience in differential diagnostic formulations, differential therapeutics, integrative treatment for comorbid presentations, and recommendations for improved clinical trial designs.
Learning Objective 1: 1) To describe phenomenological similarities and differences in the clinical features of bipolar disorder and borderline personality disorder, and the distinct roles for pharmacotherapy versus structured psychotherapies to target core symptoms of each
Learning Objective 2: 2) To understand ways in which patients with borderline personality disorder who enroll in clinical trials for bipolar disorder, or have dual-diagnostic comorbidity, may adversely influence clinical outcomes
Literary References: 1) Gunderson JG, Weinberg I, Daversa MT, et al. Descriptive and longitudinal observations on the relationship of borderline personality disorder and bipolar disorder. Am J Psychiatry 2006; 163: 1173-1178
2) Zimmerman M, Balling C, Chelminski I, et al. Patients with borderline personality disorder and bipolar disorder: a descriptive and comparative study. Psychol Med 2021; 51: 1479-1490

THE RESEARCHER'S DILEMMA: OVERLAPPING PHENOMENOLOGY AND COMORBIDITY

Holly Swartz, University of Pittsburgh School of Medicine

Individual Abstract: When treating bipolar disorder (BD), either in the context of clinical care or a research study, identification and management of co-occurring borderline personality disorder (BPD) remains a major dilemma, both because of the challenges associated with distinguishing the two disorders and the impact of comorbidity on disease course and outcomes. This workshop presentation will focus on the impact of overlapping phenomenology and comorbidity of BD and BPD on research recruitment and study outcomes. We will review findings from two separate research studies examining a) rates of screen fails due to BPD when recruiting a BD sample and b) impact of co-occurring BPD on outcomes of treatment for BD
Study 1: Adult outpatients were recruited from provider referrals, advertisements, and research registries to participate in a randomized controlled trial of interpersonal and social rhythm therapy (IPSRT) plus placebo or IPSRT plus quetiapine as treatments for BD II depression. Patients were excluded from study participation if they met DSM IV criteria for BPD based on the SCID II. 207 individuals were screened for eligibility; 23/207 (11%) met criteria for BPD and were excluded from study participation. A screen fail rate of 11% is

lower than expected given a 20% estimated prevalence of co-occurring BD and BPD, perhaps because BPD was advertised a priori as an exclusion criteria from the trial.
Study 2: In a quasi-experimental, matched case-control study, we compared acute treatment outcomes of individuals who met criteria for both BD I and BPD (n=12) to those who met criteria for BD I only (n=58). Participants received psychotherapy (IPSRT or supportive clinical management) and mood stabilizing medication. Median time to stabilization in the comorbid group was 95 weeks versus 35 weeks in the BD I only group. The comorbid group also received significantly more atypical mood-stabilizing medications per year than the BD I-only group (Z = 4.3, p LESS THAN 0.0001).
Conclusions: Taken together, these two studies underscore the importance screening for BPD in the context of clinical trials for BD. Inclusion of individuals with comorbid BD and BPD is probable if BPD is not systematically excluded. Further, as evidenced by Study 2, those with BD-BPD comorbidity will likely have worse outcomes when treated with interventions targeting BD. Future work is needed to identify treatment approaches that better address BD-BPD given the high prevalence of comorbidity and relatively worse clinical prognosis.
Literature References: Swartz HA, Rucci P, Thase ME, Wallace M, Carretta E, Celedonia KL, Frank E. Psychotherapy Alone and Combined With Medication as Treatments for Bipolar II Depression: A Randomized Controlled Trial. J Clin Psychiatry. 2018 Mar/Apr;79(2):16m11027. doi: 10.4088/JCP.16m11027. PMID: 28703949; PMCID: PMC5823786.
Swartz HA, Pilkonis PA, Frank E, Proietti JM, Scott J. Acute treatment outcomes in patients with bipolar I disorder and co-morbid borderline personality disorder receiving medication and psychotherapy. Bipolar Disord. 2005 Apr;7(2):192-7. doi: 10.1111/j.1399-5618.2005.00179.x. PMID: 15762861.

SCREENING FOR BIPOLAR DISORDER AND FINDING BORDERLINE PERSONALITY DISORDER

Mark Zimmerman, Brown University

Individual Abstract Introduction: Bipolar disorder and borderline personality disorder share some clinical features and have similar correlates. It is therefore not surprising that differential diagnosis is sometimes difficult. The Mood Disorders Questionnaire (MDQ) is the most widely used screening scale for bipolar disorder. In the present report from the Rhode Island Methods to Improve Diagnostic Assessment and Services (MIDAS) project we examined whether psychiatric outpatients who screened positive on the MDQ would be more often diagnosed with borderline personality disorder than patients who did not screen positive, and they would be more often diagnosed with borderline personality disorder than with bipolar disorder.
Methods: Five hundred thirty-four psychiatric outpatients were interviewed with the Structured Clinical Interview for DSM-IV (SCID) and Structured Interview for DSM-IV Personality Disorders (SIDP-IV), and they were asked to complete the MDQ. Missing data on the MDQ reduced the sample size to 480.
Results: In the sample of 480 patients who completed the MDQ, 10.8% (n=52) were diagnosed with a lifetime history of bipolar disorder. The majority of the 52 patients with bipolar disorder were diagnosed with bipolar I (n=18) or bipolar II (n=21) disorder. In addition, 8 patients were diagnosed with bipolar disorder not otherwise specified and 5 were diagnosed with cyclothymia. The prevalence of borderline personality disorder (9.2%, n=44) was slightly lower than the prevalence of bipolar disorder. Borderline personality disorder was four times more frequently diagnosed in the MDQ positive group than the MDQ negative

group (21.5% vs. 4.1%, p LESS THAN .001). The results were essentially the same when the analysis was restricted to patients with a current diagnosis of major depressive disorder (27.6% vs. 6.9%, p=.001). Of the 98 patients who screened positive on the MDQ in the entire sample of patients, 23.5% (n=23) were diagnosed with bipolar disorder and 27.6% (n=27) were diagnosed with borderline personality disorder.
Conclusion: Positive results on the MDQ are as likely to indicate that a patient has borderline personality disorder as bipolar disorder. The clinical utility of the MDQ in routine clinical practice is uncertain.
Literature References: Hirschfeld R, Williams J, Spitzer R, et al. Development and validation of a screening instrument for bipolar spectrum disorder: The Mood Disorder Questionnaire. Am J Psychiatry 2000;157:1873-1875.
Zimmerman, M. Positive predictive value: a clinician's guide to avoid misinterpreting the results of screening tests. Journal of Clinical Psychiatry, 2022, 83(5), 14513.

PHARMACOTHERAPIES FOR MOOD INSTABILITY: WHAT ARE WE TREATING?

Joseph Goldberg, Icahn School of Medicine at Mount Sinai

Individual Abstract: Popular use of the term "mood stabilizer" connotes efficacy to diminish the frequency and intensity of emotional excursions from euthymia that occur on a moment-to-moment basis. By that conceptualization, no psychotropic compound has demonstrated efficacy to stabilize mood, inasmuch as antimanic agents treat or prevent full affective syndromes (rather than mood reactivity), and no pharmacotherapy trials in borderline personality disorder have examined "affective instability" as the primary outcome target of treatment. Environmental factors believed to perturb euthymia fundamentally differ between bipolar disorder and borderline personality disorder; the former involves sensitivity to disruptions in circadian and social rhythm patterns, whereas the latter appears triggered mainly by interpersonal difficulties, including perceived rejection. Given the fundamental differences in exogenous factors that might provoke disruptions to euthymia in bipolar versus borderline personality disorders, alongside the expectations of pharmacological interventions based on drug classification, the term "mood stabilizer" would seem to be an imprecise and potentially misleading anachronism, lacking justifiable extrapolation from the FDA's unique product labeling of lithium.
This presentation will review empirical evidence for the use of "mood stabilizers," as well as monoaminergic antidepressants and second generation antipsychotics, for targeting affective instability as a distinct treatment focus in both bipolar and borderline personality disorders. From the available database, it will be argued that little evidence exists to apply the term "mood stabilizer" for intended efficacy against transitory mood shifts. Moreover, by popularizing and perpetuating this misconstrued terminology, the field may have unwittingly reformulated and reshaped borderline personality disorder as being an entity driven more by mood dysregulation than by its original conceptualization as straddling the border of psychosis. Whereas bipolar disorder is viewed in DSM-5 as fundamentally a disorder of energy, borderline personality disorder is not; and the core features of borderline personality disorder (e.g., identity diffusion, rejection sensitivity, chronic feelings of emptiness) diverge substantively from bipolar disorder, casting doubt on the rationale for assuming shared pharmacological efficacy for both conditions. A recent Cochrane Database review concluded that "no pharmacological therapy seems effective in specifically treating borderline personality disorder pathology." We shall consider the foundations for this conclusion and its implications for future pharmacology studies that presume borderline personality disorder to

fall more closely within the “bipolar” rather than the “psychosis” spectrum of major psychiatric disorders.
Literature References: 1) Crawford MJ, Sanatinia R, Barrett B, et al. Lamotrigine for people with borderline personality disorder: A RCT. Health Technol Assess 2018; 22: 1-68
2)Stoffers-Winterling JM, Storebø OJ, Pereira Ribeiro J, et al. Pharmacological interventions for people with borderline personality disorder. Cochrane Database Syst Rev. 2022 Nov 14;11(11):CD012956

AN INTEGRATIVE FRAMEWORK FOR TREATMENT INDIVIDUALS WITH COMORBID BIPOLAR DISORDER AND BORDERLINE PERSONALITY DISORDER

Christina Temes, Harvard Medical School, Massachusetts General Hospital

Individual Abstract: Bipolar disorder (BD) and borderline personality disorder (BPD) are diagnostically distinct conditions that nonetheless commonly co-occur, with a comorbidity rate of approximately 20% on average. Individuals with comorbid BD/BPD appear to have a markedly more severe and phenomenologically distinct clinical course when compared to those with BD alone, with greater instability of mood symptoms, increased risk for suicidal thoughts and behaviors, and poorer psychosocial functioning noted. The more complicated symptom profile and distinct trajectory observed in this subgroup necessitates a different approach to treatment for these patients. Psychosocial treatments have generally not been evaluated within this specific population, and currently no formal treatment guidelines exist for this subgroup of patients. However, there are several empirically-supported psychotherapies for BPD—for which psychosocial treatments are first-line interventions—as well as evidence-based adjunctive psychosocial treatments for BD. Adaptation and integration of these existing interventions is likely to be a fruitful avenue for identifying effective treatments for comorbid BD/BPD.
The goal of the current workshop is to discuss which psychosocial treatment approaches may be most beneficial for patients with this comorbidity based on the existing evidence base. This presentation will first include a review of the epidemiological and descriptive research on the phenomenology, course, and treatment response of those with comorbid BD/BPD compared to those with BPD alone. We will then review the current findings on evidence-based psychosocial treatments for both BD and BPD with an emphasis on interventions that appear to demonstrate promising outcomes for both conditions (i.e., dialectical behavior therapy, psychoeducation, and others). Finally, we will discuss potential avenues for integrating existing psychosocial interventions in treating patients with comorbid BD/BPD and briefly highlight the role of psychopharmacology in this subgroup.
In presenting these findings, we also will discuss practical ways in which existing evidence can be immediately integrated into clinical practice. Discussion will also focus on both small-scale and large-scale suggestions for future research directions to better understand this specific patient population and its treatment.
Literature References: Frías Á, Baltasar I, Birmaher B. Comorbidity between bipolar disorder and borderline personality disorder: Prevalence, explanatory theories, and clinical impact. J Affect Disord. 2016;202:210-219. doi:10.1016/j.jad.2016.05.048
Temes CM, Boccagno C, Gold AK, Kobaissi H, Hsu I, Montinola S, Sylvia LG. Comorbidity of bipolar disorder and borderline personality disorder: Phenomenology, course, and treatment considerations. Bipolar Disorders. 2024 Sep;26(6):548-55.

Wednesday, May 28, 2025

8:30 a.m. - 10:00 a.m.
Henry Nasrallah Awardee: Stephen Stahl

TEACHING THE TEACHERS OF PSYCHOPHARMACOLOGY: WHERE SHOULD THE FOCUS BE, ON THE CONTENT, ON THE PRESENTER OR ON THE PARTICIPANT?

Henry Nasrallah, University of Cincinnati College of Medicine

Overall Abstract: This will be a plenary talk done by Dr. Steven Stahl the Henry Nasrallah Award Winner. The goals in presenting this inaugural lecture reflect two main propositions: 1) anyone with a basic understanding of mental illness can increase their understanding of how the brain works, how its functions can go awry, and how to compensate for broken circuitry using pharmacological interventions properly, and 2) people learn best when they are engaged (and not so much if they aren't). Great teachers bring subject matter to life, spark curiosity, and make the learner ask their own questions as they make discoveries and draw intellectual connections that reflect true understanding of a complex subject.

TEACHING THE TEACHERS OF PSYCHOPHARMACOLOGY: WHERE SHOULD THE FOCUS BE: ON THE CONTENT, ON THE PRESENTER, OR ON THE PARTICIPANT?

Stephen Stahl, University of California San Diego

Abstract: It is an enormous honor to be named the inaugural recipient of the Henry Nasrallah Award for Excellence in Clinical Psychopharmacology Education. Henry Nasrallah has been, and remains, a giant in our field not only for his contributions to advancing knowledge about psychotic and mood disorders and their treatments, but moreover, for dedicating so much of his career to helping psychiatrists and other mental health professionals better understand their craft. This award rightfully acknowledges the importance with which education in clinical psychopharmacology is a pillar of our collective mission as clinicians, scientists, and academicians. How to most effectively teach psychopharmacology has been a sorely neglected topic, and one that I hope this award will make front-of-mind for all of us who devote our energies to advancing knowledge about clinical psychopharmacology.
My goals in presenting this inaugural lecture reflect two main propositions: 1) anyone with a basic understanding of mental illness can increase their understanding of how the brain works, how its functions can go awry, and how to compensate for broken circuitry using pharmacological interventions properly, and 2) people learn best when they are engaged (and not so much if they aren't). Great teachers bring subject matter to life, spark curiosity, and make the learner ask their own questions as they make discoveries and draw intellectual connections that reflect true understanding of a complex subject.
Our fundamental question is, how do great psychopharmacologists impart their knowledge, wisdom and expertise to others? Begin by appreciating that the word "doctor" derives from the latin root docere – to teach – making medical practice and education opposite sides of the same coin. Anyone who treats enough patients or conducts enough clinical trials will eventually develop a formidable knowledge base. How does that individual then most effectively transmit their knowledge to others? How do they engage a learner to absorb what they know? It's not simply by osmosis. Or, even better, how can an educator help the learner truly understand a problem in ways that lets them grasp implications, generate original insights, recognize contradictions or missing pieces, and draw their own conclusions? Truly

great educators do not merely communicate factual information; they inspire a sense of wonder and awe that makes learning adventuresome. In that sense, masterful teaching is something of a tripartite configuration: the star of the show is the content – like the plated meal at a 3-star Michelin restaurant -- while the presenter is the chef who knows how to enthrall the diner. Rock star chefs wow diners and leave them wanting more. Stellar educators make the content come alive by making participants care about it. The presenter's job, either from in front of or behind the curtain, is to keep the audience mesmerized by the content. Tricks of the trade can be taught to help accomplish this. Hacks can be learned. Metaphors and building blocks of knowledge can be constructed. But above all, "limbic learning" – where new knowledge is paired with high emotional valence – is a captivating paradigm that psychopharmacology educators at all levels of their own training and expertise can hone as a mastery skill.

Learning Objective 1: anyone with a basic understanding of mental illness can increase their understanding of how the brain works, how its functions can go awry, and how to compensate for broken circuitry using pharmacological interventions properly

Learning Objective 2: people learn best when they are engaged (and not so much if they aren't). Great teachers bring subject matter to life, spark curiosity, and make the learner ask their own questions as they make discoveries and draw intellectual connections that reflect true understanding of a complex subject

10:15 a.m. - 11:15 a.m.
ASCP Awards Ceremony and ASCP Lifetime Awardee Talk - John M. Kane, M.D.

THE EVOLUTION OF MY RESEARCH IN THE TREATMENT OF SCHIZOPHRENIA AND UNANSWERED QUESTIONS

Joseph Goldberg, Icahn School of Medicine at Mount Sinai

Overall Abstract: I am very honored to receive this award. I have been asked on numerous occasions where I get the ideas that I have been able to turn into successful grant applications. I believe that a clear source of my success has been that my research has often been driven by frequently encountered clinical dilemmas and unanswered questions.

During my residency in psychiatry, I was struck by how often I could not find compelling evidence to influence the critical clinical decisions with which I was confronted in day-to-day practice. In teaching and mentoring I ask my trainees to make a note each time they feel anxious about making a clinical decision and I try to point out that each such situation potentially reveals a research question. (If they never feel a sense of anxiety, I suggest that they come and talk to me.)

Some of the questions that I encountered very early in my career included: if and for how long is maintenance treatment indicated in someone who was relatively asymptomatic after being treated for a first episode of schizophrenia; what is the minimal dose of antipsychotic medication necessary to significantly reduce the risk of relapse; are long-acting injectable medications superior to oral medications in preventing relapse and rehospitalization; to what extent does psychosocial treatment influence risk of relapse; how common is tardive dyskinesia, how frequently does it go un- or misdiagnosed and what are the risk factors; how do we treat someone who has not responded adequately to a standard course of antipsychotic medication; what influences placebo response in schizophrenia; how relevant are blood levels in explaining heterogeneity of treatment response?

In this presentation I will discuss some of the studies that were designed to address these questions and their current status years later. At this stage of my career, I am struck by the uncertainty that remains for many of these issues, as well as the striking challenges in implementing research findings in day-to-day practice.

THE EVOLUTION OF MY RESEARCH IN THE TREATMENT OF SCHIZOPHRENIA AND UNANSWERED QUESTIONS

John Kane, The Donald and Barbara Zucker School of Medicine

Abstract: I am very honored to receive this award. I have been asked on numerous occasions where I get the ideas that I have been able to turn into successful grant applications. I believe that a clear source of my success has been that my research has often been driven by frequently encountered clinical dilemmas and unanswered questions.

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In this presentation I will discuss some of the studies that were designed to address these questions and their current status years later. At this stage of my career, I am struck by the uncertainty that remains for many of these issues, as well as the striking challenges in implementing research findings in day-to-day practice.

Learning Objective 1: To educate attendees about the process involved in designing impactful clinical research

Learning Objective 2: To bring attendees up-to-date on current controversies in the pharmacologic management of schizophrenia

Literature References: 1. Kane JM, Rifkin A, Quitkin F, Nayak D, Ramos-Lorenzi J. (1982-01). Fluphenazine vs placebo in patients with remitted, acute first-episode schizophrenia. Archives of general psychiatry. 39(1): 70 - 73. 10.1001/archpsyc.1982.04290010048009

2. Kane J, Honigfeld G, Singer J, Meltzer H. (1988-09). Clozapine for the treatment-resistant schizophrenic. A double-blind comparison with chlorpromazine. Archives of general psychiatry. 45(9): 789 - 796. 10.1001/archpsyc.1988.01800330013001

1:00 p.m. - 2:30 p.m.
Clinical Updates in Neurotherapeutics

CLINICAL UPDATES IN NEUROTHERAPEUTICS

Michael Henry, Massachusetts General Hospital

Overall Abstract: Advances in our understanding of brain physiology and the brain circuits involved in neuropsychiatric illnesses, combined with improvements in the engineering of devices has led to an explosion of neurotherapeutic treatments for severe psychiatric illness. This Plenary session will provide state of the art updates in the clinical applications of these

treatments. It will include Low Intensity Focused Ultrasound, Transcranial Magnetic Stimulation (TMS), and Vagal Nerve Stimulation.

THE SOUND OF THE FUTURE? AN INTRODUCTION TO LOW INTENSITY FOCUSED ULTRASOUND

Noah Philip, Alpert Medical School of Brown University

Abstract: Low intensity focused ultrasound is poised to become a paradigm-shifting technology with the potential to deliver non-invasive, reversible, and focal deep brain stimulation. This approach uses acoustic energy to modulate regional brain activity, reaching deep and subcortical brain regions implicated in psychiatric disorders at millimeter precision. In contrast to high intensity focused ultrasound, which is thermally ablative and available as a lesion treatment for movement disorders and other indications, low intensity focused ultrasound uses energy at or below limits for diagnostic ultrasound and appears to reversibly modulate neural activity, presumably without injury.
As with any new field, there is no shortage of important questions. First and foremost, is low intensity focused ultrasound safe? Current ultrasound safety standards were developed before the current technology existed, underscoring the need to carefully establish safe use. Since ultrasound uses acoustic (i.e., mechanical) energy, and many deep brain regions are adjacent to important components of the cerebral vasculature (i.e., circle of Willis), careful implementation is warranted. Whether this technology can reliably modulate deep brain regions is an active area of inquiry; if successful, low intensity focused ultrasound will open a novel way to evaluate neurophysiological and clinical effects from direct target engagement. This session is designed for attendees to who wish to learn more about the use of low intensity focused ultrasound in humans and potential for future use in non-invasive and non-ablative neuromodulation. This presentation will include perspective from an investigator actively engaged in first-in-human applications of its technology and will touch upon other exciting and ongoing areas of research in this space.
Learning Objective 1: Describe the difference between high and low intensity focused ultrasound
Learning Objective 2: Discuss potential safety considerations for low intensity focused ultrasound neuromodulation
Literature References: Philip NS, and Arulpragasam AR (2023). Reaching for the unreachable: low intensity focused ultrasound for non-invasive deep brain stimulation. Neuropsychopharmacology: official publication of the American College of Neuropsychopharmacology, 48(1), 251–252. https://doi.org/10.1038/s41386-022-01386-2
Cox SS, Connolly DJ, Peng X, Badran BW. A Comprehensive Review of Low-Intensity Focused Ultrasound Parameters and Applications in Neurologic and Psychiatric Disorders. Neuromodulation. 2024 Sep 3:S1094-7159(24)00662-7. doi: 10.1016/j.neurom.2024.07.008. Epub ahead of print. PMID: 39230530.

TMS IN THE AGE OF EXPERIMENTAL MEDICINE AND PRECISION NEUROMODULATION

Joan Camprodon, Massachusetts General Hospital, Harvard Medical School

Abstract: Transcranial Magnetic Stimulation (TMS) has evolved since the mid-1980s from its initial role as an innovative tool to probe human motor neurophysiology in vivo, to a powerful therapeutic option for complex and treatment-resistant brain disorders. In this presentation, we will start by defining the biological, clinical, and technological triple paradigm that defines the modern practice of TMS (specifically) and interventional

psychiatry (broadly). This circuit neuroscience framework has facilitated the implementation of experimental medicine strategies for the development of therapeutic innovations informed by response biomarkers: critically, this paradigm shift in treatment discovery has placed TMS (and other neuromodulation technologies) at the forefront of precision psychiatry, moving beyond population-based TMS protocols to patient-specific algorithms. We will review these concepts and highlight multiple recent examples of precision TMS innovations that are changing the clinical neurosciences and, importantly, offering new, safe, and effective therapies for patients with brain disorders. Finally, we will discuss some of the current challenges and future directions, including the need for treatment-selection algorithms in the face of rapidly emerging therapies with overlapping indications, and the complexities around training and professional development in the space of interventional psychiatry.
Learning Objective 1: To understand the framework for biomarker-driven treatment development in neuromodulation and TMS.
Learning Objective 2: To understand strategies for precision neuromodulation using TMS
Literature References: Camprodon JA. Therapeutic Neuromodulation for Bipolar Disorder-The Case for Biomarker-Driven Treatment Development. JAMA Netw Open. 2021;4(3):e211055. Epub 2021/03/13. doi: 10.1001/jamanetworkopen.2021.1055. PubMed PMID: 33710284.
Camprodon JA, Barbour T. Introduction. Interventional Neuropsychiatry and Neuromodulation: an emerging subspecialty in brain medicine. Harvard review of psychiatry. 2023;31(3):97-100. Epub 2023/05/12. doi: 10.1097/HRP.0000000000000368. PubMed PMID: 37171470.

VAGUS NERVE STIMULATION FOR TREATMENT-RESISTANT DEPRESSION: THE RECOVER TRIAL

Charles Conway, Washington University in St. Louis

Abstract Background: Few treatments are available for marked treatment-resistant depression (TRD). The RECOVER trial is a double-blind, multi-center (N=81), sham-controlled, prospective trial of vagus nerve stimulation (VNS) in a sample of marked TRD patients (minimum of 4 failed treatments in the current depressive episode). The study examined effects on depressive symptoms, quality of life (QoL), functional improvements, and global clinical improvement.
Objective: Evaluate the safety and effectiveness of FDA-approved adjunctive vagus nerve stimulation (VNS) in patients with marked TRD.
Methods: 493 adults with TRD and ≥4 adequate but unsuccessful antidepressant treatment trials (current episode) were randomized to active (n=249) or sham (n=244) VNS (plus treatment as usual) over a 12-month observation period. For the depressive symptom outcome, the primary outcome was percent time in response across months 3 to 12, with response defined as a ≥50% change from baseline on the Montgomery-Åsberg Depression Rating Scale (MADRS); several other measures of depressive symptom scales were also assessed. QoL was assessed via quarterly evaluations using the Q-LES-Q, Mini-Q-LES-Q, and EQ-5D-5L, and function with the WHODAS 2.0 and Work Productivity and Activity Impairment Questionnaire (WPAI) item 6. Differences between treatment groups in change in scores from baseline and percentage of time with a meaningful response in Q-LES-Q, Mini-Q-LES-Q, and WPAI item 6 scores were analyzed. Overall improvement was assessed via the Clinical Global Impression-Improvement (CGI-I).
Results: Overall, 88.4% of participants completed the trial. Percent time in MADRS response did not distinguish active from sham VNS. However, ratings from on-site clinicians (CGI-I), patients (Quick Inventory of Depressive Symptomology–Self Report [QIDS-SR]),

and offsite masked raters (Quick Inventory of Depressive Symptomology–Clinician [QIDS-C]) revealed antidepressant benefits significantly favoring active VNS. Active VNS demonstrated significantly more percent time in response on the CGI-I (P=0.004) and QIDS-SR (P=0.049), and significantly more percent time in partial response (PR; symptom improvement ≥30%) on the CGI-I (P LESS THAN 0.001) and QIDS-C (P=0.006) versus sham VNS. Active VNS was superior to sham in mean change in QoL using the Mini-Q-LES-Q (P=0.050) and WPAI item 6 (health condition's effect on regular activities [P=0.050] used as continuous variables, with a similar trend for Q-LES-Q [P=0.061]). Active VNS was superior to sham in time spent in clinically meaningful benefit (categorical analyses) using the Q-LES-Q (P=0.029), Mini-Q-LES-Q (P=0.011), and WPAI item 6 (P=0.039). The WHODAS 2.0 (P=0.304) and EQ-5D visual analog scale (P=0.125) failed to reveal between-group differences.
Conclusions: Percent time in MADRS response did not distinguish the treatment groups, but on multiple instruments time in response and PR showed a positive treatment effect. VNS was found safe and effective in participants with marked TRD. Active VNS was superior to sham VNS in improving QoL and psychosocial function in patients with TRD. VNS has a broader therapeutic impact than symptom improvement alone in patients with marked psychosocial impairment.
Learning Objective 1: Participants will understand the design of the double-blinded RECOVER vagus nerve stimulation trial.
Learning Objective 2: Participants will become familiar with the results of the RECOVER trial, including those pertaining to depressive symptoms, quality of life, and functional improvements.
Literature References: Aaronson ST, Sears P, Ruvuna F, Bunker M, Conway CR, Dougherty DD, et al. A 5-Year Observational Study of Patients With Treatment-Resistant Depression Treated With Vagus Nerve Stimulation or Treatment as Usual: Comparison of Response, Remission, and Suicidality. Am J Psychiatry. 2017;174(7):640-8.
Conway CR, Olin B, Aaronson ST, Sackeim HA, Bunker M, Kriedt C, et al. A prospective, multi-center randomized, controlled, blinded trial of vagus nerve stimulation for difficult to treat depression: A novel design for a novel treatment. Contemp Clin Trials. 2020;95:106066.

VAGUS NERVE STIMULATION FOR TREATMENT-RESISTANT DEPRESSION: RE-EVALUATING OUTCOME MEASURES

Scott Aaronson, Sheppard Pratt

Abstract: Outcome measures used in the investigation of treatments for depression such as the Hamilton Depression Rating Scale (HDRS) or the Montgomery Asberg Depression Rating Scale (MADRS) often fail to capture the most critical potential benefits for patients with the most difficult to treat depressions. These scales focus on somatic markers and do not capture changes in quality of life or ability to engage in daily functioning. As well, remission, the gold standard for depression outcomes, is very rarely seen in individuals who have been depressed and disabled for many years. Even response rates, determined by a 50% drop in a MADRS or HDRS may be too optimistic a goal. Often small, measurable improvements in ability to function may represent a meaningful improvement in the quality of life for someone who has been depressed for decades.
This lecture will introduce the evolving concepts of meaningful benefit and how outcome evaluation is changing as more treatments are introduced with the potential to improve the lives of individuals with the most difficult to treat depressions.
Learning Objective 1: Participants will understand the design of the double-blinded RECOVER vagus nerve stimulation trial

Learning Objective 2: Participants will become familiar with the results of the RECOVER trial, including those pertaining to depressive symptoms, quality of life, and functional improvements.

Literature References: Aaronson ST, Sears P, Ruvuna F, Bunker M, Conway CR, Dougherty DD, et al. A 5-Year Observational Study of Patients With Treatment-Resistant Depression Treated With Vagus Nerve Stimulation or Treatment as Usual: Comparison of Response, Remission, and Suicidality. Am J Psychiatry. 2017;174(7):640-8.
Conway CR, Olin B, Aaronson ST, Sackeim HA, Bunker M, Kriedt C, et al. A prospective, multi-center randomized, controlled, blinded trial of vagus nerve stimulation for difficult to treat depression: A novel design for a novel treatment. Contemp Clin Trials. 2020;95:106066.

3:00 p.m. - 4:30 p.m.
~Individual Research Reports (IRRs): Innovations in Novel Therapeutics for Mood, Anxiety and Related Disorders

RAPID NONINVASIVE MODULATION OF ANTERIOR CINGULATE CORTEX FOR MOOD AND PAIN DISORDERS

Brian Mickey[*1], Daniel Feldman[1], Brandon Cooper[1], Vincent Koppelmans[1], Akiko Okifuji[1], Thomas Riis[1], Jan Kubanek[1]*
[1]*University of Utah*

Brian Mickey*, University of Utah

Abstract Background: The anterior cingulate cortex (ACC) is a deep limbic hub that plays key roles in the generation of mood and perception of pain. Chronic mood and pain disorders are thought to arise from dysfunction of the ACC, and direct ACC stimulation with surgically implanted electrodes can ameliorate depression and pain in treatment-resistant patients. However, current non-invasive approaches cannot directly and selectively modulate deep targets like the ACC, so ACC-targeted interventions have been available only to those who are surgical candidates. To address this gap, we developed and validated a new device based on ultrasound arrays that can deliver low-intensity focused ultrasound transcranially to sub-regions of the ACC with millimeter precision. Recently published work has demonstrated that this approach can directly modulate ACC activity and safely improve depression and pain symptoms. Here we describe immediate subjective reports and rapid changes in brain functional connectivity elicited with direct ACC stimulation.
Methods: Subjects with treatment-resistant depression (n = 22) or chronic pain (n = 20) participated in two separate randomized, blinded, sham-controlled studies. Ultrasound was delivered at low intensity to subgenual, pregenual, and dorsal sub-regions of the ACC using individualized MRI guidance. Real or sham sonication trials (duration, 30–180 seconds) were administered during one-hour stimulation sessions. Immediate subjective self-reports from each trial (589 real, 502 sham) were scored as positive, neutral, or negative in valence. Resting-state functional MRI was acquired from 15 depressed participants immediately before and after 10 minutes of intermittent subgenual ACC stimulation. Changes in brain functional connectivity were quantified using subgenual seed-based analyses.
Results: Subjective responses to sham sonication were neutral in 94% of trials, positive in 3.6%, and negative in 2.4%, demonstrating a low sham response rate and a lack of bias in valence ($p = 0.28$). In contrast, real sonication often elicited immediate subjective changes in depression, anxiety, pain, or mental clarity. Responses to real sonication were 58% neutral, 36% positive, and 7% negative, which differed significantly from the sham condition ($p<0.0001$). Sonication of subgenual ACC was associated with a decrease in resting

functional connectivity of the target with Brodmann area 9 in the medial prefrontal cortex, representing a rapid shift from positive to negative connectivity ($p = 0.04$, FDR corrected).
Conclusions: Ultrasonic neuromodulation uniquely combines non-invasiveness with focality at depth, opening up new possibilities for selective engagement of deep brain circuits. Direct ACC neuromodulation can immediately alter subjective experiences and brain functional connectivity. These findings highlight the potential for development of transcranial focused ultrasound into rapid, safe, circuit-targeted interventions for neuropsychiatric disorders.
Learning Objective 1: Appreciate that transcranial focused ultrasound is a promising neuromodulation approach that can directly and selectively engage deep brain circuits
Learning Objective 2: Understand the role of the anterior cingulate cortex in mood and pain disorders and the potential for low-intensity ultrasound to safely and rapidly modulate mood, pain, and brain functional connectivity
Literature References: Riis TS, Feldman DA, Kwon SS, Vonesh LC, Koppelmans V, Brown JR, Solzbacher D, Kubanek J, Mickey BJ. Noninvasive Modulation of the Subcallosal Cingulate and Depression With Focused Ultrasonic Waves. Biol Psychiatry. 2024 Oct 11:S0006-3223(24)01662-7.
Riis T, Feldman D, Losser A, Mickey B, Kubanek J. Device for Multifocal Delivery of Ultrasound Into Deep Brain Regions in Humans. IEEE Trans Biomed Eng. 2024 Feb;71(2):660-668.

ASSESSING COGNITIVE OUTCOMES IN TREATMENT-RESISTANT DEPRESSION FOLLOWING PSILOCYBIN-ASSISTED PSYCHOTHERAPY

Danica Johnson[*1], Erica Kaczmarek[1], Noah Chisamore[1], Zoe Doyle[2], Orly Lipsitz[1], Rodrigo Mansur[1], Roger McIntyre[1], Joshua Rosenblat[1]*
[1]University of Toronto, [2]University Health Network

Danica Johnson*, University of Toronto

Abstract Background: Cognitive deficits, including impairments in processing speed, attention, and executive function, are prevalent in treatment-resistant depression (TRD) and are associated with poorer outcomes and reduced quality of life. Despite their clinical significance, conventional treatments often fail to address these deficits, highlighting the need for novel interventions. Psilocybin-assisted psychotherapy (PAP) has emerged as a promising treatment for the affective symptoms of TRD, but its effects on cognition remain underexplored.
Completed Pilot Study: In this post-hoc analysis of a pilot PAP trial (NCT05029466), we assessed cognitive outcomes in TRD patients randomized to an immediate treatment arm (n=12; 25 mg psilocybin plus psychotherapy) or a delayed-treatment waitlist control arm (n=14). We analyzed within- and between-group changes with paired and independent t-tests or nonparametric equivalents (Wilcoxon and Mann-Whitney U tests). We also conducted a mediation analysis to examine whether depressive symptom changes (Montgomery-Åsberg Depression Rating Scale scores) mediated cognitive outcomes. After two weeks, we observed significant within-group improvements in the treatment arm on the TMT-A (mean difference= -8.67, $p<001$, $d = 1.29$) and TMT-B (median difference = -13.50, $z = -2.554$, $p = .011$), but no significant changes in the waitlist arm for any cognitive outcomes. Between-group comparisons revealed significantly greater TMT-B improvements in the treatment arm compared to the waitlist arm ($p = .016$), while TMT-A improvements did not significantly differ ($p = .133$). Our mediation analysis revealed depressive symptom reductions did not significantly mediate TMT-B performance gains ($b = 0.81$, 95% CI [-6.57, 16.62]), suggesting mood-independent cognitive benefits.

Ongoing RCT: Building on these findings, we launched a federally-funded, triple-blind, randomized, placebo-controlled trial in February 2024 to rigorously evaluate the efficacy, safety, and tolerability of one versus two 25 mg doses of psilocybin for TRD (NCT06341426). Participants (n=90) are randomized to receive either a 1 mg placebo dose or a 25 mg therapeutic dose of psilocybin, followed by an open-label phase where all participants receive the 25 mg dose. Neuropsychological assessments are conducted at baseline, three weeks after each dose, and at three- and six-month follow-ups, enabling the evaluation of acute and sustained changes in executive function, verbal learning/memory, attention, processing speed, verbal fluency, and subjective cognitive functioning. Linear mixed-effects models will analyze treatment-related cognitive changes over time, and mediation analyses will examine whether observed cognitive improvements are independent of changes in depressive symptoms. The trial is progressing steadily, with 43 participants enrolled to date, and is projected for completion by April 2026.
Significance: The pilot results demonstrate psilocybin's potential to improve cognitive functioning in TRD, independent of mood changes. Our ongoing RCT addresses key limitations of the pilot, including the small sample size, short follow-up, and lack of placebo controls. By providing a robust evaluation of psilocybin's effects on cognition, this research has the potential to transform therapeutic paradigms for TRD and inform interventions for cognitive impairment across other psychiatric and neurological disorders.
Learning Objective 1: Evaluate the potential of psilocybin-assisted psychotherapy to address cognitive impairment in treatment-resistant depression and its implications for clinical practice and future research.
Learning Objective 2: Discuss the design and methodology of a psilocybin clinical trial, including neuropsychological assessments and strategies for evaluating mood-independent cognitive effects.
Literature References: Colwell MJ, Tagomori H, Chapman S, et al. Pharmacological targeting of cognitive impairment in depression: recent developments and challenges in human clinical research. Transl Psychiatry. 2022; 12:484.
Doss MK, Považan M, Rosenberg MD, et al. Psilocybin therapy increases cognitive and neural flexibility in patients with major depressive disorder. Transl Psychiatry. 2021; 11:574.

PHARMACOKINETIC/PHARMACODYNAMIC ANALYSIS OF THE BNC210 ATTUNE PHASE 2B DATASET ENABLES DOSE SELECTION FOR PLANNED PHASE 3 PTSD STUDY

Spyros Papapetropoulos[1], Elisabeth Doolin[1], Dharam Paul[1], Michael Odontiadis[1], Mark A Smith[1]*
[1]Neuphoria Therapeutics Inc

Spyros Papapetropoulos*, Neuphoria Therapeutics Inc

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 (Shalev et al. 2024). 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 PTSD. 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.

In a 12-week Phase 2b (ATTUNE) study, 900 mg BID BNC210 demonstrated a statistically significant improvement compared to placebo on the primary endpoint of mean change from baseline 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) (Papapetropoulos et al. 2025).

To assess dose selection for the upcoming Phase 3 study of BNC210 in PTSD, we evaluated the AUC/CAPS-5 total symptom severity exposure/response relationship of 900 mg BID. We then estimated the modeled mean AUC0-12 for potential doses for Phase 3: 450 mg BID and 600 mg BID vs 900 mg BID (assuming dose linear PK and 20% CV based on Phase 1 PK data).

ATTUNE only had a modest exposure/response correlation with BNC210 900 mg BID. This suggests that lower BNC210 doses (450 mg or 600 mg BID) may deliver therapeutic exposures and justify dose-ranging evaluation in the planned Phase 3 trial. Additionally, these proposed lower doses may contribute to an overall improved safety and tolerability profile of BNC210.

In summary, the ATTUNE-modeled AUC dataset and exposure/response analysis are expected to enable dose selection for the planned Phase 3 study with BNC210 in PTSD.

Learning Objective 1: Dose selection rationale for future planned Ph3 trial in PTSD with BNC210

Learning Objective 2: The use of pharmacometric modeling in drug development

Literature References: Shalev A, Cho D, Marmar CR. Neurobiology and treatment of posttraumatic stress disorder. Am J Psychiatry. 2024;181(8):705-19.

Papapetropoulos S, Doolin E, O'Connor S, et al. BNC210, an α7 Nicotinic Receptor Modulator, in Post-Traumatic Stress Disorder. NEJM Evid. 2025 Jan;4(1):EVIDoa2400380.

PHASE 3 TRIAL DESIGN AND METHODOLOGY: TREATMENT WITH MM120 (LYSERGIDE) FOR GENERALIZED ANXIETY DISORDER AND MAJOR DEPRESSIVE DISORDER

Daniel Karlin, MD, MA[1], Paula L. Jacobsen, PhD[2], Todd M. Solomon, PhD[2], Sarah M. Karas, PsyD[2], Jamie M. Freedman, BS[2]*

[1]Mind Medicine Inc., Tufts University School of Medicine, [2]Mind Medicine Inc.

Daniel Karlin, MD, MA, Mind Medicine Inc., Tufts University School of Medicine

Abstract Introduction: Generalized anxiety disorder (GAD) and major depressive disorder (MDD) affect 10% and 7.1% of the US population and have significant impact on daily functioning and quality of life. GAD manifests as a range of chronic and episodic psychiatric and somatic symptoms. MDD shares similar symptomology and is often comorbid with GAD.1 Medical management struggles to balance limited efficacy of current treatments with quality-of-life (QoL) considerations of treatment-associated side effects. Effective and well-tolerated pharmacotherapies are needed for both disorders. MM120 (lysergide D-tartrate) is under development as a potential treatment for GAD and MDD.

Methods: A phase 2b (NCT05407064) study evaluated the dose-response relationship of efficacy, safety, and tolerability of single-dose 25, 50, 100, or 200µg MM120 vs placebo in participants with moderate-to-severe GAD.2 Three phase 3, multicenter, randomized, placebo-controlled, double-blind studies within the development program of MM120 are ongoing. In the US, Voyage and Emerge will evaluate MM120 100µg for treatment of GAD and MDD, respectively. Panorama is a global study of GAD and includes a 50µg arm to mitigate functional unblinding. Participants with the Hamilton Anxiety Rating Scale (HAM-A)≥20 in GAD studies or with the Montgomery-Åsberg Depression Rating (MADRS)≥26 and CGI-S≥4 for the MDD study are eligible for enrollment. All studies include a single

treatment administered at the beginning of the 12-week randomized period and a 40-week extension period with an opportunity for up to four open-label treatments (OLE) to assess longer-term safety and efficacy and define retreatment paradigms. The assessment for open-label treatment incorporates symptom severity and utilizes a unique methodology for clinical trials which mimics real-world clinical practice. Consistent with phase 2b, to isolate drug-only effects and mitigate methodological concerns with co-administered therapies, these three studies do not include psychotherapy.
Results: The phase 2b study demonstrated a statistically significant dose-response relationship at the week 4 primary and week 8 key secondary endpoints. The 100µg dose achieved the highest level of clinical activity with a 21.3-point reduction in HAM-A, representing a 7.6-point reduction compared to placebo at week 4 (P=0.0004). Further, 50% of participants treated with MM120 100µg achieved remission (HAM-A ≤7) versus 17.95% with placebo. On the MADRS, an 18.1-point change from baseline and -5.7-point improvement over placebo (P LESS THAN 0.05) were observed at week 4. Improvements in HAM-A and MADRS persisted to week 12. Treatment-emergent adverse events (TEAEs) occurred in 97.5% of participants in the MM120 100µg group versus 56.4% in the placebo group. Most events were mild to moderate, occurred on dosing day, and were consistent with the expected acute effects of MM120. One serious AE occurred, and no deaths were reported in the study.
Conclusion: A single treatment with MM120, provided without the use of psychotherapy, demonstrated a rapid and durable clinical response in participants with moderate-to-severe GAD and improvement in comorbid depressive symptoms and no identified safety concerns. This suggests that MM120 may be a treatment option for GAD, MDD, or co-occurring illness. Phase 3 studies of MM120 for GAD and MDD are ongoing.
Learning Objective 1: To understand the clinical development programs for MM120 (lysergide D-tartrate) in participants with generalized anxiety or major depressive disorders.
Learning Objective 2: To evaluate the phase 2b findings demonstrating primary efficacy, safety, and tolerability and secondary reduction in depressive symptoms for single-dose MM120 (lysergide D-tartrate) in participants with generalized anxiety disorder.
Literature References: 1. Goodwin GM, Stein DJ. Generalised anxiety disorder and depression: contemporary treatment approaches Adv Ther. 2021;38(Suppl 2):45-51.
2. Karlin, D et al. Rapid and durable response to a single dose of MM120 (lysergide) in generalized anxiety disorder: A dose-optimization study. Poster P03-026. Presented at: American Psychiatric Association Annual Meeting; May 4-8, 2024; New York City, NY. 2024.

3:00 p.m. - 4:30 p.m.
Individual Research Reports (IRRs): Advances in Psychosis and Neurocognitive Disorders Research

ENHANCING DRUG MEMORY FORGETTING IN DRUG ADDICTION: THE NEURAL SIGNATURE OF METHYLPHENIDATE- AND RECONSOLIDATION-ENHANCED EXTINCTION IN COCAINE USE DISORDER

Ahmet Ceceli[*1], Sarah King[1], Kathryn Drury[1], Natalie McClain[1], John Gray[1], Jeffrey Newcorn[1], Daniela Schiller[1], Nelly Alia-Klein[1], Rita Z. Goldstein[1]*
[1]*Icahn School of Medicine at Mount Sinai*

Ahmet Ceceli, Icahn School of Medicine at Mount Sinai

Abstract: Salient drug cue memories can hinder abstinence goals in drug addiction. Promoting new (non-drug) memories via ventromedial prefrontal cortex- (vmPFC) and

amygdala-guided extinction has yielded mixed success. Post-retrieval extinction (RE) destabilizes memories during reconsolidation, improving extinction. Supplementing RE, we tested methylphenidate (MPH), a dopamine-agonist that promotes PFC-dependent learning and memory in cocaine use disorder (CUD). In a double-blind randomized within-subjects design, participants received oral MPH (20 mg) or placebo before the retrieval of some of the conditioned stimuli (i.e., reminded CS+ as compared to non-reminded CS+ and CS-) followed by extinction; a next-day lab-simulated drug-seeking measure followed. Lower vmPFC activity to non-reminded CS+ (standard extinction) under placebo replicated impairments in CUD, which were alleviated separately by both RE (a trend) and MPH, yet showing overreliance on the vmPFC. Crucially, MPH-supplemented RE normalized cortico-limbic processing, bypassing the vmPFC and its amygdala connectivity; an association between RE's overreliance on the vmPFC and enhanced drug-seeking was only evident under placebo. This mechanistic account for pharmacologically-enhanced behavioral drug memory modulation can inform the development of multi-modal interventions for addiction recovery.
Learning Objective 1: The ventromedial prefrontal cortex function is altered during the extinction of drug associated cues in people with cocaine use disorder.
Learning Objective 2: The combined use of the partial dopamine agonist methylphenidate alongside memory reconsolidation normalizes extinction related neural function in cocaine use disorder.
Literature References: Konova, A. B. et al. Neural mechanisms of extinguishing drug and pleasant cue associations in human addiction: role of the VMPFC. Addiction Biology. 2019; 24: 88–99.
Schiller, D. et al. Preventing the return of fear in humans using reconsolidation update mechanisms. Nature. 2010; 463: 49–53.

MODERATORS OF ANTIDEPRESSANT TREATMENT IN LATE-LIFE TREATMENT-RESISTANT DEPRESSION: AN ANALYSIS OF THE OPTIMUM RANDOMIZED CONTROLLED TRIAL

Helena Kim[*1], Jordan F. Karp[2], Helen Lavretsky[3], Daniel Blumberger[1], Patrick Brown[4], Alastair J. Flint[5], Emily Lenard[6], Philip Miller[6], Charles Reynolds III[7], Steven Roose[4], Eric Lenze[6], Benoit H. Mulsant[1]*
[1]University of Toronto, [2]University of Arizona,[3]UCLA, Semel Institute, [4]Columbia University Medical Center, [5]University Health Network,[6]Washington University in St. Louis, [7]University of Pittsburgh School of Medicine

Helena Kim*, University of Toronto

Abstract: Pharmacotherapy for late-life treatment-resistant depression (LLTRD) can be challenging. Augmentation of the current antidepressant with another medication was shown to be more beneficial than switching to a different medication in the Outcomes of treatment resistant depression (TRD) in Older Adults (OPTIMUM) randomized controlled trial. Identifying moderators that influence the effectiveness of these two treatment strategies is useful for advancing personalized medicine. Age, executive dysfunction, comorbid physical burden, comorbid anxiety, and the number of previous adequate antidepressant trials were previously reported to impact treatment outcomes in depression. In this moderation analysis, we examined whether these five patient factors moderate the superiority of augmentation over switching in LLTRD.
Our pre-planned moderation analysis was performed using data from the OPTIMUM trial consisting of 742 participants who are 60 years old or older with TRD. The OPTIMUM trial was a multicenter, pragmatic open-label trial. TRD was defined as having two or more adequate antidepressant trials in the current depressive episode. The participants were

randomized to treatment with either augmentation (N = 480) with aripiprazole (2.5-15mg), bupropion (150-450mg), or lithium (target serum drug level 0.6mmol/L); or switch (N = 262) to bupropion (150-450mg) or nortriptyline (target serum drug level 80-120ng/mL). The treatment duration was 10 weeks. The two main outcomes of this analysis were change in depression severity from baseline to week-10 as measured by the Montgomery-Asberg Depression Rating Scale (MADRS) and remission, which was defined as week-10 MADRS score of 10 or less.
In our analysis, the number of adequate previous antidepressant trials was identified as the only significant moderator of change in depression severity (b = -1.6, t = -2.1, p = 0.033, 95%CI [-3.0, -0.1]), where augmentation's superiority over switching decreased with increasing number of previous antidepressant trials. Augmentation was superior to switching only in participants with fewer than three trials (effect = 3.62, p = 0.0001 in participants who have fewer than 3 trials vs. effect = 0.88, p = 0.337 in participants who have more than 3 trials). Post-hoc analyses showed that this moderating effect was independent of the specific medication used for augmentation or switching (b = -0.2, t = -0.2, p = 0.839, 95%CI [-1.9, 1.6]) or whether the previous trial was an augmentation or a switch trial (b = -2.7, t = -1.2, p = 0.214, 95%CI [-7.1, 1.6]). The remaining four patient factors did not have a significant moderating effect on the change in depression severity. There were no significant moderators of remission.
The findings of this analysis can inform physicians on selecting optimal treatment strategies using a readily available patient factor (the number of previous adequate antidepressant trials) that can be collected during a routine assessment. Different intervention strategies, such as ketamine or brain stimulation, can be considered in patients with LLTRD with more than three previous antidepressant trials.
Learning Objective 1: Understand how the number of previous antidepressant trials moderate the effect of treatment strategies in late life treatment resistant depression.
Learning Objective 2: Understand how moderators can be used in clinical settings to advance personalized medicine in psychiatry.
Literature References: Lenze E, Mulsant B, Roose S, et al. Antidepressant Augmentation versus Switch in Treatment-Resistant Geriatric Depression. N Engl J Med. 2023;388(12):1067-1079.
Kim H, Blumberger D, Karp J, et al. Venlafaxine XR treatment for older patients with major depressive disorder: decision trees for when to change treatment. Evid Based Ment Health. 2022;25(4):156-162.

MEASUREMENT OF SCHIZOPHRENIA SYMPTOMS THROUGH SPEECH PHENOTYPING FROM PANSS RECORDINGS: A CROSS-STUDY VALIDATION

Michelle Worthington[*1], Anzar Abbas[1], Georgios Efstathiadis[1], Vijay Yadav[2], Tej Patel[3], Colin Sauder[3], Inder Kaul[3], Steve Brannan[3]*
[1]Brooklyn Health, [2]Brooklyn Health; University of New South Wales, [3]Bristol Myers Squibb

Michelle Worthington*, Brooklyn Health

Abstract Introduction: Speech is a clinically meaningful indicator of schizophrenia symptom severity and speech phenotyping often requires dedicated task paradigms on proprietary platforms using closed-source code to phenotype speech. Here, we use audio recordings of Positive and Negative Syndrome Scale (PANSS) interviews and open source code to calculate speech measures and evaluate them as meaningful indicators of schizophrenia symptom severity.

We previously demonstrated that such clinical interactions are a reliable source of audio for speech phenotyping (under review at Biological Psychiatry). Here, we report results from an expansion of this project using ~2,000 hours of PANSS interview recordings from three separate clinical trials, leading to what we believe is the largest study on speech-based digital phenotyping in psychiatry to date.

Methods: Audio recordings of PANSS interviews from three schizophrenia clinical trials (NCT03697252, NCT04659161, NCT04738123) were analyzed. Speech features, including amount of speech, rate of speech, pause characteristics, emotional sentiment, and lexical richness, were extracted using the OpenWillis open-source Python library (github/bklynhlth/openwillis). Mixed effects models were used to examine the association between speech measures and PANSS scores, controlling for age, sex, and race.

Results: Approximately 1,984 hours of audio data were analyzed from a total of 3,482 PANSS interviews. PANSS positive symptom subscale scores were associated with a greater amount of speech (adjusted speech length in minutes β=3.355; p-value LESS THAN 0.01; adjusted speech length in words β=0.027; p-value LESS THAN 0.01), an increased rate of speech (words per minute β=0.015; p-value LESS THAN 0.01; syllables per minute β=0.009; p-value LESS THAN 0.01), a change in pause characteristics (pause length mean β=-3.819; p-value LESS THAN 0.01), and reduced lexical richness (moving-average token-type ratio (MATTR) β=-13.008; p-value LESS THAN 0.01).

By contrast, the score on the PANSS negative subscale was associated with a reduced amount of speech (adjusted speech length in minutes β=-2.905; p-value LESS THAN 0.01; adjusted speech length in words β=-0.025; p-value LESS THAN 0.01), a decreased rate of speech (words per minute β=-0.017; p-value LESS THAN 0.01; syllables per minute β=-0.010; p-value LESS THAN 0.01), a change in pause characteristics (pause length mean β=4.969; p-value LESS THAN 0.01; increased pause between the clinician's question and the patient's response β=0.784; p-value LESS THAN 0.01), and increased lexical richness (MATTR β=5.302; p-value LESS THAN 0.01).

Conclusions: This study demonstrates the feasibility and value of using clinical interview recordings for large-scale speech analysis in schizophrenia, confirming and expanding on previous findings linking specific speech patterns to symptom severity. This approach allows for efficient and scalable analysis of readily available data, potentially enhancing clinical assessment and treatment development.

Future research will explore higher-order linguistic features to capture more complex aspects of schizophrenia, such as disorganized thought. Speech measures may also be used to develop predictive models of disease severity and stratify patients for personalized interventions. This methodology can be extended to other psychiatric and neurological conditions where speech may be affected.

Learning Objective 1: Become familiar with speech-based digital phenotyping measures.

Learning Objective 2: Understand associations between speech measures and symptoms of schizophrenia.

Literature References: Insel TR. Digital phenotyping: technology for a new science of behavior. JAMA. 2017;318(13):1215-1216.

Abbas A, Schultebraucks K, Galatzer-Levy IR. Digital measurement of mental health: challenges, promises, and future directions. Psychiatr Ann. 2021;51(1):14-20.

Brannan SK, Sawchak S, Miller AC, Lieberman JA, Paul SM, Breier A. Muscarinic cholinergic receptor agonist and peripheral antagonist for schizophrenia. N Engl J Med. 2021;384(8):717-726.

COULD RIGHT MEDIAL ORBITOFRONTAL CORTEX DAMAGE FROM TRAUMATIC BRAIN INJURY PLAY A ROLE IN SUICIDALITY? PILOT NEUROIMAGING RESULTS TOWARDS DEVELOPMENT OF A NOVEL NEUROSTIMULATION TREATMENT

Alexandra Aaronson[*1], Niki Sabetfakhri[2], Olusola Ajilore[2], Noah Philip[3], Lei Wang[4], Maheen Adamson[5], Amy Herrold[1]*
[1]Edward Hines VA Hospital, [2]University of Illinois, [3]Alpert Medical School, Brown University, [4]Ohio State University, [5]Stanford University

Alexandra Aaronson*, Edward Hines VA Hospital

Abstract Background: Mild traumatic brain injury (mTBI) and impulsivity are both established risk factors for suicidality. Also, impulsivity is known to frequently follow mTBI. Our laboratory recently demonstrated that impulsivity appears to mediate the relationship between TBI and suicidality, though the underlying mechanisms of this relationship remain unknown. The medial orbitofrontal cortex (mOFC) is known to be involved in impulse control and is commonly damaged in TBI. This study investigates mOFC volume differences between Veterans with mTBI and controls to understand its role in suicidality.
Methods: We explored volume difference in the mOFC between Veterans with mTBI (n=43) and Veteran controls (n=8). We processed structural MPRAGE MRI data using Freesurfer. We reviewed medical charts to identify which Veterans with mTBI had a history of suicidal ideation (SI) (SI n = 28, no SI n=15). We calculated effect sizes using Cohen's d and ran linear regression models to compare groups.
Results: Veterans with mTBI and suicidality showed a significant reduction in right mOFC volume compared to controls (B = -629.7, SE 241.95, p=.01) per linear regression analysis. Veterans with mTBI without SI did not significantly differ from controls (B=-441.6, SE=259.9, p=.1).
Conclusions: Our study reveals a significant reduction in right mOFC volume among Veterans with mTBI and SI, furthering our belief that damage to this cortical area is implicated in the development of SI following mTBI. We are conducting an ongoing pilot randomized clinical trial, where we administer intermittent theta burst stimulation to the right frontal pole of Veterans with mTBI and SI to target the mOFC. Three subjects have completed the trial to date without serious adverse events, and all have found the treatment tolerable and acceptable.
Learning Objective 1: Understand the relationship that exists between traumatic brain injury, impulsivity and suicidality.
Learning Objective 2: Learn that there appears to be a link between damage to the r medial orbitofrontal cortex, specifically, TBI, impulsivity and suicidality.
Literature References: Aaronson AL, Smith B, Krese K, Barnhart M, Adamson M, Philip N, de Wit H, Brenner L, Bender-Pape T, Herrold A. Impulsivity and Mental Illness Diagnoses as Mediators of Suicidal Ideation and Attempts Among Veterans with Traumatic Brain Injury. The Journal of Neuropsychiatry Clin Neurosci. 2024. April; 36(2):125-133.
Mosti C, Coccaro EF. Mild Traumatic Brain Injury and Aggression, Impulsivity, and History of Other- and Self-Directed Aggression. J Neuropsychiatry Clin Neurosci. 2018; 30:220-227.

3:00 p.m. - 4:30 p.m.
Individual Research Reports (IRRs): Update on Biomarkers Research

TREATING ACUTE SUICIDALITY IN A MEDICAL SETTING - APPROACH, KNOWLEDGE AND CURRENT PRACTICES AROUND KETAMINE INFUSION

H. Nur Eken[*1], Sharvari Shivanekar[1], Priya Gopalan[1], Anthony Pizon[1], Crystal Spotts[1], Nicholas Cruz[1], Michael Lightfoot[1], Rebecca Rohac[1], Andrew Baumeister[1], Iya Cooper[1], Mohemmed Aslam[1], Shelly Kucherer[1], Alex Israel[1], Manivel Rengasamy[1], Rebecca Price[1]*
[1]University of Pittsburgh

H. Nur Eken*, University of Pittsburgh Medical Center

Abstract Background: Ketamine has shown to rapidly reduce suicidal thoughts 2–24 h after a single infusion in patients, which can be maintained up to 90 days after infusion [1]. An open-label real-world effectiveness study published from our research team suggested that intravenous ketamine administration in a consultation-liaison setting was safe, feasible, and that patients reported rapid, statistically significant decreases in suicidality and depression starting 24-hours after infusion, with improvements from baseline maintained up to 6 months past infusion [2]. In this follow-up descriptive study, we aimed to understand patient and front line staff approach, perspectives and current practices around ketamine administration in a tertiary care hospital.
Methods: We analyzed survey data obtained surrounding acceptability of ketamine treatment by medical hospital staff who had been involved in administering a single ketamine infusion on their floor as part of an effectiveness-focused clinical trial. Survey questions assessed various aspects of the ketamine infusion, including monitoring vitals during ketamine administration, monitoring of psychiatric symptoms during/after infusion, knowing how to properly handle/waste ketamine, concerns about side effects experienced by patients, and others. We also surveyed patients who participated in the study to understand their perspectives, satisfaction and acceptability ratings of the treatment protocol. We used descriptive statistics to analyze responses to the questionnaire items.
Results: Of the 33 people who filled out the provider survey, the majority were medical-surgical inpatient unit nurses (n=29, 87.9%), 1 was a physician (3%) and 3 (9.1%) were ICU nurses. The majority of participants found the aspects of ketamine administration, as listed on the survey questions, to be “not at all problematic”. On a scale from 0 to 100, providers had an average score of 77.70 when they were asked to “rate the overall acceptability of the ketamine infusion process as a treatment option in your setting.” In addition, patient surveys revealed acceptability ratings exceeded 90%, with all individual acceptability items scoring above 70%.
Discussion: Overall, the majority of the participants reported minimal challenges with the process, and both the providers and patients in the study rated the acceptability of ketamine infusion highly. These findings underscore feasibility and significant promise for infusion of ketamine for treatment of depression and suicidality in the medical hospital, facilitated by the consultation-liaison (CL) psychiatry teams, prior to patients being able to initiate care in an inpatient psychiatric setting. Future research should focus on understanding the perspectives and practices of other key stakeholders, including medicine teams and CL psychiatry providers, as well as identifying barriers to widespread adoption of ketamine treatment protocols.
Learning Objective 1: Evaluate the effectiveness and safety of intravenous ketamine administration in a real-world sample of individuals with recent suicide attempts

Learning Objective 2: Understand the perspectives of healthcare providers and patients regarding the acceptability and feasibility of intravenous ketamine treatment for suicidality in a hospital setting

Literature References: 1. Price, R. B. et al. A Novel, Brief, Fully Automated Intervention to Extend the Antidepressant Effect of a Single Ketamine Infusion: A Randomized Clinical Trial. Am. J. Psychiatry. 2022; 179, 959–968.
2. Shivanekar, S. et al. Ketamine infusion after suicide attempt: New frontiers in treating acute suicidality in a 'real world' medical setting. J. Acad. Consult. Liaison Psychiatry. 2022; 63, S106–S107.

BRAIN AGE AND TELOMERE LENGTH IN PARTICIPANTS WITH MAJOR DEPRESSIVE DISORDER AND HEALTHY CONTROLS

Nefize Yalin[*1], Jennifer Evans[1], Claire Punturieri[1], Peixiong Yuan[1], Yoojin Lee[1], Carlos Zarate[1]*
[1]Experimental Therapeutics and Pathophysiology Branch, National Institute of Mental Health, National Institute of Health

Nefize Yalin*, Experimental Therapeutics and Pathophysiology Branch, National Institute of Mental Health, National Institute of Health

Abstract Introduction: Latest literature suggests that major depressive disorder (MDD) might be associated with accelerating biological aging processes (1). Telomere length and brain-predicted age difference (Brain-PAD) were among the most studied aging biomarkers in MDD and according to the latest meta-analyses, patients with MDD have a significantly larger brain-PAD of +0.90 and shorter telomere length with a moderate effect size in comparison to healthy controls (HC) (2, 3). On the other hand, the interaction between aging biomarkers in the context of MDD, their combined impact on MDD progression and treatment response and the effect of different clinical characteristics of MDD on these biomarkers are still not well understood (1). This study aims to address all these three points with a focus on ketamine in terms of treatment response.
Methods: This study used the initial T1-weighted magnetic resonance imaging (MRI) data acquired from participants with major depressive disorder (MDD) (n=142) and healthy subjects (HC) (n=116) aging between 18 and 65 who participated different clinical studies in our department between 2004 and 2020. Biological age was estimated using brainageR (https://github.com/james-cole/brainageR) and the BrainPAD was calculated per participant. For telomere length analysis, blood samples collected within the same year of MRI scanning were used. DNA was extracted using Qiagen Puregene Blood Core Kit and telomere length was determined by real time PCR using the Sciencell Absolute Human Telomere Length Quantification qPCR Assay Kit according to the manufacturers' specifications. Statistical analyses were completed using SPSS v29.02 and chi-square, independent samples t-test, analysis of covariance and bivariate pearson correlation were used where appropriate.
Results: Preliminary results showed that MDD group (37.39±0.98) was significantly older than HC group (32.65± 0.89) (t=-3.3, p LESS THAN 0.001) but groups were well-matched for sex (p=1.0, Female:54%). Estimated age and chronological age were strongly positively correlated in both depressed and healthy groups (R=0.77, p LESS THAN 0.001). There was no significant difference in BrainPAD between MDD (-0.25±0.64) and HC (1.96 ± 0.59) groups controlling for age (F (1,245) =1.2, p=0.26) or age and MRI strength (F (1,244) =1.01, p=0.32). Telomere length per chromosome was significantly higher in MDD group (8.55±0.48 kb) compared to HC group (6.46 ±0.46 kb) when controlled for age (F(1,216)=12.99, p LESS THAN 0.001) or age and gender (F(1,215)=12.94, p LESS THAN 0.001). BrainPAD and telomere length per chromosome were not significantly correlated in

both MDD (R=-0.16, p=0.13) and HC (R=0.007, p=0.94) groups. The remaining findings addressing the association of these aging biomarkers with clinical characteristics and treatment response to ketamine in MDD will be presented at the meeting.
Discussion: We did not find any significant difference in BrainPAD between MDD and HC groups and telomere length per chromosome was significantly higher in the MDD compared to HC group. Our findings are in contrast with the available literature, which could be related to several reasons including the clinical characteristics MDD group or variations in analysis techniques for both Brain-PAD and telomere length. The further analysis of our data that including clinical and available biological variables in addition to telomere length and BrainPAD would help us to better understand and interpret these results.
Learning Objective 1: The interaction between different aging biomarkers in the context of major depressive disorder
Learning Objective 2: The association of taging biomarkers with clinical characteristics and treatment response in major depressive disorder
Literature References: 1. Lorenzo EC, Kuchel GA, Kuo CL, Moffitt TE, Diniz BS (2023): Major depression and the biological hallmarks of aging. Ageing Res Rev. 83:101805.
2. Blake KV, Ntwatwa Z, Kaufmann T, Stein DJ, Ipser JC, Groenewold NA (2023): Advanced brain ageing in adult psychopathology: A systematic review and meta-analysis of structural MRI studies. J Psychiatr Res. 157:180-191.
3. Darrow SM, Verhoeven JE, Revesz D, Lindqvist D, Penninx BW, Delucchi KL, et al. (2016): The Association Between Psychiatric Disorders and Telomere Length: A Meta-Analysis Involving 14,827 Persons. Psychosom Med. 78:776-787.

MODELING RAPID ANTIDEPRESSANT MECHANISMS IN TREATMENT-RESISTANT DEPRESSION USING IPSC-DERIVED NEURONS AND CSF PROTEOMIC CLINICAL CORRELATION

*Gregory Jones**[1], Jenessa Johnston[1], Shiyong Peng[1], Peixiong Yuan[1], Nirmala Akula[1], Anton Schulmann[1], Mani Yavi[1], Brandi Quintanilla[1], Mark Kvarta[1], Francis McMahon[1], Carlos Zarate, Jr.[1]*
[1]National Institute of Mental Health

Gregory Jones, National Institute of Mental Health

Abstract Introduction: Treatment-resistant depression (TRD) remains an unmet need, with limited therapeutic advancements in two decades due in part to challenges in modeling its complex, polygenic nature. Induced pluripotent stem cell (iPSC)-derived neurons offer a promising approach to address this gap. This study aimed to validate this technique by: (1) characterizing transcriptomic responses to racemic ketamine and (2R,6R)-HNK, and (2) comparing these responses to serial cerebrospinal fluid (CSF) proteomics collected at 6 timepoints over 24 hours from human participants (n = 9; NCT03065335) treated with a single ketamine infusion at standard TRD dosage (0.5 mg/kg over 40 min).
Methods: iPSC neurons were generated from TRD patients (n = 5) enrolled in a crossover trial (NCT02484456) and healthy controls (n = 5). Differentiated cortical neurons were treated with vehicle (0.1%), (2R,6R)-HNK (1 μM), or racemic ketamine (1 μM) for 6 hours. Bulk RNA-seq was conducted at 6 and 24 hours, and single-cell RNA-seq (scRNA-seq) was performed on a subset (2 TRD, 2 HC lines; 24-hour timepoint). Differential expression and pathway enrichment were analyzed using dream/zenith (bulk) and MAST (scRNA-seq). Overlapping genes/proteins from RNA-seq and CSF proteomics were evaluated for enrichment, expression alignment, and correlation. Pathway analysis was performed using clusterProfiler.

Results: Treatment with (2R,6R)-HNK upregulated immune-related pathways (Interferon, IL6-Jak-STAT3, IL2-STAT5) and mTORC1 signaling. ScRNA-seq revealed cell-type specificity, primarily affecting one inhibitory (IN_Mid_2) and one excitatory (EX_Matute_1) cell type. Opposing effects were observed on the same set of pathways: mTORC1 signaling, oxidative phosphorylation, and β-oxidation. Excitatory cells showed upregulation of these pathways, while inhibitory cells exhibited downregulation. Marker genes for these two cell types were enriched for opioid signaling (excitatory) and oxytocin signaling (inhibitory), consistent with known ketamine mechanisms. Differentially expressed genes in iPSC-neurons at 24 hours revealed that (2R,6R)-HNK (and not racemic ketamine) significantly overlapped with differentially expressed proteins in the CSF of human ketamine recipients ($p = 0.043$). 89% of the overlapping genes/proteins were differentially expressed in the same direction in both datasets, far above what would be expected by chance ($p = 1.3e-5$). Correlations were strongest at the 12-hour CSF timepoint ($\rho = 0.61$, p_fdr = 0.008) and remained nominally significant at the 24-hour CSF draw ($\rho = 0.34$, p_fdr = 0.075)—an interval of near-maximal (2R,6R)-HNK metabolite concentration in the CSF. Pathway analysis confirmed inflammatory cytokine signaling as a key shared feature.
Conclusion: These findings strongly validate iPSC neuron models as effective in recapitulating treatment-specific effects of rapid acting antidepressants. Overlap between CSF proteomics and (2R,6R)-HNK responses, but not ketamine, highlights the metabolite's potential as a key therapeutic driver. The observed patterns in our single cell data support the excitation-inhibition balance hypothesis for ketamine and its most robust in vivo biomarker (increased cortical γ-power)(1). Additionally, enrichment of opioid and oxytocin signaling in responsive cell types aligns with established ketamine mechanisms, advancing our understanding of (2R,6R)- HNK as a novel experimental therapeutic(2).
Learning Objective 1: Understand the major signaling pathways altered in iPSC neurons treated with ketamine and its major metabolite (2R,6R)-HNK
Learning Objective 2: Understand the correlations between changes in iPSC gene expression with ketamine and HNK and CSF proteomic expression in participants treated with intravenous ketamine .
Literature References: 1. Medeiros GC, Matheson M, Demo I, Reid MJ, Matheson S, Twose C, et al. Brain-based correlates of antidepressant response to ketamine: a comprehensive systematic review of neuroimaging studies. The Lancet Psychiatry. 2023 Oct 1;10(10):790–800.
2. Johnston JN, Kadriu B, Allen J, Gilbert JR, Henter ID, Zarate CA. Ketamine and serotonergic psychedelics: An update on the mechanisms and biosignatures underlying rapid-acting antidepressant treatment. Neuropharmacology. 2023 Mar 15;226:109422.

CROSS-FREQUENCY DIALOGUE DURING SLEEP IS DISRUPTED IN DEPRESSION

Samika Kumar[*1], Nadia Hejazi[1], Dede Greenstein[1], Elizabeth Ballard[1], Carlos Zarate[1], Mark Kvarta[1]*
[1]*National Institute of Mental Health, NIH*

Samika Kumar*, National Institute of Mental Health, NIH

Abstract Introduction: Both depression and sleep disturbances are linked with reduced brain plasticity, yet pharmacological interventions aimed at restoring sleep have no more than modest effects in treating depression. We posit that these sleep enhancers neglect a critical component of sleep that may be relevant for depression and plasticity: cross-frequency coupling. Neuronal slow waves during natural sleep herald cross-frequency dialogue in the

brain that is crucial for learning and plasticity, but little is known about how this neural dialogue changes with depression. Here, we propose that depressive symptoms relate not only to disrupted slow waves during sleep but also to their capacity to integrate information via cross-frequency dialogue in key brain areas.
Methods: 204 adults were recruited across several mental health research protocols at the National Institutes of Health Clinical Center (Bethesda, MD, USA). Of those recruited, 39 were healthy volunteers, and 163 met criteria for either major depressive disorder or bipolar disorder. Participants completed a Montgomery–Åsberg Depression Rating Scale (MADRS) and participated in a sleep polysomnography recording. Electroencephalography (EEG) data were entered into a slow wave detection algorithm to identify individual EEG slow waves (0.4-2.5 Hz). Analysis focused on the first four hours of the sleep recording, which had fewer awakenings and was predicted to have the highest density of slow wave sleep. We first examined how specific slow wave features relate to depressive symptoms. Then we examined how cross-frequency coupling during these slow waves relates to depressive symptoms by performing a phase-amplitude coupling analysis between slow and fast (7-30 Hz) EEG frequencies. We performed regression analyses between sleep features and clinical outcomes, in which we corrected for age and biological sex.
Results: The number of detected slow waves decreased with age (t=-5.8, p LESS THAN 0.001) but was not significantly associated with MADRS score (t=0.4, p GREATER THAN 0.6). Slow waves with higher frequency in the second and third hours of the sleep recording were associated with higher MADRS scores ($t \geq 2.4$, $p \leq 0.02$), while slow wave amplitude had no significant effects ($t \leq 0.3$, $p \geq 0.2$). Across participants, the ultraslow wave (0.5-1Hz) showed weak phase-amplitude coupling with all faster tested frequencies, although this coupling peaked in the fast sleep spindle (13-16 Hz) range. Higher MADRS scores were associated with reduced phase-amplitude coupling in this slow wave-spindle range only in the third hour of the sleep recording ($p \leq 0.01$). In the middle hours of the sleep recording (hours 2-4), higher MADRS scores corresponded with reduced phase-amplitude coupling between ultraslow wave and slow sleep spindle (8-10 Hz) frequency ranges ($p \leq 0.01$).
Conclusion: Our results expand on the role of EEG slow waves in depression by highlighting their disrupted cross-frequency relationships. Novel treatment targets for depression are urgently in need. Future work should confirm whether the restoration of cross-frequency dialogue during sleep treats depressive symptoms. This causality could help identify directions for future treatments and risk stratification.
Learning Objective 1: Understand how different sleep patterns are related in healthy adults.
Learning Objective 2: Understand how the relationship between different sleep patterns is altered during depression.
Literature References: Monteiro BC, Monteiro S, Candida M, et al. Relationship between brain-derived neurotrofic factor (Bdnf) and sleep on depression: a critical review. Clinical practice and epidemiology in mental health: CP and EMH. 2017;13:213.
Vallat R, Walker MP. An open-source, high-performance tool for automated sleep staging. Elife. 2021;10:e70092.

3:00 p.m. - 4:30 p.m.
Individual Research Reports (IRRs): Bipolar Disorder

NEUROSTRUCTURAL CORRELATES OF POLYGENIC RISK FOR CORONARY ARTERY DISEASE IN RELATION TO YOUTH BIPOLAR DISORDER

Nidhi Kulkarni[*1], Clement Zai[2], Kody Kennedy[1], Megan Mio[1], L. Trevor Young[3], Bradley MacIntosh[4], Benjamin Goldstein[5]*

[1]Centre for Youth Bipolar Disorder, CAMH, [2] Family Mental Health Research Institute, CAMH; University of Toronto, [3]CAMH; University of Toronto; [4]Centre for Youth Bipolar Disorder, CAMH; Sunnybrook Research Institute; University of Toronto; Oslo University Hospital, [5]Centre for Youth Bipolar Disorder, CAMH; University of Toronto

Nidhi Kulkarni*, Centre for Youth Bipolar Disorder, CAMH

Abstract Introduction: Bipolar disorder (BD), characterized by anomalous neurostructural phenotypes, is also strongly associated with cardiovascular disease. Here we examined polygenic risk for coronary artery disease (CAD) in relation to grey matter structure in youth BD.
Methods: Youth participants (mean age 17.1 years; n=66 BD, n=45 healthy controls [HC]) underwent T1-weighted magnetic resonance imaging. CAD polygenic risk scores (CAD-PRS) were calculated using independent, adult genome-wide summary statistics. Covariate adjusted vertex-wise analyses examined the association of CAD-PRS with cortical volume, thickness, and surface area (SA) in the overall sample, and within BD and HC groups. Additional region-of-interest (ROI) analyses were conducted to examine the anterior cingulate cortex (ACC) and hippocampus. Exploratory sex-stratified analyses were also undertaken.
Results: In the overall sample, higher CAD-PRS was associated with lower right inferior temporal gyrus volume (β=-0.32, p=0.03). There were also negative associations between CAD-PRS and brain structure within BD (5 cortical thickness clusters) and HC (1 SA cluster). Within the BD group, sex-stratified analyses revealed significant findings for females, but not for males. ROI analyses revealed a nominal association of higher CAD-PRS with lower ACC thickness in the BD group (β=-0.31, p[uncorrected]=0.05, p[corrected]=0.20).
Conclusion: Higher CAD-PRS was associated with lower regional grey matter structure in youth, in regions implicated in BD. Findings were more pronounced in the BD group, particularly among females, and related to cortical thickness specifically. Future longitudinal studies are needed to examine the association of CAD-PRS with neurodevelopmental changes over time, and to discern mechanisms underlying the observed findings.
Learning Objective 1: Elucidate the impact of cardiovascular genetics on the brain in bipolar disorder
Learning Objective 2: Identify high-risk groups in whom cardiovascular-brain implications in the context of bipolar disorder are especially relevant (i.e. youth, females)
Literature References: Goldstein BI, Baune BT, Bond DJ, et al. Call to action regarding the vascular-bipolar link: A report from the Vascular Task Force of the International Society for Bipolar Disorders. Bipolar Disord. 2020;22(5):440-460.
Fürtjes AE, Coleman JRI, Tyrrell J, Lewis CM, Hagenaars SP. Associations and limited shared genetic aetiology between bipolar disorder and cardiometabolic traits in the UK Biobank. Psychol Med. 2022;52(16):4039-4048.

CORTISOL INFUSION PUMPS AND THEIR IMPACT ON PSYCHIATRIC AND PHYSIOLOGICAL OUTCOMES IN ADRENAL INSUFFICIENCY: A TRANSLATIONAL APPROACH TO PSYCHOPHARMACOLOGY

*Ryan Berry**[1]
[1]*Authority Health, FQHC*

Ryan Berry*, Authority Health, FQHC

Abstract Purpose: Glucocorticoid therapy remains the cornerstone of adrenal insufficiency management, yet current oral and intramuscular regimens fail to mimic physiologic cortisol rhythms, leading to fatigue, mood instability, and increased hospitalizations. Continuous cortisol infusion offers a way to restore natural hormone patterns, but real-world U.S. data on its impact are limited. This study evaluates the effect of continuous cortisol infusion on fatigue, anxiety, sleep quality, and hospitalization rates, reinforcing the role of physiologic treatment patterns in optimizing both endocrine and neuropsychiatric outcomes.

Content and Methodology: A retrospective cohort study was conducted at an academic-affiliated endocrinology center in Metro Detroit, analyzing 33 adrenal insufficiency patients who transitioned from conventional steroid therapy to continuous cortisol infusion between 2013 and 2023. We assessed:

- Quality of life via Addison's Disease-Specific Quality of Life Questionnaire
- Fatigue via Chalder Fatigue Scale
- Sleep via Pittsburgh Sleep Quality Index
- Mental health via SF-36 Composite Score
- Hospitalization rates and serum adrenocorticotropic hormone and cortisol levels Wilcoxon signed-rank tests and mixed-effects regression modeling evaluated differences before and after treatment.

Results:

- Hospitalizations due to adrenal crisis dropped by 95.54% (p LESS THAN 0.00022), demonstrating a strong clinical impact.
- Fatigue scores improved by 47% (p LESS THAN 0.00002), reinforcing the link between cortisol regulation and energy levels.
- Mood symptoms, including anxiety and irritability, significantly decreased (Addison's Disease-Specific Quality of Life mean increase +33.47 points, p LESS THAN 0.0001).
- Patients reported improved sleep quality, including fewer nocturnal awakenings (Pittsburgh Sleep Quality Index, p LESS THAN 0.009).
- Serum adrenocorticotropic hormone levels declined following continuous cortisol infusion, indicating improved hypothalamic-pituitary-adrenal axis regulation (p LESS THAN 0.002).

Importance and Implications for the Field: This study reinforces that treatments following physiologic hormone patterns lead to superior clinical outcomes. Patients reported better energy in the morning, aligning with the role of cortisol's natural circadian surge in promoting wakefulness. These findings serve as a reminder that therapeutic interventions, particularly in endocrinology, achieve greater efficacy when they restore intrinsic biological rhythms.

Additionally, this study provides the foundation for a larger randomized controlled trial currently in development, aimed at further validating the clinical and economic benefits of continuous cortisol infusion. Beyond adrenal disease, these findings clarify that symptoms of fatigue and mood disturbances attributed to psychiatric distress may, in some cases, stem

from endocrine dysfunction, reinforcing the need for precision medicine approaches in psychopharmacology and endocrinology.
Learning Objective 1: Describe how continuous cortisol infusion reduces fatigue and improves morning wakefulness by restoring physiologic cortisol rhythms.
Learning Objective 2: Differentiate endocrine-mediated fatigue and anxiety from primary psychiatric conditions by understanding cortisol dysregulation's role in symptom presentation.
Literature References: Øksnes M, Bjørnsdottir S, Isaksson M, et al. Continuous subcutaneous hydrocortisone infusion versus conventional glucocorticoid replacement therapy for Addison's disease: a randomized clinical trial. J Clin Endocrinol Metab. 2014;99(5):1665-1674.
Russell G, Kalafatakis K, Durant C, et al. Ultradian hydrocortisone replacement alters neuronal processing, emotional ambiguity, affect, and fatigue in adrenal insufficiency: The PULSES trial. J Intern Med. 2024;295(1):51-67.

AN INTERIM BLINDING INTEGRITY ANALYSIS OF A RANDOMIZED, DOUBLE-BLIND, MIDAZOLAM-CONTROLLED PHASE II CLINICAL TRIAL INVESTIGATING REPEATED KETAMINE INFUSIONS FOR TREATMENT RESISTANT BIPOLAR DEPRESSION

Diana Orsini[*1], Sara Di Luch[1], Tayyeba Shaikh[2], Roger McIntyre[1], Rodrigo Mansur[1], Joshua Rosenblat[1]*
[1]University of Toronto, [2]University Health Network

Diana Orsini*, University of Toronto

Abstract Introduction: Psychedelic therapies have emerged as promising treatments for a range of psychiatric disorders, including treatment-resistant bipolar depression (TRBD). However, the lack of robust results in psychedelic studies has often been attributed to issues with functional unblinding, where participants are able to guess their treatment allocation based on subjective experiences. This can lead to biased outcomes and undermine the reliability of clinical trial results. Despite these challenges, the potential of psychedelics, particularly intravenous ketamine, for treating TRBD warrants further investigation, especially under conditions that minimize bias.
Methods: A randomized, double-blind, midazolam-controlled phase II clinical trial will investigate repeated ketamine infusions for TRBD (NCT05004896). An interim blinding integrity analysis will be completed using participants' Blinding Assessment Tool responses after the first infusion to evaluate midazolam's suitability as an active control for ketamine.
Results: A total of 34 participants (N=34) with TRBD have completed treatment making this the largest randomized control trial investigating ketamine for TRBD to date. After the first infusion, 44.1% of participants correctly guessed their treatment allocation. Participants correctly guessed what medication they received 26.7% of the time in the ketamine arm and 57.9% of the time in the midazolam arm.
Discussion: Our results suggest midazolam is a suitable active control for ketamine to minimize bias. Future investigation of the relationship between Clinician-Administered Dissociative States scores and Blinding Assessment Tool results is encouraged to understand the influence of a strong dissociative experience to participants' treatment allocation guesses. Understanding of participants' expectancy bias may offer more insight into this relationship.
Learning Objective 1: Describe the need for randomized control trials investigating psychedelic pharmacotherapies that minimize bias.
Learning Objective 2: Evaluate the suitability of midazolam to act as an active control for ketamine.

Literature References: Szigeti B, Heifets BD. Expectancy Effects in Psychedelic Studies. Biol Psychiatry Cogn Neurosci Neuroimaging 2024;9(5):512-521. https://doi.org/10.1016/j.bpsc.2024.02.004
Fancy F, Rodrigues NB, Di Vincenzo JD, Chau EH, Sethi R, Husain MI, Gill H, Tabassum A, Mckenzie A, Phan L, McIntyre RS, Rosenblat, JD. Real-world effectiveness of repeated ketamine infusions for treatment-resistant bipolar depression. Bipolar Disord 2022;25(2):99–109. https://doi.org/10.1111/bdi.13284

HOW MANY CRITERIA SHOULD BE REQUIRED TO DEFINE THE DSM-5 MIXED FEATURES SPECIFIER IN DEPRESSED PATIENTS?

Mark Zimmerman[*1], Daniel Mackin*[2]
[1]*Brown University,* [2]*Dartmouth University*

Mark Zimmerman*, Brown University

Abstract Background: During the past 2 decades there has been intense interest in the clinical significance of the concurrence of manic symptoms in depressed patients. DSM-5 introduced a mixed features specifier for both bipolar depression and major depressive disorder. Studies of the DSM-5 mixed features specifier have generally found a low prevalence of mixed depression. One approach towards increasing the sensitivity of the DSM-5 mixed features criteria is to lower the classification threshold. In the present study we examine the impact of lowering the DSM-5 diagnostic threshold from 3 to 2 criteria on the prevalence and validity of the DSM-5 mixed features specifier for depression. Previous studies have found that as many, if not more, depressed patients report 2 co-occurring manic symptoms as 3 or more manic symptoms. However, little research has directly examined whether a 2-symptom threshold is valid. We compare 3 groups of depressed patients: 0-1 DSM-5-TR mixed features, 2 mixed features, and 3 or more mixed features (the DSM-5-TR threshold) on variables that have previously been found to distinguish patients with and without mixed depression such as family history of bipolar disorder, age of onset, number of episodes of depression, suicidality, symptom severity, comorbidity with other psychiatric disorders, and impairment in functioning.
Methods: Four hundred fifty-nine psychiatric patients in a depressive episode were interviewed by a trained diagnostic rater who administered semi-structured interviews including the DSM-5 Mixed Features Specifier Interview. The patients were rated on clinician rating scales of depression, anxiety and irritability, and measures of psychosocial functioning, suicidality, and family history of bipolar disorder.
Results: When the DSM-5 diagnostic threshold was lowered from 3 to 2 symptoms the prevalence of mixed features based on the DSM-5 majority of episode time frame tripled from 3.9% to 13.1% (n=60). Based on a past week time frame, the prevalence of mixed features more than doubled from 9.4% to 22.9% (n=105) upon lowering the threshold from 3 to 2 criteria. However, there was no difference between the patients with 2 mixed features and patients with 0 or 1 mixed features on family history of bipolar disorder, psychosocial impairment, presence of comorbid disorders, age of onset, history of suicide attempts or psychiatric hospitalization.
Conclusions: The results of the present study do not support lowering the DSM-5-TR diagnostic threshold for the mixed features specifier in depressed patients from 3 to 2 criteria.
Learning Objective 1: Become familiar with how to validate different thresholds in defining mixed features in depressed patients.
Learning Objective 2: Become familiar with the impact of diagnostic threshold on the prevalence and validity of the mixed features specifier in depression.

Literature References: Zimmerman M. Measures of the DSM-5 mixed-features specifier of major depressive disorder. CNS Spectr. 2017;22:196-202.
Mineo L, Rodolico A, Spedicato GA, et al. Which mixed depression model? A comparison between DSM-5-defined mixed features and Koukopoulos' criteria. Bipolar Disord. 2022;24:530-538.

7:00 p.m. - 8:30 p.m.
FREE Satellite Symposium: Schizophrenia: What's New About Dopamine and How It Is Regulated? Pre-Registration is Required

SCHIZOPHRENIA: WHAT'S NEW ABOUT DOPAMINE AND HOW IT IS REGULATED?
Joseph Goldberg, Icahn School of Medicine at Mount Sinai

Overall Abstract Symposium Focus and Relevance:
Explore new research on dopamine regulation in schizophrenia, including presynaptic modulation and muscarinic receptor agonism
Address unmet needs in drug efficacy, side effect management, and clinical applicability
Designed to benefit clinicians, researchers, regulatory partners, and new investigators
Supported by robust needs assessments from past ASCP attendees (900+ professionals)

SCHIZOPHRENIA: WHAT'S NEW ABOUT DOPAMINE AND HOW IT IS REGULATED?
Leslie Citrome, New York Medical College

Abstract Symposium Focus and Relevance:
Explore new research on dopamine regulation in schizophrenia, including presynaptic modulation and muscarinic receptor agonism
Address unmet needs in drug efficacy, side effect management, and clinical applicability
Designed to benefit clinicians, researchers, regulatory partners, and new investigators
Supported by robust needs assessments from past ASCP attendees (900+ professionals)
Learning Objective 1: Describe how the dopamine model in psychosis has evolved, from rodent studies to human applications
Learning Objective 2: Differentiate between presynaptic and postsynaptic dopamine dysregulation in schizophrenia
Literature References: Schizophrenia Prevalence and Burden. National Institute of Mental Health. Accessed 02/21/2025, 2025. https://www.nimh.nih.gov/health/statistics/schizophrenia
Kessler RC, Birnbaum H, Demler O, et al. The prevalence and correlates of nonaffective psychosis in the National Comorbidity Survey Replication (NCS-R). Biol Psychiatry. Oct 15 2005;58(8):668-76. doi:10.1016/j.biopsych.2005.04.034

Thursday, May 29, 2025

8:15 a.m. - 9:15 a.m.
Keynote Plenary: The New and the Old of is Newer Better

KEYNOTE: THE NEW AND THE OLD OF IS NEWER BETTER
Carlos Blanco, National Institute on Drug Abuse

Overall Abstract: After a decade or more of stagnation, we are enjoying a rejuvenation of interest in new psychopharmacologic approaches. Yet foes old and new threaten the promise of this attention. The placebo effect continues to pose grave challenges to success. Marketing and hype drive enthusiasm that threatens to outstrip evidence. Tech start-ups are a double-edged sword, promising innovation but too often pushing the boundaries and forgoing traditional evidence accumulation strategies. I will discuss innovation in the context of an evidence-base, touching on psychedelics, novel antipsychotic approaches, and precision psychiatry, addressing the theme of ASCP 2025: When is Newer Better?

THE NEW AND THE OLD OF IS NEWER BETTER
Joshua Gordon, Columbia University/New York State Psychiatric

Abstract: After a decade or more of stagnation, we are enjoying a rejuvenation of interest in new psychopharmacologic approaches. Yet foes old and new threaten the promise of this attention. The placebo effect continues to pose grave challenges to success. Marketing and hype drive enthusiasm that threatens to outstrip evidence. Tech start-ups are a double-edged sword, promising innovation but too often pushing the boundaries and forgoing traditional evidence accumulation strategies. I will discuss innovation in the context of an evidence-base, touching on psychedelics, novel antipsychotic approaches, and precision psychiatry, addressing the theme of ASCP 2025: When is Newer Better?
Learning Objective 1: Understand the interplay between innovation and evidence.
Learning Objective 2: Describe the evidence base for novel therapeutic advances including psychedelics, antipsychotics, and precision psychiatry.
Literature References: Vokow, ND, Gordon JA, and Wargoo EM. Psychedelics as Therapeutics-Potential and Challenges. JAMA Psychiatry. 2023;80(10):979-980.
Brady, LS, Lisanby SH, and Gordon JA. New Directions in Psychiatric Drug Development: Promising Therapeutics in the Pipeline. Expert Opin Drug Discov. 2023; 18(8):835-80.

9:30 a.m. - 11:30 a.m.
Update from Federal and Other Funding Agencies Plus Plenary

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 2025 Update From Federal and Other Funding Agencies Plenary. Alphabet soup never tasted so good! Hear updates from NIAAA, PCORI, NIDA, and the VHA.

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 140,000 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. Unfortunately, these medications do not work for everyone, and

their effect sizes are modest, due in part to considerable heterogeneity in AUD. 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, Alcohol Pharmacotherapy Evaluation Program (APEP), and preclinical program. 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 Objective 1: To understand NIAAA's Medications Development Program, including the AUD medication pipeline, current portfolio, and programmatic priorities.
Learning Objective 2: To understand NIAAA-sponsored public resources related to the treatment of AUD.
Literature References: 1Litten 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.
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.

PATIENT-CENTERED COMPARATIVE EFFECTIVENESS RESEARCH

Yu-Ping Wang, Patient-Centered Outcomes Research Institute

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 Objective 1: Learn about funding opportunities patient-centered comparative clinical effectiveness research
Learning Objective 2: 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.

NIDA UPDATE

Ivan Montoya, DHHS/National Institute on Drug Abuse

Abstract: The National Institute on Drug Abuse (NIDA) funds and conducts research and development of safe and effective therapeutics for Substance Use Disorders (SUD), including medications (small molecules and biologics), therapeutic devices, digital therapies, behavioral interventions. This Therapeutics Development Program (TDP) supports a diverse array of preclinical and clinical research projects that span from identification of lead compounds, IND enabling studies, IND filing, and all phases of clinical trials (including

Phase III clinical trials). The ultimate goal of the TDP is to advance therapeutics towards FDA approval or acceptance and implementation in clinical practice. The program funds research via grants and contracts. The majority of the research is funded by cooperative agreement grants, which can be submitted by profit and non-for-profit organizations at a national or international level. The purpose of this presentation is to provide an overview of the NIDA TDP and the pipeline of medications and other therapeutics that are currently investigated to treat SUDs and overdose. More information about funding opportunities for therapeutics development at NIDA can be found at https://nida.nih.gov/about-nida/organization/divisions/division-therapeutics-medical-consequences-dtmc/research-programs#PDP

Learning Objective 1: 1. Learn about the NIDA Therapeutics Development Program for substance use disorders, including opioid, cocaine, methamphetamine and cannabis use disorders.

Learning Objective 2: 2. Become familiar with the pipeline of medications and other therapeutics currently investigated under this program to treat substance use disorders and overdose.

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.

Volkow ND. Drugs and Addiction Science: NIDA Celebrates 50 Years of Research and Looks to the Future. Am J Psychiatry. 2024 May 1;181(5):349-352. doi: 10.1176/appi.ajp.20230880. PMID: 38706329.

UPDATE FROM DEFENSE HEALTH AGENCY PSYCHOLOGICAL HEALTH RESEARCH PORTFOLIO

Fuad Issa, Defense Health Agency

Abstract: Department of Defense has multiple mechanisms of funding research in the psychological health arena. A review of funded work from the last fiscal year will be presented. Additionally, highlight of work to de-risk scientific research and to identify potential drug targets will be reviewed.

Learning Objective 1: Understand the different funding mechanisms available for researchers

Learning Objective 2: Outline potential approaches in successful identification of pharmacologic targets

Literature References: - Blalock ZN, Wu GWY, Lindqvist D, et al. Circulating cell-free mitochondrial DNA levels and glucocorticoid sensitivity in a cohort of male veterans with and without combat-related PTSD. Transl Psychiatry. 2024 Jan 10;14(1):22. doi: 10.1038/s41398-023-02721-x. PMID: 38200001

- Gary NC, Misganaw B, Hammamieh R, et al. Exploring metabolomic dynamics in acute stress disorder: amino acids, lipids, and carbohydrates. Front Genet. 2024 Jul 25;15:1394630. doi: 10.3389/fgene.2024.1394630. PMID: 39119583

UPDATE ON VA RESEARCH INITIATIVES IN MENTAL HEALTH

Lori Davis, Veterans Affairs Medical Center

Abstract: This year marks the centennial anniversary of VA research. The strategic priorities for VA research include increasing Veterans' access to high-quality clinical trials, increasing the substantial real-world impact of VA research, and putting VA data to work with Veterans. Investigators, Scientific Review and Management (ISRM) is the VA Office of Research and Development's organizational unit for review and management of funded medical research

across the continuum, from preclinical to clinical and health services research. VA ISRM has shifted to Actively Managed Portfolios that include Gulf War Illness, Military Exposures, Pain/Opioid Use, Precision Oncology, Suicide Prevention and Traumatic Brain Injury. VA ISRM also has four broad portfolios in 1) Brain, Behavior and Mental Health, 2) Health Systems Research, 3) Medical Health and 4) Rehabilitation Research, Development and Translation. This presentation will give updates on VA accomplishments in mental health research and review the portfolios as they pertain to mental health research.
Learning Objective 1: The participant will have a better understanding the VA priorities for mental health research and the actively managed and broad portfolios.
Learning Objective 2: The participant will have greater knowledge of VA achievements in mental health research over a century of research enterprise.
Literature References: Besterman-Dahan K, Hahm B, Chavez M, Heuer J, Melillo C, Lind J, Dillahunt-Aspillaga C, Ottomanelli L. Enhancing Veteran Community Reintegration Research (ENCORE): Protocol for a Mixed Methods and Stakeholder Engagement Project. JMIR Res Protoc. 2023 Mar 14;12:e42029. doi: 10.2196/42029. PMID: 36917162; PMCID: PMC10131720.
Haibach JP, Hoerster KD, Dorflinger L, McAndrew LM, Cassidy DG, Goodrich DE, Bormann JE, Lowery J, Asch SM, Raffa SD, Moin T, Peterson AL, Goldstein MG, Neal-Walden T, Talcott GW, Hunter CL, Knight SJ. Research translation for military and veteran health: research, practice, policy. Transl Behav Med. 2021 Mar 16;11(2):631-641. doi: 10.1093/tbm/ibz195. PMID: 32043529; PMCID: PMC8786496.

UPDATE FROM FEDERAL AND OTHER FUNDING AGENCIES PLUS
Anita Clayton, University of Virginia

Abstract: Drs. Rapaport and Clayton will provide their perspectives on the changing federal funding landscape that builds on their roles as leaders in academic medical centers as well as leading organizations that foster clinical research including American Psychiatric Association with Dr. Rapaport as the incoming president and American Society of Clinical Psychopharmacology with Dr. Clayton as the incoming president.

UPDATE FROM FEDERAL AND OTHER FUNDING AGENCIES PLUS
Mark Rapaport, University of Utah Huntsman Mental Health Institute

Abstract Drs. Rapaport and Clayton will provide their perspectives on the changing federal funding landscape that builds on their roles as leaders in academic medical centers as well as leading organizations that foster clinical research including American Psychiatric Association with Dr. Rapaport as the incoming president and American Society of Clinical Psychopharmacology with Dr. Clayton as the incoming president.

1:15 p.m. - 2:45 p.m.
Panel Sessions/Workshops

***CAN WE MAKE COGNITIVE ENHANCEMENT A MORE ACHIEVABLE THERAPEUTIC TARGET IN SMI CLINICAL TRIALS?**
Joseph Goldberg, Icahn School of Medicine at Mount Sinai

Overall Abstract: Cognitive dysfunction has long been an elusive target for clinical trials in patients with serious mental illnesses (SMIs). Both global and discrete elements of impaired cognitive performance, across varying magnitudes of severity and with possibly different

profiles, are well-recognized in schizophrenia, bipolar disorder, and major depression. Subjective cognitive complaints do not always track linearly with objective cognitive performance and may be confounded by affective, anxiety, or psychotic symptoms, as well as iatrogenic factors (e.g., antihistaminergic/anticholinergic effects, sedative-hypnotic drugs, or substance use disorders). Yet, even when affective or psychotic symptoms are optimally treated and confounding factors have been accounted for, cognitive dysfunction often persists, correlating with episode number and lifetime chronicity. SMIs may differ in the extent to which associated cognitive deficits longitudinally follow static or progressive trajectories. Persistent cognitive symptoms adversely impact quality of life, impede functional recovery, and pose a substantial unmet need in the pharmacotherapy of mood and psychotic disorders.

This panel presentation will examine the existing database of candidate pharmacotherapies and neuromodulation devices to improve cognitive function in SMI patients. We will identify and discuss methodological strengths and weaknesses of clinical trials; the role for novel therapeutics (including procholinergics, dopamine agonists, anti-inflammatory agents, serotonergic modulators, glutamate and GABA modulators, computerized learning, and neurostimulation); the impact of early intervention; and ways for future studies to best detect signals involving changes in global cognition and key subdomains. From the standpoint of methodology and trial design, we will discuss key take-away points from published consensus statements and expert opinions that identify a) the need to adopt systematic and validated pre-screens for cognitive impairment prior to subject randomization, b) enrich study samples to match cognitively impaired subgroups across treatment arms, c) use diagnostically appropriate cognitive measures, d) control for cumulative illness burden and chronicity as influencing neuroprogression, and e) assay cognitive deficits via performance-based cognitive measures rather than self-report. Despite a burgeoning focus on the role of neuroprotection from effective psychotropic agents, a key obstacle remains the technological limitations of existing pharmacotherapies for mood and psychotic disorders to target associated cognitive dysfunction – including agents with antidepressant, antipsychotic, or mood stabilizing effects. As new candidate pro-cognitive agents enter clinical trials, recommendations for optimal trial designs will be discussed in the context of treating other core symptom domains across SMIs.

Learning Objective 1: 1) To identify methodological obstacles within clinical trials for the screening and longitudinal assessment of cognitive dysfunction in mood, psychotic and major cognitive disorders

Learning Objective 2: 2) To discuss strategies to improve signal detection in the course of drug or device development for targeting cognitive impairment as a primary or co-primary outcome in clinical trials for severe mental illnesses

Literary References: 1) Nuechterlein KH, Nasrallah H, Velligan D. Measuring cognitive impairments associated with schizophrenia in clinical practice: overview of current challenges and future opportunities. Schizophr Bull 2024 Aug 1:sbae051. doi: 10.1093/schbul/sbae051. Online ahead of print.

2) Miskowiak KW, Ott CV, Petersen JZ, et al. Systematic review of randomized controlled trials of candidate treatments for cognitive impairment in depression and methodological challenges in the field. Eur Neuropsychopharmacol 2016; 26: 1845-1867.

THE CHALLENGES OF TREATING THE COGNITIVE DYSFUNCTION OF DEMENTIA PRAECOX: A MAJOR UNMET NEED IN SCHIZOPHRENIA

Philip Harvey, University of Miami Miller School of Medicine

Individual Abstract: Before the term "schizophrenia" was coined by Bleuler a century ago, it was labeled as "dementia praecox" by his contemporary Kraepelin, who was more impressed by the cognitive deficits in youth afflicted by the illness than their psychotic symptoms. Since the serendipitous discovery of antipsychotic drugs 70 years ago, it became obvious that even after the psychotic symptoms remitted with antipsychotic medications, patients with schizophrenia (SZ) remained functionally impaired due to two other symptom domains: Negative symptoms and Cognitive deficits, for which no treatments are yet available.

Cognitive dysfunction has been shown to precede the onset of the first psychotic episode. Cognitive deficits in SZ include impairments in working memory, attention, executive functions and processing speed. In addition, first-degree relatives have been shown to have low cognitive performance as well, suggesting that cognitive dysfunction in SZ may be an endophenotype of this neuropsychiatric disorder.

Why are there no treatments yet for cognitive impairments in SZ, despite the association with imitation in school or work social functioning and poor quality of life? It is a major unmet need that has not been successfully addressed despite the urgent need. But it has become evident that there are many challenges that have impeded progress in developing therapies for cognitive dysfunction in SZ, including the following:

1. The neurochemical and physiological underpinnings of cognitive impairments in SZ remain unknown, although pathology in the glutamate pathways (especially hypofunction of the NMDA receptor) has been a primary focus.
2. It is possible that cognitive impairment in SZ is a neuro-developmental/neuroplasticity condition that may not be amenable to pharmacological modulation.
3. Recurrent psychotic episodes may produce neurodegeneration which worsens cognitive deficits. For example, a college student who develops SZ in the sophomore year is unable to return to college after a second-psychotic episode.
4. The extensive heterogeneity of SZ (several hundred genetic and non-genetic biotypes) with variable severity in different cognitive functions, makes drug development quite challenging.
5. The current official diagnostic schema (DSM-5) does not include cognitive deficits as one of the criteria, and clinicians focus mostly on psychotic symptoms.
6. Standard assessments of cognition are too long and are not practical to use in the busy clinical settings of the real world.
7. Training clinicians and their staff to use even the shortest cognitive tool (e.g., BACS:30-minutes) is costly and logistically time-consuming.
8. Patients with SZ rarely inform their clinicians about how their cognitive limitations interfere with their daily functions.
9. Non-pharmacological therapies like cognitive remediation training (CRT) and neuromodulation are limited to a few centers for research purposes.
10. Vocational rehabilitation for SZ rarely employs cognitive assessment to match the job with the patient's unimpaired cognitive functions.

To tackle those monumental challenges, there needs to be a joint multi-disciplinary collaboration among the research and clinical stakeholders.

Literature References: 1. Nuechterlein KH, Nasrallah HA, Velligan D: Measuring cognitive impairments associated with schizophrenia in clinical practice: overview of current challenges and future opportunities. Schizophrenia Bulletin 2024; DOI: 10.1093/schbul/sbae051

2. Keefe RSE: Why are there no approved treatments for cognitive impairment in schizophrenia? World Psychiatry 2019; 18: 167-168

OVERCOMING METHODOLOGICAL OBSTACLES TO IMPROVE COGNITIVE DYSFUNCTION IN CLINICAL TRIALS FOR BIPOLAR DISORDER AND MAJOR DEPRESSION

Joseph Goldberg, Icahn School of Medicine at Mount Sinai

Individual Abstract: Cognitive dysfunction is evident to varying degrees in about half of adults with bipolar disorder and nearly 40% of those with major depressive disorder. In contrast to schizophrenia or other major cognitive disorders, select domains are more evident than global cognitive dysfunction in mood disorder patients. Bipolar disorder probands (and to a lesser extent their unaffected first-degree relatives) typically manifest problems with attentional processing, verbal memory, and executive functioning. It is often misconstrued as de facto attention deficit-hyperactivity disorder (regardless of age at symptom onset) and is subject to influence by undertreated mood or anxiety symptoms. While subsyndromal affective symptoms are often implicated as drivers of persistent functional impairment in mood disorder patients, far less attention has been paid to the impact of cognitive impairment as an independent obstacle to global recovery. Few randomized trials, to date, have targeted performance-based cognitive impairment either as a co-primary outcome (covarying for changes in mood symptoms) or as a primary outcome in nonsyndromal mood disorder patients with only mild-to-moderate subthreshold affective symptoms.
This presentation will focus on methodological challenges in clinical trial design and implementation for the timing and assessment of global cognitive functioning as well as known subdomains of cognitive dysfunction in major depression and bipolar disorder. We will identify lessons learned from failed or negative trials of proposed cognitive enhancers, such as novel 5HT7 antagonists, pramipexole, and docosahexaenoic acid, as well as more favorable provisional findings with lurasidone, modafinil and vortioxetine. To elucidate the optimal potential efficacy of candidate interventions, we will discuss study design-based factors that likely moderate or mediate outcomes, including the use of optimal performance-based measures (e.g., the MATRICS Consensus Cognitive Battery composite score), anticipated effect sizes and statistical underpowering, sample enrichment for baseline cognitive status and mood symptoms, histories of psychosis, cumulative lifetime illness burden and episode number, concomitant pharmacotherapies, and statistical control for residual affective or anxiety symptoms.
Literature References: 1) Miskowiak KW, Burdick KE, Martinez-Aran A, et al. Methodological recommendations for cognition trials in bipolar disorder by the International Society for Bipolar Disorders Targeting Cognition Task Force. Bipolar Disord 2017; 19: 614-626
2) Miskowiak KW, Seeberg I, Jensen MB, et al. Randomised controlled cognition trials in remitted patients with mood disorders published between 2015 and 2021: A systematic review by the International Society for Bipolar Disorders Targeting Cognition Task Force. Bipolar Disord 2022; 24: 354-374

NOVEL MECHANISMS TARGETING NEUROCOGNITIVE DYSFUNCTION

Dan Iosifescu, New York University School of Medicine

Individual Abstract: Cognitive deficits are common across a range of psychiatric disorders (including schizophrenia, mood disorders, PTSD, substance abuse), affecting domains such as memory, attention, executive function, and processing speed. These cognitive deficits can persist even when mood or psychotic symptoms are controlled and can contribute to functional impairments, reduce quality of life, and complicate treatment outcomes, highlighting the need for targeted novel interventions.

We will review critically the available data on several novel classes of pharmacological and neuromodulation strategies examined for their cognitive-enhancing properties. This includes muscarinic and nicotinic acetylcholine receptor agonists, NMDA glutamate receptor modulators (like D-cycloserine and memantine), serotonergic agents (specifically those targeting 5-HT6 and 5-HT7 receptors), inflammation-modulating drugs (tested given the link between cognition and inflammation), and other drugs targeting BDNF (brain-derived neurotrophic factor) pathways. In parallel, neuromodulation strategies such as transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS), and transcranial photobiomodulation (t-PBM) can specifically alter activity within brain cognitive circuits and may represent innovative approaches to alleviate cognitive deficits.
While the new avenues represented by these interventions are promising, the large number of options available underscores that none of them have demonstrated robust, generalizable efficacy so far. Several methodological limitations explaining this will be discussed, and also potential ways to circumvent them, in order to accomplish the ultimate goal of improving the quality of life and functional outcomes in severe mental illness.
Literature References: 1. Colwell MJ, Tagomori H, Chapman S, et al. Pharmacological targeting of cognitive impairment in depression: recent developments and challenges in human clinical research. Transl Psychiatry. 2022; 12(1):484.
2. Gaggi NL, Collins KA, Gonzalez-Castillo J, et al. Transcranial photobiomodulation increases intrinsic brain activity within irradiated areas in early Alzheimer's disease: Potential link with cerebral metabolism. Brain Stimul. 2024; 17(2):208-210.

*~NOVEL THERAPIES FOR INDIVIDUALS WITH COCAINE/METHAMPHETAMINE USE DISORDER: FINDINGS FROM STUDIES WITHIN THE NIDA CLINICAL TRIALS NETWORK

Manish Jha, University of Texas Southwestern Medical Center

Overall Abstract: There are no US Food and Drug Administration (FDA)-approved pharmacotherapy options for the treatment of cocaine or methamphetamine use disorder (or referred to together as stimulant use disorder). The landmark Accelerated Development of Additive Treatment for Methamphetamine Disorder (ADAPT-2) trial that was conducted within the NIDA Clinical Trials Network (CTN; study# CTN-0068) demonstrated that combination of extended-release naltrexone (NTX, intramuscular injection) plus bupropion (BUP, oral) was associated with significantly greater reduction in methamphetamine use over six weeks of treatment. While a follow-up study based on ADAPT-2 was recently launched to compare NTX-BUP combination versus placebo over a 12-week intervention phase, there is still an urgent need to identify other novel treatments, given that over 2 million adults in the United States suffer from these disorders. This proposed panel brings together Investigators of NIDA CTN who will present findings related to their recent and ongoing work. The first presentation will focus on the use of artificial intelligence to identify drug repurposing candidates (CTN-0114), including the potential utility of drugs targeting GLP-1 receptors, and the rationale for her recently initiated study to evaluate effects of tirzepatide and semaglutide in stimulant and in opioid use disorders (CTN-0153). The second presentation will focus on findings from the randomized controlled trial of monthly injectable buprenorphine for methamphetamine use disorder with comorbid opioid misuse (CTN-0110). The third presentation will include rational and design of a four-site clinical trial of transcranial magnetic stimulation for stimulant use disorders (CTN-0108). The final presentation will be secondary analysis from ADAPT-2 trial demonstrating that improvement in depressive symptoms partly mediated the methamphetamine treatment response with naltrexone-bupropion combination.

Learning Objective 1: Understand the public health burden of cocaine/methamphetamine use disorder in the United States.
Learning Objective 2: Identify potential novel therapies that may be effective in treatment of cocaine/methamphetamine use disorder.
Literary References: Trivedi MH, Walker R, Ling W, Dela Cruz A, Sharma G, Carmody T, Ghitza UE, Wahle A, Kim M, Shores-Wilson K, Sparenborg S, Coffin P, Schmitz J, Wiest K, Bart G, Sonne SC, Wakhlu S, Rush AJ, Nunes EV, Shoptaw S. Bupropion and Naltrexone in Methamphetamine Use Disorder. N Engl J Med. 2021 Jan 14;384(2):140-153.
Volkow ND, Xu R. GLP-1R agonist medications for addiction treatment. Addiction. 2024 Jul 24. doi: 10.1111/add.16626

DRUG DISCOVERY FOR STIMULANT USE DISORDERS USING ARTIFICIAL INTELLIGENCE AND REAL-WORLD TARGET TRIAL EMULATION
Rong Xu, Case Western Reserve University

Individual Abstract: In 2023, among Americans aged 12 or older, 2.6 million reported using methamphetamine, 5 million reported using cocaine in the past year, and 3.9 million misused prescription stimulants. Provisional data from CDC's National Center for Health Statistics indicate there were an estimated 107,543 drug overdose deaths in the US during 2023, with 36,251 deaths (33.7%) due to psychostimulants (including methamphetamine) and 29,918 (27.8%) due to cocaine. Currently, no treatments are approved by the U.S. Food and Drug Administration for stimulant use disorders.
Advanced artificial intelligence (AI) algorithms that integrate, model and analyze vast amounts of biological and clinical data have great potential to facilitate drug discovery and clinical validation to treat stimulant use disorders. I will present our recent work in identifying and validating ketamine to treat cocaine and methamphetamine use disorders by combining AI prediction and clinical evaluation. I will also present our work conducting emulation target trials in millions of real-world patients to demonstrate the benefits of semaglutide and tirzepatide, a new generation and potential Glucagon-like peptide-1 receptor agonists (GLP-1RAs), in treating substance use disorders.
Literature References: Gao Z, Winhusen TJ, Gorenflo M, et al. Repurposing ketamine to treat cocaine use disorder: Integration of artificial intelligence-based prediction, expert evaluation, clinical corroboration and mechanism of action analyses. Addiction. 2023 Jul;118(7):1307-19.
Wang W, Volkow ND, Berger NA, et al. Association of semaglutide with tobacco use disorder in patients with type 2 diabetes: Target trial emulation using real-world data. Annals of Internal Medicine. 2024 Aug;177(8):1016-27.

REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION FOR STIMULANT USE DISORDERS (STIMULUS): RATIONALE AND PRELIMINARY FINDINGS
Karen Hartwell, Medical University of South Carolina

Individual Abstract: The prevalence of cocaine and methamphetamine use disorders (CUD/MUD) have increased significantly in the United States (US) from 2020 to 2022. The disorders have serious public health burden as well as medical and psychiatric consequences. Yet, there are no US Food and Drug Administration (FDA) approved treatments available for CUD or MUD. Studies exploring rTMS for stimulant use disorders remain limited by small sample sizes, as well as great heterogeneity in defined study population, treatment parameters, length of retention in treatment, and number of treatment exposures. The STIMULUS study is a multi-site trial sponsored by the National Institute on Drug Abuse Treatment Clinical Trials Network (NIDA CTN), that aims to investigate the feasibility and

preliminary efficacy of repetitive transcranial magnetic stimulation (rTMS) as a potential treatment for moderate to severe CUD/MUD. The study is a randomized, double-blind, sham-controlled trial comparing rTMS treatment to sham. The project enrolled participants (n=129), aged 18 to 65, with a current moderate to severe CUD or MUD diagnosis, randomized to receive active rTMS (10-Hz stimulation at 120% of the motor threshold over the left dorsolateral prefrontal cortex) or sham. Participants were presented with methamphetamine or cocaine-related cues immediately before intervention is delivered to stimulate craving. Feasibility of this intervention was assessed by a target of at least 20 treatment sessions administered within an 8-week period. In addition, the study evaluated the efficacy of rTMS in reducing cocaine or methamphetamine use and craving, and examine the impact of rTMS on mood, anxiety, sleep, and other measures via a battery of psychological assessments and daily monitoring. An electroencephalography (EEG) was also obtained at baseline and week 4 to assess the utility of resting connectome as a treatment response biomarker. It is hoped that the data collected will lay the groundwork for a robust randomized controlled trial of rTMS as a therapeutic intervention for individuals with CUD/MUD.
Literature References: Mehta DD, Praecht A, Ward HB, Sanches M, Sorkhou M, Tang VM, Steele VR, Hanlon CA, George TP. A systematic review and meta-analysis of neuromodulation therapies for substance use disorders. Neuropsychopharmacology. 2024 Mar;49(4):649-680.
Ballester J, Marchand WR, Philip NS. Transcranial magnetic stimulation for methamphetamine use disorder: A scoping review within the neurocircuitry model of addiction. Psychiatry Res. 2024 Aug;338:115995.

EARLY CHANGE IN DEPRESSIVE SYMPTOM SEVERITY WITH NALTREXONE-BUPROPION COMBINATION AND ITS ASSOCIATION WITH REDUCTION IN METHAMPHETAMINE USE IN ADAPT-2 TRIAL

Abu Minhajuddin, The University of Texas Southwestern Medical Center

Individual Abstract Background: This study evaluated whether depressive symptom severity improved early with extended-release naltrexone and bupropion combination (naltrexone-bupropion) in individuals with moderate/severe methamphetamine use disorder and predicted subsequent use of methamphetamine.
Methods: This unplanned secondary analysis of Accelerated Development of Additive Treatment for Methamphetamine Disorder (ADAPT-2) trial included N=326 individuals with 9-item Patient Health Questionnaire (PHQ-9) score ≥5 at baseline. Repeated-measures mixed model analyses evaluated early (baseline-to-week-4) changes in depressive symptom severity with naltrexone-bupropion versus placebo and provided slope estimates for PHQ-9 change. Additional depression outcomes included response (≥50% reduction in PHQ-9 from baseline) and remission (PHQ-9 ≤4). Methamphetamine treatment response was ascribed if three out of four urine drug screens were negative during weeks 5 and 6. Logistic regression analyses evaluated if changes in depression predicted methamphetamine treatment response. Covariates included age, sex, race, ethnicity and baseline PHQ-9.
Results: There was greater reduction in PHQ-9 scores at week-4 with naltrexone-bupropion versus placebo [estimate= 2.52; 95% confidence interval: 0.94, 4.11]. At week-4, depression response [odds ratio (OR)=2.54; 95% confidence limit (CL): 1.42, 4.55] and remission (OR=3.04; 95% CL: 1.57, 5.87) were more likely with naltrexone-bupropion versus placebo. Greater baseline-to-week-4 reduction in PHQ-9 was associated with higher likelihood of methamphetamine treatment response [OR=3.74, 95% Confidence Limits (CL): 1.28, 10.93] and explained 24.8% (95% CI: 6.7%, 60.3%) of the effect of naltrexone-bupropion on methamphetamine treatment response.

Conclusion: Use of naltrexone-bupropion was associated with early reduction in depressive symptom severity which was associated with higher likelihood of reduction in subsequent methamphetamine use.
Literature References: Trivedi MH, Walker R, Ling W, Dela Cruz A, Sharma G, Carmody T, Ghitza UE, Wahle A, Kim M, Shores-Wilson K, Sparenborg S, Coffin P, Schmitz J, Wiest K, Bart G, Sonne SC, Wakhlu S, Rush AJ, Nunes EV, Shoptaw S. Bupropion and Naltrexone in Methamphetamine Use Disorder. N Engl J Med. 2021 Jan 14;384(2):140-153.
Li MJ, Chau B, Belin T, Carmody T, Jha MK, Marino EN, Trivedi M, Shoptaw SJ. Extended observation of reduced methamphetamine use with combined naltrexone plus bupropion in the ADAPT-2 trial. Addiction. 2024 Oct;119(10):1840-1845.

OUTCOMES FROM THE RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL OF MONTHLY INJECTABLE BUPRENORPHINE FOR METHAMPHETAMINE USE DISORDER

Mariah Kalmin, RAND Corporation

Individual Abstract Introduction: Negative emotional and cognitive experiences can cause persons with methamphetamine use disorder who co-use opioids to maintain or return to use. This 12-week, randomized, placebo-controlled trial, Methamphetamine Use Reduction with Buprenorphine (MURB; Clinical Trials Network-0110) sought to test the kappa antagonist property of buprenorphine to relieve these negative experiences and thus reduce methamphetamine use.
Methods: Eligible participants across six sites in the U.S. self-reported methamphetamine use on ≥ 18 days and opioid use on ≥ 2 days in the past month and met MINI-verified diagnoses of moderate-to-severe methamphetamine use disorder and mild opioid use disorder/opioid misuse. After randomization, all participants began a 2–3-day sublingual induction onto buprenorphine. After induction and every four weeks thereafter, unmasked study staff administered injectable study medications (buprenorphine 300mg or placebo). Participants attended clinic twice weekly for urine drug screens and cognitive behavioral therapy sessions with a clinician. The primary outcome was defined as the number of urine drug screens negative for methamphetamine during weeks 9-12. Secondary outcomes collected measured symptoms of craving, anxiety and depression, social determinants of health, and quality of life.
Results: Enrollment began March 2023 and was stopped by the DSMB in September 2023 due to unacceptable sedating effects of the sublingual medication and inadequate prevalence of this group to populate the trial. Of the 575 participants who pre-screened for the study, a total of 19 (3.3%) were eligible and randomized to receive either injectable buprenorphine or placebo (one participant withdrew consent prior to receiving a dose of sublingual buprenorphine). Of the 18 participants randomized who received at least one dose of sublingual buprenorphine (n=5 randomized to injectable buprenorphine and n=13 randomized to placebo), six completed sublingual induction and received injectable buprenorphine (n=2) and injectable placebo (n=4). The primary reason that 12 participants did not complete the SL-BUP induction phase was adverse events (1 serious, 5 moderate, and 19 mild). One of the two participants who were randomized to and received injectable buprenorphine did not complete the study. Over the 12-week medication phase, there were only 4 urine drug screens negative for methamphetamine across all participants.
Discussion: Findings show moderate-to-severe methamphetamine use disorder and mild opioid use disorder/opioid misuse is not prevalent. Using buprenorphine in individuals with methamphetamine use disorder and no opioid dependence produces sedating effects that are unacceptable for participants. While the rationale for the kappa antagonist mechanism

remains reasonable, there is little evidence for using buprenorphine monotherapy in this population. There may be better acceptability to pairing an opioid antagonist with buprenorphine for those with moderate-to-severe methamphetamine use disorder and mild opioid use disorder or opioid misuse.
This study was supported by funds from the NIH Heal Initiative.
Literature References: Salehi M, Emadossadat A, Kheirabadi GR, et al. The Effect of Buprenorphine on Methamphetamine Cravings. J Clin Psychopharmacol. 2015;35(6):724-727.
Haight BR, Learned SM, Laffont CM, et al. Efficacy and safety of a monthly buprenorphine depot injection for opioid use disorder: a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2019;393(10173):778-790.

^RE-EVALUATING METHODOLOGIES IN PSYCHIATRIC CLINICAL TRIALS: LESSONS FROM PSYCHEDELIC STUDIES AND BEYOND

Scott Aaronson, Sheppard Pratt

Overall Abstract: Many of the methodologies developed for psychiatric clinical trials decades ago have not evolved as the field has. As psychiatry continues to progress towards an increased ability to offer interventions for more difficult to treat illnesses and novel interventions are introduced that appear to improve psychiatric symptoms in ways different than classic medications, there is an urgent need to reassess the methodologies employed in clinical trials.
Recent studies across multiple disease targets across the life spectrum with psychedelic compounds and other treatments highlight this critical need.
Speakers for our workshop are recognized leaders in the development of novel treatment paradigms. Gerard Sanacora will lead off with one of the most challenging hurdles in the development of psychedelics, functional unblinding due to the unique nature of psychedelic administration. Dr. Sanacora will point out that this is not a qualitatively new research problem but an old one with new quantitative concerns. Rebecca Hendrickson will focus on the interaction between medication and non-medication effects in clinical trials whether those non-medication effects are a formal psychotherapy or the experience of being in a clinical trial. Dr. Hendrickson will discuss how the potential for interplay meaningfully shapes clinical outcomes as highlighted by recent psychedelic studies but may have a more far reaching effect in many more psychiatric studies. Manpreet Singh will focus on the challenges of pediatric clinical trials where the high placebo response rates have challenged capturing the effect from the studied intervention. Dr. Singh will suggest the path forward and what needs to be done to make the future of research in youth different. Scott Aaronson will outline the need for a reassessment of outcome measures typically used in mood disorder research as we try to capture the unique ways study participants improve in psychedelic studies where effects on cognition outstrip the effects on typical vegetative symptoms. Dr. Aaronson will then address the need to refocus outcomes in studies on subjects with severe, chronic, difficult to treat depressions where quality of life and functionality measures capture more of the meaningful benefit than a standard depression rating scale. This will be followed by an opportunity for an open discussion.
Learning Objective 1: Participants will be able to list three psychedelic treatment outcome measures not captured by standard depression severity scales.
Learning Objective 2: Participants will be able to describe two strategies to mitigate the challenge of functional unblinding in a placebo controlled trial.

Literary References: van Elk M and Fried E I, History repeating: guidelines to address common problems in psychedelic science. Ther Adv Psychopharmacol. 2023 Sep 25;13:20451253231223609.
McIntyre RS, Alsuwaidan M, Baune BT et. al., Treatment-resistant depression: definition, prevalence, detection, management, and investigational interventions. World Psychiatry 2023; 22(3): 394-412.

ADDRESSING THE ISSUES OF FUNCTIONAL UNBLINDING AND PATIENT/PARTICIPANT EXPECTATIONS IN THE CURRENT LANDSCAPE OF TREATMENT DEVELOPMENT

Gerard Sanacora, Yale University

Individual Abstract: Starting at the dawn of the era of randomized placebo-controlled clinical trials, maintaining study treatment assignment blinding for both patient/participants and investigators has been a challenge. For decades the issue of functional unblinding has remained a relatively minor concern in the design of randomized placebo-controlled clinical trials. Several approaches have been employed, largely to help ensure investigator blinding. However, there has historically been a limited focus on ensuring adequate masking of patient/participants. The more recent development and study of treatments such as esketamine and psychedelic-like medications like psilocybin and MDMA has brought the issue of functional unblinding front and center for investigators and regulators. We are no longer able to disregard the potential effects of treatment expectancy and functional unblinding in the interpretation of study findings. This new reality is forcing us to develop and employ novel methods of measuring the adequacy of functional unblinding and the direction and magnitude of patient/participant expectations. We will discuss approaches being developed and employed in efforts to measure, control, and interpret the contributions of functional unblinding and patient expectations to treatment outcome. However, considering the likelihood that we will never achieve complete masking of treatment assignment, especially for drugs with blatantly obvious unique transient effects, we will need to draw some consensus on how we consider functional unblinding when interpreting clinical trial outcome measures in the future and what levels will be considered acceptable. We hope to stimulate discussion on this topic with a goal of building consensus that could be used in guiding future studies in this area.
Literature References: Food and Drug Administration. Psychedelic Drugs: Considerations for Clinical Investigations, Silver Spring, Maryland, 2023.
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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:

ARE THE EFFECTS OF PHARMACOTHERAPY EVER REALLY INDEPENDENT OF CONTEXT? HOW LESSONS FROM PSYCHEDELIC CLINICAL TRIALS MAY HELP US BETTER UNDERSTAND CLINICAL TRIAL RESULTS ACROSS PSYCHIATRY – AND DESIGN BETTER TRIALS IN THE FUTURE.

Rebecca Hendrickson, VA Puget Sound Health Care System

Individual Abstract Summary: In this portion of the workshop, we will focus on what it means for the effect of a medication to depend at least in part on the context in which it is provided – and whether such context-dependent effects may be more widely prevalent in psychiatric clinical trials than is typically acknowledged. Drawing on lessons from both psychedelic research and traditional clinical trials, we will explore how a better

understanding of such effects may better explain phenomenon such as the robust and dramatic placebo effects seen even in clinical trials of well-characterized treatment-resistant populations, and may guide improved clinical trial designs in the future, with reduced failure rates and better relevance to clinical care.

Background: Psychedelic compounds are often touted as "plasticity enhancers", and their mechanism of action is posited to at least in part depend on opening up a window of time when individuals are able respond with increased flexibility and capacity for learning to both their own memories and thoughts, and to their ongoing experiences. Some but not all psychedelic clinical trials have sought to maximize the potential benefit of the medications by pairing them with varying forms of psychotherapy or supportive connection. A question often asked of these trials is to what extent the observed benefits are due to the medication alone, versus to context or psychotherapy components alone, versus an interactive effect between the two; in part due to the concern that the dissemination of pharmacotherapies whose not just safety but efficacy depends significantly on the context in which they are given, when that context may not be similar between the randomized clinical trials used to support regulatory approval and guide prescribing, may risk misleading both clinicians and patients about the risks and benefits of treatments.

However, many of the issues raised here are not unique to psychedelic medications. Increasing evidence suggests that 1) plasticity enhancement may be a core mechanism of action for many if not most psychiatric medications, particularly for mood and anxiety disorders, and 2) the context of clinical trials may be importantly different from the context of clinical care, in ways that have real implications for patient outcomes.

Topics covered: Here, we will review some of the public results of the clinical trials of psychedelics discussed above, and compare what has been learned to patterns seen in clinical trials more widely in our field. We will touch briefly on reasons to expect that 'plasticity enhancement' and context-dependent effects of pharmacotherapy may well be widely prevalent in psychopharmacology, including for such widely used medications as SSRI/SNRI medications and mood stabilizers. We will examine whether these ideas may provide new ways to better understand the mechanisms behind and the meaning of placebo effects in psychopharmacology clinical trials, drawing on results from both traditional clinical trial designs, and designs that include e.g. comparisons between "placebo" and no treatment conditions, or transitions between blinded and unblinded periods on and off treatment for individual participants. We will also explore how the ideas discussed here may help to explain the gap that can be observed between the results of clinical trials and the at times lower rates of efficacy in clinical practice. Finally, we will start thinking about how clinical trials may be designed to better address the not just potential but likelihood of significant interactions between psychopharmacologic interventions and the context in which it's given, whether or not that context includes explicit psychotherapeutic components.

Literature References: Rief, W., Barsky, A. J., Bingel, U., Doering, B. K., Schwarting, R., Wöhr, M., and Schweiger, U. (2016). Rethinking psychopharmacotherapy: The role of treatment context and brain plasticity in antidepressant and antipsychotic interventions. In Neuroscience and Biobehavioral Reviews (Vol. 60, pp. 51–64). Elsevier Ltd. https://doi.org/10.1016/j.neubiorev.2015.11.008

Hróbjartsson, A., and Gøtzsche, P. C. (2004). Is the placebo powerless? Update of a systematic review with 52 new randomized trials comparing placebo with no treatment. In Journal of Internal Medicine (Vol. 256, Issue 2, pp. 91–100). https://doi.org/10.1111/j.1365-2796.2004.01355.x

PLATFORM TRIALS FOR PEDIATRIC MAJOR DEPRESSIVE DISORDER AND OTHER INDICATIONS

Manpreet Singh, University of California, Davis

Individual Abstract: Drug development for pediatric major depressive disorder has several challenges, including, but not limited to, multiple past trial failures, high placebo response rates, difficulty with sufficient and efficient participant enrollment due to off-label use of products approved for adults, uncertainty related to the regulatory acceptability and feasibility of extrapolation approaches, and the limited market size of the population. Fulfilling the US FDA and Europe's EMA mandates for pediatric product development requires stakeholders (including industry sponsors, clinical research leaders, investigators, patient and patient advocacy groups, health authorities, and other stakeholders in the clinical trial ecosystem) to commit substantial resources even though the affected population is only rarely a commercial priority, and this is particularly true for pediatric investigational products that are developed on the backbone of adult indications. Often, companies are developing different products for the same indication, raising questions not only as to which is better but, perhaps more importantly, whether all are necessary, while competing for (relatively) rare populations. Platform studies evaluating more than one investigational product simultaneously may offer substantial efficiencies were stakeholders were able to collaborate, speeding the delivery of safe and effective medicines to children. This talk will aim to explore how multi-sponsor registrational pediatric platform trials could be leveraged to speed delivery of innovative therapies to pediatric patient populations in association with adult approval.

Literature References: 1. Gold et al., Platform trials and the future of evaluating therapeutic behavioural interventions, 2022
Nature Reviews Psychology 1(1):7-8; DOI:10.1038/s44159-021-00012-0
2. Wathen JK, Jagannatha S, Ness S, Bangerter A, Pandina G. A platform trial approach to proof-of-concept (POC) studies in autism spectrum disorder: Autism spectrum POC initiative (ASPI). Contemp Clin Trials Commun. 2023 Jan 16;32:101061.

RE-THINKING DEPRESSION OUTCOME MEASURES IN RAPIDLY ACTING AND SLOWLY ACTING INTERVENTIONS

Scott Aaronson, Sheppard Pratt

Individual Abstract: Research into depression outcomes has traditionally relied on standardized scales that often fail to capture the unique effects observed in studies involving psychedelics or in the meaningful improvements seen with device interventions, such as vagus nerve stimulation or deep brain stimulation in participants with the most treatment resistant depressions. As these innovative therapies gain traction, it becomes increasingly clear that current measurement tools are inadequate for evaluating the multifaceted nature of depression improvement.
This presentation will explore the limitations of existing scales and propose a shift towards incorporating quality of life and functional improvement measures.
Looking at the nuanced experiences of patients undergoing psychedelic treatments, the field needs to re-consider what changes we need to capture. For many psychedelic study participants there are changes to their sense of themselves and the world around them that often leads to an improved sense of themselves. Also the time course towards improvement may be much more rapid than the timeframe offered for the most commonly used scales. A hyperfocus on vegetative symptom outcomes at this juncture appears anachronistic. Possible avenues to improved outcome assessments will be discussed. We aim to foster a more comprehensive understanding of treatment outcomes.

Within the realm of slower acting therapies such as vagus nerve stimulation or deep brain stimulation, these interventions are limited to depressed individuals with many year histories of severe, treatment resistant depression with frequent failed interventions including ECT. Often a less than 50% drop in a depression rating scale may still signify a meaningful benefit for patients disabled by their depression. Use of quality of life, functionality and patient assessment scales for these studies will be discussed.

Literature References: Breeksema JJ, Niemeijer AR, Krediet E, Vermetten E, Schoevers RA. Psychedelic Treatments for Psychiatric Disorders: A Systematic Review and Thematic Synthesis of Patient Experiences in Qualitative Studies. CNS Drugs. 2020 Sep;34(9):925-946.

Conway CR, Kumar A, Xiong W, Bunker M, Aaronson ST, Rush AJ. Chronic Vagus Nerve Stimulation Significantly Improves Quality of Life in Treatment-Resistant Major Depression. J Clin Psychiatry. Aug 21;79(5), 2018

*^PRACTICAL CONSIDERATIONS FOR DEPRESCRIBING PSYCHIATRIC MEDICATION

Joshua Rosenblat, University of Toronto

Overall Abstract: In the field of psychopharmacology, the large majority of research and education is focused on the effects of prescribing medications. In medical school and psychiatry residency programs, trainees receive hundreds of hours of teaching and hands on experience learning how to effectively start and titrate up psychotropics. Conversely, there is minimal research and education on deprescribing. The idea to stop a medication may arise from patients, family members or prescribers. The lack of training and experience with deprescribing often creates significant apprehension for care providers when considering stopping medications. Furthermore, this hesitancy to consider deprescribing contributes to the growing prevalence of polypharmacy in psychiatry.

In this Presidentially Invited Workshop, members of the ASCP Deprescribing Task Force will provide an overview of research evidence, expert opinions and practical considerations for stopping psychiatric medications. Results from our Delphi consensus project on deprescribing will also be presented.

This highly interactive session will blend didactic teaching with case-based learning, discussing a variety of clinical case examples to illustrate an approach to deprescribing a variety of medications in diverse clinical settings.

The informed consent process for deprescribing will be reviewed including risks, benefits and alternatives to stopping medications, describing the risk-benefit analyses before deprescribing and managing adverse effects. Evidence will be reviewed to support considerations for risk of relapse with medication discontinuation along with risks of continuing medications that are causing side effects. The shared decision making process will be described.

Risk mitigation strategies while tapering off medications will be discussed including selecting the appropriate rate of tapering, use of short-term medications to alleviate withdrawal symptoms and application of psychosocial strategies to reduce side effects and risk of relapse.

The following medication classes will be discussed: antidepressants, benzodiazepines, sleep aids, antipsychotics, lithium, anti-convulsants and anticholinergics.

The following special topics will also be explored through case discussion:

-Discontinuing medications for pregnancy and lactation

-Deprescribing in older adults and the medically ill

-Discontinuing baseline medications for the purpose of enrolling into clinical trials

-Considerations for stopping lithium when renal complications have been identified

Learning Objective 1: Understand practical considerations for deprescribing psychiatric medications
Learning Objective 2: Appreciate the elements of informed consent when stopping various psychiatric medications
Literary References: Boland M, Higgins A, Beecher C, et al. Identifying priorities for future research on reducing and stopping psychiatric medication: results of a James Lind Alliance priority-setting partnership. BMJ Open 2024;14:e088266. doi: 10.1136/bmjopen-2024-088266
Gupta and Cahill. A Prescription for "Deprescribing" in Psychiatry. Psychiatr Serv. 2016 Aug 1;67(8):904-7. doi: 10.1176/appi.ps.201500359.

PSYCHOLOGICAL FACTORS ASSOCIATED WITH DEPRESCRIBING PSYCHOTROPIC MEDICATIONS

Holly Swartz, University of Pittsburgh School of Medicine

Individual Abstract: Deprescribing, the process of reducing or discontinuing psychotropic drugs under supervision, may mitigate the negative effects of inappropriate prescribing and polypharmacy on patient outcomes. Although understanding the pharmacological impacts of deprescribing on human physiology is essential to the process of safe medication cessation, recognition of psychological factors affecting deprescribing is also critically important to the success of this process. This presentation will focus on identification of patient psychological factors that may influence deprescribing and psychosocial strategies that may be employed to address psychological barriers to deprescribing.

For most patients, medications have meaning independent of their physiologic effects. For instance, medications may give patients a sense of control over their illness or represent valued self-guided tools for lessening suffering and improving functioning. Pills may serve as transitional objects, providing patients with tangible evidence that their physician cares for them and has not abandoned them despite lack of physical proximity. Medications may also be perceived as validating the legitimacy of their psychiatric illness, providing patients with evidence that their struggles are real and not “all in their head.”

Patient fears of discontinuation are often identified as barriers to deprescribing. Patients may unconsciously fear the loss of medication as a valued object. They may experience deprescribing as a rejection by their doctor, a threat to the medical legitimacy of their experiences, or an attempt to remove a valued introject. They may may also fear negative outcomes based on prior personal experiences (e.g., withdrawal symptoms related to SSRI discontinuation) or (mis)information garnered from friends or social media. Even among those reporting no benefit from the current medication regimen, some are nevertheless fearful that they will feel worse without it. Patients may doubt their ability to handle stressors without medication, especially if they lack access to adequate therapeutic support or knowledge of alternative coping mechanisms.

In some cases, patients’ psychological reactions to medications may facilitate rather than hinder deprescribing. For instance, some individuals view taking psychiatric medication as undesirable or stigmatizing, signaling that the patient is “crazy.” They may see medication use as a sign of weakness, dependency, or failure to heal naturally. Ingesting medication might symbolize reliance on an external entity (the medication itself or the prescriber) for well-being, evoking feelings of passivity or dependency and challenging their sense of autonomy. In these cases, deprescribing might be perceived positively as a step toward recovery or "normalcy."

Understanding patients’ psychological relationship to medication will aid prescribers to more effectively work with patients around deprescribing. It may lead to adoption of strategies

directly targeting psychological barriers to deprescribing, including psychoeducation, collaborative tapering plans, adjunctive coping skills, and regular monitoring with support. Understanding and addressing psychological factors implicated in medication management can significantly enhance the likelihood of successful deprescribing while preserving the integrity of the patient-provider relationship.

Literature References: Mintz DL, Flynn DF. How (not what) to prescribe: nonpharmacologic aspects of psychopharmacology. Psychiatr Clin North Am. 2012 Mar;35(1):143-63. doi: 10.1016/j.psc.2011.11.009. Epub 2011 Dec 15. PMID: 22370496.
Reeve E, To J, Hendrix I, Shakib S, Roberts MS, Wiese MD. Patient barriers to and enablers of deprescribing: a systematic review. Drugs Aging. 2013 Oct;30(10):793-807. doi: 10.1007/s40266-013-0106-8. PMID: 23912674

THE SCOURGE OF ANTICHOLINERGIC LOAD

Leslie Citrome, New York Medical College

Individual Abstract: The deleterious effects of excess anticholinergic load are discussed within the context of the unbiquitous use of medications with anticholinergic properties, including concommitant benztropine. Strategies to deprescribe anticholinergic agents are described, together with alternative medications for the management of drug-induced movement disorders.

Literature References: 1. Vanegas-Arroyave N, Caroff SN, Citrome L, Crasta J, McIntyre RS, Meyer JM, Patel A, Smith JM, Farahmand K, Manahan R, Lundt L, Cicero SA. An Evidence-Based Update on Anticholinergic Use for Drug-Induced Movement Disorders. CNS Drugs. 2024 Apr;38(4):239-254. doi: 10.1007/s40263-024-01078-z. Epub 2024 Mar 19. PMID: 38502289; PMCID: PMC10980662.
2. Vinogradov S, Fisher M, Warm H, Holland C, Kirshner MA, Pollock BG. The cognitive cost of anticholinergic burden: decreased response to cognitive training in schizophrenia. Am J Psychiatry. 2009 Sep;166(9):1055-62. doi: 10.1176/appi.ajp.2009.09010017. Epub 2009 Jul 1. PMID: 19570929; PMCID: PMC3735363.

THE WHAT, WHEN, AND HOW OF DEPRESCRIBING PSYCHIATRIC MEDICATIONS IN MEDICALLY-ILL OLDER ADULTS

Rajnish Mago, Simple and Practical Medical Education, LLC

Individual Abstract: The term “deprescribing” was originally used in reference to older adults—and with good reason. Older adults are more likely to have multiple comorbid medical conditions and be on multiple medications. They are also more susceptible to adverse effects of medications with anticholinergic, sedative, and hypotensive effects. In older adults, polypharmacy contributes to impaired cognition, falls, deficits in functioning, hospitalizations, and even increased mortality.

A routinely applied, systematic, and multidisciplinary approach to medication review and deprescribing can lead to substantial benefits for the individual, healthcare system, and society. The use of structured instruments can aid this systematic approach by identifying potentially inappropriate medications and providing an overall estimate of their additive effects.

The American Geriatrics Society’s Beers Criteria®, updated in 2023, are useful as an authoritative overview of “potentially inappropriate medications” that are “typically best avoided by older adults in most circumstances or under specific situations, such as in certain diseases…”

Falls: Falls are the most common cause of accidental death in older adults. We should routinely check orthostatic vitals and use the STOPPFall tool to identify fall-risk-increasing drugs (FRIDs) and deprescribe them where possible, using its guidelines.
Anticholinergic burden: Many older adults, including those with cognitive impairment or dementia—and even some who are on a cholinesterase inhibitor—are taking one or more medications with significant anticholinergic activity. The anticholinergic burden of these medications is associated with a variety of negative outcomes, including cognitive impairment, confusion, delirium, falls, urinary retention, etc. The routine use of a rating scale for anticholinergic burden and systematic deprescribing of these medications is recommended. Which of the many anticholinergic burden rating scales we should use to guide evaluation and deprescribing will be discussed.
QTc prolongation: Busy clinicians need a strategy for quickly looking up the risk of QTc prolongation with each medication as well as its clinical significance; that is, has torsade de pointes been reported? Combining this information with systematically identified non-medication risk factors for QTc prolongation allows clinicians to develop a rational plan for deprescribing medications that are associated with the greatest risk.
Syndrome of Inappropriate Anti-Diuretic Hormone (SIADH) secretion / Hyponatremia: Oxcarbazepine, carbamazepine, and serotonergic antidepressants are among the psychiatric medications that can cause clinically significant hyponatremia. Older adults are much more likely than others to develop hyponatremia associated with these medications. It is also important to know that the risk of hyponatremia is markedly higher in patients who are also on non-psychiatric medications that can also cause hyponatremia, like diuretics, angiotensin-converting-enzyme inhibitors, angiotensin II receptor blockers, and proton pump inhibitors. This is relevant because when it is important to continue the particular antidepressant that was associated with hyponatremia, we should discuss possibly deprescribing these non-psychiatric medications instead.
Literature References: 1. By the 2023 American Geriatrics Society Beers Criteria® Update Expert Panel. American Geriatrics Society 2023 updated AGS Beers Criteria® for potentially inappropriate medication use in older adults. J Am Geriatr Soc. 2023;71(7):2052-2081.
2. Al Rihani SB, Deodhar M, Darakjian LI, et al. Quantifying Anticholinergic Burden and Sedative Load in Older Adults with Polypharmacy: A Systematic Review of Risk Scales and Models. Drugs Aging. 2021;38(11):977-994.

RETROSPECTIVE TRACKING OF THE VALUE AND TOLERABILITY OF MULTIPLE MEDICATIONS PRIOR TO DEPRESCRIBING

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

Individual Abstract: Although the idea of polypharmacy was once an anathema, "rational cotherapy" is now practiced by most psychopharmacologists. For patients who do not respond quickly to first-line therapies, "rational cotherapy" may result in taking two or three psychotropic medications. This pattern may be amplified when the patient suffers from several co-occurring conditions. Such "extremely complex pharmacotherapy" is seen commonly in people with more difficult to treat forms of depression and bipolar disorder: five medications was found to be the modal number some years ago and today we are not infrequently asked to evaluate people who are taking eight or even more psychotropic medications. Often, one or more of these rationally prescribed medications have been added to lessen the adverse effects of other, earlier prescribed drugs. As many of the patients taking more complex regimens are still quite symptomatic and impaired, it is quite simply not possible that all of the prescribed medications are helpful and iatrogenic complications are likely. This portion of the workshop will illustrate the use of life charting and the a

modification of the timeline follow-back strategieies to identify the most likely medications to target when trying to implement a "rational de-prescripton" approach to overly complex psychopharmacological treatment.
Literature References: Kim, A. M., Salstein, L., and Goldberg, J. F. (2021). A Systematic Review of Complex Polypharmacy in Bipolar Disorder: Prevalence, Clinical Features, Adherence, and Preliminary Recommendations for Practitioners. The Journal of clinical psychiatry, 82(3), 20r13263. https://doi.org/10.4088/JCP.20r13263
Brooks, J. O., 3rd, Goldberg, J. F., Ketter, T. A., Miklowitz, D. J., Calabrese, J. R., Bowden, C. L., and Thase, M. E. (2011). Safety and tolerability associated with second-generation antipsychotic polytherapy in bipolar disorder: findings from the Systematic Treatment Enhancement Program for Bipolar Disorder. The Journal of clinical psychiatry, 72(2), 240–247. https://doi.org/10.4088/JCP.09m05214yel

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

^HARNESSING EDUCATIONAL TECHNOLOGY TO ADVANCE EDUCATION: THE NEXT GENERATION ASCP MODEL PSYCHOPHARMACOLOGY CURRICULUM

Matthew Macaluso, The University of Alabama at Birmingham

Overall Abstract: The goal of this panel is to present the initial phase of the next generation Model Psychopharmacology Curriculum: Crash Course, to the American Society of Clinical Psychopharmacology (ASCP) leaders, members, and other key stakeholders. The workshop will also review the current status of the Curriculum. The presentation will also demonstrate the current iteration of the online Curriculum.
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 to improve the knowledge gained by trainees to enhance patient care. 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 demonstrated the need for integration of advanced technology to ensure that both educators and learners were optimally engaged. By the 11th edition of the ASCP curriculum, published in 2021, the ASCP leadership agreed that the curriculum would be re-formulated to meet the needs of modern learners, whose education has largely occurred in a digital space.
A committee appointed by the ASCP Board has worked to integrate modern technology to include educational material developed by content experts to meet the needs of end users. End users could be psychiatry 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.
The newest iteration of the ASCP Model Psychopharmacology Curriculum consists of several parts: 1. A series of online presentations presented by recognized experts in the respective areas; 2. A short high yield reading on each topic; and 3. A chat feature into which

learners can ask questions of an artificial intelligence teaching assistant that is built out of specific readings provider by the presenters.5 The curriculum will consist of three parts: a "crash course" intended for first year residents; a basic course, which will be the core psychopharmacology curriculum for second year residents; and an advanced course for third year residents, that will be more mechanistic in focus. To date, the crash course is complete and ready for distribution. The editors and committee are currently hard at work on the basic course, which we anticipate will be complete by next year's ASCP Annual Meeting.
Learning Objective 1: Review the history of the ASCP model psychopharmacology curriculum.
Learning Objective 2: Understand the process being used to revamp, update and modernize the curriculum (and provide feedback).
Literary References: 1. Glick ID, Janowsky DS, Salzman C, Shader RI. A Model Psychopharmacology Curriculum for Psychiatric Residents. Nashville, Tennessee, The American College of Neuropsychopharmacology, 1984.
2. 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. PMID: 15937259. Erratum in: Acad Psychiatry. 2005; 29:324. Erratum in: Acad Psychiatry. 2005; 29:324.
3. Wulsin and Kramer: Teaching Psychopharmacology in the 21st Century, Acad Psychiatry 2001; 25:102-106.
4. Das T, Kaur G, Nematollahi S, et al. Medical Education in the Digital Era. JACC Adv. 2022; 1:100031. PMID: 38939313
5. Sun L, Yin C, Xu Q, Zhao W. Artificial intelligence for healthcare and medical education: a systematic review. Am J Transl Res. 2023; 15:4820-4828. PMID: 37560249.

REBOOTING THE ASCP MODEL PSYCHOPHARMACOLOGY TEACHING CURRICULUM

Richard Shelton, University of Alabama at Birmingham

Individual Abstract: The newest iteration of the ASCP Model Psychopharmacology Curriculum consists of several parts: 1. A series of online presentations presented by recognized experts in the respective areas; 2. A short high yield reading on each topic; and 3. A chat feature into which learners can ask questions of an artificial intelligence teaching assistant that is built out of specific readings provider by the presenters.5 The curriculum will consist of three parts: a "crash course" intended for first year residents; a basic course, which will be the core psychopharmacology curriculum for second year residents; and an advanced course for third year residents, that will be more mechanistic in focus. To date, the crash course is complete and ready for distribution. The editors and committee are currently hard at work on the basic course, which we anticipate will be complete by next year's ASCP Annual Meeting.
Dr Shelton will review the process by which the curriculum pilot was developed, how a needs assessment was conducted, how feedback was solicited on the pilot module and from whom, and how the crash course was developed. The goal of the crash course is to teach early psychiatry residents and other trainees what they need to know to function as new practitioners. We plan to release the crash course around the time of the 2025 ASCP Annual Meeting in Arizona. Subsequent to releasing the crash course, a basic course will be developed for trainees and will build on the crash course, covering what is needed for the second and third years of training. The last portion of the curriculum to be developed will be the advanced course, which will be for advanced level trainees and also include aspirational content, such as new developments in the field and ongoing research efforts. Portions, if not

all, of each (crash course, basic and advanced courses) will be useful to non-psychiatric trainees, non-psychiatric physicians and other practitioners including advanced practice providers.

Literature References: 1. Glick ID, Janowsky DS, Salzman C, Shader RI. A Model Psychopharmacology Curriculum for Psychiatric Residents. Nashville, Tennessee, The American College of Neuropsychopharmacology, 1984.
2. 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. PMID: 15937259. Erratum in: Acad Psychiatry. 2005; 29:324. Erratum in: Acad Psychiatry. 2005; 29:324.
3. Wulsin and Kramer: Teaching Psychopharmacology in the 21st Century, Acad Psychiatry 2001; 25:102-106.
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5. Sun L, Yin C, Xu Q, Zhao W. Artificial intelligence for healthcare and medical education: a systematic review. Am J Transl Res. 2023; 15:4820-4828. PMID: 37560249.

HARNESSING EDUCATIONAL TECHNOLOGY TO ADVANCE EDUCATION: THE NEXT GENERATION ASCO MODEL PSYCHOPHARMACOLOGY CURRICULUM

Gemma Espejo, University of California

Individual Abstract: The goal of this workshop is to present the initial phase of the next generation Model Psychopharmacology Curriculum: Crash Course, to the American Society of Clinical Psychopharmacology (ASCP) leaders, members, and other key stakeholders. The workshop will also review the current status of the Curriculum. The presentation will also demonstrate the current iteration of the online Curriculum.

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While the ASCP curriculum was widely used throughout the 1990's and into the 2010's, follow up evaluations of the curriculum's effectiveness demonstrated the need for integration of advanced technology to ensure that both educators and learners were optimally engaged.2,3 By the 11th edition of the ASCP curriculum, published in 2021, the ASCP leadership agreed that the curriculum would be re-formulated to meet the needs of modern learners, whose education has largely occurred in a digital space.4

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2. 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. PMID: 15937259. Erratum in: Acad Psychiatry. 2005; 29:324. Erratum in: Acad Psychiatry. 2005; 29:324

REBOOTING THE NEXT GENERATION MODEL CURRICULUM: WHAT RESIDENCY TRAINING PROGRAMS NEED

Lillian Houston, Southern Illinois University

Individual Abstract: While the ASCP curriculum was widely used throughout the 1990's and into the 2010's, follow up evaluations of the curriculum's effectiveness demonstrated the need for integration of advanced technology to ensure that both educators and learners were optimally engaged.2,3 By the 11th edition of the ASCP curriculum, published in 2021, the ASCP leadership agreed that the curriculum would be re-formulated to meet the needs of modern learners, whose education has largely occurred in a digital space.
Residency training programs often struggle to find content experts to teach psychopharmacology. Even resource rich programs often lack experts in all content areas or have experts who are unable to teach or teach at the required effort needed. Moreover some new programs or rural based programs may lack content experts altogether or even lack the experience or pedagogy to teach psychopharmacology at a state of the art level. This leads to disjointed education and likely to lack of standardization of practice nationally. Dr Houston will present needs to fill this gap from the residency program perspective based on available literature, her experience as a training director and now education vice chair, and the results of focus group meetings with Dr Macaluso, Dr Shelton and other GME leaders.
Literature References: 1) Macaluso M, Houston LJ, Kinzie JM, Cowley DC (book editors) (2022). Graduate Medical Education in Psychiatry: From Basic Processes to True Innovation, Vol. 1, Springer Nature, Switzerland. August 2022. ISBN: 978-3-031-00836-8.
2) Wulsin and Kramer: Teaching Psychopharmacology in the 21st Century, Acad Psychiatry 2001; 25:102-106.
3) Das T, Kaur G, Nematollahi S, et al. Medical Education in the Digital Era. JACC Adv. 2022; 1:100031. PMID: 38939313
4) Sun L, Yin C, Xu Q, Zhao W. Artificial intelligence for healthcare and medical education: a systematic review. Am J Transl Res. 2023; 15:4820-4828. PMID: 37560249.

***A HEALTHY MIND IN A HEALTHY BODY: FINDINGS FROM TRANSLATIONAL RESEARCH INTO CAUSES, TREATMENTS, AND THEIR IMPACTS**

Mahavir Agarwal, Centre for Addiction and Mental Health

Overall Abstract: Cardiometabolic comorbidities such as 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. The etiology of metabolic disturbances in mental illness is multifactorial, arising from a complex interplay of intrinsic risk, lifestyle factors, reduced access to medical care, and iatrogenic causes such as psychotropic treatment side effects. Concerningly, modifiable cardiovascular risk factors are often under-screened and under-treated in the psychiatric context, further perpetuating the health disparity among these individuals.

This symposium, chaired by Dr. Mahavir Agarwal (University of Toronto, Canada), will present an array of translational research that seeks to further explore the predictors and increased prevalence of cardiometabolic risk in psychiatric patients, disentangle potential mechanisms underlying cardiometabolic comorbidity in mental illness, and examine the real-world effectiveness of metabolic agents in this population.

Dr. Katharine Liang (University of Washington, USA) will present an analysis of medical records from nearly 5 million Veterans to explore the prevalence of metabolic comorbidity in individuals with post-traumatic stress disorder (PTSD). A particular focus will be made on identifying potential mediators of this relationship, including but not limited to sex, age, body mass index, and psychotropic use. The findings of this work suggest that the relationship between PTSD and glucose metabolism in this population may potentially be distinct from canonical mechanisms of metabolic dysfunction.

Dr. Nicolette Stogios (Centre for Addiction and Mental Health (CAMH), Canada) will present data from a proof-of-concept pilot investigation that employed an MRI-based assay of brain insulin resistance to investigate the effect of acute antipsychotic administration on brain insulin action in relation to various neurocognitive processes and outcomes. This work is novel as it demonstrates, for the first time in humans, that a widely prescribed antipsychotic medication may perturb insulin action in the brain by impairing its effects on network functional connectivity. This in turn may affect both the metabolic and cognitive sequalae of these medications.

Finally, Kateryna Maksyutynska (University of Toronto, Canada) will present data from a psychiatrist-led mental health and metabolism clinic that aims to improve the metabolic health of individuals with severe mental illness on psychotropic medications. This is the largest study, to date, investigating the impact of metabolic monitoring and interventions in the management of weight gain in antipsychotic-treated patients in a real-world clinical setting. It provides a recommendation for an integrated care pathway algorithm which would streamline the process of implementing these monitoring strategies and interventions in a systematic manner.

Dr. Rebecca Hendrickson (University of Washington, USA) will serve as the discussant to review the implications of cardiometabolic risk in individuals' with mental illness, its potential causes and treatment, as well as insights for future directions that can help propel the field forward.

The symposium brings together women (Drs. Liang and Stogios, and Ms. Maksyutynska), doctoral trainees (Ms. Maksyutynska), postdoctoral fellows (Dr. Stogios), early career scientists (Drs. Liang, and Agarwal), and clinicians (Drs. Liang, Agarwal, and Hendrickson).

Learning Objective 1: To provide novel perspectives into the pathophysiological mechanisms of cardiometabolic disturbances that are highly prevalent in mental illnesses.
Learning Objective 2: To highlight the potential of targeting cardiometabolic comorbidity to meaningfully improve physical and cognitive health outcomes in patients with mental illness.
Literary References: 1. Polcwiartek C, O'Gallagher K, Friedman DJ, et al. Severe mental illness: cardiovascular risk assessment and management, European Heart Journal. 2024;45(12):987-997.
2. Henderson DC, Vincenzi B, Andrea NV, Ulloa M, Copeland PM. Pathophysiological mechanisms of increased cardiometabolic risk in people with schizophrenia and other severe mental illnesses. Lancet Psychiatry. 2015;2(5):452-464.

INTERVENTIONS TO MITIGATE PSYCHOTROPIC ASSOCIATED WEIGHT GAIN USING AN ALGORITHMIC MEASUREMENT-BASED INTEGRATED CLINICAL PATHWAY: A RETROSPECTIVE CHART REVIEW STUDY

Kateryna Maksyutynska, Centre for Addiction and Mental Health, University of Toronto

Individual Abstract Background: Individuals with severe mental illness (SMI) have a 20% reduced life expectancy compared to the general population, largely owing to an increased risk for cardiometabolic comorbidities. Psychotropic drugs undoubtedly contribute to this increased cardiometabolic risk with their propensity to cause metabolic adverse effects. Several non-pharmacological and pharmacological interventions are available to mitigate these metabolic adverse effects [2]. However, data on the utility of these interventions in real-world settings are limited. This study presents real-world data from a Mental Health and Metabolism Clinic that specializes in providing psychiatrist-led care for metabolic dysfunction in those with mental illness.
Methods: We conducted a retrospective chart review of all patients attending the Mental Health and Metabolism Clinic at the Centre for Addiction and Mental Health (CAMH) in Toronto, Canada, between 2016 and 2023. The primary outcome measures were change in weight at 3, 6, 9, and 12 months, the percentage of patients that lost ≥5% of their baseline weight at each time point, and the number needed to treat (NNT) to achieve this outcome with each intervention.
Results: The sample consisted of 383 patients (males: 46.5%, mean age: 34.6 ± 11.81 years) who were followed in the clinic for at least 6 months. The mean baseline body weight of the sample was 97.5 ± 23.0 kg. Overall Clinic Effect: A significant effect of the clinic (including all interventions) was observed on body weight over time (F=7.87, p LESS THAN 0.001). The mean change in weight was -0.79 ± 0.49 (p=0.06), -0.83 ± 0.42 kg (p=0.048), -2.05 ± 0.47 kg (p LESS THAN 0.001) and -2.46 ± 0.52 kg (p LESS THAN 0.001) at 3, 6, 9, and 12 months, respectively. Moreover, 132 (37%) patients lost ≥5% of their baseline body weight during the 12-month study period. Effect by Intervention: In this sample, 287 were receiving add-on therapy with a pharmacological intervention (Metformin: N=229, Topiramate: N=14, Semaglutide: N=9, Other treatment combinations: N=35), while the remaining 93 received lifestyle counselling only. No significant change in weight was observed at any of the time points for patients on non-pharmacological (lifestyle only) interventions. Among the pharmacological interventions, significant weight loss was observed at 6, 9 and 12 months with metformin (-1.02 ± 0.47, -1.68 ± 0.51, and -2.28 ± 0.58 kg, respectively), at 3, 6, 9 and 12 months with topiramate (-2.93 ± 1.21, -2.68 ± 1.18, -4.05 ± 1.41, and -4.17 ± 1.48 kg, respectively), and 6, 9 and 12 months with semaglutide (-1.29 ± 2.27, -6.63 ± 2.29, -8.41 ± 2.29, and -10.03 ± 2.59 kg, respectively). The number needed to achieve ≥5% weight loss was 2.86 for lifestyle interventions, 2.76 for metformin, 2.17 for topiramate, and 1.29 for

semaglutide. Among the remaining patients on combination treatment (N=35), there were very small samples for each of the individual combinations, precluding meaningful analysis.
Conclusions: This large naturalistic retrospective cohort study demonstrates the effectiveness of pharmacological interventions in managing weight gain in individuals with mental illness. It provides real-world clinical evidence to support that psychiatrist-led care for metabolic dysfunction in mental illness is effective in reducing weight gain associated with psychotropic medications. This approach may streamline the implementation of monitoring strategies and interventions in a systematic manner.
Literature References: [1] Polcwiartek C, O'Gallagher K, Friedman DJ, et al. Severe mental illness: cardiovascular risk assessment and management, European Heart Journal; 2023;45(12).
[2] The American Psychiatric Association Practice Guideline for the Treatment of Patients With Schizophrenia Practice Guidelines
https://psychiatryonline.org/doi/book/10.1176/appi.books.9780890424841

INVESTIGATING THE EFFECTS OF ANTIPSYCHOTICS ON BRAIN INSULIN ACTION: A RESTING-STATE FUNCTIONAL CONNECTIVITY STUDY IN HEALTHY CONTROLS

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

Individual Abstract Background: Antipsychotics (APs) are associated with serious metabolic adverse effects including weight gain and type 2 diabetes [1]. Brain insulin resistance has emerged as a possible explanatory mechanism underlying these effects [2]. Preclinical studies have shown that an acute dose of olanzapine (OLA) has a direct anti-insulin effect in the brain that is independent of weight gain. While currently there are no methods to investigate brain insulin resistance directly, the neurophysiological response to intranasal insulin (INI) can be used as a reliable albeit surrogate marker. In this proof-of-concept study, we leveraged neural signatures of brain insulin action with INI to examine if an acute dose of OLA can disrupt brain insulin action in healthy humans.
Methods: This was a single blind, crossover study in which 24 healthy volunteers (N=14 females; age = 21.8 years; BMI = 21.9 kg/m2) received 4 different treatment combinations, 2-4 weeks apart, in a random sequence. Participants received 5 and 10 mg of OLA (or PL) over two days, which was followed by functional MRI (fMRI) testing on a third day. A 10-minute resting state fMRI scan was acquired 15 minutes after administering 160 IU of INI or INP. A repeated measures ANOVA was conducted to determine any changes in resting-state functional connectivity (rsFC) with INI/PL relative to INP/PL (a whole-brain false discovery rate (FDR) corrected threshold of p LESS THAN 0.05 was used). The subsequent effect of OLA was investigated by restricting the second-level analysis to the seeds that were noted to have significant rsFC changes with INI/PL.
Results: Significantly higher rsFC was found in the INI/PL condition compared to INP/PL between the anterior cingulate cortex (ACC) of the salience network (SN) and the right lateral parietal cortex (LPC) of the default mode network (DMN) (T= 3.64, whole brain p-FDR=0.029). These findings were significant while controlling for age, sex, and BMI. rsFC between SN-ACC and DMN-LPC in the INI/PL condition was significantly higher than that in the INP/OLA (T=2.30, p- FDR=0.032) and INI/OLA (T=3.08, p-FDR=0.006) conditions. There was no difference in rsFC between the INI/OLA and INP/OLA or INP/PL conditions. Interestingly, these findings were only observed among male participants alone.
Conclusion: In this pilot investigation, increased rsFC was observed between regions of the salience and default mode networks with INI/PL compared to INP/P; this was subsequently diminished with the introduction of OLA. Interestingly, this finding was only observed

among the male participants, suggesting that there may be an intrinsic sex difference between males and females in terms of brain insulin sensitivity. Further research is needed to unequivocally delineate how APs may induce deficits in brain insulin action in relation to neurocognitive processes.
Unique Data: This finding is novel as it demonstrates, for the first time in humans, that OLA perturbs insulin action in the brain by impairing its effects on network functional connectivity. This observation extends an earlier preclinical finding that OLA directly abolishes the well-established ability of central insulin to suppress endogenous glucose production. Thus, we have translated this concept to humans and provided a separate line of evidence to suggest that OLA induces brain insulin resistance, which in turn may affect both the metabolic and cognitive sequalae of these medications.
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(7):686-694.
[2] Kullmann S, Heni M, Hallschmid M, Fritsche A, Preissl H, Haring HU. Brain Insulin Resistance at the Crossroads of Metabolic and Cognitive Disorders in Humans. Physiol Rev 2016;96(4):1169-209.

ASSESSING THE RELATIONSHIP BETWEEN PTSD AND TYPE 2 DIABETES IN A LARGE-SCALE ANALYSIS OF VETERAN HEALTH RECORDS

Katharine Liang, VA Puget Sound Health Care System

Individual Abstract: Background: Post-traumatic stress disorder (PTSD) affects up to 15% of Veterans following deployment and is strongly associated with insulin resistance (IR), with over half of people with PTSD also exhibiting IR, and PTSD severity prospectively predicting increased risk of both worsening IR severity and new-onset type 2 diabetes mellitus (DM2), leading to premature mortality. Mounting evidence suggests the possibility of biologically distinct trauma-specific mechanisms leading to IR; however, it remains unclear whether other factors such as demographics, medications or obesity may be at play. Here, we present preliminary analyses of data from post-9/11 US military Veterans examining the influence of PTSD on likelihood of DM2 diagnosis and blood glucose (hemoglobin A1c [HbA1c]), with a goal of informing future research addressing this important physiological relationship with potential significant clinical impact in the mental health population.
Methods: Data were extracted from the Department of Veterans Affairs (VA) Corporate Data Warehouse clinical database using the VA Informatics and Computing Infrastructure (VINCI). Included Veterans served ≥2 years of post-9/11 military service and exited service before age 30. Diagnoses were identified by ICD codes and PTSD symptoms quantified by PTSD Checklist (PCL) scores. Veterans with DM1, non-diabetic endocrine disorders, bipolar, or psychotic disorders were excluded, as were those receiving anti-glycemic or corticosteroid medication at the point of prescription for regression analyses. Multivariable linear mixed effects models (nlme package, R) assessed HbA1c as the dependent variable with PCL, age, body mass index (BMI), and selected medications as predictors, analyzed separately by sex. Mediation analyses used the psych package in R.
Results: Over 4.9 million Veterans ages 22-45 were identified for analysis with a full sample prevalence 28.1% for PTSD and 1.2% for DM2; conditional prevalence of DM2 given PTSD diagnosis was 1.8% and conditional prevalence of PTSD given DM2 diagnosis was 40.9%. While DM2 prevalence increased with age, the relative risk of DM2 given a PTSD diagnosis

was 1.2-1.5 across age and remained elevated when individuals were excluded following antipsychotic or antidepressant prescriptions.
In multivariable mixed effects models, PTSD symptom burden was a significant predictor of HbA1c (normalized β and 95% CI =0.015 [.013-.017] for M and β=0.010 [.004-.015] for F, both p LESS THAN .001). In secondary analyses, the effect of PTSD symptom burden on HbA1c was greater in males, at younger ages, and at lower BMI. In mediation analysis, BMI did not mediate the relationship between PTSD symptom severity and HbA1c.
Conclusion: In analyses of medical records from nearly 5 million Veterans, we found that PTSD diagnosis increased risk of DM2 independent of antipsychotic or antidepressant use. Furthermore, increased PTSD severity was correlated with worsened glycemic control, a relationship not mediated by BMI, suggesting a relationship between PTSD and glucose metabolism in this population potentially distinct from canonical mechanisms of metabolic dysfunction. Future research exploring mechanisms linking PTSD and IR has potential to influence existing treatment algorithms, lead to new treatments for IR-related comorbidities largely influencing morbidity and mortality in Veterans with PTSD, expand our understanding of PTSD biology and possible treatment targets.
Literature References: Boyko EJ, Jacobson IG, Smith B, et al. Risk of diabetes in U.S. military service members in relation to combat deployment and mental health. Diabetes Care. Aug 2010;33(8):1771-7.
Rosenbaum S, Stubbs B, Ward PB, Steel Z, Lederman O, Vancampfort D. The prevalence and risk of metabolic syndrome and its components among people with posttraumatic stress disorder: a systematic review and meta-analysis. Metabolism. Aug 2015;64(8):926-33.

*BIPOLAR ACTION NETWORK: A PROTOTYPE FOR A LEARNING HEALTH NETWORK

Andrew Nierenberg, Massachusetts General Hospital

Overall Abstract: The purpose of the Bipolar Action Network is to improve the health and well-being for people living with bipolar disorder. The network uses a successful learning health network model from the Anderson Center Healthcare System Excellence at Cincinnati Children's Hospital. These networks have a proven track record of improving outcomes for complex chronic diseases. Based on these other networks, the Bipolar Action Network brings together patients, families, clinicians, researchers, quality improvement specialists, experts in system change, and data analysts to radically collaborate to get better outcomes.
Fundamentally, the network uses human-centered and idealized design principles, along with quality improvement methods to systematically change the system of care. Data from each clinical encounter builds the database, and then the healthcare systems exploit variations in outcomes to learn from each other, facilitated by a culture of curiosity, generosity, and humility.
Mark Rapaport will discuss the Bipolar Action Network from his perspective as a leader of a large healthcare system and how the network fits with strategic priorities to get better outcomes. Erika Saunders will discuss the success of her department in using measurement-based and guideline-informed care. Steven Strakowski will discuss lessons learned from re-designing Austin State Hospital. Finally, Andrew Nierenberg will discuss the progress made in planning, designing, and implementing the Bipolar Action Network.
Learning Objective 1: The participant will know the elements required to build a learning health network.
Learning Objective 2: The participant will know specifics about the construction of the Bipolar Action Network and how it can improve outcomes.

Literary References: Nierenberg AA, Margolis P, Strakowski S, Trivedi M, Yatham LN, Blumberg HP, DelBello M, Duckworth K, Gorrindo T, Iosifescu D, Jackson J. A Bipolar Learning Health Network: An innovation whose time has come. Bipolar Disorders. 2023;25(3).
Ramsey LB, Mizuno T, Vinks AA, Margolis P. Learning health systems as facilitators of precision medicine. Clinical pharmacology and therapeutics. 2017;101(3):359.

LEARNING HEALTH SYSTEMS: THE PROMISE AND THE CHALLENGE FOR HEALTH SYSTEMS

Mark Rapaport, University of Utah Huntsman Mental Health Institute

Individual Abstract: The concept of the learning health system is important and admirable: the use of real-world data from patients, their families and clinicians to advance our knowledge of the effectiveness of current best practices and to facilitate the development of new treatment approaches. Learning health systems and networks have been successfully employed in pediatrics - particularly in the national network of children's hospital health systems. These environments have several unique advantages: 1) being health systems solely focused on the care of children, and 2) many of these health systems have significant financial resources (from profitable specialty care programs and extensive philanthropic resources). The translation of these success stories to diverse academic health systems is challenging. These challenges are intensified when one attempts to mobilize the already stretched IT infrastructure of an academic health system to focus on a service that is traditionally considered a lower resource priority area, psychiatry. In this presentation we will discuss the work of our team to: 1) align our priorities for participating in a national learning health system with our institution's priorities, 2) describe the steps necessary for formalizing adult and child bipolar disorder specialty programs in a large "undifferentiated" outpatient clinical system, 3) discuss the legal and administrative processes that need to align for data sharing, 4) describe educational and administrative efforts needed to demonstrate the importance and value of devoting time to conferences where the team reviews the progress of patients. Understanding these obstacles and how to overcome them are important because the potential value of data and new interventions developed by a learning health network will be one of the most effective ways to rapidly bring clinical advances to our patients.
Literature References: Greene SM, Reid RJ, Larson EB, Implementing the Learning Health System From Concept to Action. Ann Intern Med. 2012;157: 207-210.
Menear M, BlanchetteM-A, Demers-Payette O, RoyD, A Framework for Value-Creating Learning Health Networks. Health Research Policy and Systems. 2019. doi.org/10.1186/s12961-019-0477-3

HOW CAN A LEARNING HEALTH NETWORK IMPROVE CARE? THE USE OF MEASUREMENT AND PRACTICE GUIDELINES IN CARE FOR MOOD DISORDERS

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

Individual Abstract: Approximately 1/3 of patients achieve remission in major depressive disorder in real-world clinical estimates. To improve this, practice guidelines have been developed, however it is not well understood to what extent guidelines improve outcomes. To examine this issue, we queried a real-world quality registry derived from electronic medical record data and patient reported outcomes. We hypothesized that: 1) adherence to practice guidelines in real-world clinics would demonstrate better symptomatic and functional outcomes 2) implementing measurement-based care (MBC) in the clinic affected health outcomes and total healthcare costs.

Methods: Study #1: In a cohort of 1,403 adults seen from February 2015 to April 2021, we evaluated concordance to the Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines for MDD with a novel metric and using up to 1 year of treatment data per patient. We then examined the associations between this score and the Patient Health Questionnaire depression (PHQ-9) and World Health Organization Disability Assessment Schedule 2.0 (WHODAS) scores.
Study #2: The overall sample was 3,426 adults: 571 adults were propensity score matched 1:5 with 2,855 adults from a claims-based sample enrolled with the insurer between 2015 and 2023. We measured the time to the first general and psychiatric emergency department (ED) visits within six months after the index visit. Per member per month (PMPM) costs and utilization were compared between the matched and MBC samples from baseline through follow-up. To determine whether the intensity of MBC influenced outcomes and costs, we calculated the proportion of visits with a completed PHQ-9 questionnaire among the MBC group. We then examined the associations between this proxy measure and patterns of care, outcomes, and costs.
Results: Study #1: Among those who switched drugs (n = 671), 81% (n = 542) did not have their dose increased to the recommended maximum before switching. Each 1 SD increase in the guideline concordance score was associated with a 0.78 improvement in the mean PHQ-9 score (P LESS THAN .001). Likewise, a 1 SD increase in the guideline concordance score was associated with a 0.48-point reduction in the mean disability score (P = .02). In an exploratory cross-sectional analysis, we also found that the remediation in functional disability associated with higher guideline concordance could be owed entirely to the preceding improvement in MDD symptom severity (P LESS THAN .001).
Study #2: Among participants who received MBC, those who had a higher proportion of visits with a completed PHQ-9 (greater MBC intensity) demonstrated a significantly lower rate of all-cause ED (P = .03) and psychiatric ED visits (P = .02). A higher proportion of visits with a completed PHQ-9 was also associated with a lower cost of care (P = .01); the MBC sample had more consistent reductions in medical costs than the comparison (P = .04), and had a larger decline in total costs during 36 months of follow-up, though not statistically significantly different (P = .07).
Conclusions: We observed better symptom and functional recovery among those whose treatment followed guidelines more closely, including via MBC, and better improvements in healthcare utilization and medical costs with more intense MBC. Through a learning health network, we can build upon these observations to 1) determine generalizability and 2) design interventions to improve use of process measures and decision-support tools for clinicians.
Literature References: 1. Breitzig MT*, He F, Kong L, Liu G, Waschbusch DA, Yanosky JD, Saunders, EFH, Liao D. Novel Quality Control Metric for the Pharmacotherapy of Major Depressive Disorder: Measuring Guideline Concordance and Its Impact on Symptom Severity. J Clin Psychiatry. 2024 Jan 3;85(1):23m14916. doi: 10.4088/JCP.23m14916.
2. Breitzig MT*, He F, Kong L, Liu G, Waschbusch DA, Yanosky JD, Liao D, Saunders, EFH. Pharmacotherapy Guideline Concordance for major depressive disorder and its link to functioning via symptom change. Journal of Clinical and Translational Science. in press, 2024.

LESSONS FROM THE AUSTIN STATE HOSPITAL REDESIGN: A SYSTEMS APPROACH

Stephen Strakowski, Indiana University School of Medicine

Individual Abstract: In 2013, the Texas Department of Health and Human Services requisitioned a consultation to evaluate the condition of its state psychiatric hospital

infrastructure, only to learn that the hospitals were in poor condition, many not reparable. The Austin State Hospital was one of these. Discussion began regarding how to replace it that ultimately led to an academic/public partnership between the Dell Medical School (UT Austin) and Texas' Health and Human Services Commission to develop a new approach to the redesign; namely, to replace the hospital while also positioning it within the larger mental health continuum of care. Dr. Strakowski and Dell Med were selected to lead the process that formally began in 2018. A Steering Committee was established of critical regional stakeholders to design a modern and functional facility while also addressing common missing components and barriers within the large care continuum. Work groups were spawned from the Steering Committee to address specific issues, ultimately bringing more than 100 participants into the plan, thereby garnering public support. Based on the best evidence available, the process designed a modern recovery - oriented 240 bed hospital (that is now open) and defined a care continuum, available at www.ashredesign.org. The care continuum places the person being served as the 'north star' and acknowledges that, despite building a hospital, ideal care is largely ambulatory. The teams focused on minimizing over-reliance on crisis management and defined more clearly the role a state mental hospital serves within this continuum. The public/academic partnership was adopted in several other state hospital replacements/renovations and is now the standard in Texas. This partnership brings broad expertise and experience across the mental healthcare landscape. In this presentation, Dr. Strakowski will review the steps toward building an effective partnership, the care continuum model that was and continues to be used in planning Texas public mental healthcare and provide suggestions for incorporating these types of approaches in other venues.

Literature References: Bray TE, Harris SS. Building new hospitals in Texas. In: SS Harris and SM Strakowski, Redesigning the US Mental Health Care System. Oxford University Press, NY, NY 2024; pp. 145-158.

Harris SS, Strakowski SM. Pulling it all together: Solutions for the US mental health system. In: SS Harris and SM Strakowski, Redesigning the US Mental Health Care System. Oxford University Press, NY, NY 2024; pp. 283-302.

^CHARTING A COURSE IN CHANGING TIMES: ALTERNATIVE RESEARCH MODELS BEYOND FEDERAL FUNDING

Michael Henry, Massachusetts General Hospital

Overall Abstract: Government based funding has been an important foundation for many people pursuing academic careers – both directly through awarded grants, and more indirectly through shared resources and training opportunities. With the current changes in Federal spending and policy, it is important to be aware of other sources of funds to support academic endeavors, as well as alternative models for conducting clinical research.

This workshop is intended to provide a forum to consider options for maintaining active and effective research programs in a changing research landscape. It will start by identifying a few of the specific areas of current challenge, including ensuring that core skill sets such as the conduct of clinical trials research continue to be taught to early career researchers. It will include a focus on options for non-Federal sources of research support, including how to engage with industry at the different stages of drug development, the use of large clinical databases generated by electronic medical records for initial hypothesis testing and generation of pilot data, and how to apply to foundations and obtain private philanthropic support for research. It will also consider how approaches for conducting research that do not directly receive federal funding may be affected by changes in federal policy and support, and to prepare for such possible changes. Finally, it will consider how collaboration across

research teams and institutions, including nonacademic settings, may facilitate productive research during this period of change, and how we can work to build connections that will support this goal.
The workshop will begin with brief presentations by speakers with experience following a variety of models for conducting clinical psychiatric research, but will encourage active discussion by all attendees as we consider these topics together as a community.
Learning Objective 1: Participants will increase their awareness of non-Federal funding sources for supporting academic research.
Learning Objective 2: Participants will have an increased understanding of how to improve the chances of obtaining financial support from the different funding sources.
Literary References: 1. Gabbe SG, Lockwood CJ, Marsh CB. Commentary: a ray of hope for medical school research funding. Acad Med. 2012 Nov;87(11):1464-5. doi: 10.1097/ACM.0b013e31826b84dd. PMID: 23111257.
2. Hein P, Michel MC. Project-Based Public-Private Collaborations. Handb Exp Pharmacol. 2024;286:21-31. doi: 10.1007/164_2024_722. PMID: 39120768.

CHARTING A COURSE IN CHANGING TIMES: ALTERNATIVE RESEARCH MODELS BEYOND FEDERAL FUNDING

Scott Aaronson, Sheppard Pratt

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CHARTING A COURSE IN CHANGING TIMES: ALTERNATIVE RESEARCH MODELS BEYOND FEDERAL FUNDING

Rebecca Hendrickson, VA Puget Sound Health Care System

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2. Hein P, Michel MC. Project-Based Public-Private Collaborations. Handb Exp Pharmacol. 2024;286:21-31. doi: 10.1007/164_2024_722. PMID: 39120768.

CHARTING A COURSE IN CHANGING TIMES: ALTERNATIVE RESEARCH MODELS BEYOND FEDERAL FUNDING

M. Crismon, The University of Texas at Austin

Individual Abstract: Government based funding has been an important foundation for many people pursuing academic careers – both directly through awarded grants, and more indirectly through shared resources and training opportunities. With the current changes in Federal spending and policy, it is important to be aware of other sources of funds to support academic endeavors, as well as alternative models for conducting clinical research.
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and to prepare for such possible changes. Finally, it will consider how collaboration across research teams and institutions, including nonacademic settings, may facilitate productive research during this period of change, and how we can work to build connections that will support this goal.
The workshop will begin with brief presentations by speakers with experience following a variety of models for conducting clinical psychiatric research but will encourage active discussion by all attendees as we consider these topics together as a community.
Literature References: 1. Gabbe SG, Lockwood CJ, Marsh CB. Commentary: a ray of hope for medical school research funding. Acad Med. 2012 Nov;87(11):1464-5. doi: 10.1097/ACM.0b013e31826b84dd. PMID: 23111257.
2. Hein P, Michel MC. Project-Based Public-Private Collaborations. Handb Exp Pharmacol. 2024;286:21-31. doi: 10.1007/164_2024_722. PMID: 39120768.

CHARTING A COURSE IN CHANGING TIMES: ALTERNATIVE RESEARCH MODELS BEYOND FEDERAL FUNDING: FINDING NON-FEDERAL WAYS TO FUND YOUR ACADEMIC LIFE
Michael Henry, Massachusetts General Hospital

Individual Abstract: The career path of an academic clinician does not always require federal funding. Alternative sources of funding include philanthropy, and various types of industry collaborations. It also requires data. Today more than ever electronic medical records can be used to examine the evidence behind treatment guidelines and other standard clinical practices.
Literature References: 1. Wade BSC, Pindale R, et al. Prediction of individual treatment allocation between electroconvulsive therapy or ketamine using the Personalized Advantage Index. NPJ Digit Med 2025 Feb 27;8(1):127.
2. Henry ME, Lauriat TL, et al. Effects of citalopram and escitalopram on fMRI response to affective stimuli in healthy volunteers selected by serotonin transporter genotype. Psychiatry Res. 2013 Sep 30;213(3):217-24.

CHARTING A COURSE IN CHANGING TIMES: ALTERNATIVE RESEARCH MODELS BEYOND FEDERAL FUNDING: ARE THERE OTHER CAREER PATHS WHERE YOU CAN DO RESEARCH AND MAKE A DIFFERENCE?
Leslie Citrome, New York Medical College

Individual Abstract: The presenter will describe a career path in academic clinical psychopharmacology that diverged 30 years ago from the traditional route of obtaining a federal NIH R01 grant as Principal Investigator. This alternate path consisted of running an in-patient unit at a State-operated research institute, executing Investigator Initiated Research that leveraged existing staff and/or by obtained funding from pharmaceutical companies either directly for the specific project, or indirectly by utilizing revenue generated through contracted research ranging from Phase I Pharmacokinetic studies to Phase II-IV RCTs. This was followed by becoming a self-employed consultant, continuing a clinical practice, and becoming a voluntary faculty member "instead of involuntary." By selecting specific themes on what to focus on in terms of executing data analyses, writing, and teaching, this resulted in a coherent body of work that when combined with other activities such as collaboration with colleagues, mentorship of others, editorship on medical journals, and participation in professional organizations, permitted the presenter to "make a difference."
Literature References: 1. Citrome L, Epstein H, Nolan KA, Trémeau F, Elin C, Roy B, Levine J. Public-academic partnerships: integrating state psychiatric hospital treatment and

clinical research. Psychiatr Serv. 2008 Sep;59(9):958-60. doi: 10.1176/ps.2008.59.9.958. PMID: 18757586.
2. Citrome L, Ketter TA. When does a difference make a difference? Interpretation of number needed to treat, number needed to harm, and likelihood to be helped or harmed. Int J Clin Pract. 2013 May;67(5):407-11. doi: 10.1111/ijcp.12142. PMID: 23574101.

CHARTING A COURSE IN CHANGING TIMES: ALTERNATIVE RESEARCH MODELS BEYOND FEDERAL FUNDING
Manish Jha, University of Texas Southwestern Medical Center

Individual Abstract: Government based funding has been an important foundation for many people pursuing academic careers – both directly through awarded grants, and more indirectly through shared resources and training opportunities. With the current changes in Federal spending and policy, it is important to be aware of other sources of funds to support academic endeavors, as well as alternative models for conducting clinical research.
This workshop is intended to provide a forum to consider options for maintaining active and effective research programs in a changing research landscape. It will start by identifying a few of the specific areas of current challenge, including ensuring that core skill sets such as the conduct of clinical trials research continue to be taught to early career researchers. It will include a focus on options for non-Federal sources of research support, including how to engage with industry at the different stages of drug development, the use of large clinical databases generated by electronic medical records for initial hypothesis testing and generation of pilot data, and how to apply to foundations and obtain private philanthropic support for research. It will also consider how approaches for conducting research that do not directly receive federal funding may be affected by changes in federal policy and support, and to prepare for such possible changes. Finally, it will consider how collaboration across research teams and institutions, including nonacademic settings, may facilitate productive research during this period of change, and how we can work to build connections that will support this goal.
The workshop will begin with brief presentations by speakers with experience following a variety of models for conducting clinical psychiatric research but will encourage active discussion by all attendees as we consider these topics together as a community.
Literature References: 1. Gabbe SG, Lockwood CJ, Marsh CB. Commentary: a ray of hope for medical school research funding. Acad Med. 2012 Nov;87(11):1464-5. doi: 10.1097/ACM.0b013e31826b84dd. PMID: 23111257.
2. Hein P, Michel MC. Project-Based Public-Private Collaborations. Handb Exp Pharmacol. 2024;286:21-31. doi: 10.1007/164_2024_722. PMID: 39120768.

4:30 p.m. - 6:30 p.m.
Plenary Panel: GLP-1 Agonists and Neuropsychiatric Disorders

GLP-1 AGONISTS AND NEUROPSYCHIATRIC DISORDERS
Ivan Montoya, DHHS/National Institute on Drug Abuse

Overall Abstract: Glucagon Like Peptide-1 receptor agonists (GLP-1 RAs) are approved by the FDA to treat diabetes and obesity. They have emerged as an area of research in neuropsychiatric disorders given their potential efficacy for their treatment. The GLP-1 brain circuit involves both peripherally and centrally produced GLP-1. GLP-1 receptors are widely expressed throughout the brain, with high concentrations in hypothalamus, nucleus tractus solitarius (NTS) of the brainstem, and area postrema. The GLP-1 brain circuit is involved in feeding behavior, glucose homeostasis, energy balance, and neuroprotection. GLP-1 appear

to depolarize neurons and increase firing rates, affect glutamatergic and GABAergic neurotransmission, and may act as a neurotransmitter, being stored in synaptic vesicles and released at axon terminals. Therefore, GLP-1 RAs appear to promote neurogenesis, enhance synaptic plasticity, modulate stress response pathways, reduce β-amyloid plaques, prevent synaptic loss, and decrease oxidative stress and inflammation in the brain. In consequence, GLP-1RAs have emerged as promising candidates for treatment of multiple neuropsychiatric disorders, including substance use disorders (SUD) and age-related disorders. The purpose of this symposium is to provide an overview of the GLP-1 circuitry and its involvement in the neuropathophysiology of multiple neuropsychiatric disorders followed by overviews of the safety and potential efficacy of GLP-1 agonists on neuropsychiatric disorders, including SUD and age-related disorders.

GLP-1RAS IN SEVERE MENTAL ILLNESS - OPPORTUNITIES AND CHALLENGES

Mahavir Agarwal, Centre for Addiction and Mental Health

Abstract: Glucagon-like peptide 1-receptor agonists (GLP-1RA)s, of which semaglutide is the most famous example, are a newer class of drugs that mimic the effects of GLP-1, an endogenous peptide synthesized in the intestinal mucosa. GLP-1RAs have been shown to bring about remarkable weight loss as well as a lower risk of major adverse cardiovascular endpoints, including cardiovascular mortality, and non-fatal strokes and myocardial infarctions. These studies have largely excluded individuals with severe and persistent mental illness (SPMI) such as schizophrenia and bipolar disorder. However, given the several fold higher incidence of cardiovascular disease in those with SPMI, GLP-1RAs are a potential game changer in this vulnerable population. Semaglutide is being actively investigated in the SPMI population in several ongoing trials across the world.
This presentation will review ongoing clinical trials of GLP-1RA for SPMI. Additionally, clinical results from the Mental Health and Metabolism Clinic at CAMH/University of Toronto will be presented. The discussion will focus on the benefits, common side effects, and caveats around the enthusiasm for these medications.
Learning Objective 1: To review the need and promise of GLP-1RAs in SPMI
Learning Objective 2: To review the available evidence supporting the use of GLP-1RAs in SPMI
Literature References: Agarwal SM, Hahn M. Semaglutide in Psychiatry-Opportunities and Challenges. JAMA Psychiatry. 2024 Oct 1;81(10):955-956.
Prasad F, De R, Korann V, Chintoh AF, Remington G, Ebdrup BH, Siskind D, Knop FK, Vilsbøll T, Fink-Jensen A, Hahn MK, Agarwal SM. Semaglutide for the treatment of antipsychotic-associated weight gain in patients not responding to metformin - a case series. Ther Adv Psychopharmacol. 2023 Apr 19;13:20451253231165169.

GLP-1 AND NEURODEGENERATIVE DISEASES

Nigel Greig, National Institute on Aging, NIH

Abstract: Glucagon-like peptide-1 (GLP-1) receptor agonist (RA)-based drugs (incretin mimetics) have meaningfully impacted the current clinical treatment of type 2 diabetes mellitus (T2DM), and their actions on satiety and weight loss have led to their approved use as an obesity medication. With multiple pleotropic effects beyond their insulinotropic and weight loss ones that include cytoprotective, trophic, anti-inflammatory and anti-insulin-resistant actions that are mediated via their G protein-coupled receptors present within numerous organs, this drug class offers potential efficacy for an increasing number of systemic and neurological disorders whose current treatments are inadequate. Among these

are a host of neurodegenerative disorders that are prevalent in the elderly, such as Parkinson's and Alzheimer's disease, which have bucked previous therapeutic approaches. GLP-1 receptors are found throughout the brain, including on neuronal and glial cells, and an increasing preclinical, clinical, and epidemiological literature suggests that incretin mimetics may provide an effective treatment strategy, but 'which GLP-1RAs?' For 'which disorders?' And 'when should they best be administered?' remain important and largely unresolved questions.
Learning Objective 1: Drug repurposing from type 2 diabetes mellitus to neurological disorders
Learning Objective 2: Neuroprotective/trophic and anti-inflammatory action of GLP-1-based drugs in neurological disorders
Literature References: Kopp KO, Glotfelty EJ, Li Y, Lahiri DK, Greig NH. Type 2 diabetes mellitus/obesity drugs: A neurodegenerative disorders savior or a bridge too far? Ageing Res Rev. 2024; 98:102343.
Kopp KO, Glotfelty EJ, Li Y, Greig NH. Glucagon-like peptide-1 (GLP-1) receptor agonists and neuroinflammation: Implications for neurodegenerative disease treatment. Pharmacol Res. 2022; 186:106550.

PHASE 2 RANDOMIZED TRIALS OF GLP-1 RECEPTOR AGONISTS FOR SUBSTANCE USE DISORDER

Christian Hendershot, UNC at Chapel Hill

Abstract: Converging evidence from preclinical, observational, and pharmacoepidemiology studies supports potential therapeutic applications of glucagon-like peptide-1 receptor agonists (GLP-1RA) for substance use disorders (SUD). Data from randomized clinical trials with SUD participants is critical to informing the safety and efficacy of GLP-1RA for the indication of SUD. However, these findings are only beginning to emerge. This presentation will review ongoing clinical trials of GLP-1RA for SUD, and will review evidence from trials completed through 2024. Additionally, results from new Phase 2A clinical trials of semaglutide in non-treatment-seeking adults with tobacco use disorder and alcohol use disorder will be presented. The discussion will focus on the steps required to move these findings toward clinical applications of GLP-1RA medications for substance use disorder.
Learning Objective 1: To gain familiarity with ongoing clinical trials of GLP-1RA in populations with substance use disorder.
Learning Objective 2: To learn about findings from recently completed Phase 2A trials of semaglutide in tobacco use disorder and alcohol use disorder.
Literature References: Hendershot CS, Bremmer MP, Paladino MB, et al. One-weekly semaglutide in adults with alcohol use disorder: A randomized clinical trial. 2025; Epub ahead of print.
Leggio L, Hendershot CS, Farokhnia M, et al. GLP-1 receptor agonists are promising, but unproven treatments for alcohol and substance use disorders. Nature Medicine. 2023; 29(12), 2993-2995.

THE NEUROBIOLOGY OF GLP-1: FROM PHYSIOLOGY TO CLINICAL APPLICATIONS

Rodrigo Mansur, University of Toronto

Abstract: There has been increasing interest and speculation on the potential neuropsychiatric effects of incretin-based pharmacological agents. Incretins are multifaceted peptides. Endogenous glucagon-like peptide-1 (GLP-1) acts both as a gut hormone and as a neuropeptide within the central nervous system (CNS). In this presentation, we will review

the physiological and neurobiological underpinnings of GLP-1 actions, with a focus on its distinct central and peripheral roles, as well as its relationships with the broader energy homeostasis network. We will critically review the extant literature on the behavioral effects of GLP-1 signaling, focusing on their potential impact on cognitive functioning and reward response. Finally, we will present the results of the first completed randomized clinical trial that tested the effects of a GLP-1 receptor agonist in individuals with major depressive disorder (MDD).
Learning Objective 1: To understand the physiological roles of central and peripheral GLP-1 signaling.
Learning Objective 2: To discuss the results of the first RCT testing the safety and efficacy of a GLP-1RA on a mood disorders population.
Literature References: Trapp S, Brierley DI. Brain GLP-1 and the regulation of food intake: GLP-1 action in the brain and its implications for GLP-1 receptor agonists in obesity treatment. Br J Pharmacol 2022; 179(4): 557-70.
Mansur RB, Di Vincenzo JD, Badulescu S, Gill H, Tabassum A, López CL, Rosenblat JD, McIntyre RS. Are glucagon-like peptide-1 receptor agonists anti-consummatory drugs? CNS Spectr. 2024 Dec;29(6):536-541.

Friday, May 30, 2025

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

*A BD2 ROADMAP TO IMPROVE HEART AND DIABETES HEATH IN BIPOLAR DISORDER

Fernando Goes, Johns Hopkins University School of Medicine

Overall Abstract: The significant cardiometabolic burden associated with bipolar disorder (BD) contributes to elevated morbidity and mortality, compounded by common adverse effects of psychotropic medications such as weight gain, diabetes, and dyslipidemia. To develop a roadmap for improving cardiometabolic health in individuals with bipolar disorder, the BD² (Breakthrough Discoveries for Thriving with Bipolar Disorder) initiative partnered with individuals with lived experience through the Depression and Bipolar Support Alliance to identify primary and secondary drivers of cardiometabolic health and develop actionable, measurable strategies for improvement. Preliminary findings from this work will be presented alongside data from an ongoing longitudinal study exploring the intersection of obesity, cardiovascular health, and mental health in BD. As of November 2024, 281 participants have been enrolled, providing a robust dataset to evaluate obesity prevalence, focusing on WHO BMI classifications, HbA1c levels, and glucose levels, and its correlations with mood and functional outcomes. The session will feature three key presentations: (1) an analysis of obesity prevalence and its metabolic and psychiatric correlates in BD; (2) a proposal for a participant-centered wellness plan aimed at improving cardiometabolic health; and (3) a conceptual framework addressing the role of behavioral and systemic changes in achieving long-term health outcomes for individuals with BD and comorbid conditions. By leveraging comprehensive data through BD², this symposium highlights the potential to advance scientific understanding, foster innovative treatments, and enhance wellness by addressing the complex interplay of metabolic and mental health in bipolar disorder.
Learning Objective 1: Understand the prevalence and correlates of obesity in bipolar disorder and its impact on cognitive and psychiatric outcomes.

Learning Objective 2: Explore practical, patient-centered strategies to promote cardiovascular and metabolic health in individuals with BD

Literary References: Cuellar-Barboza, A.B., Cabello-Arreola, A., Winham, S.J., Colby, C., Romo-Nava, F., Nunez, N.A., Morgan, R.J., Gupta, R., Bublitz, J.T., Prieto, M.L., De Filippis, E.A., Lopez-Jimenez, F., McElroy, S.L., Biernacka, J.M., Frye, M.A., Veldic, M., 2021. Body mass index and blood pressure in bipolar patients: Target cardiometabolic markers for clinical practice. J Affect Disord 282, 637–643.
Maksyutynska, K., Stogios, N., Prasad, F., Gill, J., Hamza, Z., De, R., Smith, E., Horta, A., Goldstein, B.I., Korczak, D., Graff-Guerrero, A., Hahn, M.K., Agarwal, S.M., 2024. Neurocognitive correlates of metabolic dysregulation in individuals with mood disorders: a systematic review and meta-analysis. Psychol Med 54, 1245–1271.

CLINICAL AND BIOLOGICAL DETERMINANTS OF OBESITY AND INFLAMMATION IN BIPOLAR-I DISORDER: INSIGHTS FROM THE BD2 INTEGRATED NETWORK STUDY

Balwinder Singh, Mayo Clinic

Individual Abstract Background: Obesity has emerged as a global epidemic, with prevalence rates doubling over the past four decades. Projections indicate that 50% of the world's adult population may meet criteria for obesity by 2030. Among individuals with bipolar disorder (BD), obesity rates are even higher, contributing to an increased burden of cardiovascular disease and systemic inflammation. Identifying clinical and biological correlates of obesity and inflammation in BD could inform targeted interventions to reduce cardiovascular risk in this vulnerable population.
In this symposium, we present findings from the BD2 Integrated Network, a multi-site longitudinal initiative. Initial results from one site will be expanded to include data from five additional sites.
Methods: Adults aged 18–75 years with bipolar I disorder (BD-I) enrolled at Mayo Clinic completed diagnostic interviews and comprehensive baseline assessments. The obesity phenotype was defined as a baseline BMI GREATER THAN 30 kg/m², while the inflammation-positive phenotype was characterized by elevated inflammatory markers, including CRP, IL-6, IL-10, IL-18, MCP-1, and TNF-α. Comparisons were made between obese and non-obese participants and between inflammation-positive and inflammation-negative individuals based on demographic, clinical, social, and biological factors, including inflammatory and lipid profiles.
Results: Among 43 participants (mean age 43 years, BMI 31 kg/m², 48.6% female), 23 (53%) had obesity. Participants with obesity had significantly higher BMI (32.8 vs. 25.3, p LESS THAN 0.001), lower median free T4 levels (1.0 vs. 1.3, p = 0.02), and lower testosterone levels (304 vs. 607.5, p = 0.008) compared to those without obesity.
Immune profile data were available for 26 participants (60%), of whom 12 (46%) were classified as inflammation-positive. Compared to inflammation-negative individuals, inflammation-positive participants exhibited higher CRP levels (3.5 vs. 1.0, p = 0.03), elevated IL-18 levels (GREATER THAN 468 pg/mL in 40% vs. 0%, p = 0.074), and elevated MCP-1 levels (40% vs. 0%, p = 0.074). Inflammation-positive participants also had a higher median BMI (30.6 vs. 25.9), though this difference did not reach statistical significance, likely due to the small sample size.
Conclusions: Preliminary findings suggest significant differences in inflammatory profiles among individuals with BD-I, particularly in those with obesity or an inflammation-positive phenotype. These results highlight the high rates of obesity and inflammation in individuals with BD. Larger studies are needed to further explore these relationships and inform tailored

interventions. Expanded data from over 300 participants across all BD2 sites will be presented at the symposium.
Literature References: 1. Kambey PA, Kodzo LD, Serojane F, Oluwasola BJ. The bi-directional association between bipolar disorder and obesity: Evidence from Meta and bioinformatics analysis. Int J Obes (Lond). 2023 Jun;47(6):443-452. doi: 10.1038/s41366-023-01277-6.
2. Rosenblat JD, McIntyre RS. Bipolar Disorder and Inflammation. Psychiatr Clin North Am. 2016 Mar;39(1):125-37. doi: 10.1016/j.psc.2015.09.006

WELLNESS PLANS FOR CARDIOVASCULAR AND DIABETES HEALTH

Mark Frye, Mayo Clinic

Individual Abstract Background: Individuals living with bipolar disorder (BD) are at elevated risk for developing obesity, type 2 diabetes, and major adverse cardiovascular events (MACE). Reducing this burden is critical to facilitate the global aim of the newly created Breakthrough Discoveries for Thriving with Bipolar Disorder (BD2). The BD2 Integrated Network has developed a roadmap wellness plan for improved heart and diabetes health that focuses on lived experience, measurement-based care, and best practices embedded in a learning health network (LHN).
Methods: In partnership with the Depression Bipolar Support Alliance (DBSA), BD2 convened a work group to identify a meaningful goal or smart aim of improving physical wellness in bipolar disorder. Key Driver Diagrams (KDD), an improvement science tool, were utilized to identify factors that drive physical wellness, similar to Quality Improvement initiatives, measurement-based change ideas, or interventions to improve physical wellness.
Results: Collaborative treatment planning emerged as a primary driver for improved physical wellness. Lived experience experts noted key factors outside the medical system, emphasizing conventional clinical trials and regulatory outcome measures that were not necessarily meaningful to them. Primary drivers to improved physical wellness included effective management of medical comorbidity, emphasizing improved cardiometabolic health, optimizing treatment adherence, mood stabilization, improving sleep quality, and increasing physical activity. Secondary drivers included more effective management of cardiometabolic side effects of pharmacotherapy, understanding the role of diet/exercise and assessing the level of motivation to improve these lifestyle factors, access to medication, awareness of how medication can be helpful, and how substance use can drive mood instability and sleep problems. Multiple change ideas were identified, spanning the use of smartphone technology to track sleep, physical fitness, and risk of mood relapse, quantifying social determinants of health impact on wellness, utilization of peer support groups to foster accountability, studying prescribing behavior and cost, and adoption of shared decision-making principles to develop meaningful outcome measures of physical wellness. The measurement-based strategy to the interventions proposed is robust given the deep phenotyping research protocol (comprehensive rating scales, laboratory studies of inflammation, lipids, hormones, cognitive testing) and electronic health record common data elements access to vital signs, BMI, use of metformin, GLP1- agonists, and SGLT-2 inhibitors. An educational curriculum is also being developed to support these change initiatives, fostering a comprehensive, data-driven approach to promoting physical wellness in bipolar disorder.
Conclusion: The BD2 Learning Health Network (LHN) implementation workgroup has developed a road map to improve physical wellness in bipolar disorder.

Literature References: 1. Cuellar-Barboza AB, Cabello-Arreola A, Winham SJ, Colby C, Romo-Nava F, Nunez NA, et al. Body mass index and blood pressure in bipolar patients: Target cardiometabolic markers for clinical practice. J Affect Disord. 2021;282:637-43.
2. Foroughi M, Medina Inojosa JR, Lopez-Jimenez F, Saeidifard F, Suarez L, Stokin GB, et al. Association of Bipolar Disorder With Major Adverse Cardiovascular Events: A Population-Based Historical Cohort Study. Psychosom Med. 2022;84(1):97-103.

CONCEPT OF CHANGE: TRANSFORMING CARE THROUGH DATA-DRIVEN INNOVATIONS FOR TREATING BIPOLAR DISORDER WITH METABOLIC COMORBIDITIES

Emily Baxi, Breakthrough Discoveries for Thriving with Bipolar Disorder

Individual Abstract Background: Despite advancements in mental health research, the translation of scientific discovery into effective care for bipolar disorder (BD) remains slow, with an estimated 17-year gap. Addressing this challenge, BD² (Breakthrough Discoveries for Thriving with Bipolar Disorder) aims to accelerate discovery, develop novel treatment options, and promote wellness for individuals living with BD. By leveraging a centralized, data-driven platform, BD² integrates clinical, behavioral, and biological data to improve the precision and timeliness of care, particularly for individuals with metabolic comorbidities.
Methods: BD² utilizes a multimodal approach, integrating data from electronic health records (EHRs), wearable devices, app-based actigraphy, and biosamples into a centralized data platform. The BD² Integrated Network serves as a longitudinal cohort study embedded within a learning health network. The cohort study enables deep phenotyping, while the learning health network drives continuous improvement in care through iterative cycles of data collection, analysis, and evidence-based implementation. This dual design facilitates the rapid translation of scientific findings into clinical practice.
Results: Preliminary data from the BD² platform highlight the potential for improved care through personalized treatment strategies and the identification of novel intervention targets. The effective integration of multimodal data holds the potential to create a collaborative information-sharing system for clinicians and patients. This approach aligns with BD²'s goals to advance measurement-based care and promote sustainable cardiovascular health improvements.
Conclusion: BD² represents a paradigm shift in bipolar disorder care, integrating multimodal data into a unified platform that accelerates discovery, drives personalized care, and bridges the gap between passive health monitoring and proactive cardiovascular care. This approach will empower both clinicians and patients to make informed decisions, ultimately improving cardiovascular outcomes in individuals with bipolar disorder.
Literature References: 1. Altimus CM, Baxi EG, Frye MA, Nestler EJ, Pham DL, Burdick KE. Supercharging collaboration for bipolar research-Breakthrough discoveries for thriving with bipolar disorder (BD2). Bipolar Disord. 2023 Dec;25(8):619-623. doi: 10.1111/bdi.13398. Erratum in: Bipolar Disord. 2024 Jan 29. doi: 10.1111/bdi.13407. PMID: 38127002.
2. Leboyer M, Soreca I, Scott J, Frye M, Henry C, Tamouza R, Kupfer DJ. Can bipolar disorder be viewed as a multi-system inflammatory disease? J Affect Disord. 2012 Dec 1;141(1):1-10. doi: 10.1016/j.jad.2011.12.049. Epub 2012 Apr 11. PMID: 22497876; PMCID: PMC3498820.

***#NEW CLINICAL TRIALS FOR AUTISM: ENDPOINTS, STUDY DESIGN, BIOMARKERS AND RESULTS FOR A FAAH INHIBITOR, GABA-B AGONIST, PREGNENOLONE, AND VASOPRESSIN**

Paul Wang, Clinical Research Associates, LLC

Overall Abstract: More than 15 years have passed since the approvals of risperidone and aripiprazole for the treatment of "irritability associated with autistic disorder." There remain no approved treatments for the diagnostic, "core symptoms" of autism – impairment in social-communicative function, repetitive and restricted interests and behaviors, and sensory atypicalities. While many autistic individuals neither require nor desire therapeutic treatments, many others do, and the effort to identify treatments that are safe and effective for the core symptoms continues.

Recently published trials in autism include those for bumetanide, oxytocin, and balovaptan (vasopressin 1a antagonist). Although these studies were negative, newer trials continue to be motivated by mechanistic hypotheses related to E:I imbalance, and the role of oxytocin and vasopressin in social function. As well, there is strong interest in the role of endocannabinoid signaling in autism. Questions related to trial design for autism studies, including endpoint selection and the potential utility of biomarkers, also remain unsettled. This panel will describe the design and results of 4 recent trials for youth and young adults with autism.

JNJ-42165279 is a potent, selective, and orally bioavailable inhibitor of fatty acid amide hydrolase, which degrades the endocannabinoids anandamide (AEA), oleoylethanolamide (OEA), and palmitoylethanolamine (PEA), and other fatty acid amides. It is hypothesized that the endocannabinoid system and FAAH inhibition could modulate the core symptoms of autism. A 12 week, randomized, double-blind, placebo-controlled, study was conducted in the United States to evaluate the efficacy, safety, pharmacokinetics, and tolerability of JNJ-42165279. In addition to clinician and caregiver ratings of clinical outcomes, a suite of biomarkers assessments, including eye-tracking and EEG, was administered.

Arbaclofen was studied in a previous P2 trial for autism, with negative results on the 1° endpoint (Aberrant Behavior Checklist – Social Withdrawal/Lethargy, ABC-LSW), but positive post-hoc results on the Vineland-Socialization score, especially in subjects with fluent language. New studies in Canada and the EU were designed with these learnings in mind, enrolling a total of 212 autistics, age 5 – 17 years. Neither study was positive on the Vineland-Soc scale, but both were nominally positive on the ABC-LSW and multiple other secondaries. No unexpected safety issues were found. A subject-level meta-analysis of the 2 studies will be presented.

Data from controlled trials of arginine vasopressin (AVP) and pregnenolone also will be discussed. A recently completed investigation used AVP to target social deficits as assessed by the Social Responsiveness Scale in youth with autism (N=108; age 6-17 years), by implementing an 8-week Sequential Parallel Comparison Design. The second trial is ongoing and consists of a randomized placebo-controlled 14-week trial of pregnenolone, a neurosteroid and dietary supplement, that aims at targeting irritability in adolescents and young adults with autism (N=28; age range 14-25 years), as assessed by the ABC-Irritability subscale.

The discussant will summarize the state of autism trial design, the utility of biomarkers in autism trials, and leading candidates for further study.

Learning Objective 1: Describe mechanistic hypotheses for autism that are addressed by experimental treatments

Learning Objective 2: Recognize critical challenges in clinical trial design for autism

Literary References: Siafis S, Ciray O, Schneider-Thoma J, et al. Placebo response in pharmacological and dietary supplement trials of autism spectrum disorder (ASD): systematic review and meta-regression analysis. Mol Autism. 2020;11(1):66.
Sikich L, Kolevzon A, King BH, et al. Intranasal Oxytocin in Children and Adolescents with Autism Spectrum Disorder. New Engl J Med. 2021;385(16):1462-1473.

UTILITY OF CLINICAL OUTCOME ASSESSMENTS AND BIOMARKERS TO FACILITATE DRUG DEVELOPMENT ACROSS CLINICAL DRUG DEVELOPMENT PHASES - AN EXEMPLAR PROOF-OF-CONCEPT STUDY
Gahan Pandina, Johnson and Johnson, Titusville

Individual Abstract: Clinical trials investigating efficacy and safety of treatment for clinically relevant and impairing symptoms associated with autism spectrum disorder have yielded few drug candidates progressing to Phase 3: none have led to approval for core symptoms of ASD. A 12-week, randomized, double-blind, placebo-controlled, Phase 2 PoC clinical trial was conducted with JNJ-42165279, a potent, selective, and orally bioavailable inhibitor of fatty acid amide hydrolase in the United States to evaluate the efficacy, safety, pharmacokinetics, and tolerability of JNJ-42165279. In addition to clinician and caregiver ratings of clinical outcomes, a suite of biomarkers assessments, including eye-tracking, EEG, actigraphy, and facial affect recognition, was employed (Ness et al, 2019).
Features from putative biomarkers and clinical outcome assessments were assessed at baseline and periodically throughout the trial and utilized to predict change and measure between-group change from baseline over time. Biomarkers and experimental paradigms were selected to facilitate identification of a potentially responsive subpopulation (stratification), and to correlate with clinical change over time, to increase signal detection. While the study did not achieve it's primary objective (Klein et al, 2024), further analysis of a biomarker-enriched subpopulation was suggestive of potential efficacy in the treatment of core symptoms.
This talk will review the utility of biomarkers and clinical measures to facilitate change detection, and their relevance to different phases of clinical development.
Literature References: Ness, S. L., Bangerter, A., Manyakov, N. V., Lewin, D., Boice, M., Skalkin, A., ... and Pandina, G. (2019). An observational study with the Janssen Autism Knowledge Engine (JAKE®) in individuals with autism spectrum disorder. Frontiers in neuroscience, 13, 111.
Klein, M.E., Bangerter, A., Halter, R.J. et al. Efficacy and safety of JNJ-42165279, a fatty acid amide hydrolase inhibitor, in adolescents and adults with autism spectrum disorder: a randomized, phase 2, placebo-controlled study. Neuropsychopharmacol. (2024). https://doi.org/10.1038/s41386-024-02001-2

CANADA AND EUROPEAN TRIALS OF ARBACLOFEN FOR AUTISTIC YOUTH
Paul Wang, Clinical Research Associates, LLC

Individual Abstract: A previous 12-week, Phase 2 trial of arbaclofen in youth with autism (Veenstra-Vanderweele et al., 2017) was negative on the primary endpoint of the Aberrant Behavior Checklist – Social Withdrawal/Lethargy (ABC-LSW) subscale, with a large placebo effect found. A nominally significant effect was found on the CGI-S, and post-hoc analyses showed benefit on the Vineland-Socialization scale, with a larger effect in subjects who had fluent language or higher IQ. The data also suggested that a longer treatment period and a higher dosing limit might be more likely to show a drug effect.

Two new randomized, double-blind, placebo-controlled trials of arbaclofen recently completed in Canada and in Europe, respectively. They had nearly identical protocols to each other, featuring learnings from the previous P2 trial, and were prospectively coordinated. They enrolled 5–17-year-olds of either sex who met DSM5 and ADOS Module 3 or 4 criteria. The treatment period was 16 weeks, with maximum dose 15 mg TID (age 5-11 yrs) or 20 mg TID (12-17 yrs). The studies had independent statistical analysis plans, but both declared the Vineland-Socialization (VABS-Soc) scale to be the 1° endpoint, and both identified the ABC-LSW, CGI-I, and VABS-Communication as secondaries. The Autism Impact Measure (AIM), BOSCC, Pediatric Quality of Life (PedQL), and VABS-Daily Living Skills (DLS) were designated as secondary in one study but exploratory in the other. The SRS-2 was administered only in the European study.

The trials were conducted before, during, and after COVID lockdowns. 212 subjects were enrolled in total (72 male, 18 female in Canada; 102, 20 in the EU). Mean age ± SD was 12±3 across the studies, and fullscale IQ was 95±18 for subjects on arbaclofen, and 98±18 for placebo. Across the 2 studies, completion rates were 87% on arbaclofen vs. 94% on placebo. Safety and tolerability were substantially similar to that in previous studies of arbaclofen, with somnolence, problems with attention, and problems with sleep among the most common adverse events. Two SAEs of decreased level of consciousness were reported, both in Canada, and both resolving upon drug withdrawal, without other intervention. No SAEs were reported in Europe.

Efficacy was analyzed in each study independently, using logistic regression. Neither study showed a statistically significant effect on the VABS-Soc. Nominally significant improvement on the ABC-LSW was found in both studies, but not on the other secondary outcomes shared across both studies. Both studies also showed nominally significant benefit on the AIM, and the European study also showed nominally significant improvement on the PedQL, VABS-DLS, and the SRS-2.

A “meta-regression” across the 2 studies also was performed. This analysis showed robust statistical significance on the ABC-LSW and the AIM, and nominal significance on the PedQL and VABS-DLS. In addition, a meta-analysis combining subject-level data from both studies is underway.

While negative on their shared primary endpoint, these data show multiple efficacy signals for arbaclofen, demanding further investigation. 4 of 7 shared endpoints showed at least nominally significant improvement in the meta-regression, and the other shared endpoints all favored active treatment numerically. Data from the Brief Observation of Social Communication Change (BOSCC) and from EEG and tactile psychophysics assessments also are under analysis.

Literature References: Parellada M, San Jose Caceres A, Palmer M, et al. A Phase II Randomized, Double-Blind, Placebo-Controlled Study of the Efficacy, Safety, and Tolerability of Arbaclofen Administered for the Treatment of Social Function in Children and Adolescents with Autism Spectrum Disorders: Study Protocol for AIMS-2-TRIALS-CT1. Front Psychiatry 2021;12:701729.

Veenstra-VanderWeele J, Cook EH, King BH, et al. Arbaclofen in Children and Adolescents with Autism Spectrum Disorder: A Randomized, Controlled, Phase 2 Trial. Neuropsychopharmacology. 2017;42(7):1390-1398.

INNOVATIVE RANDOMIZED CONTROLLED TRIALS IN AUTISM: FROM NEUROPEPTIDES TO NEUROSTEROIDS

Antonio Hardan, Stanford University

Individual Abstract: Limited progress has been made in the psychopharmacological treatment of autism spectrum disorder (ASD). Therefore, the search continues for novel molecules that aims at targeting the core features as well as the associated behaviors. Data from two controlled trials will be discussed examining the efficacy of arginine vasopressin (AVP), a neuropeptide, and pregnenolone (PNO), a neurosteroid and dietary supplement. The first study applied a Sequential Parallel Comparison Design (SPCD) to examine the efficacy and safety of AVP in children and adolescents with ASD between the ages of 6 and 17 years in targeting autistic symptomatology, including social deficits, as assessed by the social responsiveness scale (SRS-2). Participants randomized to the active group received AVP (20 IU BID) intra-nasally or placebo (BID) for either 4 or 8 weeks. The second trial is ongoing and consists of a randomized placebo-controlled 14-week trial of PNO that included a 2-week single blind placebo lead. After the initial phase, participants received PNO or placebo for 12 weeks. PNO was started at 60 mg PO BID and was progressively titrated up every 2 weeks until the maximum dose of 250 mg BID. This study aimed at targeting irritability in adolescents and young adults with autism (age range 14-25 years), as assessed by the irritability subscale of the aberrant behavior checklist (ABC-I).

The AVP trial was recently completed, and 157 youth were enrolled, 108 randomized, and 93 completed the 8-week trial. Data analyses is ongoing, and findings will be summarized during the presentation. The PNO trial is ongoing, and 62 participants were enrolled, 29 randomized, and 28 completed the study to date. PNO was overall well tolerated with limited adverse events. Preliminary efficacy analyses indicate that a strong placebo effect as evidenced by a 30% decrease in ABC-I across all participants during the placebo lead in phase (t(df) = 5.090, p LESS THAN 0.001). Improvement in irritability was observed in the PNO (n=12; Average ABC-I at baseline = 23.3 □ 7.95; End of treatment = 16.7 □ 8.9; t= 2.731, p=0.02) but not in the placebo group (n=12; Average ABC-I at baseline = 19.9 □ 4.6; End of treatment = 15.7 □ 10.9; t= 1.440, p=0.178). Interestingly, improvement in autistic symptomatology, as assessed by the SRS-2, was observed in the PNO (n=12; SRS-T score at baseline = 83.00 □ 11.3; End of treatment = 76.3 □ 16.1; t= 2.524, p=0.028) but not the control group (n=12; SRS T score at baseline = 82.6 □ 9.2; End of treatment = 81.64 □ 10.7; t=0.375, p=0.751).

An accumulating body of literature research points to AVP and PNO as promising ASD treatment. It has been known that AVP plays a critical role in promoting mammalian social behavior and that dysregulation of the AVP signaling pathway produces social deficits in rodents. Similarly, mounting evidence suggest that neurosteroids, such as PNO can exert rapid, potent actions at the cell membrane via allosteric interactions with the GABA A receptor, and consequently modulating the excitation/inhibition balance, known to be abnormal in ASD. Therefore, finding from the above discussed trials, once finalized, will provide confirmatory evidence about the role of AVP and PNO in targeting core autism features as well as associated behaviors and might represent a breakthrough in ASD therapeutics.

Literature References: 1. Parker KJ, Oztan O, Libove RA, Mohsin N, Karhson DS, Sumiyoshi RD, Summers JE, Hinman KE, Motonaga KS, Phillips JM, Carson DS, Fung LK, Garner JP, Hardan AY. A randomized placebo-controlled pilot trial shows that intranasal vasopressin improves social deficits in children with autism. Sci Transl Med. 2019 May 8;11(491): eaau7356. doi: 10.1126/scitranslmed.aau7356. Epub 2019 May 1. PMID: 31043522; PMCID: PMC6716148.

2. Fung LK, Libove RA, Phillips J, Haddad F, Hardan AY. Brief report: an open-label study of the neurosteroid pregnenolone in adults with autism spectrum disorder. J Autism Dev Disord. 2014 Nov;44(11):2971-7. doi: 10.1007/s10803-014-2144-4. PMID: 24849255; PMCID: PMC4194260.

*^NEW TARGETS, NEW HOPE: ADVANCES IN NOVEL TREATMENT DISCOVERY FOR DEPRESSION

James Murrough, Icahn School of Medicine at Mount Sinai

Overall Abstract: There have been rapid advances in our understanding of basic and molecular mechanisms of brain function relevant to psychiatric disorders. Despite this progress, the translation of new insights from basic science into new effective, mechanistically novel, treatments have been slow. Recently however, a series of new targets, approaches, and compounds are emerging from both early and late phase clinical trials and the first mechanistically novel antidepressant agents in decades have recently come to market. The hypothesis of the current panel is that the field is entering a new era of novel treatment discovery, representing a long-awaited payoff following decades of investment in neuroscience and experimental medicine studies. The panel brings together a diverse group of speakers with significant experience in clinical and translational neuroscience and experimental therapeutics in mood disorders and related conditions. The first speaker will present new data concerning the safety, efficacy, and mechanisms of action of a completely novel pharmacological target for depression and anhedonia in KCNQ (a.k.a., Kv7) potassium channels. The second speaker will provide an overview of promising immune targets for depression, as well as new data concerning the safety and efficacy of a monoclonal antibody (mAb) against interleukin 17 (IL-17) in patients with treatment-resistant depression (TRD). The third speaker shifts focus to the role of cognitive neuropsychological mechanisms in antidepressant treatments, highlighting neuroimaging insights that emphasize the potential of pharmacologically targeting the lateral habenula (LHb), a critical brain region implicated in major depressive disorder (MDD). Finally, the fourth speaker will focus on targeting specific neurobiological and cognitive aspects of hopelessness to advance novel treatment approaches for depression and suicide risk. All talks will include new, unpublished data. At the conclusion of the panel, it is anticipated that the audience will have a substantially enhanced understanding of the current state of field regarding new and emerging targets and mechanistically novel agents for depression.
Learning Objective 1: To understand the current state of evidence supporting the KCNQ channel and immune components as novel targets for antidepressant treatments
Learning Objective 2: To appreciate the role of human neuroimaging and cognitive testing in advancing novel treatment discovery for depression
Literary References: Costi S, Han MH, Murrough JW. The Potential of KCNQ Potassium Channel Openers as Novel Antidepressants. CNS Drugs. 2022 Mar;36(3):207-216.
Rizk MM, Bolton L, Cathomas F, He H, Russo SJ, Guttman-Yassky E, Mann JJ, Murrough J. Immune-Targeted Therapies for Depression: Current Evidence for Antidepressant Effects of Monoclonal Antibodies. J Clin Psychiatry. 2024 Jun 24;85(3):23nr15243.

KCNQ (KV7) POTASSIUM CHANNELS AS NOVEL TARGETS FOR DEPRESSION AND ANHEDONIA

James Murrough, Icahn School of Medicine at Mount Sinai

Individual Abstract Background: Depression is one of the largest causes of disability, and mechanistically new treatment approaches are urgently needed to address this public health

problem. Basic research suggests that enhancing signaling at KCNQ (a.k.a., Kv7) type potassium channels in the brain may represent a promising new strategy for drug discovery for depression and related conditions.
Methods: We conducted a proof of concept randomized, controlled clinical trial of the KCNQ2/3 (a.k.a., Kv7.2/3) positive allosteric modulator ezogabine in N=45 adults with depression and prominent anhedonia. Participants underwent fMRI and clinical assessments at baseline and following a 5-week treatment period under double-blind conditions. The primary outcome, previously reported, was a change in brain response to reward in the context of task-based fMRI. Herein we report new, unpublished results based on a region of interest approach focused on the ventral tegmental area (VTA), as well as results based on resting-state fMRI (rs-fMRI). Depressive symptom changes were assessed with the MADRS while anhedonia was explored via completion of the SHAPS.
Results: As previously reported, treatment with ezogabine was associated with improvement in MADRS and SHAPS score, compared to placebo. New neuroimaging results focusing on the VTA show a significant drug-by-time interaction in VTA activation during anticipation ($F(1,34) = 4.36$, $p=0.044$), where VTA activation was reduced from pre-to-post ezogabine, compared to placebo. Mesocortical connectivity was also reduced from pre-to-post ezogabine, compared to placebo (significant drug-by-time interaction, $F(1,33)=4.317$, $p=0.046$).
Conclusion: These new 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. Our results are consistent with preclinical findings highlighting VTA hyper-activity in individuals with depression, suggesting a mechanism of action for KCNQ channel openers in normalizing this hyper-activity in individuals with both depression and anhedonia.
Literature References: Costi S, Han MH, Murrough JW. The Potential of KCNQ Potassium Channel Openers as Novel Antidepressants. CNS Drugs. 2022 Mar;36(3):207-216.
Costi S, Morris LS, Kirkwood KA, Hoch M, Corniquel M, Vo-Le B, Iqbal T, Chadha N, Pizzagalli DA, Whitton A, Bevilacqua L, Jha MK, Ursu S, Swann AC, Collins KA, Salas R, Bagiella E, Parides MK, Stern ER, Iosifescu DV, Han MH, Mathew SJ, Murrough JW. 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.

NOVEL IMMUNE TARGETS FOR DEPRESSION

James Murrough, Icahn School of Medicine at Mount Sinai

Individual Abstract Background: Immune dysregulation is consistently implicated in the pathogenesis of major depressive disorder (MDD) and may contribute to treatment-resistant depression (TRD). Monoclonal antibodies (mAbs) targeting specific immune pathways have revolutionized the treatment of inflammatory disorders. Notably, some mAbs are associated with improvement of comorbid depressive symptoms in patients with inflammatory disorders, independently of physical symptom relief. Ixekizumab is a mAb targeting the pro-inflammatory cytokines interleukin (IL)-17A and thus mitigates the dysregulated T-helper 17 (Th 17) pathway in inflammatory disorders, such as psoriasis. Ixekizumab has a favorable safety profile and has demonstrated potential in alleviating depressive symptoms in clinical trials of psoriasis, offering hope for patients unresponsive to standard antidepressants.
Methods: We conducted two studies to evaluate targeted immunomodulatory approaches in MDD. Study 1: Blood samples collected from 108 participants (aged 18–70; 44% female) were analyzed using the proteomic Olink assay covering 353 proteins across four panels of general, cardiovascular, and neural inflammation 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. Study 2: A pilot 6-week, randomized, placebo-controlled trial was conducted to assess the safety and efficacy of ixekizumab for TRD (n=7; aged 18–55) with elevated CRP (GREATER THAN 1 mg/dL). Primary outcome measures included dropout and adverse effect rates as well as reduction in depression severity.
Results: Study 1: Compared with the other three 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). Study 2: Ixekizumab (n=4) demonstrated a favorable safety profile (no dropouts, 1 mild side effect with ixekizumab vs. 7 with placebo) compared to placebo (n=3). However, there were no differences in depressive symptom reduction between the two groups.
Conclusions: Our findings highlight the involvement of Th2 and Th17 signaling in MDD and the potential of mAbs targeting this pathway as novel treatments. The lack of antidepressant efficacy observed with ixekizumab underscores the need for further exploration of patient subgroups and therapeutic targets. Future research should focus on direct clinical trials of mAbs in primary depressive disorders to refine their use as antidepressants.
Literature References: 1. Rizk MM, Bolton L, Cathomas F, et al. Immune-Targeted Therapies for Depression: Current Evidence for Antidepressant Effects of Monoclonal Antibodies. J Clin Psychiatry. 2024;85(3):23nr15243.
2. Griffiths, C.E.M., et al., Impact of Ixekizumab Treatment on Depressive Symptoms and Systemic Inflammation in Patients with Moderate-to-Severe Psoriasis: An Integrated Analysis of Three Phase 3 Clinical Studies. Psychother Psychosom. 2017;86(5):260-267.

THE LATERAL HABENULA AS A NOVEL TARGET FOR ANTIDEPRESSANT DEVELOPMENT: INSIGHTS FROM KETAMINE'S MECHANISTIC EFFECTS

Sara Costi, University of Oxford

Individual Abstract Background: The lateral habenula (LHb) is an evolutionarily conserved brain region densely populated with glutamatergic neurons and plays a critical role in cognitive processes associated with major depressive disorder (MDD), including negative emotion encoding, reward processing, and stress adaptation. Often described as the brain's "antireward" system, the LHb regulates reward behaviours through its inhibitory projections to the dopaminergic ventral tegmental area (VTA) and serotonergic raphe nucleus. Ketamine, a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist, has demonstrated rapid and sustained antidepressant effects in clinical settings. However, the neurocognitive mechanisms underlying these effects in humans remain largely unexplored. Recent preclinical studies suggest that ketamine's ability to block NMDAR-dependent bursting activity in the LHb may underlie its rapid antidepressant action. By inhibiting LHb bursting activity, ketamine temporarily lifts the inhibitory brake on the reward system, potentially restoring reward processing and alleviating depressive symptoms. In rodent models of depression, ketamine reduces LHb bursting activity and overall firing rates, which

are elevated in depression models. Importantly, ketamine targets neurons with high basal burst frequencies by blocking NMDARs in their open state, leading to sustained suppression of LHb activity lasting up to 24 hours in mice.
Methods: Using an experimental medicine model, 70 healthy volunteers (aged 18-45) were randomised in a double-blind design to receive either ketamine (0.5 mg/kg) or placebo (saline 0.9%). High-field 7T fMRI was performed 24 hours post-administration. The analyses focused on habenula responses during a Pavlovian learning task involving monetary reward, loss, punishment (win or loss of money), and the administration of a shock. The primary outcome measure was habenula activation during the Pavlovian conditioning task in response to the conditioned stimulus associated with pain stimuli and the receipt of shock. This study was registered on ClinicalTrials.gov (NCT04850911).
Results: Data available from n=66 subjects (34 males; 35 receiving ketamine) who completed fMRI revealed that ketamine attenuated habenula activity in response to the delivery of aversive stimuli (drug group × run interaction: $F(2, 128)=6.028$, $p=.003$) compared to placebo. However, ketamine did not significantly affect the expectation phase or mood and depression ratings.

Conclusions: These results provide valuable insights bridging preclinical findings to human applications and support the LHb as a target for ketamine's effects. Further research in clinical populations is necessary to validate and expand these findings.
Literature References: Lawson RP, Seymour B, Loh E, et al. The habenula encodes negative motivational value associated with primary punishment in humans. Proc Natl Acad Sci U S A. 2014; 111(32):11858-63.
Yang Y, Cui Y, Sang K, et al. Ketamine blocks bursting in the lateral habenula to rapidly relieve depression. Nature. 2018;554(7692):317-322

HOPELESSNESS AS A TREATMENT TARGET FOR SUICIDE RISK AND DEPRESSION
Elizabeth Ballard, National Institute of Mental Health

Individual Abstract: Suicide is a leading cause of death. There is a critical need to determine which interventions reduce suicide risk. Suicidal ideation is often used as a proxy outcome for suicide risk in clinical trials but is limited due to its dynamic nature, stigma and reactivity to the placebo effect. Hopelessness is a key suicide risk factor and is implicated in the relationship between suicide risk and depression. In this presentation, I will discuss hopelessness as a potential treatment target for suicide risk and depression. I will review recent findings on the neurobiology of hopelessness, demonstrating that hopelessness is associated with decreased salience network activity using magnetoencephalography (MEG)(n = 108). I will also present data on a cognitive task used to probe hopelessness and future expectancy, which could be used in clinical trials of depression and suicide risk, including unpublished data on future expectancies pre and post ketamine. Lastly, I will review recent data suggesting that ketamine may have a stronger effect on hopelessness than suicidal thoughts. Implications for future treatment of depression and suicide risk will be discussed.
Literature References: Aupperle RL, Kuplicki R, Tsuchiyagaito A, Akeman E, Sturycz-Taylor CA, DeVille D, Lasswell T, Misaki M, Berg H, McDermott TJ, Touthang J, Ballard ED, Cha C, Schacter DL, Paulus MP. Ventromedial prefrontal cortex activation and neurofeedback modulation
during episodic future thinking for individuals with suicidal thoughts and behaviors. Beh Res Therapy. 2024: 176, 104522.

Ballard ED, Nischal RP, Burton CR, Greenstein DK, Anderson GE, Waldman L, Zarate CA, Gilbert JR. Clinical and electrophysiological correlates of hopelessness in the context of suicide risk. Euro Neuropsychopharm, 2024; 80:38-45.

*NOVEL TREATMENTS AND BIOMARKERS FOR COGNITIVE DEFICITS IN MOOD DISORDERS

Adam Fijtman, NIH/NIMH

Overall Abstract: Cognitive deficits are a pervasive and debilitating aspect of mood disorders. These challenges severely impact daily functioning and diminish quality of life. Despite their prevalence, effective treatments remain scarce, and there is a critical lack of biomarkers to elucidate the underlying pathophysiology of these deficits and their relationship to other clinical features. This panel aims to provide a comprehensive exploration of novel treatments and biomarkers for cognitive impairments in unipolar and bipolar depression, showcasing recent cutting-edge research on innovative psychiatric interventions, neuroimaging techniques, and blood-based biomarkers.

The discussion will begin with an overview of the evidence supporting the use of serotonergic psychedelics and glutamatergic modulators, such as ketamine, for improving cognitive function in major depressive disorder and bipolar disorder. Presenters will examine how these treatments impact cognitive domains and correlate with neuroimaging findings alongside blood-based biomarkers of inflammation.

The first presenter of the panel will detail a randomized, double-blind, placebo-controlled crossover trial assessing ketamine's effects on working memory in treatment-resistant depression. Using the N-back task during fMRI, the study found that while ketamine did not enhance working memory accuracy, it significantly altered brain activity in regions responsible for working memory. Increased activation in the left parieto-occipital junction and a treatment-by-diagnosis interaction in the right superior temporal gyrus were observed, suggesting neural mechanisms underlying ketamine's cognitive effects.

The second presentation will focus on reward processing deficits in depression, utilizing magnetoencephalography and a monetary reward task to examine reward circuitry connectivity deficits in patients with a mood disorder compared to healthy participants. A subset of patients also received ketamine infusion. At baseline, patients exhibited reduced prefrontal-to-hippocampal connectivity compared to healthy controls, particularly for monetary loss trials, and ketamine increased this connectivity during both reward anticipation and feedback. These findings suggest a potential biomarker for ketamine's antidepressant effects.

Next, the panel will shift to psilocybin, highlighting results from an open-label trial of psilocybin-assisted psychotherapy in TRD assessing workplace and psychosocial functioning outcomes. Significant improvements were observed in social functioning in patients at 2 weeks, with medium-to-large effects sustained at six months. Small-to-medium improvements were also noted in workplace presenteeism and family functioning at 2 weeks and 6 months, underscoring the potential for serotoninergic psychedelics psychotherapy to enhance psychosocial outcomes.

Finally, the panel will delve into the interplay between body mass index, inflammation, and cognition in bipolar disorder. The presenter will discuss a study that revealed that higher BMI was associated with poorer global cognition in bipolar disorder after controlling for several factors including clinical symptomatology. Across the entire sample of patients and healthy participants, interleukin-6 levels mediated the relationship between BMI and global cognition. These findings position BMI and inflammation as critical targets for addressing cognitive impairments in mood disorders.

This panel will synthesize groundbreaking research, offering insights into novel therapeutic approaches and elucidating potential biomarkers aimed at improving cognitive function and reducing the burden of mood disorders.
Learning Objective 1: Gain a comprehensive understanding of recent research on biomarkers—both blood-based and imaging—associated with neurocognitive deficits in mood disorders.
Learning Objective 2: Understand recent research advancements in cutting-edge treatments for cognitive deficits and functional impairments in mood disorders.
Literary References: Gill H, Gill B, Rodrigues NB, et al. The Effects of Ketamine on Cognition in Treatment-Resistant Depression: A Systematic Review and Priority Avenues for Future Research. Neurosci Biobehav Rev. 2021;120:78-85.
Nicoloro-SantaBarbara J, Majd M, Miskowiak K, et al. Cognition in Bipolar Disorder: An Update for Clinicians. Focus (Am Psychiatr Publ). 2023;21(4):363-369.

TREATMENT-RESISTANT DEPRESSION WORKING MEMORY FMRI BRAINACTIVITY AFTER IV KETAMINE

Adam Fijtman, NIH/NIMH

Individual Abstract Background: Treatment-resistant depression (TRD) often involves working memory (WM) deficits.
Emerging evidence suggests that ketamine may improve WM and alter brain activity in key cognitive circuits. This study examined changes in WM performance and brain activity, measured via functional magnetic resonance imaging (fMRI) during an N-back task, in TRD patients and healthy volunteers (HV) following ketamine. We hypothesized that ketamine would enhance WM in TRD and produce increased activity in regions important for WM compared to placebo and HV.
Methods: 22 TRD patients and 19 HV participated in a randomized, double-blind, placebo-controlled, crossover intravenous ketamine trial (single dose, 0.5 mg/kg over 40 minutes). Participants completed 1-back and 3-back tasks during a 3 Tesla fMRI at baseline and two days post-infusions. Blood-oxygen-level-dependent (BOLD) activity in four regions of interest (dorsolateral prefrontal cortex, parieto-occipital junction (POJ), superior temporal gyrus (STG), and inferior frontal gyrus) was analyzed for the 3-back vs. 1-back and 3-back vs. rest contrasts. Linear models assessed the effects of ketamine and diagnosis on WM accuracy and BOLD activity, controlling for infusion order and baseline performance and activity.
Results: Ketamine's effect on WM accuracy did not differ by diagnosis ($t = 0.75$, $p = 0.45$). A significant treatment-x-diagnosis interaction was observed in the right STG (TRD - placebo: -0.03 ± 0.2, TRD - ketamine: -0.09 ± 0.19; HV - placebo: -0.09 ± 0.23, HV - ketamine: 0.09 ± 0.22; $t = 2.61$, $p = 0.02$), and ketamine increased left POJ activity ($t = 2.71$, $p = 0.01$). No significant differences were found in other regions (p GREATER THAN 0.05).
Conclusions: Ketamine did not improve WM in TRD or HV but altered brain activation in WM-related regions. STG activity may underlie the procognitive effects of glutamatergic modulators in mood disorders.
Literature References: Park H, Kang E, Kang H, et al. Cross-frequency power correlations reveal the right superior temporal gyrus as a hub region during working memory maintenance. Brain Connect. 2011;1(6):460-472.
Souza-Marques B, Santos-Lima C, Araújo-de-Freitas L, et al. Neurocognitive Effects of Ketamine and Esketamine for Treatment-Resistant Major Depressive Disorder: A Systematic Review. Harv Rev Psychiatry. 2021;29(5):340-350.

KETAMINE INCREASES REWARD CIRCUITRY CONNECTIVITY IN DEPRESSION: EVIDENCE FROM MAGNETOENCEPHALOGRAPHY

Jessica Gilbert, National Institute of Mental Health

Individual Abstract Background: Depression is characterized by altered connectivity in reward-processing regions including prefrontal cortex, hippocampus, and striatum. To study these altered circuits, the Monetary Incentive Delay (MID) task was used to investigate differences in brain connectivity in participants with a mood disorder diagnosis (MDs) compared with healthy volunteers (HVs). Ketamine was also administered to a subset of MDs. The study had two primary aims: 1) to measure connectivity differences within reward-related circuitry in MDs compared to HVs, and 2) to examine whether ketamine normalizes reward circuitry connectivity.
Methods: Forty-five participants (33 MD, 12 HV) completed the MID while undergoing magnetoencephalography (MEG) scanning. Nineteen MDs completed a second scan after subanesthetic ketamine infusion. Task-related stages of interest included reward anticipation (-600 to -100 ms preceding target) and feedback (500 to 1000 ms following target). Effective connectivity between regions-of-interest in prefrontal cortex, hippocampus, and striatum was probed using dynamic causal modeling. Parametric empirical Bayesian analysis was used to measure differences in parameter estimates of connectivity.
Results: HVs had significantly lower depression scores at baseline and greater prefrontal-to-hippocampal connectivity for loss compared to win trials during reward anticipation than MDs. Ketamine significantly reduced depression scores in MDs and increased prefrontal-to-hippocampal connectivity during both reward anticipation and feedback. In addition, trial-specific increases in prefrontal-to-hippocampal connectivity were found for loss compared to win trials during reward anticipation following ketamine.
Conclusions: Ketamine increased connectivity in reward circuitry in MDs. Changes in prefrontal cortex to hippocampus connectivity, particularly for loss trials, might serve as a putative biomarker of ketamine antidepressant response.
Literature References: Gilbert J, Wusinich C, Zarate Jr C. A predictive coding framework for understanding major depression. Front Hum Neurosci. 2022;16:787495.
He Z, Zhang D, Muhlert N, et al. Neural substrates for anticipation and consumption of social and monetary incentives in depression. Soc Cogn Affect Neurosci. 2019;14(8):815-826.

BODY MASS INDEX AND INFLAMMATION AS MODIFIABLE TARGETS FOR ADDRESSING OBESITY-RELATED COGNITIVE IMPAIRMENT IN BIPOLAR DISORDER

Marzieh Majd, Brigham and Women's Hospital, Harvard Medical School

Individual Abstract Background: Despite growing recognition of the interplay between obesity, inflammation, and cognitive function, research on the link between body mass index (BMI) and cognition and the mediating role of inflammation remains limited, particularly in individuals with mental illness. This study aimed to investigate 1) whether BMI and peripheral inflammation are associated with cognitive performance in patients with bipolar disorder (BD) and healthy controls (HC), and 2) the potential mediating role of inflammation in the BMI-cognition link.
Methods: As part of an ongoing study, 127 participants (79 individuals with BD and 48 HCs) were recruited. 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. Global cognition was measured by the MATRICS composite score. C-reactive protein (CRP), interleukin (IL)-6

and tumor necrosis factor (TNF)-α levels were quantified in blood. A composite inflammation index of CRP, IL-6 and TNF-α was created and utilized in primary analyses. Mediation analysis was conducted by the PROCESS macro for SAS.
Results: The BD group had a mean depression score of 7.7 ± 7.1 (as measured by the Hamilton Depression Rating Scale-24) and a mean mania score of 2.5 ± 3.2 (as measured by the Young Mania Rating Scale), reflecting the affective stability of participants. In the entire sample, higher BMI was associated with poorer global cognition, controlling for age, sex, diagnosis, education and medical comorbidity (beta=-.22, p=.006), and this association remained significant within BD after controlling for clinical factors (p=.02). Inflammation was associated with worse global cognition (beta=-.19, p=.024) across the entire sample. This association was no longer significant within BD after controlling for clinical factors (p=.08). The inflammation-cognition association remained significant for IL-6 after controlling for relevant covariates, but not for CRP or TNF-α. Hence, in the subsequent mediation analysis, we focused specifically on IL-6 as a mediator. We found that the indirect effect of BMI on global cognition through IL-6 was statistically different from zero (ab: beta=-.09, CI=-.18, -.01) in the entire sample, as revealed by a 95% confidence interval that is entirely below zero, suggesting that the negative effect of BMI on cognition is partly carried through IL-6.
Conclusions: The findings highlight BMI as a potential biomarker and treatment target for obesity-related cognitive impairment in BD and the broader population, with IL-6 as a key mediator.
Literature References: Lackner N, Bengesser SA, Birner A, et al. Abdominal obesity is associated with impaired cognitive function in euthymic bipolar individuals. The World Journal of Biological Psychiatry. 2016;17(7):535-546.
Misiak B, Stańczykiewicz B, Kotowicz K, Rybakowski JK, Samochowiec J, Frydecka D. Cytokines and C-reactive protein alterations with respect to cognitive impairment in schizophrenia and bipolar disorder: A systematic review. Schizophrenia Research. Schizophrenia Research. 2018;192:16-29.

NOVEL TREATMENTS TO IMPROVE WORKPLACE AND PSYCHOSOCIAL FUNCTION IN TREATMENT-RESISTANT DEPRESSION: EXPLORATORY OUTCOMES FROM AN OPEN-LABEL FEASIBILITY TRIAL OF PSILOCYBIN-ASSISTED PSYCHOTHERAPY

Orly Lipsitz, University of Toronto

Individual Abstract: Background: Cognitive concerns associated with treatment-resistant depression (TRD) are especially relevant due to their strong association with functional impairment. Given the profound functional impairment experienced by individuals with TRD, there is an urgent need to identify treatments that are effective in promoting workplace and psychosocial functioning. The aim of the present exploratory analysis is to identify whether there are changes in self-reported psychosocial and workplace functioning two weeks after psilocybin-assisted psychotherapy, and whether these changes are maintained at six months after beginning treatment.
Method: 31 participants with TRD were randomized in an open-label waitlist control trial of psilocybin-assisted psychotherapy (25 mg). Participants were followed for a period of six months after the first dose. Functional outcomes were measured using the Sheehan Disability Scale at baseline, week 2 (n = 29), and 6 months (n = 21). Paired t-tests were conducted between baseline to week 2 and baseline to six months. Given the small sample size and exploratory nature of these analyses, effect sizes are emphasized. Sensitivity analyses were conducted to identify the smallest detectable effect that may be found in this sample. To achieve 80% power in a two-tailed paired samples t-test with an alpha level of .05 and a

sample size of 29, an effect size of .54 or greater is required. With a sample size of 21, an effect size of .64 or greater is required.
Results: Family role functioning did not significantly improve from baseline to week 2 (Cohen's d = 0.28) or from baseline to month 6 (Cohen's d = 0.23). Social functioning significantly improved from baseline to week 2 with a medium effect ($t(27) = 2.60$, $p = .015$, Cohen's d = 0.49), and a large effect was sustained at month 6 ($t(19) = 3.81$, $p = .001$, Cohen's d = 0.85). Workplace functioning did not significantly improve from baseline to week 2 or month 6, with small-to-medium effects (Cohen's d = 0.33; Cohen's d = 0.49). Workplace presenteeism significantly improved from baseline to week 2 ($t(27) = 2.08$, $p = .047$, Cohen's d = 0.39). Effects remained small-to-medium at month 6 but were not statistically significant (Cohen's d = 0.31). Workplace absenteeism did not significantly improve at week 2 or month 6, with small effects (Cohen's d = 0.30; Cohen's d = 0.16).
Conclusions: These open-label exploratory findings in a small sample suggest that psilocybin-assisted psychotherapy may particularly improve social functioning, with maintained effects over time, as well as improvements in workplace presenteeism. Effects of psilocybin-assisted psychotherapy on functioning should be explored as a primary outcome in future studies. Although functional outcomes have been identified as a treatment priority by individuals with MDD and are being prioritized in new conceptualizations of TRD, 44% of individuals with MDD do not experience functional remission with pharmacotherapy; furthermore, improvements in depressive symptoms are often discordant with improvements in functioning. There is a need to identify treatments for depression that not only improve depressive symptoms but also improve functioning.
Literature References: Goodwin, GM, Aaronson, ST, Alvarez, O, et al. Single-dose psilocybin for a treatment-resistant episode of major depression: Impact on patient-reported depression severity, anxiety, function, and quality of life. Journal of Affective Disorders. 2023;327,120-127.
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Wednesday, May 28, 2025

Poster Session I with Lunch

W1. TRANSLATION AND VALIDATION STUDY OF THE ADULT ADHD INVESTIGATOR SYMPTOM RATING SCALE - JAPANESE (AISRS-JAPANESE)

Akira Iwanami[1], Dan Nakamura[1], Joan Busner[2], Kensuke Ito[3], Nobutaka Sakayoshi[3], Dorothee Oberdhan[4], Sayaka Machizawa[5], Lenard A. Adler[6]*

[1]Showa University, School of Medicine [2]Signant Health and Virginia Commonwealth University School of Medicine, [3]Headquarters of Clinical Development, Otsuka Pharmaceutical Co Ltd, Japan, [4]Otsuka Pharmaceutical Development and Commercialization, Inc. USA, [5]Signant Health, [6]NYU School of Medicine

Abstract Background: The Adult ADHD Investigator Symptom Rating Scale (AISRS) is a widely used gold standard clinician-administered assessment of DSM-5 ADHD symptoms in adults. Until today a Japanese translated version of the scale has been unavailable. With the involvement of the scale author (LAA) and other members of our group, a Japanese version of the AISRS was created with linguistic translation and cognitive debriefing and then studied for validity and reliability in a sample of adult ADHD patients in Japan.

Method: 61 ADHD patients (mean age=33.3 (10.8) years, 47% female; 53% male) at 2 university hospitals in Japan were included in this IRB-approved 2-month noninterventional study. For inclusion, ADHD was required to be at least mild in severity (CGI-S > 3), with or without any current treatment, and to have been diagnostically confirmed with the Conners Adult ADHD Diagnostic Inventory (CAADID) and DSM-5. Major or unstable comorbidities were not allowed. Raters were site clinicians who had been trained and qualified in the use of the AISRS-Japanese and CGI-S using materials developed by the scale author (LAA) and translated into Japanese. Interrater, intra-rater, and test-retest reliability of the AISRS-Japanese total score and Hyperactive/Impulsive (HI) and Inattentive (IA) subscale scores were assessed by ICCs after administering the scale twice, approximately 1 month apart, by the same rater with a second rater also scoring at the second timepoint. Convergent validity was examined via correlations of the total and subscale scores with those of the subject-completed Adult ADHD Self-Report Scale, v1.1, 18-Question symptoms checklist - Japanese (ASRS-Japanese) and the rater-completed CGI-S. Item-level reliability and internal consistency of the AISRS-Japanese were assessed by Cronbach's alpha.

Results: 59 subjects completed the study. Mean (SD) scores for the AISRS-Japanese were 27.1 (9.0), 10.4 (5.3), 16.7 (5.0) for the total, HI, and IA subscale scores, respectively. Mean (SD) scores for the (self-report) ASRS-Japanese were 40.7 (11.1), 16.6 (6.6), and 24.1(5.7), for the total, HI, and IA subscale scores, respectively. The CGI-S mean (SD) was 4.0 (0,5), with 75% of subjects having a CGI-S score of 4 (moderate). AISRS-Japanese internal consistency was high (Cronbach's alpha=0.82, 0.74, and 0.75, for the total, HI, and IA subscale scores, respectively), as was test-retest reliability, with respective ICCs ranging from 0.77-0.84). Intra-rater reliability was high (ICCs = 0.76-0.83), and interrater reliability was excellent (ICCs=0.95-0.97) for the total and subscale AISRS-Japanese scores. The (self-

report) ASRS-Japanese correlations with the AISRS-Japanese were high (r's=0.83-0.88 for total and subscale scores). Correlations of the CGI-S with the AISRS-Japanese were low (r's =0.20, 0.05, 0.29 for total, HI, and IA subscale scores, respectively), which may have been due to the restricted CGI-S range.

Conclusions: The results support the validity and reliability of the AISRS-Japanese for evaluating DSM-5 adult ADHD symptoms in Japan. Heretofore, although other scales have been used, there has been no validated Japanese measure of DSM-5 adult ADHD symptoms. Future work by our group will examine the scale's utility as a primary efficacy measure for pharmacologic treatment in Japan. In addition to its role in research, the newly developed and validated AISRS-Japanese is expected to assist clinicians in Japan in evaluating and tracking outcome of their adult ADHD patients.

W2. TELEHEALTH PSYCHOTHERAPY AND HEALTHCARE RESOURCE UTILIZATION AMONG VETERANS WITH ALCOHOL USE DISORDERS: AN ANALYSIS OF NATIONWIDE VETERANS HEALTH ADMINISTRATION DATA

Teresa Ann Granger[1], Joshua Richman[2], Regina Grebla[3], Lori Davis[4]*

[1]Tuscaloosa VA Medical Center, [2]Birmingham VA Health Care System, [3]Alkermes, [4]Veterans Affairs Medical Center

Abstract Purpose: This study examines the impact of the COVID-19 pandemic on healthcare resource utilization (HRU) and psychotherapy service delivery modalities for U.S. military veterans with alcohol use disorder (AUD) within the Veterans Health Administration (VHA). The research focuses on the rapid transition to telehealth during the pandemic, assessing changes in HRU and psychotherapy patterns over a four-year period spanning pre- and post-COVID emergency declarations.

Methods: Using a retrospective analysis, nationwide VHA electronic health records were reviewed to identify veterans with at least two AUD-related encounters (≥14 days apart) between March 13, 2018, and March 12, 2022. Diagnoses included AUD codes F10.1x and F10.2x. Veterans older than 89 years and those with non-AUD seizure or opioid use disorders were excluded to mitigate confounding medication overlaps. Monthly HRU metrics, including telehealth, outpatient, pharmacy, inpatient, emergency department (ED) visits, and AUD medications, were analyzed for the 24-month pre- and post-COVID periods. Outcomes were correlated with exposures assessed the previous month. Temporal trends were assessed using penalized splines for smoothing, and statistical comparisons were conducted using t-tests and chi-square tests.

Results: The cohort included 441,678 unique veterans (93.0% male; mean age 57 ± 14.5 years), with a demographic distribution of 66% White, 24.8% Black, 1.2% Native American/Alaskan, 0.9% Pacific Islander, 0.7% Asian, and 8.0% Hispanic.

Telehealth psychotherapy utilization was negligible pre-COVID but increased substantially post-COVID, particularly for non-physician therapy (NPT) services. This growth was driven by group telehealth psychotherapy, which offset a decline in in-person group therapy that did not recover post-COVID. Conversely, in-person individual psychotherapy experienced a decline post-COVID but later rebounded.

Prior month telehealth psychotherapy use was associated with fewer ED visits, lower suicidality, and fewer mental health admissions, particularly during the post-COVID period.

The relationship between telehealth psychotherapy and medication for AUD (MAUD) use was also explored. Veterans with an active MAUD prescription in the preceding month were significantly more likely to engage in telehealth psychotherapy, a trend that intensified post-COVID. Furthermore, telehealth psychotherapy participants were more likely to maintain an active MAUD prescription, with consistent and exponential increases observed during the study period.

Importance: The findings highlight telehealth psychotherapy's transformative role in improving healthcare outcomes for veterans with AUD, particularly during the COVID-19 pandemic. Increased telehealth utilization correlated with significant reductions in acute mental health crises and enhanced medication adherence. These results emphasize the critical need to sustain and expand telehealth services within the VHA and beyond to promote equitable, effective care for vulnerable populations. The study provides valuable insights into the long-term benefits of integrating telehealth into mental health care delivery, underscoring its potential to enhance service accessibility, continuity of care, and patient outcomes in diverse healthcare settings.

W3. EFFECTS OF MAZINDOL ON FENTANYL DEPENDENCE: PRECLINICAL EVIDENCE FROM STUDY KO-943

Eric Konofal[1], Jean-Charles Bizot[2], Maxime Robin[3], Anh-Tuan Lormier[4], Alexander Zwyer[5]*

[1]University of Paris, Robert-Debré Hospital, [2]Key-Obs SAS, [3]Aix-Marseille Université Institut de Chimie Radicalaire, [4]CayLab

Abstract: Fentanyl, a potent synthetic opioid, poses significant challenges in addiction treatment due to its high affinity for mu-opioid receptors (MOP) and its profound effects on the mesolimbic reward pathway. Chronic fentanyl use often results in tolerance, dependence, and opioid-induced hyperalgesia, complicating pain management and withdrawal. Current treatments, such as opioid substitution therapies, are associated with their own risks of dependence and limited efficacy in addressing the underlying reward circuitry.
A past preclinical study (Study KO-572-577; Key-Obs 2017) showed that mazindol both attenuated the rewarding effects of heroin in a place preference test in C57BL/6 mice and reduced heroin withdrawal symptoms in Sprague-Dawley rats.

Based on these results, the present study (Study KO-943), using the same preclinical models was designed to evaluate the potential of Mazindol to mitigate both the rewarding effects of fentanyl and its associated withdrawal symptoms, leveraging unique pharmacological profile of Mazindol targeting MOP, 5-HT1A receptors, and orexin-2 receptors (OX2R). Mazindol acts as a triple monoamine reuptake inhibitor (dopamine, norepinephrine, serotonin) with additional modulation of MOP through partial agonism to reduce withdrawal symptoms while limiting euphoria-induced dependence, 5-HT1A receptors to address stress, pain, and mood disturbances during opioid withdrawal, and partially OX2R to enhance wakefulness and counter sedation associated with opioid use.

Preclinical studies were designed to assess the effects of Mazindol in rodent models of fentanyl dependence using two validated approaches. In the conditioned place preference (CPP) model, C57BL/6 mice were trained using fentanyl in a two-compartment CPP paradigm. Post-conditioning, Mazindol (0.25–0.5 mg/kg) or vehicle was administered to test its effect on time spent in fentanyl-paired compartments. In the naloxone-precipitated withdrawal model, Sprague-Dawley rats were rendered fentanyl-dependent through escalating doses. Naloxone (3 mg/kg) was used to precipitate withdrawal symptoms after Mazindol (0.25–0.5 mg/kg) administration.

Based on previous results obtained in models of heroin dependence, mazindol should reduce time spent in the fentanyl-associated paired compartment, indicating a decrease in the rewarding effect of fentanyl, and should reduce fentanyl withdrawal symptoms.

Mazindol offers a novel, multi-faceted approach to fentanyl dependence treatment, targeting both the reward and withdrawal pathways. Its modulation of MOP and 5-HT1A receptors, combined with its OX2R activity, provides a promising non-opioid therapeutic strategy. These preclinical findings from Study KO-943 lay the foundation for clinical development in opioid dependence, with Mazindol ER poised as a safer and potentially more effective alternative to existing treatments.

The unique pharmacological profile of Mazindol may also be extended to other opioid use disorders, paving the way for expanded indications in addiction medicine. Future clinical studies will further validate its efficacy and dosing regimens in fentanyl-dependent populations.

W4. POST-LAUNCH ADVERSE EVENTS REPORTED TO FAERS FOR LONG-ACTING INJECTABLE BUPRENORPHINE

Brian Dawson[1], Michael P. Frost[2], Natalie R. Budilovsky-Kelley[3], Adam Friedman[3], Joshua M. Cohen[3]*

[1]Ideal Option, [2]The Frost Medical Group LLC, [3]Braeburn Inc,

Abstract Background and Introduction: Two long-acting injectable (LAI) buprenorphine medications have received US Food and Drug Administration (FDA) approval for the treatment of moderate to severe Opioid Use Disorder (OUD): buprenorphine extended-release injection monthly formulation (SUBLOCADE: BUP-SB) and buprenorphine extended-release injection weekly and monthly formulations (BRIXADI: BUP-BX).

Although randomized controlled trials have demonstrated the safety of treatment with these LAI buprenorphine medications for the treatment of OUD, post-marketing data are valuable for understanding the safety of these treatments in a real-world setting in broad and diverse populations of patients not necessarily represented in a clinical trial setting.

The FDA Adverse Event Reporting System (FAERS) is a centralized, computerized information database that is used by the FDA and other pharmacovigilance experts for post-marketing drug safety surveillance and adverse event (AE) signal detection. It contains AE reports that the FDA has received from manufacturers as required by regulations, along with

voluntary reports received directly from consumers and health care professionals. Given that the data are spontaneous in nature, they are frequently used to highlight new findings or for hypothesis generation purposes. In this study, we retrospectively reviewed the FAERS data to analyze real-world AE reporting for BUP-SB and BUP-BX for the 12-month periods following their commercial launch in the United States.

Methods: This retrospective analysis evaluated AEs spontaneously reported to FAERS during the first 12 months post-launch for patients treated with BUP-SB (March 1, 2018 to February 28, 2019), and BUP-BX (September 5, 2023 to September 4, 2024).

The primary objective was to determine the reporting rates (RR) of AEs during the first 12 months post-launch, using the total number of AE reports containing a specific Medical Dictionary for Regulatory Activities (MedDRA) AE preferred term (PT) per 1000 patients treated (RRpt) and per 1000 prescriptions dispensed (RRrx). AEs with an RR ≥1 for at least one of the products are reported.

Results: A total of 799 AE reports were received for BUP-SB and a total of 393 AE reports were received for BUP-BX during the first 12 months post-launch. For BUP-SB and BUP-BX, the estimated total number of patients treated during this time period was 6,464 and 24,805, and the estimated number of prescriptions dispensed was 16,770 and 94,826, respectively.

AEs meeting the frequency threshold in the RRrx analysis (RR≥1 for either product per 1000 prescriptions dispensed) were as follows for BUP-SB and BUP-BX, respectively: “drug withdrawal syndrome”: 15.1 and 1.1, “injection site pain”: 15.0 and 0.3, “drug dependence”: 3.4 and 0.2, “injection site erythema”: 3.0 and 0.2, “injection site discharge”: 3.0 and 0, “drug abuse”: 2.6 and 0, and “nausea”: 2.4 and 0.1.

Results for AEs meeting the frequency threshold in the RRpt analysis (RR≥1 for either product per 1000 patients treated) were similar.

Conclusion and Discussion: **Overall**, AEs associated with both BUP-SB and BUP-XR were infrequent during the first 12 months post-launch. Within this period, the most frequent AE, based on RRrx, was “drug withdrawal syndrome” at 15.1 per 1000 prescriptions dispensed for BUP-SB, with all other AEs having lower RR. These findings support a favorable overall safety profile for LAI buprenorphine medications in the treatment of moderate to severe OUD in the real-world, post-marketing setting. This data is important for clinicians as it informs their decision-making when considering medications for OUD for their patients.

W5. AGE OF ONSET OF SOCIAL ANXIETY DISORDER (SAD) IN TRIALS OF FASEDIENOL (PH94B) NASAL SPRAY

Ester Salmán[1], Ross Baker[1], Stephen Coffey[1], Rita Hanover[1], Michael Liebowitz[2], Louis Monti[1], Ester Salman[1]*

[1]Vistagen Therapeutics, Inc., [2]Medical Research Network, LLC,

Abstract Introduction: Social Anxiety Disorder (SAD) is among the earliest mental illnesses to manifest, with early onset usually associated with poorer outcomes, poor

treatment response, and an elevated risk of comorbid disorders such as depression, substance use, and suicide attempts (1,2). Fasedienol (PH94B; 3β-androsta-4,16-dien-3-ol) is a neurocircuitry-focused investigational pherine nasal spray in Phase 3 clinical trials for the acute treatment of SAD. Intranasal fasedienol rapidly activates receptors in peripheral nasal chemosensory neurons connected to subsets of olfactory bulb neurons connected to neurons in the limbic amygdala that are involved in the pathophysiology of SAD. An initial study suggested fasedienol is locally metabolized in the olfactory mucosa, with subsequent studies demonstrating that fasedienol does not require systemic absorption or CNS receptor binding to achieve anxiolytic effects. The age of onset in two placebo-controlled trials and one large open-label long-term safety study (LTSS) of fasedienol are described here.

Methods: Two Phase 3, U.S., multi-center, double-blind, randomized, placebo-controlled studies (NCT04754802; NCT05011396) and one U.S. open-label long-term safety study (LTSS, NCT05030350) enrolled adults with Diagnostic and Statistical Manual of Mental Disorders, 5th edition defined SAD. As part of the psychiatric evaluation, subjects were asked via a standard questionnaire to report the age at which their symptoms of SAD started. In both randomized studies, after Screening (Visit 1), all subjects completed Baseline (Visit 2, V2), where they received a placebo nasal spray and then participated in a 5-minute public speaking challenge (PSC) during which subjects self-reported scores on the Subjective Units of Distress Scale (SUDS). Subjects reporting a SUDS score ≥ 75 during at least one of the six observation points at Visit 2were invited back a week later for Randomization (Visit 3, V3) and were allocated in a 1:1 fashion to receive intranasal fasedienol (3.2 ug; 1.6ug in each nostril) or placebo. At V3, subjects again underwent a second 5-minute PSC with SUDS scores recorded six times. ANCOVA with baseline SUDS as a covariate was used to compare change in mean SUDS from V2 to V3 for the subjects administered fasedienol at V3 vs. those who received placebo at V3. The primary objective of the LTSS, which enrolled de novo subjects and rollover subjects from the two randomized studies, was to collect fasedienol safety and tolerability data.

Results: A total of 608 subjects reported the age of SAD onset: mean years of age was 14 (7.6 SD, median 13). Of the 608 subjects who reported age of onset, nearly 1/3 (188/608) reported early childhood age of onset ≤10: mean 7.2 (2.1 SD, median 7.0). In placebo-controlled trials, one trial (PALISADE-1) did not meet the primary endpoint, while the second trial (PALISADSE-2) demonstrated a clinically meaningful and statistically significant reduction in SUDS scores. Fasedienol was well-tolerated across all studies.

Conclusion: Our results underscore that SAD manifests in childhood and affects a substantial subpopulation before the onset of puberty, which may go unrecognized or be attributed to social awkwardness. Early identification of SAD symptoms, followed by thorough diagnosis and treatment, particularly among the early childhood group, may mitigate or possibly prevent progression to more serious mental illness and comorbidities.

W6. CONVERGENT CLINICAL AND PRECLINICAL EVIDENCE SUPPORTS SAMPLE ENTROPY AS A PREDICTIVE BIOMARKER FOR TREATMENT RESPONSE TO ALTO-300 IN MAJOR DEPRESSIVE DISORDER

Michael Avissar[1], Guhan Sundar[1], Yueqi Guo[1], Li Shen[1], Joshua Jordan[1], Akshay Ravidran[1], Michael Larson[2], Scott Steffenson[2], Priyanka Takle[1], Stacey Eckert[1], Nicholas Cooper[1], Chao Wang[1], Maimon Rose[1], Faizan Badami[1], Jessica Powell[1], Amit Etkin[1], Patricio O'Donnell[1], Adam Savitz[1]*

[1]Alto Neuroscience, [2]Brigham Young University

Abstract: Drug development for depression has been hampered by a one-size-fits-all approach that does not take into account the biological heterogeneity of people with major depressive disorder (MDD). Previously, we presented a precision psychiatry approach using an enrichment strategy for development of ALTO-300 (also known as agomelatine) with a companion EEG-based predictive biomarker for the treatment of depression. Here, we describe the biomarker, gamma-band sample entropy (SE), in more detail and present supporting human and preclinical evidence demonstrating its relevance to the mechanism of action of ALTO-300.

The mechanism of action of ALTO-300 includes serotonin receptor antagonism at 5-HT2C receptors and melatonin agonism at MT1/MT2 receptors. ALTO-300 has been shown to increase dopamine release in prefrontal cortex and improve anhedonia, which has been thought to reflect deficient dopaminergic functioning. Using an agnostic, data-driven, machine learning approach in a large open-label study, higher gamma-band SE was identified as a biomarker that predicted better treatment response to ALTO-300. Its predictive utility for response to ALTO-300 was replicated in an independent MDD sample, whereas it did not predict response to SSRI/SNRIs or placebo.

We developed a working hypothesis that higher gamma band sample entropy, indexing greater neural variability and unpredictability, reflects reduced dopaminergic functioning potentially due to increased tone at the 5-HT2C receptor, a key target for ALTO-300. We tested this hypothesis using a human dopamine depletion study as well as treatment of rodents with 5-HT2C agonists.

To assess the relationship between SE and dopamine depletion, data from a double-blind placebo controlled cross-over study in 12 healthy men were analyzed comparing SE measured after a nutritionally balanced amino acid mixture (placebo) or after consumption of a mixture deficient in tyrosine and phenylalanine that results in dopamine depletion (APTD). We found that low gamma-band SE was significantly higher in the APTD condition compared to the placebo condition ($p = 0.01$, Cohen's $d = 0.93$).

To better understand the relationship of SE to 5-HT2C activity, we administered two 5-HT2C agonists (Ro60-0175 [n=13] and YM348 [n=11]) to independent cohorts of mice, comparing them to vehicle in the same mice. We found a dose-dependent increase in gamma-band SE with each of the 5-HT2C agonists (ANOVA, Ro60-0175: $p = 5\times10^{-5}$; YM348: $p = 0.007$).

To assess ALTO-300 in patients with MDD, an adjunctive double-blind placebo-controlled trial (ALTO-300-201) is currently underway, using SE as an enrichment marker. The primary outcome is change in MADRS score during the double-blind period in biomarker positive patients. The convergent human and preclinical mechanistic studies described here provide a neurobiological rationale tying this machine-learning discovered biomarker to the ALTO-300 mechanism of action, further supporting the precision psychiatry approach taken in the development of this molecule.

W7. NONLINEAR MODELING OF DEPRESSION AND ANXIETY OUTCOMES WITH BILATERAL TMS PROTOCOLS

Yosef Berlow[1], Amourie Prentice[2], Farrokh Mansouri[3], Victoria Middleton[4], Jennifer Bowman[5], Joseph Kriske[5], Nancy Donachie[5], Noah Philip[6], Jonathan Downar[7]*

[1]Alpert Medical School, Brown University, [2]Maastricht University, [3]University of Toronto, [4]Salience Research Institute, [5]Salience Health, [6]Alpert Medical School, Brown University; Providence Veterans Affairs Medical Center, [7]University Health Network, University of Toronto

Abstract Background: Depression and anxiety frequently co-occur in patients undergoing transcranial magnetic stimulation (TMS) treatment. Although the patterns of symptom improvement vary, they often follow a nonlinear trajectory best described with an exponential decay function, with large improvements early in treatment and slower gains thereafter. This study examined depression and anxiety outcomes in a large sample of patients receiving either the bilateral dorsolateral prefrontal cortex (Bilateral-DLPFC) TMS or a hybrid protocol targeting left DLPFC and right orbitofrontal cortex (Hybrid-OFC) and modelled symptom improvement using this nonlinear model.

Methods: A total of 3,544 patients from a 14-site community practice (Salience TMS Neuro Solutions, Plano, TX) were assessed weekly using the Patient Health Questionnaire-9 (PHQ-9) and Generalized Anxiety Disorder-7 (GAD-7). Patients received left-sided 10 Hz TMS followed by right-sided 1 Hz stimulation targeting either the DLPFC (Bilateral-DLPFC) (n=2763) or OFC (Hybrid-OFC) (n=781). Treatment assignment to either protocol was determined by the date the clinics began offering the Hybrid-OFC protocol. Nonlinear mixed-effects (NLME) models using the exponential decay function, D(t)=A*e^(-t/B)+C, were compared to linear mixed-effects (LME) models using the Akaike information criterion (AIC), Bayesian information criterion (BIC) and likelihood ratio test (LRT). Individual items of the PHQ-9 were modeled using nonlinear least squares. The equivalence of response and remission outcomes between protocols was assessed using the two one-sided t-test with a 5% equivalence margin.

Results: Treatment groups (Bilateral-DLPFC and Hybrid-OFC TMS) did not differ on age, sex, baseline depression or baseline anxiety scores ($p > 0.05$). Improvements in both depression and anxiety symptoms were well-modeled with the exponential decay function (all parameters $p < 0.001$). Depression ratings declined 9.8 points (A), with a time constant of 11 TMS sessions (B), approaching scores near remission 6.6 (C). The NLME model demonstrated superior fit compared to the LME model (LRT 3437.4, $p < 0.0001$). No significant protocol differences were detected for depression response (Bilateral-DLPFC: 68.2%, Hybrid-OFC: 68.5%) or remission (Bilateral-DLPFC: 41.2%, Hybrid-OFC: 41.2%) rates and equivalence tests were significant (response: Z=2.545, p=0.0055; remission: Z=2.485, p=0.0065). Nonlinear models for individual items on the PHQ-9 also demonstrated good fits to the exponential decay model and yielded similar curves for both protocols. Improvements in anxiety scores also followed this exponential decay pattern with scores decreasing by 7.8 points (A) with a time constant of 13.3 TMS sessions (B) and reaching a plateau at 5.2 points. The NLME model yielded a superior fit compared to the LME model

(LRT 1969.7, $p < 0.0001$). When comparing rates of anxiety response (Bilateral-DLPFC 64.9%, Hybrid-OFC 61.8%), no significant difference between groups was detected ($Z=1.66$, $p=0.097$), but equivalence could not be supported ($Z=0.89$, $p=0.19$). However, comparing remission rates for anxiety (GAD-7 < 5: Bilateral-DLPFC 49.3%, Hybrid-OFC 48.3%) yielded evidence of equivalent effectiveness ($Z=-1.955$, $p=0.025$).

Conclusions: Both Bilateral-DLPFC and the Hybrid-OFC TMS protocols significantly improved depressive and anxiety symptoms in an exponential decay pattern. For depression, response and remission rates were equivalent across protocols. For anxiety, equivalence was supported for remission but not conclusively for response, although overall improvements were similar.

W8. THE COMPLEX DIAGNOSTIC PROFILE OF PSYCHIATRIC OUTPATIENTS PRESENTING FOR THE TREATMENT OF BIPOLAR DEPRESSION: IMPLICATIONS FOR THE GENERALIZABILITY OF PLACEBO-CONTROLLED STUDIES OF BIPOLAR DEPRESSION

Mark Zimmerman[*1], Barbara Lu[1]*

[1]*Brown University*

Abstract Background: Co-occurring psychiatric disorders are common in individuals with bipolar disorder. Meta-analyses focused on the frequency of single disorders have found that between 15% to 30% of individuals with bipolar disorder have a lifetime history of generalized anxiety disorder, panic disorder, posttraumatic stress disorder, alcohol use disorder, cannabis use disorder and attention deficit disorder. A problem, though, with these literature reviews and meta-analyses is the variability in the methodology of the included studies. Most of these meta-analyses combined findings from general population epidemiological studies with studies of patient samples. Most studies report lifetime prevalence rates of comorbid disorders, though, in treatment studies it is more important to be aware of current disorders than disorders that may have been remitted years earlier. Few studies have examined the frequency of a broad range of psychiatric disorders presenting for the treatment of bipolar depression. In the present report from the Rhode Island Methods to Improve Diagnostic Assessment and Services (MIDAS) project we examined the following three questions: 1) What is the prevalence of current comorbid disorders in patients presenting for the treatment of bipolar depression? 2) Do patients with bipolar I and bipolar II depression differ in the comorbidity rates? 3) Do patients consider the comorbid disorder to be clinically significant insofar as they indicate their desire to have treatment directed towards the comorbid disorder?

Methods: The sample examined in the present report was derived from the 3,800 psychiatric outpatients evaluated with semi-structured diagnostic interviews, 48 of whom were in a major depressive episode and diagnosed with current bipolar I disorder, and 83 of whom were in a major depressive episode and diagnosed with bipolar II disorder. Patients were interviewed by a diagnostic rater who administered the Structured Clinical Interview for DSM-IV (SCID) and the borderline personality disorder section of the Structured Interview for DSM-IV Personality (SIDP-IV). At the end of each SCID module we added the following question about reason for seeking treatment "Are (symptoms of current disorder) a reason for coming

for treatment now?" When asking this question the interviewer reviewed the features of the disorder that had just been described so the patient understood to what the question referred.

Results: The mean number of comorbid diagnoses was similar in the patients with bipolar I and bipolar II depression (2.4+2.0 vs. 2.2+1.6, t=0.48, n.s.). Half of the patients with bipolar I depression and 43.4% of the patients with bipolar II depression were diagnosed with 3 or more comorbid disorders. There was no difference in the rate of any specific disorder between the patients with bipolar I and bipolar II depression. Two-thirds of the patients wanted treatment to address a comorbid disorder, and more than half wanted treatment to address at least 2 comorbid disorders. Social anxiety disorder, generalized anxiety disorder, and panic disorder were the comorbid disorders that the patients most frequently wanted treatment to address.

Conclusions: The majority of patients with bipolar depression have multiple comorbid disorders. The clinical significance of comorbid disorders is suggested by patients desire to have them addressed in treatment. The implications of these findings for the generalizability of treatment trials for bipolar disorder, many of which exclude patients with comorbid disorders, will be discussed.

W9. THE NEUROBIOLOGICAL EFFECTS OF PSILOCYBIN IN TREATMENT RESISTANT BIPOLAR DEPRESSION: PROTOCOL AND INTERIM ANALYSIS OF AN EMOTIONAL-PROCESSING FMRI PILOT STUDY

Erica Kaczmarek[*1], Ishrat Husain[2], Colin Hawco[2], Danica Johnson[1], Noah Chisamore[1], Zoe Doyle[3], Joshua Rosenblat[1]*

[1]University of Toronto, [2]Centre for Addiction and Mental Health, [3]University Health Network

Abstract Background: Bipolar Disorder (BD) is a severe and persistent mental illness with a lifetime prevalence of 2-3%. Individuals with BD spend a significant portion of their lives experiencing depressive episodes, yet bipolar depression remains a considerable treatment challenge. Current pharmacological treatment options are limited and are often associated with significant adverse effects. Treatment outcomes for bipolar depression are poor, with approximately one-third of patients failing to respond to two or more first-line treatments (i.e., treatment resistant bipolar depression (TRBD)). Consequently, there is an urgent need to develop novel therapeutics for bipolar depression, although progress is hindered by our limited understanding of the neurobiology of BD.

Methods: Participants (n=20) with a primary diagnosis of Bipolar II Disorder will receive a single 25 mg oral dose of psilocybin with accompanying psychotherapy (PAP) as part of an ongoing open-label clinical trial. Eligibility criteria includes a current moderate to severe major depressive episode failing two or more adequate treatment trials. The primary outcome is to evaluate neurobiological effects of psilocybin by examining the association between post-treatment right amygdala activity, measured via a facial affect task during an fMRI, and antidepressant effects over time. We hypothesize the increased right amygdala activity in response to emotional stimuli one day after psilocybin treatment will correlate with greater antidepressant effects in the one-week period post-treatment in individuals with TRBD, as

seen in unipolar TRD samples. The trial was registered on ClinicalTrials.gov (NCT06506019).

Results: Enrollment for the study opened on November 25, 2024. Recruitment for the trial is ongoing (n=6 enrolled to date) with an expected recruitment rate of 2 participants per month. An interim analysis will be completed in May 2025 (prior to the conference), which will include evaluation of antidepressant effects, tolerability, and adverse events for all participants enrolled to date.

Conclusions: This presentation will provide an overview of a novel trial investigating PAP for TRBD. To date, only two small pilot trials have included participants with Bipolar II Disorder (with n=19 BD participants in total), making this research a critical contribution to the field. Furthermore, the incorporation of neuroimaging offers a unique opportunity to elucidate both the pathobiology of bipolar depression and the neurobiological effects of psilocybin.

W10. EFFICACY OF ARIPIPRAZOLE ONCE-MONTHLY AND ARIPIPRAZOLE 2-MONTH READY-TO-USE ON SLEEP DISRUPTION IN PEOPLE WITH BIPOLAR I DISORDER: POST HOC ANALYSES OF DATA FROM TWO RANDOMIZED CONTROLLED TRIALS

Karimah S. Bell Lynum[1], Anne Walker[2], Norman Atkins[1], Zhen Zhang[1], Craig Chepke[3], Joseph F. Goldberg[4]*

[1]Otsuka Pharmaceutical Development and Commercialization, Inc., [2]Lundbeck LLC, [3]Excel Psychiatric Associates, [4]Icahn School of Medicine at Mount Sinai

Abstract Background: Sleep disruption is common in people living with bipolar I disorder (BP-I) and may impair quality of life; in addition, variability in sleep may be associated with an increase in mood episode relapses. Achieving and maintaining BP-I symptom control may involve antipsychotic treatment. Long-acting injectable (LAI) formulations of antipsychotics are associated with improved treatment adherence and better outcomes, compared with oral formulations. The objective of these exploratory post hoc analyses was to assess the effect of LAI formulations of aripiprazole – aripiprazole once-monthly 400 mg (AOM 400) and aripiprazole 2-month ready-to-use 960 mg (Ari 2MRTU 960) – on sleep disturbance in BP-I.
Methods: Data from two randomized controlled trials were analysed. Data for AOM 400 were from a double-blind, randomized withdrawal trial in which patients with BP-I currently experiencing a manic episode (n=266) were first stabilized on oral aripiprazole, then stabilized on AOM 400, and then randomized to continue on AOM 400 or switch to placebo for 52 weeks (NCT01567527; Study 250). Data for Ari 2MRTU 960 were from an open-label trial in which clinically stable patients with BP-I (n=81) were randomized to AOM 400 or Ari 2MRTU 960 for 32 weeks (NCT04030143; Study 181). Both trials included assessment of symptoms using the Young Mania Rating Scale (YMRS) and Montgomery–Åsberg Depression Rating Scale (MADRS).

In these post hoc analyses, changes from baseline in scores for the YMRS ‘sleep’ item, MADRS ‘reduced sleep’ item, and MADRS ‘lassitude’ item were evaluated. The analysis of

data from Study 250 focused on those patients with mild to severe reduction in sleep/sleep need prior to stabilization on oral aripiprazole (defined as a YMRS sleep item score of 1–4); the analysis of data from Study 181 included all patients with BP-I.

Results: In Study 250, mild to severe reduction in sleep/sleep need was reported in 181 (68.3%) patients prior to oral aripiprazole stabilization, with a mean (standard deviation [SD]) YMRS sleep item score of 2.1 (0.8). In those patients, the YMRS sleep score improved to 0.9 (0.9) following oral aripiprazole stabilization, and then to 0.4 (0.8) following AOM 400 stabilization – the improvement was maintained in those receiving AOM 400 in the randomised phase, but worsened in those who switched to placebo (Week 52 scores: 0.4 [0.8] and 0.7 [1.0], respectively). At Week 52, mild to severe reduction in sleep/sleep need was reported in 14/89 (15.7%) of those receiving AOM 400 and 20/91 (22.0%) of those in the placebo group. Overall, the results from Study 250 show an improvement in sleep/sleep need in patients with BP-I receiving treatment with aripiprazole.

In Study 181, treatment of clinically stable patients with BP-I with AOM 400 (n=40) or Ari 2MRTU 960 (n=39) resulted in a small improvement from baseline at Week 32 (presented here as least squares mean change [standard error]) in YMRS sleep item score (AOM 400, -0.41 [0.16]; Ari 2MRTU 960, -0.34 [0.16]), MADRS lassitude item score (AOM 400, -0.43 [0.26]; Ari 2MRTU 960, -0.51 [0.26]), and MADRS reduced sleep item score (AOM 400, -0.80 [0.30]; Ari 2MRTU 960, -0.70 [0.31]).

Conclusion: These results indicate that AOM 400 may improve sleep outcomes in patients with BP-I and disrupted sleep. As Ari 2MRTU 960 and AOM have comparable pharmacokinetic, safety, and efficacy profiles, Ari 2MRTU 960 may provide similar benefits to AOM 400 – exploratory analyses in a small sample support this hypothesis.

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W11. PROTOCOL FOR A RANDOMIZED, DOUBLE-BLIND, MIDAZOLAM-CONTROLLED PHASE II CLINICAL TRIAL INVESTIGATING REPEATED KETAMINE INFUSIONS FOR TREATMENT RESISTANT BIPOLAR DISORDER (NCT05004896)

*Diana Orsini**[1], Sara Di Luch[1], Tayyeba Shaikh[2], Roger McIntyre[1], Rodrigo Mansur[1], Joshua Rosenblat[1]*

[1]University of Toronto, [2]University Health Network

Abstract Introduction: Treatment resistant bipolar depression (TRBD) is a significant clinical challenge with an urgent need for novel treatments. Growing evidence supports rapid and robust antidepressant effects with sub-anesthetic doses of intravenous (IV) ketamine for treatment resistant depression. The majority of completed randomized controlled trials (RCTs) to date have been in major depressive disorder samples, excluding participants with history of mania or hypomania. Only small single dose pilot RCTs have evaluated ketamine for bipolar depression. No completed RCTs have evaluated the effects of repeated doses of IV ketamine for TRBD. Based on this minimal evidence, most guidelines consider IV ketamine to be a third-line option for acute bipolar depression.

Methods: A multi-site (University Health Network (UHN) and Ontario Shores (OS)), randomized, double-blind, midazolam-controlled, phase II clinical trial will evaluate the efficacy, safety and tolerability of four flexibly dosed ketamine infusions (0.5 – 0.75 mg/kg infused over 40 minutes) for acute treatment of moderate to severe TRBD (BDI and BDII). Exclusion criteria will include active psychosis, mania, substance use and severe medical comorbidity. Target enrollment is 70 participants (n=35 per group) to be adequately powered. The primary outcome will be change in Mongomery-Asberg Depression Rating Scale (MADRS) scores from baseline to Day 14, using analysis of covariance (ANCOVA), with 14-day MADRS as the outcome and baseline MADRS and stratification variable (sex, bipolar diagnosis) as covariates. Secondary outcomes include response and remission rates, safety (adverse events), tolerability (treatment emergent mania), suicidality, anxiety, quality of life, function and duration of effects (to Day 28).

Results: Enrollment began June 2022 at UHN and April 2024 at OS. Recruitment is ongoing with 51 participants currently enrolled (n=44 UHN, n=7 OS) and is expected to be completed by November 2025. Current recruitment rate is 2-3 participants completed per month. The mean age of the total sample is 45.0 (SD=10.8) with 52.9% female participants (n=27). 20 participants have a diagnosis of bipolar I and 31 are diagnosed with bipolar II.

Discussion: There is an urgent need to evaluate the efficacy, safety and tolerability of repeated IV ketamine for TRBD. If results find ketamine to be effective and safe, this novel intervention will have the potential to address the current lack of sufficient pharmacotherapies for TRBD and hold hope of improving clinical outcomes in this difficult to treat population. Our trial will provide critical evidence to support or refute the use of IV ketamine for TRBD to inform clinical care guidelines.

W12. PROTOCOL FOR AN OPEN-LABEL EXTENSION TRIAL INVESTIGATING MAINTENANCE KETAMINE INFUSIONS FOR TREATMENT-RESISTANT BIPOLAR DEPRESSION (NCT05339074)

Sara Di Luch[*1], Diana Orsini[2], Tayyeba Shaikh[1], Rodrigo Mansur[2], Roger McIntyre[2], Joshua Rosenblat[2]*

[1]University Health Network, [2]University of Toronto

Abstract Background: Preliminary studies have suggested clinical benefits of sub-anesthetic doses of intravenous (IV) ketamine for treatment-resistant bipolar depression (TRBD). However, previous clinical trials have only evaluated single doses with no trials evaluating maintenance ketamine infusions after the acute course in TRBD samples. The primary research goal is to determine the antidepressant efficacy, safety, and tolerability of maintenance ketamine infusions over a period of twelve weeks in individuals with TRBD that responded to acute course of ketamine treatment.

Methods: Forty (n=40) participants will be recruited from a parent trial (NCT05004896) to the present maintenance study. We are conducting a multi-site (University Health Network (UHN) and Ontario Shores Centre for Mental Health Sciences (OS)), single-arm, open-label, 12-week extension trial evaluating the effects of flexibly-dosed adjunctive ketamine infusions for TRBD to maintain antidepressant effects in patients who achieved an antidepressant

response (Montgomery–Åsberg Depression Rating Scale (MADRS) decrease by > 50%) or remission (MADRS < 12) following an acute course of four ketamine infusions. The primary outcome will be MADRS scores, determined by a linear mixed model from baseline to week 12. Secondary outcomes include evaluating response and remission rates, safety, tolerability (including treatment-emergent mania), and effects on suicidality, anxiety, quality of life, function, and the duration of effects. Open-label ketamine infusions will be provided on a flexible schedule (every 2-4 weeks) with flexible dosing (0.5-1.0mg/kg over 40 minutes) titrated to optimize benefits while minimizing the dosage and frequency over a 12-week extension period. In addition to this acute course of four infusions over two weeks, a maximum of six infusions will be provided over the 12-week period.

Results: Enrollment began in August 2022. Recruitment is ongoing with 25 participants currently enrolled and is expected to be completed by December 2025. The mean age of the total sample is 41.56 (standard deviation: 10.55) with 56% female participants (n=14). 10 participants have a diagnosis of bipolar I disorder and 15 are diagnosed with bipolar II disorder. Enrollment updates will be provided at time of abstract presentation.

Discussion: The proposed study will be the first to evaluate the effects of repeated ketamine infusions for maintaining antidepressant effects in TRBD (i.e., repeated doses post-acute response). There is an urgent need to evaluate ketamine in the maintenance phase, not only for acute treatment, as relapse post-acute course is common with ketamine. If results find ketamine to be effective and safe, this novel intervention will have the potential to address the current lack of sufficient pharmacotherapies for TRBD and hold hope of improving clinical outcomes in this difficult to treat population. Our trial will provide critical evidence to support or refute the use of maintenance ketamine infusions for TRBD to inform clinical care guidelines.

W13. KETAMINE VERSUS ELECTROCONVULSIVE THERAPY FOR NON-PSYCHOTIC TREATMENT-RESISTANT DEPRESSION: A COST-EFFECTIVENESS ANALYSIS

Michael Lebenbaum[1], Benoit Mulsant[2], Sagar Parikh[3], Jason Fletcher[1], Jeffrey Hoch[4], Paul Kurdyak[2], Daniel Blumberger[5], Manish Jha[6], Venkat Bhat[2]*

[1]Center for Demography of Health and Aging, University of Wisconsin-Madison, [2]University of Toronto, [3]University of Michigan, [4]Division of Health Policy and Management, Center for Healthcare Policy and Research, University of California Davis, [5]Temerty Centre for Therapeutic Brain Intervention, Centre for Addiction and Mental Health, Toronto, [6]Center for Depression Research and Clinical Care, O'Donnell Brain Institute, University of Texas Southwestern Medical Center

Abstract Background: Electroconvulsive therapy (ECT) is a highly effective treatment for treatment-resistant depression (TRD), however its use is limited partly due to concerns of cognitive side effects. Evidence beyond 1 month for the efficacy of ketamine versus electroconvulsive therapy (ECT) for TRD has only recently become available. No studies have examined the cost-effectiveness (i.e., costs and effect measured as quality adjusted life years (QALYs) of racemic ketamine versus ECT for TRD.

Methods: Using a decision-tree model, the QALY and costs of ketamine was compared to ECT over 29 weeks, from a healthcare and societal perspective in the Canadian setting. Deterministic and probabilistic sensitivity analyses were used to account for uncertainty.

Results: Compared to ECT, ketamine resulted in higher health related quality of life (0.024) and lower costs from both a healthcare perspective (-$1,674) and societal perspective (-$3,410). In nearly all one-way sensitivity analyses, we found ketamine to be cost-effective relative to ECT.

Conclusions: Ketamine provided additional QALYs while saving costs relative to ECT in the treatment of TRD. Health insurance plans that cover all the costs of ECT, should consider covering the costs of ketamine treatment for TRD.

W14. SUSTAINED MOOD IMPROVEMENT WITH LAUGHING GAS EXPOSURE (SMILE): A RANDOMIZED, PLACEBO-CONTROLLED PILOT TRIAL OF NITROUS OXIDE FOR TREATMENT-RESISTANT DEPRESSION

Karim Ladha[1], Jiwon Lee[2], Gabriella Mattina[2], Janneth Pazmino-Canizares[2], Duminda Wijeysundera[1], Fatemeh Nezhad[3], Vanessa Tassone[3], Fathima Adamsahib[3], Wendy Lou[4], Sidney Kennedy[5], Venkat Bhat[1]*

[1]University of Toronto, [2]St. Michael's Hospital, Toronto, [3]Interventional Psychiatry Program, St. Michael's Hospital, Unity Health Toronto, [4]Biostatistics Division, Dalla Lana School of Public Health, University of Toronto, [5]Temerty Faculty of Medicine, University of Toronto

Abstract Background: Nitrous oxide may possess antidepressant effects; however, limited data exist on repeated administrations and active placebo-controlled studies in treatment-resistant depression (TRD). We aimed to test the feasibility of a randomized controlled trial (RCT) examining a 4-week course of nitrous oxide or active placebo, midazolam.

Methods: In this randomized, active placebo-controlled pilot trial, 40 participants with TRD were assigned either a 1-hour inhalation of 50% nitrous oxide plus intravenous saline (n=20) or a 1-hour inhalation of 50% oxygen plus intravenous midazolam (0.02 mg/kg, up to 2mg; n=20) once-weekly, for 4 weeks. Feasibility was assessed by examining rates of recruitment, withdrawal, adherence, missing data, and adverse events. The primary clinical efficacy measure was the change in depression severity, assessed by the Montgomery-Åsberg Depression Rating Scale (MADRS) score, from baseline to day 42.

Results: The recruitment rate was 22.3% (95% confidence interval [CI]: 16.9-29.0). Withdrawal rates were 10% (95% CI: 2.8-30.1) in both groups and adherence rates were 100.0% (95% CI: 82.4-100) in the nitrous oxide group and 94.4% (95% CI: 74.2-99.0) in the placebo group. There were no missing primary clinical outcome data in either group (0.0%, 95% CI: 0.0-17.6). MADRS score changed by -20.5% (95% CI: -39.6 to -1.3) in the nitrous oxide group and -9.0% (95% CI: -22.6 to 4.6) in the placebo group. Nearly all adverse events were mild to moderate and transient.

Conclusion: The findings support the feasibility and the necessity of conducting a full-scale trial comparing nitrous oxide and midazolam in patients with TRD.

W15. ALZHEIMER'S DISEASE SPECIFIC DIFFERENCES IN ENGAGEMENT BY GENDER FOR ONLINE CLINICAL TRIAL RECRUITMENT

Ralph Lee[1], Yu-Jay Huoh[1], Colin Sholes[1], Craig Lewin[1]*

[1]*Irvine Clinical Research*

Abstract Background: Clinical research sites have increasingly turned to online advertising to speed up recruitment. In this study, we look at differences in the impact of gender on advertisement engagement rate when recruiting for Alzheimer's Disease trials compared to trials for other indications.

Methods: Between 2022 and 2024, a commercial site in California showed online advertisements on social media platforms to 631,506 people within a broad age group. These advertisements were intended to identify people interested in clinical trials for treatments of anxiety, depression, or Alzheimer's Disease. People interested in these trials clicked the ad to get more information and were contacted by the site.

Results: During the observed timeframes, women were 17.5% less likely to engage with anxiety trial ads (2.17% vs. 1.79%, n=12,072). Women were also 8.0% less likely to engage with depression ads (1.18% vs. 1.08%, n=111,022). In contrast, women were 53.2% more likely to engage with Alzheimer's Disease ads (2.13% vs. 3.26%, n=508,412).

This 53.2% increase in engagement of Alzheimer's Disease ads against 17.5% / 8.0% decreases for anxiety / depression was highly statistically significant - a reduction in residual deviance of 70 on 2 degrees of freedom ($p < 1e-8$; indication and time of year were controlled for).

Conclusion: Multiple studies have shown that women are less likely to participate in clinical trials, both for Alzheimer's Disease and more broadly. However, with such a dramatic increase in engagement rate by women for online Alzheimer's Disease advertisements, there is definitely interest in Alzheimer's Disease treatments within the female population. The reduced willingness for women to actually participate in these trials must be a result of something downstream in the recruitment / enrollment process. In order to have a subject roster that is more representative of the broader population, these causes should be identified and remediated.

W16. ASSESSING THE RELATIONSHIP BETWEEN DISSOCIATION AND ESKETAMINE EFFICACY IN ADULTS WITH MAJOR DEPRESSION DISORDER AND ACUTE SUICIDAL IDEATION OR BEHAVIOR

Dionne Williams[1], Dong Jing Fu[2], Carla Canuso[2]*

[1]*Janssen Pharmaceuticals and Drexel University,* [2]*Janssen Pharmaceuticals*

Abstract Background: Dissociative side effects of newer generation antidepressants, including esketamine, can lead to functional unblinding, potentially impacting the interpretation of efficacy. One published study found no association between esketamine efficacy and dissociation assessed by the Clinician-Administered Dissociation States Scale (CADSS) in adults with treatment-resistant depression (TRD) [1]. Here we aim to investigate the

relationship between esketamine efficacy and dissociation in adult participants of Major Depression Disorder with acute suicidal ideation or behavior (MDSI). This analysis was performed on the pooled ASPIRE I and II Phase 3 esketamine studies as an adjunctive therapy in adults with MDSI [2].

Methods: This post-hoc analysis included two completed, double-blind (DB), randomized, placebo-controlled studies that evaluated the efficacy of 84 mg of esketamine intranasal spray compared to placebo intranasal spray both in addition to a standard of care treatment in adults with MDSI. We examined the responder status of participants (improvement from baseline ≥50% in MADRS total score) at Day 2 (24 hours) post first dose (primary endpoint of the studies) and post-dose AE of dissociation and change in CADSS score > 4 from pre-dose to post-dose on the first dosing day. The Fisher's exact test was used to assess the relationship between esketamine efficacy and dissociation by comparing dissociation and responder status.

Results: The total N for the esketamine 84 mg and the placebo treatment groups were N=229and N=227 respectively. Data from the full efficacy analysis set shows the proportion of responders with and without AE of dissociation was 38.5% (25/65) and 34.0% (55/156) for esketamine 84 mg respectively (p=0.540). The proportion of responders from TEAE reports for the placebo group with and without dissociation was 28.6% (2/7) and 22.6% (55/215) respectively (p=1.000). Data from the full efficacy analysis set shows the proportion of responders with and without dissociation (CADSS > 4) was 33.8% (53/157) and 39.1% (25/64) for esketamine 84 mg respectively (p= 0.535). The proportion of responders with and without dissociation (CADSS > 4) was 21.4% (3/14) and 26.0% (54/208) for the placebo group respectively (p =1.000).

Conclusion: Irrespective of the presence of dissociation, esketamine response rates were similar, suggesting that esketamine efficacy is not dependent on dissociation. Our findings from this post-hoc analysis are similar to Chen et al. 2022 reporting that there is no association between response rates and dissociation in adult participants with TRD. Thus, it appears that functional unblinding does not play a major role in the antidepressant efficacy of esketamine.

W17. ARE YOUR SF RATIOS INCREASING? THE SERIAL SCREENER, A VARIANT OF THE PROFESSIONAL SUBJECT

Thomas Shiovitz[*1], Chelsea Steinmetz[2], Brittany Steinmiller[2], Brett Burbidge[2]*

[1]CenExel CNR | CTSdatabase, LLC, [2]CTSdatabase, LLC

Abstract: Duplicate and professional subjects are a significant problem in clinical trials, particularly in those in indications with subjective endpoints, such as CNS and pain. These prospective subjects can change their presentation or magnify their symptoms as they go from site to site. Duplicate subject registries, such as CTSdatabase or Verified Clinical Trials, are available to detect such subjects at screen, before they can adversely affect study data integrity. We have found that in studies of persons with schizophrenia, the duplicate subject

issue is most pronounced, with these subjects often accounting for more than 10% of screened subjects.
Recently, CTSdatabase came across a case of a professional subject attempting to screen for a Shift Work Disorder study who had presented 29 different times, often in the same week, to a remarkable 15 different sites over a span of 5 years. The majority of presentations were screening or prescreening for schizophrenia, but he also screened for a Migraine study and prescreened for studies of Bipolar Affective Disorder and Borderline Personality Disorder as well as Healthy Volunteer and vaccine studies. The outcome of all the pre-screenings are unknown. However, every study he screened for resulted in a screen failure.

Of note, this subject should have known that he would be tracked by our registry as he signed an authorization each time and would presumably have been notified if he showed up elsewhere. We propose that the motivation of this subject was to sign consent and collect stipends, even if it was soon discovered that he was not an appropriate candidate for the study: A Serial Screener.

We will present the case history of this man, define the Serial Screener, and discuss steps that might be taken to detect such persons and mitigate the effect that they and other professional subjects may have on clinical trial enrollment and outcomes.

W18. PRACTICAL CONSIDERATIONS FOR THE EVALUATION OF PHYSICAL DEPENDENCE AND DRUG WITHDRAWAL FOR NOVEL CNS-ACTIVE DRUGS IN CLINICAL TRIALS

Beatrice Setnik[1], Jadwiga Martynowicz[2], Anthony Coulson[3], Sanjay Dube[4], Samiran Ghosh[5], Denise Milovan[1], Collin Price[6], Joyce Tsai[7], Berra Yazar-Klosinski[8], Gary Zammit[9]*

[1]Altasciences, [2]Neokee Pharma Consulting LLC, [3]NTH Consulting Inc., [4]McyoMedica Life Sciences and Stanford University SOM, [5] Data Science Coordinating Center for Clinical Trials Institute for Implementation Science University of Texas School of Public Health, [6]UCLA; West LA VA Medical Center, [7]Independent, [8]Lykos Therapeutics, [9]Clinilabs Inc; Icahn School of Medicine, Mount Sinai

Abstract Introduction: Chronic exposure (over 4 weeks) to certain drugs can lead to physical dependence (PD) and withdrawal symptoms (WS), which can be severe. The FDA's 2017 guidance on the Assessment of Abuse Potential of Drugs recommends evaluating PD following the abrupt discontinuation of novel CNS-active compounds. However, current PD evaluations during Phase III patient trials face challenges due to patient non-compliance with frequent administration of drug-class-specific withdrawal scales, disease-specific scales, adverse event (AE) monitoring, measuring physiological and pharmacodynamic effects, and collecting blood samples for pharmacokinetic (PK) analysis. Many of the relevant scales are clinician-rated and are not validated for patients without substance use disorders. Additionally, many assessments cannot be self-administered (eg, cardiac or brain activity measurements) and require in-person clinic visits, limiting the frequency of data collection. When PD is identified, guidance for effective drug tapering or conversion schemes is often lacking, highlighting the need to assess PD earlier in drug development. Current study designs must be adapted to better capture withdrawal symptoms throughout the relevant timeframe.

Methods: A working group of industry leaders with clinical trial experience met monthly from February to December 2024 to review FDA requirements, identify existing methodological limitations, and propose new, pragmatic methods to address clinical trials objectives. The group identified key challenges and recommended adaptations to existing trial designs and data collection methods.

Results: The working group recommends several pragmatic methods to evaluate PD. A subject-rated withdrawal scale, the Comprehensive Drug Withdrawal Scale, is being developed for frequent use in clinical trials involving both patient and healthy populations. This tool would be administered via a daily diary, similar to how AEs and concomitant medications are tracked. Disease-specific scales and subjective measures of WS and mood states may also be adapted for repeated, clinician-assisted or self-reported, virtual evaluations. Telemedicine and wearable devices approved by regulatory agencies could enable remote collection of physiological data and reduce the need for frequent in-clinic visits. Advances in PK assays, which require large blood volumes (up to 10 mL), may soon allow for remote collection via microsampling (10-20 µL). Evaluating WS in early-phase trials with healthy volunteers may help minimize late-phase confounders such as use of concomitant medications, provide insights into rebound effects, and assist in developing tapering or conversion protocols for later patient studies. Emerging artificial intelligence (AI) technologies may further enhance the prediction and interpretation of PD safety signals.

Conclusions: PD and WS following chronic drug exposure are critical safety concerns that must be addressed during drug development. However, evaluating these requires trial designs that support frequent symptom assessments following abrupt drug discontinuation. The working group has identified several key adaptations that can be incorporated into clinical trials to facilitate frequent collection of PD and withdrawal symptoms. The integration of new instruments, telemedicine, wearable devices, microsampling, and AI can help minimize patient burden while effectively evaluating the potential for PD.

W19. CAN IMPROVEMENTS IN METABOLIC HEALTH IMPACT COGNITIVE OUTCOMES IN INDIVIDUALS WITH MOOD DISORDERS? REAL-WORLD DATA FROM A MENTAL HEALTH AND METABOLISM CLINIC

Kateryna Maksyutynska[*1], Nicolette Stogios[1], Riddhita De[1], Femin Prasad[1], Akash PrasannaKumar[2], Tariq Ahmed[1], Vittal Korran[1], Marcos Sanches[2], Daphne Korczak[3], Ariel Graff-Guerrero[1], Gary Remington[1], Margaret Hahn[1], Sri Mahavir Agarwal[1]*

[1]Centre for Addiction and Mental Health, University of Toronto, [2]Centre for Addiction and Mental Health, [3]The Hospital for Sick Children, University of Toronto

Abstract Background: Individuals with mood disorders experience significant cardiometabolic burden, such as higher rates of type 2 diabetes and obesity, which is negatively associated with illness severity and quality of life. Early evidence of the use of metabolic pharmacological therapies has shown promise in improving multifaceted symptom domains. As a result, metabolic pathways have become novel targets for addressing chronic illness due to the growing incidence of treatment resistance and limited treatment options for cognitive decline in this patient population. This study utilizes real-world data from a Mental

Health and Metabolic Clinic to explore the association between weight loss and cognition in patients with mood disorders treated for metabolic dysfunction.
Methods: A retrospective chart review was conducted of all patients diagnosed with a mood disorder and enrolled in the Mental Health and Metabolism Clinic at the Centre for Addiction and Mental Health (CAMH) in Toronto, Canada, between January 2018 and November 2024 (REB #181-2024). Data was collected from the Brief Cognitive Assessment Tool (BCAT), a cognitive battery comprised of four instruments evaluating working memory, verbal fluency, and processing speed, completed as part of the clinic's standardized assessment. Weight and other metabolic data were collected from the day of cognitive assessment completion. A Spearman's Rank correlation analysis was performed to assess the association between changes in cognitive and metabolic parameters.

Results: Forty-eight patients with mood disorders (mean age: 36.10 ± 13.02 years; 20.8% male) completed the BCAT and experienced weight loss between cognitive assessments. The primary mood disorder diagnoses of the included sample were bipolar disorder (54.2% BD-I; 16.7% BD-II; 8.3% BD-NOS) and major depressive disorder (20.8%). Patients were treated with a lifestyle (12.5%), metformin (41.7%), topiramate (6.3%), semaglutide (29.2%), or semaglutide + metformin (10.4%) intervention at the time of their greatest weight loss. On average, patients achieved weight loss of -7.28 ± 7.40 kg, with an average duration of 34.70 ± 20.02 weeks between cognitive assessments. A significant negative correlation was identified between changes in weight and verbal fluency (ρ=-0.321; p=0.026), with greater weight loss associated with improved cognitive performance. No significant correlation was found between changes in weight and global cognition, working memory, or processing speed.

Conclusions: This study highlights the close association between metabolic and cognitive outcomes, and emphasizes the importance of metabolic monitoring in the context of severe mental illness. Future research must work to identify the underlying mechanisms of this interaction and reproduce findings in randomized controlled trials.

W20. NEW META-ANALYTIC RESULTS INFORMING A PROSPECTIVE TRIAL OF PSILOCYBIN FOR CANCER-RELATED EXISTENTIAL DISTRESS

Samantha Lim[*1], Maria Lapid[2]*

[1]Our Lady of Fatima University, Philippines, [2]Mayo Clinic

Abstract Objective: Terminal cancer patients experience profound existential distress, significantly impairing their quality of life. This study presents new meta-analytic findings on the effectiveness and safety of psilocybin-assisted therapy for alleviating cancer-related existential distress. By synthesizing data from prior trials, this research provides critical insights to guide the design of a prospective clinical trial, marking a step in advancing therapeutic options for terminally ill patients.
Methods: A comprehensive search of MEDLINE, APA PsycINFO, Cochrane database, Embase, and Scopus was conducted from inception to August 26, 2024 to identify randomized controlled trials (RCTs), open-label trials, qualitative studies, and case reports evaluating psilocybin for cancer-related distress. Quantitative data were pooled using a random-effects meta-analysis to calculate standardized mean differences (SMDs).

Heterogeneity was assessed using the I^2 statistic, and subgroup analyses were performed to compare RCTs with open-label trials. Qualitative data were thematically analyzed to capture patient-centered experiences. Study quality was evaluated using the Cochrane Risk of Bias tool for RCTs and the Methodological Index for Non-Randomized Studies (MINORS) criteria. The study was registered with PROSPERO (CRD42024511692).

Results: Fourteen studies met the inclusion criteria, comprising three RCTs, five open-label trials, five qualitative studies, and one case report. The meta-analysis revealed significant reductions in depression (pooled SMD: -3.08, 95% CI: -10.34, 4.17, I^2=94.8%) and anxiety (pooled SMD: -1.74, 95% CI: -16.86, 13.38, I^2=96.5%) at early evaluation (~3 weeks). At late evaluation (~6 months), pooled effect sizes for depression (-3.39, 95% CI: -34.69, 27.90, I^2=95.9%) and anxiety (-3.22, 95% CI: -36.03, 29.59, I^2=96.0%) also demonstrated substantial heterogeneity. Subgroup analysis showed larger effect sizes in open-label trials than RCTs, with significant differences in depression ($p < 0.001$) and anxiety ($p < 0.001$). Psilocybin therapy demonstrated improvements in psychological and existential distress, with mild, transient adverse effects. Thematic analysis revealed psilocybin fostered existential relief and enhanced emotional and spiritual well-being. Participants had increased self-compassion, acceptance of mortality, and a deeper sense of meaning to life.

Conclusion: This study presents new meta-analytic findings on psilocybin-assisted therapy for cancer-related existential distress, demonstrating its potential to reduce depression and anxiety while enhancing emotional well-being. Despite high heterogeneity, analyses revealed themes of existential relief and deeper life meaning. These findings are directly informing the development of our own prospective pilot clinical trial at our cancer center, designed to investigate psilocybin therapy in advanced cancer patients with severe existential distress, aiming to improve their quality of life.

W21. COMPARISON OF MORTALITY AND MORBIDITY RISK WITH MONOCLONAL ANTIBODIES: DATA FROM MEDICAL AND STATISTICAL REPORTS FROM US FDA FOR SEVEN APPROVED MEDICATIONS CONSISTING OF A TOTAL DATABASE OF 19,721 SUBJECTS

Aishwarya Prasad[*1], Anshu Arora[1], Arun Arora[1], Arifulla Khan[1]*

[1]Northwest Clinical Research Center

Abstract Introduction: For Alzheimer's Disease, currently, two classes of medications are available; symptomatic treatment with cholinesterase inhibitors (AChEIs) or NMDA inhibitor and newer disease modifying drugs-monoclonal antibodies (mAb). Current literature shows that the newer drugs may be causing significantly more adverse effects. The safety profile of these medications are not fully established, specifically the mortality and morbidity risk. Here, we evaluated the mortality and morbidity risk among the seven FDA approved medications including the 3 new Monoclonal Antibody drugs.

Methods: We searched the FDA database(www.accessdata.fda.gov/scripts/cder/daf/index.cfm) for all approved AD treatment drugs through October 2024, focusing on verified safety data for investigational medications.

Our search targeted cholinesterase inhibitors (donepezil, galantamine, rivastigmine), memantine and monoclonal antibodies (lecanemab, aducanumab, donanemab). Mortality and Morbidity (used here interchangeably with Severe Adverse Effects) data was analyzed. PEY was calculated for all of these classes of medications with available data.

Results: Among the 19,721 clinical trial participants, 163 (0.8%) died and 1651 (8.3%) experienced protocol defined SAEs. There were no obvious trends in the frequency of SAEs and death between investigational medications and placebo controls among any of the trials (p-value not significant). Since the duration of exposure varied across the many trials, we tabulated the mortality and morbidity risk using the PEY model. There were no obvious differences in the frequency of protocol defined SAEs as well as mortality risk. The overall mortality and morbidity risk was lower among the clinical trials for AChEI medications than mAb, however higher using the PEY model. Looking specifically at ARIA, 41 subjects had a severe ARIA events (1.4%) and 2 (0.07%) out of 2856 patients exposed to an mAb had a fatal occurrence of ARIA. However, the overall mortality rate in the mAb drug group was not significantly higher than the placebo group.

Summary: The overall mortality and morbidity rates among the clinical participants were surprisingly low and there were no obvious differences between the approved AD medications and placebo. Based on this data, it appears that the currently FDA approved AD medications including mAbs are relatively safe. Interestingly, the mortality rate for comparable age range in the US general population is higher at 1978/100K/yr. This may be explained by the hypothesis that these data may not reflect the US general population, if the trials included less medically complicated, relatively early onset AD patients. Of the 2856 AD patients assigned to an mAb drug, ARIA meeting SAE criteria was found in 41 (1.4%) patients, two of whom died (0.07%); 1 after ARIA-E, 1 after ARIA-E and ARIA-H.

Conclusion and Limitations: These data from the FDA archives suggest that the 7 approved drugs have low morbidity (SAEs) and mortality risk. The risk was comparable to placebo control within trials and general age matched control. The relatively low mortality and morbidity risk compared to the general US population in that same age range may point towards a less medically complicated sample group in the trials. For the mAb trials, ambiguities include the stage of Alzheimer's disease, APOE gene status which is not fully understood with established guidelines and tests, presence of microhemorrhages or minor cerebral edema at baseline, even before considering the use of mAB for AD patients. Further studies are needed to better understand and interpret these results.

W22. 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], Emma Grassi[1], Bridget Murphy[1], Peri Barest[1], David Chitayat[2], Sonia Hernandez-Diaz[3], Adele Viguera[4]*

[1]Massachusetts General Hospital, Ammon-Pinizzotto Center for Women's Mental Health, [2]University of Toronto, [3]Harvard T.H. Chan School of Public Health, [4]Massachusetts General Hospital, Ammon-Pinizzotto Center for Women's Mental Health, Cleveland Clinic, Cleveland Clinic Neurological Institute

Abstract: Background: 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.

Methods: 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 April 4th, 2024, 3577 women were enrolled in the NPRPM, including 1269 in the exposure group and 2206 in the comparison group. Medical records were obtained for 77% of participants. A total of 2571 participants (945 exposed to an SGA in the first trimester, 1626 unexposed to an SGA during pregnancy) completed the postpartum interview and were eligible for analysis. Of 975 infants in the exposure group, 37 confirmed major malformations were identified. In the control group of 1653 infants, 33 malformations were identified. No consistent pattern of malformation was seen in either group. The absolute risk of major malformations was 3.79% in the exposure group and 1.99% 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 3.79% in the exposed group, while it was lower at 1.99% 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.

W23. EVALUATING AUGMENTATION OF ANTI-SUICIDAL EFFECTS OF INTRAVENOUS KETAMINE BY LOW ORAL DOSES OF OPIOID RECEPTOR PARTIAL AGONISM

Jason Tucciarone[*1], Igor D. Bandeira[1], Ian H. Kratter[1], Jarrod Ehrie[1], Christine Blasey[1], Boris D. Heifets[1], Alan F. Schatzberg[1]*

[1]*Stanford University School of Medicine*

Abstract Background: Ketamine has demonstrated rapid-onset antidepressant and anti-suicidal properties. Most mechanistic studies attribute the therapeutic properties of ketamine to NMDA receptor antagonism. Our group previously demonstrated that mu opioid receptor antagonism attenuates intravenous ketamine's acute antidepressant effects. Others have found that ultra-low oral doses of a partial mu receptor agonist have potent antidepressant and anti-suicidal properties. To reduce the burden and risk of repeated ketamine dosing needed to maintain therapeutic efficacy, we explored whether low dose opioid receptor agonism with buprenorphine could extend the anti-suicidal and antidepressant properties of a single administration of intravenous ketamine.

Methods: In an ongoing, double-blinded trial to be completed by mid-March 2025, 42 participants to date (average age 37.5 +/- 10.9 years, 75% female) diagnosed with treatment resistant depression have received open-label IV ketamine infusion (0.5mg/kg), followed by randomization two days later to receive either dose-escalated buprenorphine (0.2-0.8 mg QOD) or placebo for 4 weeks, followed by a post taper follow up for 2 weeks. Study entry criteria include a major depressive episode lasting ≥ 8 weeks, a history of at least one treatment failure in the current episode, a Beck Scale for Suicidal Ideation (BSSI) score ≥ 6 and a minimum score of 3 on the Columbia-Suicide Severity Rating Scale (CSSRS). The primary measure outcome was change in the BSSI. Pre-defined secondary outcomes include changes from baseline on the Montgomery–Åsberg Depression Rating Scale (MADRS), Hamilton Depression Rating Scale (HAMD-21). The time course was analyzed via mixed-effects ANOVA and Bonferroni correction.

Results: Of the 42 participants infused thus far with a single dose of IV ketamine, 33 participants have completed the day 45-day time course. On day 3 post infusion, 52.1% of participants achieved ≥ 50% reduction of BSSI; response and remission rates were 35/17.5% on the HAM-D-21 and 37.5/25% on the MADRS respectively. With recruitment ongoing, the intervention allocation remains blinded, but preliminary results for the entire study are provided here. At day 45, BSSI decreased from 15.81 to 7.15 ($F_{4,139} = 28.40$, $p < 0.0001$); mean HAM-D-21 decreased from 24.88 to 16.94 ($F_{4,128} = 20.98$, $p < 0.0001$), and mean MADRS decreased from 33.98 to 22.45 ($F_{3,117} = 18.56$, $p < 0.0001$). At day 45, 21% of participants continued to remit using HAMD, with 27% continuing to remit using MADRS criteria. As of this submission recruitment is ongoing and blinded to buprenorphine treatment but completion will be before the ASCP meeting.

Conclusion: A single dose IV ketamine infusion substantially reduced depression and suicidality at day 3, with somewhat greater effect observed for suicidality than depression. The overall therapeutic benefits were largely maintained out to day 45, beyond what has been typically reported in the literature. While this outcome could be consistent with our hypothesis that low dose mu opioid agonism in the buprenorphine arm will prolong the therapeutic benefits of ketamine > placebo, we can only speculate until study completion and unblinding. The study will be completed prior to the ASCP meeting, and unblinded results will be presented at ASCP.

W24. EFFECTS OF COMP360 ON ANHEDONIA-RELATED ITEMS OF THE MONTGOMERY-ASPERG DEPRESSION RATING SCALE (MADRS) AND POSITIVE AND NEGATIVE AFFECT SCALES (PANAS)

Matt Young[*1], *Joyce Tsai*[1], *Claudia Sisa*[1], *Lindsay Marwood*[1], *Jamie Chai-Reese*[1], *Sunil Mistry*[1], *Guy Goodwin*[1]

[1]*Compass Pathways, PLC*

Abstract Background: Both depressed mood and anhedonia are core symptoms for diagnosis of major depressive disorder (MDD). Although patients voice the importance of improvements in anhedonia and positive affect, both pharmacological and non-pharmacological antidepressant treatments (ADT) have historically addressed negative affect better than positive affect, and anhedonia is a common residual symptom in treatment-resistant depression (TRD). Recent studies suggest that psilocybin may impact anhedonia symptoms in individuals with TRD, including a 233-patient randomized controlled double-blind study of investigational COMP360 psilocybin (COMP 001). To address the paucity of data on the effects of psilocybin on measures of anhedonia, we undertook additional post-hoc analyses of data from the COMP 001 study.

Methods: Data from COMP 001 were used to assess the effect of 25 mg, 10 mg or 1 mg (n=79, 75, 79; N=233) investigational COMP360 psilocybin on items of the Montgomery-Asperg Depression Rating Scale (MADRS) and the Positive and Negative Affect Scales (PANAS) most relevant to anhedonia. These include the MADRS Anhedonia Factor (MADRS-AF; Items 1, 2, 6, 7, 8) and the PANAS positive (PANAS-P) scale, which correlate with changes on the Snaith-Hamilton Pleasure Scale (SHAPS) and/or the Dimensional Anhedonia Rating Scale (DARS). For MADRS-AF, least squares (LS) mean change from baseline (CFB) are reported for Day 2 and Weeks 1, 3, 6 and 12 after treatment administration (Day 1). For PANAS total scores, LS mean CFB is reported for Day 2 and Week 3. Mean CFBs are also reported for individual items of the MADRS-AF and PANAS-P at the same time points as their respective total scores. All analyses were conducted on observed cases without explicit imputations for missing data or control over Type-I error.

Results: Mean CFB MADRS-AF total score was numerically greater in the 25 mg group than the 10mg and 1mg groups at 1 day, 1 week, 3 weeks and 6 weeks after a single administration of COMP360. Mean CFB in MADRS-AF total score in the 25mg group stabilized from Week 1 to Week 12. Numerically greater mean CFB in all 5 items of the MADRS-AF were observed in the 25 mg group compared to the 10 mg and 1 mg groups up to Week 12. The LS Mean Difference in CFB between 25 mg and 1 mg in MADRS-AF total

score were nominally significant at Day 2 (LS Mean Difference [95% Confidence Interval] (-3.9 [-6.2, -1.7]), Week 1 (-4.2 [-6.3, -2.0]), Week 3 (-4.3 [-6.4, -2.1]) and Week 6 (-2.6 [-4.9, -0.3]). Numerically greater LS Mean CFB differences were seen at Week 9 and 12 for the COMP360 25 mg vs 1 mg comparisons, but these were not nominally significant. The mean difference CFB at Day 2 and Week 3 demonstrated numerical superiority of 25 mg but not 10 mg over 1 mg for both PANAS-P and PANAS-N total scores. For PANAS-P, the LS mean differences in CFB between the 25 mg and 1 mg groups were 6.3 (95% confidence interval [CI] [3.4, 9.2]) at Day 2 and 6.2 (95% CI [3.5, 8.8]) at Week 3. For PANAS-N, the LS mean differences in CFB between the 25 mg and 1 mg groups were -3.3 (95% CI [-5.3, -1.2]) at Day 2 and -3.2 (95% CI [-5.6, -0.8]) at Week 3. Only the 25mg group sustained improvements the day after treatment at Week 3. Individual items most improved in 25mg group compared to the 10mg or 1mg group included 'Interested', 'Enthusiastic', 'Inspired', 'Proud', and 'Determined'

Conclusion: In a post-hoc analysis of a large (N=233) Phase 2b study of participants with TRD, treatment with COMP360 25 mg improved items of the MADRS and PANAS that are most relevant to anhedonic symptoms of depression. COMP360 25 mg appeared to have nominally greater efficacy than 10 and 1 mg, suggesting a dose-related effect. Given the post-hoc nature of this analysis, future studies should prospectively study these effects.

W25. INITIATING DEXTROMETHORPHAN 45 MG-BUPROPION 105 MG (AUVELITY®) IN PATIENTS WITH MAJOR DEPRESSIVE DISORDER (MDD): EXPERT PANEL CONSENSUS RECOMMENDATIONS

Anita Clayton[*1], Gus Alva[2], Philip Bowman[3], Erin Crown[4], Bibi Das[5], Paul Doghramji[6], Brooke Kempf[7], John Miller[8], Andrew Muzyk[9], Jeremy Schreiber[10]*

[1]University of Virginia SOM, [2]University of California Riverside Medical School, [3]Bowman Medical Group, [4]Pennsylvania Mental Health Initiative, State College, [5]Dr. Bibi Das MD, [6]Pottstown Medical Specialists, [7]Indiana University, [8]Brain Health, [9]Campbell University College of Pharmacy and Health Sciences, [10]West Liberty University,

Abstract Background: Despite a multitude of approved treatments for major depressive disorder (MDD), there remains a critical need for those with novel mechanisms of action (MOAs) that may improve patient outcomes. Dextromethorphan 45 mg-bupropion 105 mg (Auvelity®; DM-BUP) is an oral, N-methyl-D-aspartate (NMDA) receptor antagonist, sigma-1 receptor agonist, and aminoketone CYP2D6 inhibitor approved for treatment of MDD in adults. Additionally, the components of DM-BUP inhibit the reuptake of monoamines. With a novel MOA, healthcare providers (HCPs) may seek real-world, evidence-informed clinical guidance on how to prescribe DM-BUP for their patients. To fill this knowledge gap, HCPs with experience treating MDD and prescribing DM-BUP participated in a modified Delphi panel to develop expert recommendations for initiating or switching to DM-BUP for MDD to complement data from published literature and the DM-BUP Prescribing Information.

Methods: The Panel was comprised of 10 HCPs from the U.S. representing primary care, psychiatry, and pharmacy. A comprehensive literature review was conducted that included both published literature and congress presentations relevant to the treatment of MDD with

DM-BUP. Guidance in comparable clinical scenarios was also assessed. Based on clinical experience and literature review, preliminary statements were drafted by the Panel's Chair. These statements were anonymously voted on by the panel for level of agreement pre-meeting and discussed as a group in 2 rounds of virtual meetings where they were refined, and anonymously re-rated. Statements required a mean score ≥3.0 on a 5-point (~75% agreement) Likert scale (Scale: 0=do not agree to 4=very much agree) to reach consensus.

Results: Panelists developed 28 final recommendation statements across two major topics (1) Overcoming perceived barriers to initiating and using DM-BUP and (2) Approaches for initiating or switching to DM-BUP for MDD treatment. Consensus was achieved on all items (mean overall score=3.6). Key recommendations (paraphrased here) included the following: 1) DM-BUP is indicated as a monotherapy for adults with MDD and should be considered as first-line treatment in appropriate patients across several target clinical populations; 2) Due to its novel MOA in MDD, DM-BUP is also recommended for those with inadequate response (e.g. residual symptoms and/or intolerable side effects) to traditional pharmacological treatments; 3) Use of DM-BUP is appropriate for individuals with MDD and anxiety symptoms; 4) When switching from, or adding to, TCAs, SSRI/SNRIs, atypical antidepressants, or adjunctive antipsychotics prescribed for MDD, the level of CYP2D6 inhibition of the current treatment must be considered when deciding whether an abrupt switch, taper, discontinuation, or dosage adjustment is appropriate prior to initiating DM-BUP, 5) When switching from, or adding to, other NMDA modulators (e.g. ketamine or esketamine) for MDD, it may be possible to start in close proximity, but should be done with caution.

Conclusions: The Delphi panel agreed DM-BUP is a first-line treatment for MDD in selected clinical populations. DM-BUP should be considered for patients who have inadequate response to antidepressant therapy, who desire a switch for tolerability or efficacy reasons, and patients with comorbid anxiety. These recommendations will provide HCPs with additional information needed to optimize and personalize treatment for their patients with MDD.

W26. EFFICACY AND SAFETY OF A SINGLE ADMINISTRATION OF THE N-METHYL-D-ASPARTATE SUBUNIT 2B-SELECTIVE NEGATIVE ALLOSTERIC MODULATOR, BI 1569912, IN PEOPLE LIVING WITH MAJOR DEPRESSIVE DISORDER: A PHASE IB RANDOMIZED CONTROLLED TRIAL

Roger S. McIntyre[1], Gerard Sanacora[2], David P. Walling[3], Elan A. Cohen[4], Shishuka Malhotra[5], Holger Rosenbrock[6], Manuela Schmitz[7], Andreas Scholz[6], Sigurd D. Suessmuth[6], Franco De Crescenzo[6]*

[1]University of Toronto, [2]Yale University, [3]CenExel CNS, [4]CenExel Hassman Research Institute, [5]Neuro-Behavioral Clinical Research, [6]Boehringer Ingelheim Pharma GmbH and Co. KG, [7]mainanalytics GmbH, Sulzbach/Taunus

Abstract Background: Although non-selective N-methyl-D-aspartate (NMDA) receptor antagonists, such as ketamine and esketamine, are efficacious in treating major depressive disorder (MDD) they are associated with safety concerns e.g., dissociation, sedation and/or abuse potential. Selective negative allosteric modulators of NR2B subunit containing NMDA receptors (NR2B NAMs) may offer efficacy with better tolerability. BI 1569912 is an oral NR2B NAM in development for MDD.

Methods: We report data from a randomized, double-blind, placebo-controlled Phase Ib trial (NCT04937829) of a single dose of BI 1569912 (5 mg or 20 mg) vs placebo adjunctive to antidepressants in adults with moderate-to-severe MDD and insufficient response to ongoing antidepressant monotherapy. Efficacy was assessed by maximum decrease from baseline in Montgomery-Åsberg Depression Rating Scale (MADRS) total score at any day within a 7-day interval (primary efficacy endpoint) and by change from baseline in MADRS total score and Leuven Affect and Pleasure (LAPS) subscales at individual timepoints. Treatment response (≥50% reduction from baseline MADRS) and remission (MADRS ≤10) were assessed. Primary safety endpoint was number/% of patients with drug-related adverse events (DRAEs). Dissociative symptoms were assessed by the Clinician Administered Dissociative States Scale (CADSS) and psychedelic effects by the Bowdle Visual Analog Scale (B-VAS).

Results: Participants (N=59) were randomized 1:1:1 to receive placebo (n=19), BI 1569912 5 mg (n=20), or 20 mg (n=20). Median age was 54.0 years, 54.2% of participants were female, and mean (SD) MADRS total score at baseline was 34.6 (5.8) points. Adjusted mean (SE) maximum decrease from baseline in MADRS within a 7-day interval was similar between groups, at -19.3 (2.3), -16.8 (2.2), and -19.9 (2.2) for placebo, BI 1569912 5 mg, and 20 mg, respectively. However, a single BI 1569912 20-mg dose provided a clinically relevant 3.4- to 4.9-point improvement in MADRS total score versus placebo at Days 2, 4, and 6, meeting predefined criteria for further development. A higher proportion in the BI 1569912 20 mg group achieved MADRS response at Days 2, 4, and 6 (50.0%, 45.0%, and 50.0%) vs placebo (21.1%, 10.5%, and 21.1%). Remission on Days 2, 4, and 6 was also achieved by a higher proportion in the BI 1569912 20 mg group (20.0%, 35.0%, and 40.0%) vs placebo (10.5%, 10.5%, and 21.1%). LAPS results showed improvements in dimensions of depression in all treatment arms.

The proportion of participants with ≥1 AE, from start of treatment to Day 15, was 31.6%, 35.0%, and 15% for placebo, BI 1569912 5 mg, and 20 mg groups, respectively. DRAEs were reported in the placebo group (n=1, 5.3%), BI 1569912 5 mg group (n=3, 15.0%), and 20 mg group (n=1, 5.0%). In BI 1569912-treated participants, DRAEs included constipation (n=2), and flatulence, increased blood pressure, decreased appetite, dizziness, and dry skin (n=1 for all). No severe/serious AEs, or AESIs were reported. CADSS scores remained low across the study with most patients reporting scores of zero. No clinically relevant signs regarding psychedelic effects were observed via B-VAS.

Conclusion: BI 1569912, an oral NR2B NAM in development for treatment of MDD, was well tolerated with no dissociation and no clinically relevant signs of human abuse potential. Preliminary efficacy signals support continued development of BI 1569912 in adults with MDD.

Funding: Boehringer Ingelheim Pharmaceuticals, Inc.

W27. FETAL BRAIN CHANGES FROM IN UTERO EXPOSURE TO SSRIS

Emily Leiderman[1], Madison Johnson[1], Mujeeb Shad[2]*

[1]*Touro University Nevada,* [2]*University of Nevada, Las Vegas*

Abstract Background: Serotonin reuptake inhibitors (SSRIs) are the most widely used antidepressants for Major
Depressive Disorder (MDD), and prenatal exposure to SSRIs has been associated with hippocampal changes in newborns. Although few human studies have reported these changes, they may explain the increased risk for depression after in-utero exposure to SSRIs. This review analyzes findings from a small number of human studies to explore SSRI-induced changes in the developing hippocampus and other regions associated with depression.

Methods: A literature search using key phrases such as "perinatal SSRIs," "hippocampal changes," and "fetal brain development" yielded six human studies exploring the potential effects of prenatalexposure to SSRIs on fetal brain areas linked to depression vulnerability.

Results: Four of the six reviewed studies in human subjects revealed significant changes in corticofugal and corticothalamic tracts after prenatal SSRI exposure; three human studies showed increased amygdala volume, and one preliminary study found decreased hippocampal volume. One study reported global brain changes, which contradicted another. Compared to only one study in human subjects, fifteen of seventeen rodent studies revealed hippocampal changes after SSRI exposure, with reduced BDNF exon mRNA. However, some inconsistent findings regarding hippocampal DNA methylation, cell proliferation, and synaptic density were reported. Two of the reviewed studies also reported decreased serotonin and dendritic density.

Conclusion: This review reinforces the connection between in-utero exposure to SSRIs and an increased risk for depression. More research is required to confirm the findings from the reviewed studies, including the risk of increased vulnerability to depression and decreased treatment response.

W28. SODIUM-GLUCOSE COTRANSPORTER-2 INHIBITOR EMPAGLIFLOZIN FOR DEPRESSION: PRELIMINARY RESULTS

David Liebers[1], Umit Tural[2], Dan Iosifescu[1]*

[1]*New York University School of Medicine,* [2]*The Nathan Kline Institute for Psychiatric Research*

Abstract Purpose and Content: Ketogenic diets have associated with large-effect improvements in depressive symptoms in case-series and open label studies. Sodium-glucose cotransporter-2 (SGLT2) inhibitors, antidiabetic medications unique for their ketogenic properties, have associated with lowest risk of incident depression in population-based studies, and improved brain energetics in preclinical studies. This pilot study seeks to test the

feasibility, safety, and preliminary efficacy of SGLT2 inhibitor empagliflozin in major depressive disorder (MDD).
Methods: To date, five participants with MDD (confirmed by MINI) have completed a six-week, single-arm, open label study of empagliflozin. Participants are administered empagliflozin 10mg for two weeks and then 25mg for four additional weeks. Baseline measures included weight, BMI, age, C-reactive protein (CRP), Montgomery-Åsberg Depression Rating Scale (MADRS), Snaith-Hamilton Pleasure Scale (SHAPS), Clinical Global Impression-Severity (CGI-S), and serum β-hydroxybuytrate (BHB) levels. Here, we report comparisons between measures at baseline, week 2 and week 6.

Results: Baseline characteristics included a mean age 33.20 (SD=14.05), BMI of 29.29 (SD=5.14), HbA1c 5.08 (SD=0.37), and CRP of 5.77 (SD=3.92). From baseline to the six-week endpoint, the mean change in BHB was 0.29 mmol/L (SD=0.544, z = 1.214, p-value=0.3125), the mean change in MADRS was -13.6 (SD=4.5, z=-2.023, p= 0.0625), and the mean change in SHAPS was 9.0 (SD=3.74; z = 1.826, p=0.125). The effect size (calculated with non-parametric assumptions) for the change in BHB was moderate (r=0.422; 95% CI = 0.06-0.93) at week 2 and large (r = 0.543; CI = 0.18-0.93) at week 6. Similarly, for the change in MADRS the non-parametric effect size was large (r = 0.548; 95% CI=0.06-0.95) at week 2 and also large (r = 0.905; 95% CI =-.9-0.95) at week 6. There were no serious adverse events or drop outs due to adverse events. There was no significant relationship between change in BHB and change in MADRS (Spearman rho=0.4; p=0.517) in this small sample.

Relevance: Treatment with the SGLT2 inhibitor empagliflozin in MDD was associated with moderate to large effect sizes in changes in serum ketone (BHB) levels, and with large effect size of change in depression severity (MADRS). While we did not observe statistically significant changes in this very small sample, these preliminary data provide support for further study of SGLT2 inhibitors in MDD.

Keywords: depression, ketogenesis, brain energetics, metabolism, SGLT2 inhibitors

W29. LONG-TERM ADJUNCTIVE LUMATEPERONE TREATMENT IN MAJOR DEPRESSIVE DISORDER: RESULTS FROM A SIX-MONTH OPEN-LABEL EXTENSION STUDY

Willie R. Earley[1], Suresh Durgam[1], Susan Kozauer[1], Changzheng Chen[1], Tobie Escher[1], Andrew J. Cutler[2]*

[1]Intra-Cellular Therapies, Inc., [2]SUNY Upstate Medical University

Abstract: Background: Current treatments for major depressive disorder (MDD) are limited by side effects including weight gain and metabolic disturbances. Approximately 50% of patients with MDD have inadequate response to antidepressant therapy (ADT) leading to reduced adherence, functioning, and quality of life.
Lumateperone is an FDA-approved, atypical antipsychotic to treat schizophrenia and depressive episodes associated with bipolar I or II disorder. The efficacy and safety of lumateperone 42mg adjunctive to ADT in patients with MDD with inadequate ADT response was recently demonstrated in 2 Phase 3 trials (Study 501 NCT04985942; Study 502

NCT05061706). This Phase 3 open-label extension trial, Study 503 (NCT05061719), investigated the long-term safety of adjunctive lumateperone 42mg in patients who completed Study 501 or 502.

Methods: Study 501 and 502 enrolled patients (18-65 years) meeting DSM-5 criteria for MDD with inadequate response to 1-2 adequate courses of ADT in the current depressive episode and Montgomery-Asberg Depression Rating Scale (MADRS) Total score ≥24 and Clinical Global Impression Scale-Severity (CGI-S) score ≥4. Patients who safely completed the 6-week double-blind treatment period could enroll in Study 503 to receive 26-week, open-label, oral, once-daily lumateperone 42mg adjunctive to continued ADT. The primary endpoint was safety and tolerability of lumateperone 42mg, measured by adverse events (AEs), extrapyramidal symptoms (EPS), suicidality, and changes in laboratory parameters, vital signs, and electrocardiogram (ECG) measures. The secondary endpoint was improvement/maintenance of depressive symptoms, measured by MADRS and CGI-S Total scores change from Study 501 or 502 baseline to Week 26 of open-label treatment.

Results: Of 809 patients enrolled and treated, 684 (84.5%) completed the treatment period. Treatment-emergent AEs (TEAEs) occurred in 548 patients (67.7%), with 292 (36.1%) experiencing a drug-related TEAE. Treatment discontinuation due to an AE occurred in 7.4% of patients. TEAEs reported in ≥5% of patients were headache (16.6%), dizziness (10.6%), dry mouth (8.0%), nausea (7.7%), somnolence (7.2%), diarrhea (6.2%), and nasopharyngitis (5.2%). Most TEAEs (98.9%) reported were mild to moderate in severity. The rates of EPS-related TEAEs based on broad standard Medical Dictionary for Regulatory Activities query were low (3.8%) with no increase in EPS scales. Mean changes from baseline to end of treatment were minimal for body morphology, cardiometabolic laboratory values, prolactin levels, pulse rate, blood pressure, and ECG measures. No patients reported emergence of serious suicidal ideation or suicidal behavior during the study. Symptoms of depression improved as measured by mean change from baseline to Week 26 in MADRS Total score (−22.9) and CGI-S Total score (−2.7).

Conclusions: Lumateperone 42mg adjunctive to ADT was safe and effective during 26-week treatment in patients with MDD and inadequate ADT response.

W30. THE EFFECTS OF ADJUNCTIVE CARIPRAZINE IN PATIENTS WITH MAJOR DEPRESSIVE DISORDER WITH AND WITHOUT COMORBID ANXIETY SYMPTOMS: A POST HOC ANALYSIS

Maurizio Fava[1], Jun Yu[2], Elizabeth Pappadopulos[2], Simranpreet Waraich[2]*

[1]Massachusetts General Hospital, [2]AbbVie

Abstract Introduction: Many individuals with major depressive disorder (MDD) experience comorbid anxiety, which may lead to poorer outcomes relative to depression without anxiety. Cariprazine, a dopamine D3-preferring D3/D2 and serotonin 5-HT1A receptor partial agonist, is approved as an adjunct to antidepressant therapy (ADT) for MDD. This post hoc analysis aimed to assess the effects of adjunctive cariprazine on anxiety symptoms, including both psychic and somatic dimensions, in patients with and without baseline anxiety and in those with at least mild, at least moderate, or severe baseline anxiety.

Methods: In a phase 3, randomized, double-blind, placebo-controlled trial (NCT03738215), the effects of cariprazine 1.5 mg/d or 3 mg/d + ADT in adults with MDD and inadequate response to ADT were evaluated. Post hoc analyses evaluated changes from baseline to week 6 in Hamilton Anxiety Rating Scale (HAM-A) total score and in HAM-A psychic (sum of items 1-6) and somatic (sum of items 7-14) subscale scores in the overall population. Changes in HAM-A total score were also examined by baseline severity subgroups as follows: at least mild (HAM-A total score > 7), at least moderate (HAM-A total score > 14), and severe (HAM-A total score > 23). In addition, Hamilton Depression Rating Scale (HAM-D) anxiety/somatization factor scores were evaluated in patients with and without baseline anxiety (HAM-D factor score ≥7 and < 7, respectively).

Results: A total of 751 patients (cariprazine 1.5 mg/d + ADT n=250; 3 mg/d + ADT n=252; placebo + ADT n=249) were included. In the overall population, the least squares mean difference (LSMD) at week 6 in HAM-A total score was statistically significant for cariprazine 1.5 mg/d + ADT vs placebo + ADT (-1.3; P=.0370). Change in HAM-A psychic subscale scores was significantly greater for cariprazine 1.5 mg/d + ADT vs placebo + ADT (LSMD: -0.7; P=.0295). Numerically greater reductions in somatic subscale scores with cariprazine + ADT vs placebo + ADT were observed. Based on HAM-A total score, most patients had at least mild (n=742; 98.8%) or at least moderate (n=620; 82.6%) baseline anxiety; 262 (34.9%) had severe baseline anxiety. LSMDs in change from baseline to week 6 in HAM-A total scores were statistically significant for cariprazine 1.5 mg/d + ADT vs placebo + ADT in patients with at least mild (-1.3; P=.0335) and at least moderate (-1.6; P=.0224) anxiety. In all anxiety subgroups, changes in HAM-A were numerically greater, though not all statistically significant, for both cariprazine doses vs placebo. Based on HAM-D factor scores, 627 patients (83.5%) had baseline anxiety symptoms and 124 (16.5%) did not. For patients with baseline anxiety, significantly greater reductions in HAM-D factor scores were observed for both cariprazine 1.5 mg/d + ADT (LSMD: -0.8; P=.0028) and 3 mg/d + ADT (-0.6; P=.0258) vs placebo. For patients without baseline anxiety, there was a greater reduction in HAM-D factor scores with both cariprazine 1.5 mg/d (-2.7) and 3 mg/d (-2.2) + ADT vs placebo (-1.8).

Conclusions: Cariprazine + ADT reduced anxiety symptoms in adults with MDD and baseline anxiety. Psychic dimensions were significantly reduced with adjunctive cariprazine 1.5 mg/d and somatic dimensions reduced numerically with adjunctive cariprazine vs placebo. Importantly, there was no worsening of anxiety in patients without baseline anxiety symptoms. These results provide a comprehensive understanding of the effects of adjunctive cariprazine on anxiety symptoms in patients with MDD.

W31. LUMATEPERONE AS ADJUNCTIVE THERAPY IN PATIENTS WITH MAJOR DEPRESSIVE DISORDER: RESULTS FROM A RANDOMIZED, DOUBLE-BLIND, PHASE 3 TRIAL

Suresh Durgam[1], Willie R Earley[1], Susan G Kozauer[1], Changzheng Chen[1], Hassan Lakkis[1], Margaret Martin[1], Roger S. McIntyre[2], Stephen Stahl[3]*

[1]*Intra-Cellular Therapies, Inc.,* [2]*University of Toronto,* [3]*University of California*

Abstract: Background: Lumateperone is an FDA-approved antipsychotic to treat schizophrenia and bipolar depression. This Phase 3, randomized, double-blind, placebo-controlled, multicenter, international trial (NCT04985942) investigated adjunctive lumateperone 42mg in patients with major depressive disorder (MDD) with inadequate response to antidepressant therapy (ADT).

Methods: Eligible males and females (18-65 years old) met DSM-5 criteria for MDD with inadequate response to 1-2 courses of ADT in the current depressive episode and had Montgomery-Asberg Depression Rating Scale (MADRS) Total score ≥24, Clinical Global Impression Scale-Severity (CGI-S) score ≥4, and Quick Inventory of Depressive Symptomatology-Self Report-16 item (QIDS-SR-16) score ≥14. Patients were randomized to outpatient 6-week placebo or lumateperone 42mg adjunctive to ADT. Primary and key secondary efficacy endpoints were change from baseline to Day 43 in MADRS Total score and CGI-S score, respectively, analyzed using a mixed-effects model for repeated measures. Additional measures included response (≥50% MADRS Total score decrease), remission (MADRS Total score ≤10), and change from baseline in QIDS-SR-16 Total score. Safety assessments included adverse events (AEs), vital signs, laboratory parameters, and extrapyramidal symptoms.

Results: Of 484 patients treated (placebo, 243; lumateperone, 241), 93% completed treatment. Primary and key secondary endpoints were met for adjunctive lumateperone, with significantly greater improvement vs adjunctive placebo from baseline to Day 43 in MADRS Total score (least squares mean difference vs placebo [LSMD]=−4.9; effect size [ES]=−0.61; P < .0001) and CGI-S (LSMD=−0.7; ES=−0.67; P < .0001). Rates of MADRS Total score response (placebo, 24%; lumateperone, 46%; P < .0001) and remission (placebo, 14%; lumateperone, 26%; P < .001) were significantly greater with lumateperone vs placebo at Day 43. Adjunctive lumateperone significantly improved self-reported depressive symptoms at Day 43 vs adjunctive placebo, as measured by QIDS-SR-16 Total score (LSMD=−2.4; ES=−0.50; P < .0001). Adjunctive lumateperone was generally safe and well tolerated, consistent with prior studies. The most common treatment-emergent AEs with lumateperone (≥5% and twice placebo) were dry mouth, fatigue, and tremor. No serious AEs occurred with lumateperone during treatment.

Conclusion: Lumateperone 42mg adjunctive to ADT demonstrated robust and clinically meaningful efficacy over adjunctive placebo to ADT and was generally safe and well tolerated, indicating lumateperone as a promising adjunctive therapy to ADT to treat MDD in adults.

W32. REAL-WORLD PRACTICE PATTERNS AND OUTCOMES IN PATIENTS WITH MAJOR DEPRESSIVE DISORDER TREATED WITH ANTIDEPRESSANTS

Maurice Ohayon[1]*, Maggie McCue*[2]*, Michael Martin**[3]*, Patricia Driscoll-Shempp*[2]*, Michelle Kirby*[2]*, Andrew D. Krystal*[4]*, Stephanie Duhoux*[5]*, Marie-Lise Cote*[6]

[1]Stanford University School of Medicine, [2]Takeda Pharmaceuticals U.S.A., Inc., [3]Takeda Pharmaceuticals North America, Inc., [4]UCSF School of Medicine, [5]Eval Research Institute, [6]Centre d'Evaluation and de Statistiques

Abstract Introduction: Major depressive disorder (MDD) is a significant mental health issue in the US, affecting an estimated 8% of the population, with only half receiving treatment.1 In patients who do receive treatment, many will have a modest response.1 Most patients are treated for MDD in primary care, while most psychiatry referrals are for patients with insufficient response to initial treatment.1,2 However, barriers related to patients, providers, and systems can hinder effective treatment and follow-up care.1 There are limited real-world data on the effectiveness and tolerability of antidepressants (ADs) in patients with MDD who have shown inadequate response. This observational study aimed to capture these data and patient experiences among the conditions and diversity found in the general population and contemporary clinical practice.

Methods: To recruit participants with mood and depressive symptoms, the study was advertised via mailing lists, social media, and advocacy groups. Between May and October 2024, 1158 individuals participated in an online interview driven by the Ad-Infer EVAL system, an AI-positive, differential diagnosis evaluation and data capture tool. Interviews addressed health-related topics with an emphasis on depressive symptoms and AD treatments. Answers provided to the Ad-Infer EVAL system dictated the length of the interview. Participants not receiving AD treatments were not included in the current analyses. The retained sample, after matching on age, sex, and treating physician specialty, was composed of 104 participants taking fluoxetine or paroxetine (GR1), 79 taking bupropion (GR2), and 72 taking vortioxetine (GR3).

Results: The proportions of women across treatments were 76% in GR1, 57% in GR2, and 79% in GR3. Participants were aged 21-62 years. In all groups, a majority were prescribed an AD by a psychiatrist. The proportion experiencing a current MDD episode was higher in GR1 (58.3%) compared with GR3 (45.8%; $P < 0.01$) and GR2 (54.9%). The recurrence of MDD episodes was significantly higher in GR1 (93.4%) and GR2 (83.9%) compared with GR3 (42.5%; $P < 0.001$). More than 60% of the participants in each group were taking the AD for ≥1 year. The proportion of those who estimated their treatment was very helpful was higher in GR3 (50.0%) compared with GR1 (24.3%) and GR2 (35.7%; all $P < 0.01$). There were also several differences in depressive symptoms between the groups: GR1 (62.4%) and GR2 (70.5%) displayed significantly more frequent cognitive impairment compared to GR3 (35.5%; all $P < 0.01$). GR1 (56.4%) and GR2 (54.9%) also reported more frequent psychomotor retardation than GR3 (20.9%; $P < 0.01$). Suicidal thoughts were higher in GR1 (49.2%) compared with GR3 (34.5%; $P < 0.01$).

Conclusion: In this real-world population, serotonin modulator ADs were more likely to reduce the risk of recurrent MDD and the likelihood of residual symptoms, implying that some ADs might work better for particular individuals or types of depressive symptomatology.

W33. THE ASSOCIATION BETWEEN AMYGDALAR SUBFILED VOLUME CHANGES AND DEPRESSIVE SYMPTOM IMPROVEMENTS AFTER REPEATED KETAMINE INFUSION IN TREATMENT-RESISTANT DEPRESSION: A DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED TRIAL

Kengo Yonezawa[*1], Shinichiro Nakajima[1], Nobuaki Hondo[1], Yohei Ohtani[1], Kie Nomoto-Takahashi[1], Taisuke Yatomi[1], Sota Tomiyama[1], Nobuhiro Nagai[2], Keisuke Kusudo[1], Koki Takahashi[1], Shiori Honda[1], Sotaro Moriyama[1], Shinsuke Koike[3], Hiroyuki Uchida[1], Hideaki Tani[1]*

[1]University School of Medicine, [2]Minami-Hanno Hospital, [3]University of Tokyo Institute for Diversity and Adaptation of Human Mind, The University of Tokyo

Abstract Introduction: The mechanism of the antidepressant effect of repeated intravenous ketamine infusion remains unclear in patients with treatment-resistant depression (TRD). The amygdala plays an important role in emotional processing and mood state. Some of the functional magnetic resonance imaging (MRI) studies reported abnormal hyperactivity in the amygdala during emotion processing tasks and ketamine administration decreased overreactions in the amygdala in patients with TRD. However, the relationship between the effect of ketamine and the amygdalar volume changes in patients with TRD has not been well investigated. To date, there is the only study that investigated amygdalar volume changes after repeated ketamine treatment in patients with depression. However, it was an open-label study, that included mixed patients with either TRD, suicidality, or both, and the volume of each subfield was not analyzed. Therefore, this study sought to examine whether changes in amygdalar subfield volumes would correlate with clinical response to ketamine in patients with TRD in an exploratory manner.

Methods: We used data from a double-blind, randomized, placebo-controlled trial to assess the efficacy of repeated intravenous ketamine in Japanese patients with TRD (jRCTs031210124). In this trial, 34 participants were randomly allocated to either ketamine or placebo groups in a 1:1 ratio and received either repeated intravenous ketamine or placebo. MRI scans were conducted before and after administration of these study drugs. The depressive symptom was assessed with the Montgomery Åsberg Depression Rating Scale (MADRS) and three MADRS subdomains: dysphoria, retardation, and vegetative symptoms. All participants were imaged on a 3T Siemens scanner using a 32-channel head coil. We focused on the volumes of three amygdalar subfields: the laterobasal, centromedial and superficial nucleus. For the analysis, we used data from the participants who underwent MRI scans both before and after the intervention. Multivariable regression analyses were conducted to explore the factors associated with the change in the MADRS total and its subdomain scores with explanatory variables, including treatment, volume change in each region of interest, and treatment by volume change interaction. Next, we also fit separate multivariable linear regression models with changes in the MADRS total and subdomain scores and amygdalar subfield volume changes in each treatment group.

Results: Of the 31 participants who completed treatment, 11 (32.6 %) in the ketamine group and 15 (44.1 %) in the placebo group underwent MRI scans before and after the intervention. For the MADRS dysphoria scores, multiple regression analyses found a positive correlation with the treatment by volume change interaction in the right laterobasal nucleus (rLB) (β = 0.61, p = 0.028). The model was statistically significant (p = 0.029) and accounted for 24.0%

of the variance in MADRS dysphoria score change. Moreover, a post-hoc multiple regression found that changes in MADRS dysphoria scores were related to volume changes only in the rLB in the ketamine group ($\beta = 0.66$, $p = 0.032$). However, there was no such association in the placebo group ($p = 0.56$).

Discussion: The volume reduction in the rLB correlated with a better clinical response to ketamine treatment in patients with TRD. The result suggests that the volume of the amygdala, particularly the rLB, may be related to the mechanism of the effects of ketamine for patients with TRD.

W34. SECONDARY ANALYSIS OF THE EFFECT OF PATIENT TREATMENT PREFERENCE ON THE CLINICAL OUTCOMES IN SUBJECTS WITH TREATMENT RESISTANT DEPRESSION ENROLLED IN ASCERTAIN-TRD STUDY

*Stefania Chaikali**[1], Clotilde Guidetti[2], Madhukar Trivedi[3], Richard Shelton[4], Dan V. Iosifescu[5], Michael E. Thase[6], Manish Jha[7], Sanjay J. Mathew[8], Charles DeBattista[9], Mehmet Dokucu[10], Olga Brawman-Mintzer[11], William V. McCall[12], Matthew Macaluso[13], Maurizio Fava[14], George Papakostas[14]*

[1]Harvard Medical School/Massachusetts General Hospital, [2]Massachusetts General Hospital, and Harvard Medical School, [3]UT Southwestern Medical Center, [4]University of Alabama At Birmingham, [5]Icahn School of Medicine at Mount Sinai, [6]Perelman School of Medicine, University of Pennsylvania, and Corporal Michael J. Crescenz VAMC, [7]University of Texas Southwestern Medical Center, [8]Baylor College of Medicine, [9]Stanford University, [10]Dartmouth Geisel School of Medicine, [11]Ralph H. Johnson VA Medical Center, Medical University of South Carolina [12]Medical College of Georgia, Augusta University, [13]The University of Alabama At Birmingham, [14]Massachusetts General Hospital

Abstract Background: Major depressive disorder (MDD) is a severe and debilitating illness. Despite the available pharmacological and non-pharmacological treatment options, clinical outcomes remain suboptimal. Therefore, it is crucial to identify factors associated with response to treatment. The present study investigated the relationship between patient treatment preferences and clinical outcomes in patients with MDD. The effect of patients' treatment preferences on response to antidepressive treatment remains unclear. Most studies have shown that patients' treatment preferences do not moderate treatment response. On the other hand, only two studies comparing pharmacotherapy versus psychotherapy have found that patients' preferences can significantly enhance clinical outcomes in patients who receive their preferred treatment.

Methods: This is a secondary data analysis investigating the relationship between treatment preference and response to treatment in the multi-site, randomized (1:1:1), open-label, effectiveness ASCERTAIN-TRD trial (NCT02977299) comparing three treatment arms (aripiprazole augmentation, repetitive transcranial magnetic stimulation (rTMS) augmentation, switching to venlafaxine XR or duloxetine) in MDD patients with TRD who are currently on ongoing, stable and adequate antidepressant therapy (ADT) as per the MGH Antidepressant Treatment Response Questionnaire (ATRQ). Patient treatment preferences were recorded in the study entry. Response to treatment was evaluated based on the change in

MADRS scores (MGH CTNI-administered by blinded raters) from baseline to week 8. For the MADRS analyses, mixed-effects models with repeated measures (MMRM) were used.

Results: In total, 278 subjects were randomly assigned to one of three treatment groups: aripiprazole (n=92), rTMS (n=70), or venlafaxine/duloxetine (n=98). Of these 278 subjects, 256 (92.1%) had at least one post-baseline MADRS score and a recorded treatment preference and were included in this secondary analysis. In the total population, participants' preferences did not affect their response to treatment, and the MADRS score change was similar in patients who received their preferred treatment, had no preference, or received treatment against their preference (p=0.59). Similarly, when analyzing preference within the context of each specific treatment group and MADRS score reduction, relationships were not statistically significant for Aripiprazole (p=0.63), rTMS (p=0.32), and Venlafaxine XR/Duloxetine (p=0.29) groups.

Conclusion: Our findings suggest that patients' preference is not a significant factor that predisposes to optimal treatment outcomes. Furthermore, our study is the first to investigate the effect of patient preference on response to r-TMS treatment. While our results indicate that patient preference towards r-TMS did not favorably affect the response to treatment, this knowledge is a step forward in understanding the complexities of treatment response. These results underscore the need for a nuanced understanding of the effect of patient preference on the efficacy of pharmacotherapy and r-TMS in treating patients.

W35. SUPERVISED MACHINE-LEARNING CLASSIFICATION OF TREATMENT-RESISTANT DEPRESSION IN U.S. CLAIMS DATA

Vicki Wing[*1], Jason Lerner[1], Patrick Clarke[1], Shane O'Connor[1], Sydney Tran[2], Jonathan Darer[2], Jaspreet Gill[1], Lucinda Orsini[1]*

[1]Compass Pathways, [2]Health Analytics, LLC

Abstract Background: Treatment-resistant depression (TRD) is defined by the Food and Drug Administration as the failure to respond to two or more antidepressant medication of adequate dose and duration. Accurate identification of patients with TRD is crucial to improving quality of care and clinical outcomes. However, this process is currently dependent upon subjective provider assessments or onerous medication calculations. To explore novel approaches to reduce the burden of TRD identification, we developed TRD classification models using data available within electronic health records and claims databases.

Methods: Adults with major depressive disorder (MDD) and commercial insurance in the United States were identified between 1/1/2019 and 12/31/2022 within Merative™ MarketScan® Commercial and Medicare Supplemental Databases. Patients who failed to respond to at least 2 MDD medications of adequate dose and duration within 2 years prior to their last pharmacy claim for an antidepressant were considered to have TRD. An initial set of 517 features, including demographics, psychiatric comorbidities, physical comorbidities, medication days supplied, drug classes, generic drug names, and mental health and non-mental health resource utilization, was pruned and used to classify TRD from non-TRD MDD patients in an automated machine learning process generating 20 models, including

distributed random forest, extremely randomized trees, regularized generalized linear models, Gradient Boosting Machine, and Extreme Gradient Boosting Machine, using a cohort-balanced 80:20 train:test split. The highest performing model based on F1 score was designated the full-feature model. A parsimonious model was developed by implementing backward elimination and a clinically oriented consolidation strategy on the full-feature model. A rule-based model was adapted from a published proxy definition.

Results: The study included 501,493 patients, with 463,485 (92.4%) patients in the non-TRD cohort and 38,008 (7.6%) in the TRD cohort. After pruning features using LASSO regression, 306 features remained and were input to the automated machine learning engine to train and refine the models. The full feature model (ridge logistic regression) demonstrated the highest overall performance (AUC=0.96, F1=0.64) with 306 features. Backward elimination and implementation of the feature consolidation strategy resulted in a parsimonious model (logistic regression) with acceptable performance (AUC=0.92, F1=0.53) comprising 8 drug-class features. The rule-based model (decision tree) had the lowest AUC (0.82) and F1 score (0.40).

Conclusions: To address the need for efficient TRD identification, we developed a machine learning model capable of identifying individuals with TRD from commercial claims data based on 8 drug class features without the need for drug dose and duration information. This model performs near the limit of what is established by the full features model, uses clinically meaningful features, and has an interpretable architecture (logistic regression). Our pragmatic approach to identifying individuals with TRD in clinical practice may facilitate adherence to reliable delivery of best practices, escalate therapy as needed including referral to advanced psychiatric care, and reinforce monitoring to avoid emergency department visits, hospitalizations, and at worst case, suicide attempts. This model may be used to support population health and outcomes research and may reduce the subjectivity and variability in approaches to the identification of TRD in clinical practice. In addition, the observed prevalence of TRD in this study aligns with prevalences reported in the literature.

W36. ARIPIPRAZOLE OR BUPROPION AUGMENTATION VS SWITCHING TO BUPROPION IN TREATMENT RESISTANT DEPRESSION: A BENEFIT-RISK ANALYSIS

William Meyerson[*1], Jordan Smoller[2]*

[1]Massachusetts General Hospital, [2]Massachusetts General Hospital and Harvard Medical School

Abstract Purpose: To determine which of three treatments has the most favorable benefit-risk profile in treatment resistant depression: aripiprazole augmentation (A-ARI), bupropion augmentation (A-BUP), or switching to bupropion (S-BUP).

Methods: We used a health state transition model to estimate the quality adjusted life years (QALYs) gained from improved depression with these treatments minus the QALYs lost from side effects due to falls, weight gain, and tardive dyskinesia using the hesim R package (v. 0.5.5). The model was applied to patient subgroups defined by age and baseline body mass index (BMI). Transition probabilities and utility values were obtained from randomized

control trials and the broader literature. We used a 1-year treatment duration and cycle length, lifetime time horizon, and 1.5% discount rate. 95% confidence intervals were obtained through 1000 runs of probabilistic sensitivity analysis, and the influence of individual model choices were examined through univariate sensitivity analyses. QALYs were converted to depression-free days (DFDs), the QALY difference between 1 day of remitted vs active depression.

Results: In the main analysis, C-BUP was preferred over S-BUP in all subgroups, with 1 year of C-BUP leading to a lifetime change in expected DFDs in ages 18-64, 65-84, and 85-89 of 20.7, 16.6, and 7.9 DFDs over S-BUP, respectively, regardless of baseline BMI. A-ARI was preferred over S-BUP only when BMI < 25: DFDs vs S-BUP in ages 18-64, 65-84, and 85-89 were 8.0, 5.1, and 10.9, respectively, when BMI < 25 and -56.6, -34.7, and -13.1 when BMI > =25. C-BUP was preferred over A-ARI in all subgroups except adults aged 85-89 with BMI < 25, where A-ARI was preferred.

Importance: For adults under age 85, A-BUP offered the best balance of risks and benefits of the three treatments studied according to the model. These results may inform shared decision-making and clinical guidelines for treatment resistant depression.

W37. RE104: A NOVEL SEROTONERGIC PSYCHEDELIC 4-OH-DIPT PRODRUG

Mark Pollack[1], Jasna Hocevar-Trnka[1], Beatrix Taylor[1], Robert Alexander[1], Nathan Bryson[1]*

[1]*Reunion Neuroscience*

Abstract RE104, a unique, proprietary 4-OH-DiPT prodrug, is a novel psychedelic investigational compound being developed for the treatment of postpartum depression (PPD) and other mental health conditions. Preclinical and clinical characterization confirmed similar pharmacology of 4-OH-DiPT to the well-characterized psychedelic active form of psilocybin (4-OH-DMT), while in vivo studies demonstrated a significantly shorter and reproducible psychedelic experience. Here we present the results of the first-in-human (FIH) phase 1 study characterizing the safety, pharmacokinetics (PK) and pharmacodynamics (PD) of RE-104, as well as an update of an ongoing Phase 2 randomized, active-dose controlled trial in women with moderate to severe PPD.

Methods: A phase 1, FIH, double-blind, parallel group trial was conducted with 6 ascending dose cohorts of 8 psychedelic experienced health volunteers (randomized 6 active, 2 placebo). Predefined dose escalation ranged from 5 mg to 47.9 mg RE104 administered subcutaneously as a single injection. Adequate set and setting included one preparatory session followed by a dosing session with a qualified and trained session monitor. Follow-up study visits occurred on days 2 and 10. Study objectives included assessing safety and tolerability, PK and PD (Drug Effect Questionnaire (DEQ) and Mystical Effect Questionnaire 30 (MEQ)). A "complete" mystical experience (CME) was defined as > /=60% max value in total MEQ score. DEQ < /= 1 represented a subjective end of the psychoactive experience.

Results: A total of 48 subjects with a mean age of 36 years, 27% female and 88% white were enrolled across 6 cohorts. There were no serious AEs and no clinically significant vital signs, clinical laboratory, or electrocardiogram findings at doses up to and including 40 mg RE104. PK demonstrated dose-proportionality. At 30 mg RE104, mean experience duration

was 3.7 hours, with all participants having a score off < /=1 at 5 hours post-dose. 66.7% of participants in the RE104 30 mg treatment group had a CME predictive of clinical efficacy. This data informed the dose selection of RE104 at 30 mg for the phase 2 trial.

The PPD trial is a multi-center, randomized, double-blind parallel group, active dose-controlled study evaluating the safety and efficacy of a single dose of RE104 in participants aged 18-45 with PPD. The primary endpoint is MADRS at day 7.

Conclusions: *A single dose of RE104 was found to be safe and generally well-tolerated with robust PD effects and a short induced psychoactive state (approximately 4 hours). RE104 has the potential to be an accessible, fast-acting, single dose treatment for PPD.

W38. ENHANCEMENT OF COGNITION IN PRECLINICAL MODELS BY NOVEL INVESTIGATIONAL M1/M4 AGONIST, ML-007

Susmita Chatterjee[1], Abraham Vazquez[1], Revathi Kaduru[1], Hannah K Kim[1], Maritza Soria[1], Natalie Navarro[1], Kimberly R Thompson[1], James Lillie[1], Anatol C Kreitzer[1], Michael W Wood[1]*

[1]MapLight Therapeutics

Abstract: Muscarinic agonists represent a new class of therapeutic agents for the treatment of schizophrenia and potentially for other types of psychosis. Historical data with muscarinic agonists have indicated potential for cognitive improvement, which could further broaden the therapeutic utility of this class. ML-007 is a novel investigational muscarinic agonist that has strong intrinsic activity at M1 and M4 receptors, with a slight bias toward M1 signaling. Since M1 activation has been proposed to underlie procognitive effects, we explored whether ML-007 could improve hippocampal-dependent spatial memory in the Tg2576 mouse model of Alzheimer's disease (AD). In the Barnes maze task, vehicle-treated Tg2576 mice failed to recall the target location after seven days whereas treatment with ML-007 led to significant improvement in long-term memory for the target location. Consistent with a critical role for M1 in cognition, we found that knockout of M1, but not M4, disrupted Y-maze spatial memory performance. A comparative study was undertaken with xanomeline at doses that produced an equivalent effect on locomotive behavior. Notably, we found that ML-007 improved Y-maze performance in the Tg2576 mouse model of AD, while xanomeline did not. A GTPgammaS assay that utilized membranes from rat hippocampus revealed that ML-007 had higher intrinsic receptor activity relative to xanomeline, which could explain the differential enhancement of cognition with ML-007. Further consistent with the hypothesis that cognitive improvement is driven by strong activation of M1, the M4-selective PAM, emraclidine, was found to be inactive in the Y-maze assay. Together these studies suggest that M1 activity is critical for cognition in rodent models and that ML-007, due to its higher intrinsic activity at M1 receptors, could be ideally suited to address cognitive symptoms, in addition to treatment of psychosis in AD and schizophrenia.

W39. LYSERGIDE MAY ENHANCE NEUROPLASTICITY BY POST-DOSE UPREGULATION OF TRKB COMPARED TO OTHER COMPOUNDS

Julie Tripp[1], Deborah Rudin[2], Oliver V. Stöckmann[2], Matthias E. Liechti[2], Gennady N. Smagin[1]*

[1]*Mind Medicine Inc.,* [2]*University Hospital Basel*

Abstract Introduction: Psychoactive compounds that produce transient alterations in perception, cognition, and emotion partially through agonism of the serotonergic receptors (5-HT, especially 5-HT2A) are categorized as psychedelics. It was recently reported that lysergic acid diethylamide (LSD) and psilocin also directly bind to the TrkB receptor.1 MM120 (lysergide D-tartrate, a formulation of LSD) is under development as a potential treatment for generalized anxiety and major depressive disorders. As TrkB mediates brain-derived neurotrophic factor (BDNF) driven neuroplasticity, we evaluated the interaction of the TrkB receptor and several serotonergic drugs that are considered psychedelic as a key target of neuroplasticity.1-2

Methods: Activation of TrkB by BDNF was assessed by measuring inositol monophosphate 1 (IP1) accumulation. NIH/3T3 cells stably expressing human TrkB were used. Natural TrkB ligand BDNF served as positive control. We tested LSD, psilocin, N,N-dimethyltryptamine (DMT), mescaline, 2,5-dimethoxy-4-iodoamphetamine (DOI), N-2-methoxybenzyl-phenethylamine (25B-NBOMe), 4-bromo-2,5-dimethoxyphenethylamine (2C-B), methylenedioxyamphetamine (MDA), and the selective serotonin reuptake inhibitor fluoxetine. The same cells were treated with varying BDNF concentrations, combined with test drugs at fixed concentrations to assess potential allosteric modulation of TrkB activation. In a separate experiment, we assessed potential TrkB upregulating effects of LSD due to its partial antagonism.

Results: As expected, BDNF was highly potent at the TrkB receptor, activating it in the sub-picomolar range (EC50 0.2 pM). LSD, 25B-NBOMe, and fluoxetine activated TrkB (EC50 of 811, 26370, and 6040 pM respectively) with low maximal efficacies (40, 57, and 60% respectively). Psilocin, DMT, DOI, MDA, and 2C-B did not activate TrkB at concentrations up to 1 mM or, in the case of psilocin, activated it with very low efficacy.

Cotreatment with BDNF and a fixed concentration of LSD increased BDNF-induced TrkB activation (EC50 0.06 pM) and reduced activation efficacy to 60%. The other drugs tested reduced activation potency, as well as the maximal receptor activation. Fluoxetine and 25B-NBOMe did not generate activation curves. All drugs partially antagonized the effect of BDNF at the TrkB receptor. This antagonistic effect may lead to the observed induction of neuroplasticity. Pretreatment with LSD led to reduced activation potency and efficacy of BDNF after recovery for 18 and 24 hours. After 30 hours of recovery, BDNF was similarly potent but around 30% more effective in activating TrkB than without LSD treatment. Hence, LSD seems to induce TrkB upregulation, which could lead to the described neuroplastic effects observed by other research groups.

Conclusions: LSD, 25B-NBOMe, and fluoxetine activated TrkB at pharmacologically relevant concentrations as partial agonists and psilocin, DMT, DOI, MDA, and 2C-B did not. The combination of BDNF with fixed concentrations of drugs described as psychedelic or fluoxetine led to reduced activation efficacy of BDNF. LSD increased the BDNF-induced TrkB activation. Pretreatment with LSD strongly increased the activation efficacy of BDNF at the TrkB receptor without changing the activation potency. Induced TrkB upregulation may underly and provide evidence for neuroplastic effects of LSD.

W40. DEVELOPING A NEW NEUROPLASTOGEN, ITI-1549, A SEROTONIN 5-HT2A AGONIST FOR THE TREATMENT OF NEUROPSYCHIATRIC DISORDERS

Emma Lehmann[*1], Sophie Dutheil[1], Lei Zhang[1], Neelu John[1], Nora Awadallah[1], Wei Yao[1], Peng Li[1], Gretchen Snyder[1], Robert Davis[1]*

[1]*Intra-Cellular Therapies, Inc.*

Abstract: Serotoninergic psychedelics targeting 5-HT2A receptors are currently being investigated as therapeutics for several psychiatric disorders. Literature and case studies show promising and sustainable effects at various doses in both human and animal models acting presumably by normalizing disrupted serotonin signaling and by restoring brain connectivity. However, most hallucinogens bind and activate the 5-HT2B receptor, which is associated with heart valvulopathy in humans. In addition, it is widely reported that these drugs elicit strong physiological responses, altering aspects of cognition, mood, and perceptions of reality that can put individuals at risks, encourage abuse, and ultimately limit their distribution. Intra-Cellular Therapies designed a novel class of small molecules that are 5-HT2A receptor biased agonists, exemplified by a novel drug named ITI-1549. In vitro assays were performed to identify receptor binding profiles, post-receptor signaling pathways, and to determine effects on cortical neurite outgrowth. Drug pharmacokinetic profiles were determined in mice at time points ranging from 5 minutes to 24 hours (n=3 per route of administration per timepoint). For in vivo behavioral experiments, male or female rodents received ITI-1549 at various dosing regimens (N= 8-17/group). Gene and protein changes related to neuroplasticity and synaptogenesis were analyzed using western blotting, rt-qPCR, or NanoString technology. Statistical analyses were performed using GraphPad Software.

Results show that ITI-1549 exhibits high affinity binding to the 5-HT2A receptor subtype (Ki = 10.2), demonstrating biased signaling through the activation of β-arrestin but not G-protein pathways. It also binds to 5-HT2C (Ki = 21.1) receptor subtypes. Importantly, it is an antagonist at 5-HT2B receptors (Ki = 4.8), thus lacking cardiac liabilities associated with 5-HT2B agonism. Pharmacokinetic analyses show that ITI-1549 has high bioavailability with a Tmax of 15 minutes and a Cmax of 41.3 ng/mL and 112 ng/g in the plasma and brain, respectively. Protein analyses indicate that ITI-1549 acutely increases signaling pathways associated with synaptogenesis in the medial prefrontal cortex while in vitro ITI-1549 treatment of rat cortical neuronal culture with ascending concentrations induces a significant increase in measured neurite network parameters as compared to control cultures. When administered in vivo, ITI-1549 does not elicit hallucinogen-like behaviors (ie, head twitches), and provides beneficial effects, such as increasing social interaction, rescuing transient anhedonic-like behavior, and reducing anxiety-like behavioral symptoms in male and female rodents, with no effects on overall locomotion.

In conclusion, as neuropsychiatric disorders are often associated with a dysregulation of serotonergic signaling in the brain, our new data show that ITI-1549 is a biased non-hallucinogenic neuroplastogen that has the potential to safely treat mood and other neuropsychiatric disorders in humans.

W41. THE SIRT6 ACTIVATOR, FORVISIRVAT (SP0624), SHOWS PRO-COGNITIVE AND ANTIDEPRESSANT EFFECTS ON QEEG BRAIN ANALYTICS: A PHASE 1 STUDY

Walter Duffy[1], Joel Raskin[2], Gil Issachar[3], Offir Laufer[3], Chuck Moser[4], Kelly Abernathy[2], Greg Rigdon[5]*

[1]Alivation Research [2]Sirtsei Pharmaceuticals, [3]Firefly Neuroscience, [4]New Light Clinical, [5]Arrivo Bioventures

Abstract Background: Brain network analytics (BNA) can identify patterns of electrophysiological signals characteristic of diverse neurological and psychiatric conditions, including depression. Depression is associated with increased delta activity and P200 latency and amplitude. Forvisirvat is a novel epigenetic, orally active, first-in-class, selective SIRT6 activator, being studied for treatment of major depressive disorder (MDD).

Methods: Objectives for the first cohort of this study were to determine if forvisirvat changed BNA profiles relative to placebo after 1 day or 2 weeks of daily treatment. Healthy participants received 20 mg forvisirvat (n=8) or placebo (n=4) once daily. Electroencephalograms (EEG) and Event Related Potential (ERP) assessments were done on days 1 and 15 (pre-dose and 3 hours post-dose) using 64 electrode EEG headsets. EEGs were recorded while healthy participants were resting with eyes closed (EC) and open (EO) (5 minutes each) and during auditory oddball (AOB) and visual go no-go (VGNG) tasks (20 minutes each). The power spectrum analysis focused on absolute and relative power in delta (1-4Hz), theta (4-8Hz), alpha (8-12Hz), beta 1 (12-18Hz) and beta 2 (18-25Hz) frequency bands, and on alpha peak frequency. ERP analysis focused on amplitude and time measures of P200, N2, P3a and P3b extracted from the VGNG task and P200, P3a, and P3b extracted from the AOB task. Analyses included a linear mixed effects model with treatment (forvisirvat/placebo) and session (pre-/post-dose) as fixed effects, and age and sex as covariates, controlling for healthy participants as a random effect. Adverse events (AEs) were also collected.

Results: All healthy participants completed the study. On day 1, compared with placebo, forvisirvat treatment resulted in significant ($p \leq 0.1$) treatment-by-session interaction effects, showing increases in beta2 relative power (EC), alpha and beta1 relative power (EO), and decreases in delta relative power (EO), P200 amplitude (AOB), and P3b latency (VGNG). On day 15, forvisirvat treatment resulted in significant increases from pre-dose to post-dose in beta2 and theta relative power (EC) and beta1 absolute and relative power (EO). Significant increases from day 1 pre-dose to day 15 post-dose were observed for beta2 relative power (EC), beta1 relative power (EO), and N2 amplitude (VGNG). All AEs were mild. Two (25%) forvisirvat-treated participants had 3 AEs: fatigue, abdominal pain, and headache. One (25%) participant who received placebo had headache, lethargy, and sinus congestion.

Conclusions: Forvisirvat treatment changed BNA profiles relative to baseline after 1 day and 2 weeks in healthy participants. Observed post-dose increases across high-frequency bands alpha, beta1, and beta2 suggest enhanced synaptic plasticity and neuronal connectivity. Beta activity plays a role in cognitive processing, attention, and arousal. Reduction in delta power also supports forvisirvat's potential antidepressant effects. Decrease in post-dose P200

amplitude suggests enhanced neural efficiency in early perceptual processing. Of note, increased P200 amplitude during the AOB task is common in people with depression. Faster P3b latency during the VGNG task reflects improved decision-making speed and context updating. Increased N2 amplitude points to enhanced conflict monitoring and inhibitory control, functions often impaired in MDD. These findings are consistent with forvisirvat 20 mg exerting antidepressant and pro-cognitive effects by improving neuronal connectivity and cortical efficiency and normalizing brain activity.

W42. REAL-WORLD SLEEP MEDICATION TREATMENT PATTERNS FOR PATIENTS WITH BIPOLAR I DISORDER, SCHIZOPHRENIA, OR MAJOR DEPRESSIVE DISORDER BEFORE AND AFTER CARIPRAZINE INITIATION

Roger S. McIntyre[1], Lauren Aronin[2], Huy-Binh Nguyen[2]*

[1]University of Toronto, Brain and Cognition Discovery Foundation BCDF, [2]AbbVie,

Abstract Introduction: Sleep disturbances occur in many psychiatric diseases, including bipolar I disorder (BP-I), schizophrenia (SCZ), and major depressive disorder (MDD), and are associated with poor outcomes. Polypharmaceutical approaches that add sleep medication may treat sleep disturbances but may also increase the risk of drug-drug interactions, adverse events, and non-adherence and pose economic burdens to patients and payers. Cariprazine is a dopamine D3-preferring D3/D2 and serotonin 5-HT1A receptor partial agonist that is approved to treat SCZ, manic/mixed and depressive episodes of BP-I, and as an adjunct to antidepressant therapy for MDD. This real-world, claims-based study examined sleep medication treatment patterns before and after cariprazine treatment in patients with BP-I, SCZ, or MDD.

Methods: Claims data from Optum's Market Clarity database (October 2014-June 2022) were used to identify adults (aged ≥19 years) with BP-I, SCZ, or MDD who initiated cariprazine between October 2015 and May 2022. Prescription sleep medication treatment patterns, determined by prescription fills, were assessed during the baseline period (1 year before index; index=date of first cariprazine fill) and follow-up period (time from index to the earliest of: end of the study period, end of insurance enrollment, cariprazine runout [end of days' supply], or death). Outcomes included the proportion of patients using sleep medication at baseline and follow-up and the rates (per 100 person-years) of sleep medication initiation and discontinuation during follow-up. Discontinuation was defined as a gap of > 60 days between the runout of one dispensed prescription and the date of any subsequent dispensed prescriptions.

Results: A total of 67,236 patients (BP-I=50,728; SCZ=4,388; MDD=12,120) with a mean (SD) age of 39.9 (12.9) years were included in the study. The mean follow-up length was 4.7 (4.1) months. Most patients (70%) were female. At baseline, 13.2% of patients used sleep medication, with zolpidem being the most common (8.5%). The MDD cohort had the highest proportion of patients with sleep medication use (15.0%), followed by BP-I (13.1%) and SCZ (9.4%). Among patients who used sleep medication at baseline, the overall discontinuation rate during follow-up was 50.2 per 100 person-years (BP-I=51.0; SCZ=45.7; MDD=48.2). During follow-up, the overall initiation rate for sleep medication among patients who did not use sleep medication at baseline was 10.7 per 100 person-years (BP-I=11.3; SCZ=8.1;

MDD=9.2). Among patients who began using sleep medication during follow-up, the overall discontinuation rate was 124.2 per 100 person-years (BP-I=119.5; SCZ=128.3; MDD=152.6). The prevalence of sleep medication use was numerically lower during follow-up (11.0%) versus baseline (13.2%), which was consistent across all indications (BP=11.2%; SCZ=7.8%; MDD=11.7%).

Conclusions: This real-world, claims-based study examining sleep medication treatment patterns in patients with BP-I, SCZ, or MDD before versus after cariprazine treatment found a numerically lower prevalence of sleep medication use during the follow-up period after cariprazine initiation compared with baseline before cariprazine initiation. Following cariprazine initiation, the sleep medication discontinuation rate was high and the initiation rate was low. These findings suggest that cariprazine may have a potential role in reducing the need for concomitant sleep medications for some patients.

W43. MOOD TRIAL RESULTS: MULTICENTER RANDOMIZED CONTROLLED TRIAL OF A HOME-USE EXTERNAL COMBINED OCCIPITAL AND TRIGEMINAL AFFERENT STIMULATION THERAPY FOR MAJOR DEPRESSION

Jeffrey Rado[*1], Andrew Leuchter[2], Mark George[3], Linda Carpenter[4]*

[1]Northwestern University, [2]UCLA, [3]MUSC, [4]Brown University

Abstract Background: Major Depressive Disorder (MDD) is a leading cause of disability worldwide, with limited options for patients unresponsive to antidepressants. Access to most neurostimulation therapies is limited to clinical settings. Proliv Rx, a novel neuromodulation system delivering external combined occipital and trigeminal afferent stimulation (eCOT-AS), offers an accessible, physician-supervised, at-home therapy for MDD.

Methods: A multicenter, randomized, double-blind, parallel-group, sham-controlled trial evaluated the efficacy and safety of Proliv Rx in adults with MDD who showed inadequate response to antidepressants and had baseline Hamilton Depression Rating Scale (HDRS21) scores ≥20. Participants were randomized to active Proliv Rx therapy or sham stimulation for 8 weeks, followed by an additional 8 weeks of open-label active therapy.

Results: Of 124 participants, 97 were included in the mITT analysis. Baseline HDRS17 scores averaged 22 in both groups. At 8 weeks, the active therapy group achieved a significantly greater mean HDRS17 reduction (8.6 vs. 6 points; p=0.02), higher remission rates (21.3% vs. 6%), and greater clinically substantial improvement (62% vs. 32%). During the open-label phase, both groups improved further; by week 16, remission rates reached 32% in the continued-active group and 22% in the initially sham group after crossing over to active therapy. Blinding was highly effective with 90% unable to guess treatment assignment. Both groups exhibited excellent compliance, and no serious unanticipated adverse events were reported.

Conclusion: This multicenter randomized controlled trial provides robust evidence of the safety and efficacy of a physician-supervised, at-home neurostimulation therapy for patients with treatment-resistant MDD. Proliv Rx demonstrates significant clinical effectiveness while offering an accessible and convenient treatment option. This innovation represents a pivotal

advancement in neurostimulation therapy for MDD, effectively transitioning its delivery from the clinical setting to the home environment.

W44. A PILOT STUDY OF SEQUENCED TMS AND ATBS DOSING IN ADOLESCENTS WITH MAJOR DEPRESSIVE DISORDER

Cicek Bakir[1], Paul A. Nakonezny[2], Dicle Buyuktaskin[1], Lucero Sangster-Carrasco[1], Irem Azamet[1], Jennifer Vande Voort[1], Paul E. Croarkin[3]*

[1]Mayo Clinic, [2]UT Southwestern Medical Center, [3] Mayo Clinic Children's Research Center, and Mayo Clinic Depression Center

Abstract: Background: Major depressive disorder (MDD) affects approximately 11% of adolescents, with 40% being treatment-resistant to conventional therapies. Transcranial magnetic stimulation (TMS), FDA-cleared for adolescents aged 15–21 as an adjunctive therapy for depression, is a promising neuromodulation therapy. Theta burst stimulation (TBS), a high-frequency TMS modality, has shown efficacy in treatment of MDD and modulation of cortical excitability. However, its clinical use is limited by high variability individual response rates, and unclear optimal dosing and sequencing strategies, warranting need for research on personalized and targeted treatments. Intracortical facilitation (ICF) is a promising biomarker of glutamatergic N-methyl-D-aspartate (NMDA) receptor–mediated neurotransmission and cortical excitability. This exploratory study investigates whether ICF-guided TBS can improve outcomes in adolescents with MDD unresponsive to conventional TMS.

Methods: Adolescents (N=6) aged 12-17 with MDD who did not respond to standard 1 Hz or 10 Hz TMS were recruited. Those with baseline ICF values ≤1.5 received intermittent TBS (iTBS), while those with ICF > 1.5 received continuous (cTBS). Treatment involved 10 sessions of TBS over two weeks targeting the left dorsolateral prefrontal cortex (LDLPFC) using the Beam F3 method. Depression severity was assessed using the Children's Depression Rating Scale-Revised (CDRS-R) at baseline, weeks 1 and 2, and at six months. Secondary measures included suicidal ideation severity (Columbia Suicide Severity Rating Scale, CSSRS) and changes in ICF. A within-subjects linear mixed model analyzed changes in each outcome over time.

Results: A significant reduction in depressive symptoms was observed from baseline to six months (p=0.02; d=0.82). Pairwise analyses demonstrated significant reductions in CDRS-R scores at week 2 [LSM decrease = -5.83 (SE=2.21), adjusted p=0.04] and 6-month follow-up [LSM decrease = -18.39 (SE=7.05), adjusted p=0.04]. No significant changes were observed in suicidal ideation or ICF values. The intervention was well tolerated, with no serious adverse events reported.

Discussion: This pilot study suggests biomarker-guided TBS is a safe, feasible and effective intervention for adolescents with MDD, with sustained symptom improvement at six months. Limitations include small sample size, absence of a control group, and reliance on Beam F3 rather than neuronavigation. The stability of ICF during treatment suggests it may serve as a stable, trait-like baseline biomarker for guiding intervention rather than a dynamic indicator of neuroplasticity.

Conclusion: Biomarker-driven TBS guided by ICF variability offers a novel and promising approach to personalize and improve MDD treatment in adolescents. Future large-scale, randomized controlled trials are needed to validate findings and refine biomarker-based personalization of TBS.

W45. PREDICTING DEPRESSION TREATMENT OUTCOMES USING MOBILE HEALTH (MHEALTH) TECHNOLOGY

Jayesh Kamath[1], Soumyashree Sahoo[2], Dongjiin Song[2], Alexander Russel[2], Bing Wang[2]*

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

Abstract Background: Evidence indicates that only 35% of patients remit after an initial antidepressant treatment. However, approximately 40% of patients who failed first antidepressant will remit when switched to an alternate antidepressant or with an adjunctive treatment. It is highly desirable to predict if the patient will respond to treatment as early as possible after treatment initiation. The present study investigated whether smartphone data collected early, during the initial 2-4 weeks of treatment, can predict treatment outcomes at week 12.

Methods: Participants were recruited if they had at least moderate level of depression (QIDS score of 11 or more) and starting a new antidepressant treatment. Exclusion criteria include bipolar disorder, primary psychotic disorder, and clinically significant substance use disorder.

Four types of smart phone collected data include daily self-rating of mood and anxiety, weekly self-reported depression questionnaire, 16-item Quick-Inventory of Depression Symptomatology (QIDS), weekly medication-related questionnaire (side effects, tolerability, and adherence), and automatic sensory data. Treatment response was defined as 50% improvement in week 12 QIDS compared to baseline QIDS. Analyses included correlational analyses and development of machine learning models using GRU-D and BRITS.

Results: A total of 147 participants were recruited. Participants were predominantly Caucasian and of female gender. The smart phone data was collected over a 3-month period. The data from 87 participants (30 Android and 57 iOS users) was used for analyses due to missing data and based on minimum data requirements. A total of 8 location features were extracted from the weekly sensory data collected.

The smart phone data collected early (2 to 4 weeks) during treatment predicted treatment outcomes at 12 weeks with promising F1 scores. The F1 scores were substantially higher when all three types of data (daily mood and anxiety rating, weekly medication related questionnaires, and weekly sensory data) was used for analyses. When using data from the first two weeks, the predicted F! score was 0.60 when using single type of data and improved to 0.68 when all three types of data are combined. Prediction accuracy improved when 4 weeks of data was used for analyses compared to shorter time period (F1 score 0.73 vs 0.68) combining all three types of data. Adding baseline QIDS and 4-week QIDS to the smart phone data further enhanced prediction accuracy with a maximum F1 score of 0.77.

Discussion and Conclusion: Our results indicate that brief ecological momentary assessments (EMA) collected remotely early during treatment period combined with location features extracted from the automatic sensory data can predict treatment outcomes at 12

weeks with substantial accuracy. The EMA included depression-related assessments as well as medication-related safety, tolerability, and adherence self-reports. Our results also highlight the importance of using complementary data for depression treatment prediction

W46. MEMANTINE AND MEMANTINE-ACETYLCYSTEINE COMBINATION FOR TREATMENT-RESISTANT OBSESSIVE-COMPULSIVE DISORDER

Christy Alhannat[*1], Kristine Hawkins[1], Maju Koola[2]*

[1]Cooper Medical School, [2]Mental Health and Behavioral Services, Veterans Affairs New Jersey Health Care System

Abstract: Obsessive-compulsive disorder (OCD) is a chronic psychiatric disorder characterized by intrusive obsessions and compulsions that significantly impair functioning. The lifetime prevalence of OCD is estimated to be 3% globally. While selective serotonin reuptake inhibitors, selective norepinephrine reuptake inhibitors, and cognitive behavioral therapy remain first-line treatments, approximately 40%–60% of patients fail to achieve remission, highlighting the urgent need for novel treatment strategies. Clomipramine was approved by the US Food and Drug Administration for OCD in 1989, and fluoxetine was approved in 1994. Clomipramine, the gold standard, is now rarely used due to its side effect profile. We looked at all the randomized controlled trials (RCTs) and meta-analyses of adjuvant/augmentation strategies in OCD. We found memantine to be the most effective, followed by N-acetylcysteine (NAC). The N-methyl-D-aspartate (NMDA) receptor plays a central role in OCD pathophysiology through its involvement in cortico-striato-thalamo-cortical circuitry and excitotoxicity. Memantine is an NMDA receptor antagonist, and NAC is a glutathione precursor and NMDA modulator. Despite promising findings, previous trials utilizing single-agent NMDA modulators in OCD have shown mixed results. A systematic review of RCTs demonstrated that monotherapy approaches often fail to achieve clinical significance, suggesting that a multi-targeted strategy may be necessary. Addressing treatment-resistant OCD requires a paradigm shift in therapeutic approaches, moving beyond serotonergic modulation alone. In light of the growing body of evidence supporting NMDA receptor involvement in OCD, we propose the combination of memantine and NAC as a novel intervention for severe, treatment-resistant cases. This dual approach holds the potential to modulate multiple pathophysiological pathways. Future RCTs are warranted to evaluate the long-term efficacy and safety of this combination therapy in OCD.

W47. COMPLIANCE WITH 2017 FDA GUIDANCE FOR EVALUATING DRUG IMPAIRED DRIVING: APPLICATION OF GUIDANCE TO APPROVED DRUGS THROUGH 2024

Gary Kay[*1], Thomas Hochadel[1], Brandy Isaacks[1]*

[1]Cognitive Research Corporation

Abstract Purpose: The US Food and Drug Administration (FDA) issued final guidance entitled “Evaluating Drug Effects on the Ability to Operate a Motor Vehicle” in November 2017. The purpose of this presentation is to report on how this guidance has been applied to psychiatric drugs subsequently approved by the FDA (January 2018 – December 2024).
Content: Tables of the breakdown of approved drugs by category and indication and driving study conducted or not conducted to be included in poster.

Methodology: The FDA website (www.fda.gov) served as the source of information. A listing was generated of all novel drug approvals from January 2018- December 2024. For each drug the listing included: sponsor, drug name, active ingredient, approval date, approved use, adult use, driving studies conducted. In addition, information was recorded regarding CNS relevant Adverse Events (AEs). The authors applied the criteria outlined in the FDA Guidance to determine whether each of the drugs warranted a dedicated driving study.

Results: Of the 405 FDA-approved drugs (from January 2018 – December 2024), 4 drugs underwent a dedicated driving study. Based upon a conservative application of FDA criteria, there were 42 drugs that clearly met FDA criteria for a dedicated driving study. Analysis by therapeutic area shows that of the 42 drugs identified as meeting criteria for a dedicated driving study, 20 are CNS drugs. All 4 of the approved drugs for which a dedicated driving study was conducted were CNS drugs (i.e., treatments for psychiatric or neurologic conditions). For the other 38 drugs identified as warranting a driving study, the approved label explicitly instructs providers to warn patients against driving. Many of these labels state that patients should make a judgement as to whether they feel safe to drive. For example, labels instruct patients not to drive until they know how the drug affects them. This type of instruction contradicts the FDA Guidance which states that drivers often fail to recognize when a drug is impairing their ability to drive.

Importance: The FDA's published guidance does not appear to have been routinely applied to determining whether newly approved drugs are likely to impair driving and/or when it's safe for an individual to drive after taking a medication. Since the publication of the guidance only 4 approved drugs have undergone a dedicated driving study. It remains unclear as to why this guidance is not being systematically applied.

W48. A MODEL PSYCHOPHARMACOLOGY CURRICULUM FOR TEACHERS OF PSYCHIATRIC RESIDENTS AND FOR MEDICAL STUDENTS

*Ira Glick**[1]

[1]*Stanford University School of Medicine*

Abstract: Since 1984, a psychopharmacology group has developed unique and widely disseminated curricula for teaching clinical psychopharmacology to 1) Psychiatric Residents and another to 2) Medical Students and Primary Care Physicians. It has increasingly had global penetration. We present here the 12th edition of the Resident Curriculum and the Joint 6th edition for Medical Students and for Primary Care. The curriculum has developed materials related to the "what, why, and how to teach and evaluate." In addition, for each curriculum, we included both a core series of lectures as well as optional lectures developed by experts in their fields. We have done follow ups on all three curriculums within the last few years. We describe here the process of revising, updating, and moving to a web-based curriculum. We present the content for the three curriculums. Depending on the size/sources of the program, teachers use the curriculum in its entirety or in parts. It works even in non-English speaking countries as users adopt/translate to local conditions and teaching problems. For Residents, the curriculum is now in its 12th edition and has 104 lectures and over 4000 slides. For the Medical Student curriculum, there are 22 lectures for medical students who

have widely divergent career paths. Having the curriculum web-based has improved availability though some global programs still request a hard copy version.

W49. PSYCHOTHERAPY EXPERIENCE AFFECTS ANTIDEPRESSANT RESPONSE RATE MODELED USING THE PARTICIPANT AND CLINICIAN REPORTED (PCR) CIRCUMPLEX MODEL OF DEPRESSION

Hadley Nolan[*1], Zach Cole[1], Miriam Evans[1]*

[1]Adams Clinical

Abstract: Many clinical and scientific advances are currently fueled by data-driven machine learning and artificial intelligence models that allow for a more individualized approach to healthcare and psychopharmacology, with cutting edge work largely focused on topics such as identifying biomarkers capable of predicting the antidepressant treatment (ADT) response in MDD clinical trials (e.g., Malik et al., 2021). In MDD clinical trials, the primary endpoints are often determined by clinician-reported outcomes, but the ADT treatment response is largely dependent on the participant's perception of their own condition. Recent introducing the Patient and Clinical Reported Circumplex Model of Depression (PCRC-MD; Cole, Nolan, and Evans, 2025) has shown that robust response prediction from a more straightforward and holistic approach is capable of meeting the same ends as the more sophisticated and data-driven approaches, but with a more concise and theoretical foundation. The PCRC-MD maps the clinician and participant reported outcomes within the same dimensional space. Generally, MDD patients who do not respond to therapy can improve with the addition of an antidepressant (Dunlop et al., 2019). Using the PCRC-MD, there is the potential for individuals educated through exposure to psychotherapy to respond differentially within the context of the PCRC-MD. The aim of the current work is to determine how prior psychotherapy experience prediction affects ADT treatment response, within the context of the PCRC-MD.

Methods: A sample of 130 MDD trial participants with psychotherapy experience (n = 80) or therapy naïve (n = 50) were prescribed an FDA approved ADT. PCR Circumplex models were derived from PHQ-9 and HAM-D assessment outcomes for baseline, end of treatment (EOT; six weeks), and change scores (baseline - EOT). Baseline and EOT scores were categorized by PCR quadrant (1: Depressed, 2: Minimizer, 3: Euthymic, 4: Exaggerator), change score quadrants were labeled as (1: Non-responder, 2: Discrepant Responder, 3: Responder, 4: Placebo Responder).

Results: $\chi 2$ test for given probabilities indicated that participants in the PCR Depressed Category at baseline were disproportionately less likely to respond to an ADT (25.4% vs. 63.5%; $\chi 2(1) = 17.004$, $p < .001$), whereas psychotherapy-naive participants were not (28.9% vs. 46.7%; $\chi 2(1) = 2.316$, $p = .128$). PCR Depressed participants in both psychotherapy groups were both equally likely to minimize or exaggerate their symptoms as evidenced by EOT or change scores.

Conclusions: The findings of our research suggest that the PCR Circumplex Model holds significant potential as a tool for enhancing the understanding and ability to predict treatment outcomes. Participants who had experience with psychotherapy were less likely to respond to the ADT, but participants who were therapy naïve did not. Typically combining

psychotherapy with an ADT is seen as an effective approach to treating MDD, particularly when one alone did not result in a response. In this case, current or previous psychotherapy appeared to reduce the likelihood of responding to an ADT. Future research can build on these findings by investigating additional factors and demographics (such as psychotherapy experience) that influence participants' symptoms, perception, as well as their ADT response. Our research findings establish a foundation for furthering the exploration of how the combined PCR Circumplex Model can lead to enhancing antidepression treatment predictions, as well as transforming the way clinical trials are conducted. Ultimately broadening the way MDD is treated.

W50. LEVERAGING GENETIC APPROACHES TO ADVANCE THE UNDERSTANDING OF GENETIC AND ENVIRONMENTAL EFFECTS ON SEVERE MENTAL ILLNESS: THE MODERATING ROLE OF PHYSICAL ACTIVITY

Olaoluwa Okusaga[*1], Roseann E. Peterson[2], Tim Bigdeli[2], Rachel L. Kember[3]*

[1]Michael E DeBakey VA Medical Center/Baylor College of Medicine, [2]SUNY Downstate Medical Center, [3]University of Pennsylvania

Abstract Background/Aims: Patients with a severe mental illness (SMI) including major depressive disorder (MDD), bipolar disorder (BD), and schizophrenia (SCZ), are more likely to have a sedentary lifestyle with low levels of physical activity (PA) relative to people without mental illness. Low PA levels are associated with obesity and other risk factors for cardiometabolic disease which shorten the lifespan of Veterans with SMI. Although high PA has been consistently associated with reduced risk of MDD, the relationship between PA and SCZ or BD is unclear. As PA is a modifiable risk factor, it is critical to understand the relationship between PA levels and genetic liability to SMI. We therefore aimed to identify genetic variants associated with SMI whose effects are modified by self-reported PA.
Methods: In the VA Data Commons, we identified cases of SCZ (N=48,603), BD (N=51,469), MDD (314,229), and controls (N=307,545) based on the presence or absence of the corresponding phecodes. Response to section C ("Activities") of the lifestyle questionnaire was used to classify cases and controls into high or low PA categories. We then performed a genome-wide association study (GWAS) of trans-diagnostic SMI, followed by GWAS of trans-diagnostic SMI stratified by PA.

Results: Cross-ancestry meta-analysis of SMI identified 3,174 genome-wide significant variants in 79 loci. GWAS stratified by PA identified 129 variants in 20 loci containing genes associated with brain development (CNTNAP2), brain specific (CALN1), developmental processes (SOX6) and transcription (BTAF1).

Conclusions: GWAS stratified by PA identified loci not found in the overall GWAS, suggesting that PA moderates the effect of a subset of genetic variants associated with SMI. A better understanding of how the genetic architecture of an individual moderates the impact of PA on SMI may lead to the identification of novel therapeutic targets to improve mental and physical health in patients with SMI.

W51. DURATION OF ILLNESS AND RESPONSE TO PIMAVANSERIN IN PARKINSON'S DISEASE PSYCHOSIS: POST-HOC ANALYSIS OF CLINICAL TRIAL DATA

Khashayar Dashtipour[1], Alberto Espay[2], Michele Tagliati[3], Gregory Brunson[4], Xiaoshu Feng[4], Nazia Rashid[4], Lambros Chrones[4]*

[1]Loma Linda University School of Medicine, [2]University of Cincinnati Gardner Neuroscience Institute, Gardner Family Center for Parkinson's Disease and Movement Disorders, University of Cincinnati, [3]Cedars-Siani Medical Center, [4]Acadia Pharmaceuticals Inc.

Abstract Objective: To examine individual responses to treatment with pimavanserin in patients with Parkinson's disease psychosis (PDP) initiating treatment < 6 months vs ≥6 months and < 12 months vs ≥12 months after initial psychotic symptoms.

Background: Pimavanserin is the only FDA-approved medication indicated for the treatment of hallucinations and delusions associated with PDP. Data regarding the relationship between PDP symptom duration and response to treatment are limited, and information from individual response data may have greater relevance to clinical practice than simply reporting mean changes from baseline.

DESIGN/Methods: Using data from a pivotal Phase 3, randomized, double-blind, placebo-controlled trial (ACP-103-020), we performed a responder analysis based on the duration of PDP symptoms. Patients who experienced severe psychotic symptoms weekly during the month before screening and met additional baseline requirements (a global item score of ≥3 on the Scale for the Assessment of Positive Symptoms [SAPS]-Hallucinations or SAPS-Delusions, and a score ≥3 on at least 1 other non-global item using the Parkinson's disease-adapted SAPS scale [SAPS-PD]) were randomized 1:1 to receive once-daily pimavanserin (34 mg) or placebo for 6 weeks. The primary outcome was the mean change from baseline to week 6 on the SAPS-PD. Individual responses were categorized by SAPS-PD score reductions of ≥1-point, ≥3-point, ≥5-point, ≥7-point, ≥10-point, or complete response (SAPS-PD=0), as well as increases > 1-point (worsening) or no change.

Results: A total of 95 patients who received active treatment with pimavanserin were included in this analysis. Patients with PDP symptoms < 6 months (n=13) had numerically greater rates of response to pimavanserin at all levels compared to those with symptoms ≥6 months (n=82). Notably, 30.8% of those who initiated pimavanserin < 6 months after initial psychotic symptoms achieved a complete response, or no hallucinations or delusions, compared with 11.0% of patients who initiated treatment after ≥6 months, however, differences were not statistically significant. These findings were consistent with rates of response for patients with < 12-month vs ≥12-month durations of psychotic symptoms.

Conclusions: Our analysis found that, at all levels of response, a greater percentage of patients with PDP responded to pimavanserin when treated < 6 months after initial psychotic symptoms compared with patients treated ≥6 months after initial psychotic symptoms (complete response: 30.8% vs 11.0%); findings were consistent for durations of < 12 vs ≥12 months since initial symptoms.

W52. FEASIBILITY OF ACCELERATED COURSE OF REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION IN METHAMPHETAMINE USE DISORDER

Amrita Ghose[*1], Taylor Helmbrecht[1], Virgilio Garza[1], Snoben Kuruvila[1], Sidarth Wakhlu[1], Madhukar Trivedi[1], Manish Jha[1]*

[1]The University of Texas Southwestern Medical Center

Abstract: Studies of transcranial magnetic stimulation (TMS) of the left dorsolateral prefrontal cortex (DLPFC) in individuals with methamphetamine use disorder have found decreased craving and potential reduction in stimulant use. Recently, intermittent theta burst stimulation (iTBS), a form of TMS with shorter administration time, has been shown to reduce cue-induced cravings for methamphetamine. However, a common barrier to treating participants with methamphetamine use disorder is low retention rates due in part of unstable housing and transportation issues. Retention rates could be improved by using accelerated TMS protocols, such as the Stanford Intelligent Neuromodulation Therapy (SAINT) protocol that has been cleared by the United States Food and Drug Administration for the treatment of depression. Here, we report on the feasibility of using an accelerated TMS approach for individuals with moderate/severe methamphetamine use disorder who also had comorbid depression (i.e., 9-item Patient Health Questionnaire score of 5 or more). Participants received four sessions/day of 60 cycles of 10 bursts of three pulses at 50 Hz delivered in 2-second trains (5 Hz) with an 8-second intertrain intervals delivered at hourly interval for a total of 50 sessions over a three-week period. Beam F3 was used for coil placement targeting left DLPFC. The study was registered on clinicaltrials.gov before initiation of any study activities. To date, 12 individuals with methamphetamine use disorder have been enrolled. The average age of participants is 46.4 years with eight males and four females. The average number of sessions completed is 49.2 and 9/12 (75%) have completed 50/50 sessions. The mean QIDS-SR at baseline and 4-weeks after treatment initiation were 9.7 and 6.8 respectively, with response rate of 41.7% (5/12). Together, these preliminary data provide compelling evidence that accelerated approaches for TMS can facilitate delivery of therapeutic course of TMS for individuals with methamphetamine use disorder.

W53. LURASIDONE AND PREGNANCY: AN UPDATE FROM THE MGH NATIONAL PREGNANCY REGISTRY FOR PSYCHIATRIC MEDICATIONS

Marlene Freeman[*1], Adele Viguera[2], Maya Verghese[1], Hannah Yoon[1], Caroline Frisch[1], Audrey Reuman[1], Peri Barest[1], Emma Grassi[1], Bridget Murphy[1], David Chitayat[3], Sonia Hernandez-Diaz[4], Lee Cohen[1]*

[1]Massachusetts General Hospital, Ammon-Pinizzotto Center for Women's Mental Health, [2]Massachusetts General Hospital, Ammon-Pinizzotto Center for Women's Mental Health; Cleveland Clinic, Cleveland Clinic Neurological Institute, [3]University of Toronto, [4]Harvard T.H. Chan School of Public Health,

Abstract: Background: As a prospective pharmacovigilance program, the National Pregnancy Registry for Psychiatric Medications (NPRPM) has collected reproductive safety data on a range of psychiatric medications, including second generation antipsychotics (SGAs) since 2008. Lurasidone is among one of the mostly commonly prescribed SGAs. The NPRPM published data on first trimester lurasidone use in 2023 with some indication that the

medication is not a major teratogen. Given the significant expansion of the NPRPM dataset and limited available reproductive safety data for lurasidone, the goal of the present analysis is to provide an update on the risk of major malformations among infants exposed first trimester to lurasidone compared to infants not exposed to SGAs.
Methods: Pregnant women, aged 18-45, with a history of a psychiatric disorder are eligible to participate. The research team collects prospective data on medication use, obstetric, and infant health outcomes across three phone interviews—twice during pregnancy and once at approximately three months postpartum. Enrollment is ongoing. Labor and delivery and pediatric medical records are procured and reviewed for the presence of a major malformation with final adjudication by a dysmorphologist blinded to medication use. Infants born to participants with a first trimester exposure to lurasidone were compared to controls without exposure to any SGAs.

Results: As of January 22nd, 2025, N=3,872 participants have enrolled in the NPRPM. At the time of data extraction, N=229 lurasidone-exposed infants and N=1913 infants in the comparison group were eligible for analysis. Among infants exposed to lurasidone in the first trimester of pregnancy, 6 had major malformations. The absolute risk of major malformations in the exposure group was 2.62% (95% CI: 0.97, 5.62) for lurasidone compared to 1.67% (95% CI: 1.15, 2.35) in the control group. The adjusted risk ratio is 1.52 (95% CI: 0.61, 3.78) for lurasidone.

Importance: This data is consistent with previously NPRPM data on the reproductive safety on this medication, suggesting that first trimester exposure to lurasidone is unlikely to have major teratogenic effect as seen in medications like valproic acid. However, greater sample sizes with more generalizable characteristics of the study population are essential to understanding a more precise estimate of risk.

W54. TREATMENT OF ARIPIPRAZOLE ASSOCIATED AGALACTORRHEA WITH RISPERDAL: CASE SERIES

Parmis Fatih[1], Genevieve Kurapaty[1], Senada Bajmakovic-Kacila[1], Mervat Sha'ini[1]*

[1]*Rush Medical College of Rush University*

Abstract: Antipsychotics are commonly used to treat women of childbearing age with various disorders, such as depressive disorders, psychotic disorders, and bipolar spectrum disorder. Aripiprazole is generally a well-tolerated second-generation antipsychotic with reassuring literature regarding its safety during pregnancy and the peripartum period. However, Aripiprazole's partial D2 agonism could lead to decreased breast milk production. There are several cases in the literature presenting evidence of lactation failure associated with Aripiprazole [1-4]. Risperidone's D2 antagonism could result in hyperprolactinemia, and there is evidence that Risperidone could be used as a galactagogue [5]. In this case series, we present two postpartum patients with lactation failure associated with Aripiprazole who were treated with Risperdal to restore milk production while maintaining mood stabilization. Both patients demonstrated improved breast milk production after the initiation of Risperdal. This case highlights the importance of considering treatment alternatives for women of childbearing age who wish to breastfeed, as well as strategies for boosting milk production in cases of medication-induced lactation failure.

W55. CLOZAPINE AVAILABILITY AT UNITED STATES MENTAL HEALTHCARE FACILITIES

Samuel Bunting[1], *Aparna Das**[2], *Luca Lacobelli*[2], *Beth Broussard*[2], *Emily Griner*[2], *Robert Cotes*[2]

[1]*The University of Chicago,* [2]*Emory University School of Medicine*

Abstract Background: Clozapine is a highly effective antipsychotic medication approved for treatment resistant schizophrenia and patients with recurrent suicidal behavior associated with schizophrenia or schizoaffective disorder. Despite being highly effective, it faces underutilization due to various factors, including prescriber lack of comfort, patient concerns about side effects, its required hematologic monitoring, and the Clozapine REMS system. To date, little information exists about clozapine availability at the mental health facility level. Understanding current clozapine availability within health care systems is crucial for improving access to this life-saving medication.

Methodology: This cross-sectional study administered by the Substance Abuse and Mental Health Services Administration (SAMHSA) analyzed the 2023 National Substance Use and Mental Health Services Survey (N-SUMHSS) to determine clozapine prescription availability at treatment facilities. The survey also collected data on facility characteristics, services provided, and location. The primary outcome of this study was whether clozapine prescription was available at each responding facility. Respondents were presented with a list of antipsychotics and subsequently indicated which were prescribed at their facility. Only facilities that prescribed antipsychotics were included in the analysis. Additional clinical services provided by the facility were assessed in relation to clozapine prescription. These included whether the facility had on-site laboratory testing, integrated primary care, assertive community treatment (ACT) team services, a specific program for people with SMI, administration of court-ordered or assisted-outpatient treatment (AOT), all answered as yes/no on the N-SUMHSS. Frequencies were calculated to describe the facility cohort, and a logistic regression model was used to analyze the relationship between facility characteristics and clozapine availability. Statistical significance was determined using a p-value of $< .05$.

Results: The 2023 N-SUMHSS survey was distributed to 25,148 facilities in the U.S. and SAMHSA reported an overall response rate of 84.9%. It was found that 58.5% (N=3768) of mental healthcare facilities in the U.S. offered clozapine prescription, with psychiatric hospitals (80%) having the highest availability. Outpatient facilities (aOR = .041 [0.22-0.74], $p < .001$) and those in the Western US (aOR = 0.49 [0.36-0.67], $p < .001$) were less likely to offer clozapine, while those with dedicated SMI programs (aOR = 1.57 [1.34-1.85], $p < .001$) and laboratory testing (aOR = 1.69 [1.26-2.26], $p < .001$) were more likely to do so.

Conclusions: Serious gaps for clozapine access exist at the facility level, as 53% outpatient mental health facilities overall and only 64% of facilities with a dedicated SMI program had clozapine availability. If a patient needs clozapine at a facility where it is not offered, they may not be offered clozapine at all or may need to seek services elsewhere, which may not be feasible in rural or underserved areas. Quality improvement or policy initiatives should seek to ensure that clozapine is accessible anywhere where patients with serious mental illness are

treated. Targeted educational and outreach efforts should be directed toward clinic administrators to encourage the integration of clozapine within mental health facilities.

W56. FETAL BRAIN CHANGES FROM IN-UTERO EXPOSURE TO ANTIPSYCHOTICS

Golden Reeves[*1], Plaiphon Vaidyanuvatti[1], Mujeeb Shad[2]*

[1]Touro University Nevada, [2]Valley Health System

Abstract: Antipsychotic medications are commonly prescribed to manage schizophrenia, with many individuals requiring long-term treatment during pregnancy. While benefits of antipsychotic use are well-documented, concerns still remain regarding their potential impact on fetal neurodevelopment, specifically on brain areas linked to schizophrenia. This observational study utilized a primary literature search focusing on key electronic databases and journals including Pubmed, Embase, and Google Scholar for eligible articles. Key inclusion criteria for this study focused on articles exploring prenatal antipsychotic use, effects on fetal brain development, specifically brain areas linked to schizophrenia. Search phrases included "prenatal/perinatal antipsychotics", "fetal brain development", and/or "prefrontal cortex", which yielded 10 studies that met the inclusion criteria. These studies explored the effects of prenatal exposure to antipsychotics on fetal brain areas linked to schizophrenia. In all reviewed studies, in utero exposure to antipsychotics on rodent subjects demonstrated brain alterations. In studies that reviewed effects of first generation antipsychotic, Haloperidol, showed reduced midbrain dopamine neurons and effects on development of dentate neurons which are key potential impairments observed in schizophrenia. Additionally, exposure to second generation antipsychotics, Quetiapine and Risperidone, led to reduced thickness in hippocampal layers, indicating apoptotic neurodegeneration. These findings highlight the potential risks of antipsychotic exposure during pregnancy, particularly in relation to the fetal brain's vulnerability in changes that may later manifest as schizophrenia-related symptoms. However, further research is needed to better understand the potential impact of gestational antipsychotic exposure on human fetal neurodevelopmental changes associated with schizophrenia.

W57. BROAD EFFICACY OF XANOMELINE AND TROSPIUM CHLORIDE ACROSS DEMOGRAPHIC SUBGROUPS IN THE LONG-TERM EMERGENT-4 AND EMERGENT-5 TRIALS OF PEOPLE WITH SCHIZOPHRENIA

Amy Claxton[*1], Inder Kaul[1], Tejendra R Patel[1], Soumya A Charturvedi[1], Wei-Chih Lin[1]*

[1]Bristol-Myers Squibb

Abstract Background: The M1/M4 preferring muscarinic receptor agonist xanomeline combined with the peripherally restricted muscarinic receptor antagonist trospium chloride was approved by the U.S. Food and Drug Administration for the treatment of schizophrenia in adults based on results from the 5-week, phase 3 EMERGENT-2 (NCT04659161) and EMERGENT-3 (NCT04738123) clinical trials. Maintenance of efficacy of xanomeline/trospium (X/T) was demonstrated in the long-term EMERGENT-4 (NCT04659174) and EMERGENT-5 (NCT04820309) trials of adults with schizophrenia. Subgroup analysis of acute trial data showed a consistent treatment effect across baseline

clinical and demographic characteristics. Here, post hoc analyses are used to examine X/T efficacy across participant subgroups in the long-term trials.

Methods: EMERGENT-4 and EMERGENT-5 were 52-week, phase 3, open-label trials of X/T in adults with schizophrenia. EMERGENT-4 enrolled participants who previously completed the treatment period of the EMERGENT-2 or EMERGENT-3 trials. Individuals enrolled in EMERGENT-5 had no prior exposure to X/T, a Positive and Negative Syndrome Scale (PANSS) total score ≤80, and a Clinical Global Impression–Severity score ≤4. Trial participants received twice-daily oral dosing at X/T 50 mg/20 mg and titrated to a maximum dose of X/T 125 mg/30 mg. Efficacy was assessed by change in PANSS score at week 52 from acute trial baseline (EMERGENT-4) and from trial baseline (EMERGENT-5). Efficacy analyses were performed in the modified intent-to-treat (mITT) populations, defined as all randomized participants who received ≥1 trial drug dose and had a baseline and ≥1 postbaseline PANSS assessment. Change in PANSS score at week 52 was further examined in subgroups based on the baseline demographic parameters of age, sex, ethnicity, race, nationality, and body mass index (BMI).

Results: A total of 111 and 558 individuals comprised the EMERGENT-4 and EMERGENT-5 mITT populations, respectively. In both trials, X/T was associated with continued improvements in PANSS total score across the 52-week treatment periods and was generally safe and well tolerated. No new safety issues emerged. Subgroup analyses revealed an overall consistent treatment effect of X/T on PANSS total score across demographic subgroups. In EMERGENT-4, the point change in PANSS total score from acute trial baseline to week 52 was generally consistent across age (< 45 years, -38.0; ≥45 years, -26.3) and sex (male, -32.6; female, -32.6) subgroups. In EMERGENT-5, intergroup differences in PANSS score reductions were also generally consistent across age (< 45 years, -5.7; ≥45 years, -5.4), sex (male, -5.2; female, -6.1), and ethnicity (Hispanic/Latino, -6.9; non-Hispanic/Latino, 5.1) categories. Analyses of race, nationality, and BMI subgroups are under way, and results will be presented at the meeting.

Conclusion: In post hoc analyses of participant subgroups from the 52-week EMERGENT-4 and EMERGENT-5 trials of adults with schizophrenia, people treated with xanomeline/trospium showed consistent symptom improvement regardless of demographic characteristics. Additional subgroup analyses are underway. To date, results indicate that the long-term efficacy of xanomeline/trospium is broadly applicable to a range of individuals living with schizophrenia.

W58. LONG-TERM SAFETY AND TOLERABILITY OF XANOMELINE/TROSPIUM IN SCHIZOPHRENIA: INCIDENCE, ONSET, AND DURATION OF TREATMENT-RELATED ADVERSE EVENTS IN THE 52-WEEK, OPEN-LABEL EXTENSION EMERGENT-4 TRIAL

*Amy Claxton *[1], Soumya A Charturvedi[1], Tejendra R Patel[1], Nichole Neugebauer[1], Pierre Nicolas[1], Inder Kaul[1]*

[1]Bristol-Myers Squibb

Abstract Background: The U.S. Food and Drug Administration recently approved the dual M1/M4 preferring muscarinic receptor agonist xanomeline combined with the peripherally restricted pan muscarinic receptor antagonist trospium for the treatment of adults with schizophrenia. In the 5-week, randomized, double-blind, placebo-controlled EMERGENT-1 (NCT03697252), EMERGENT-2 (NCT04659161), and EMERGENT-3 (NCT04738123) trials, xanomeline/trospium improved symptoms and was generally well tolerated in people with schizophrenia experiencing acute psychosis. Most adverse events (AEs) occurred early during the first 2 weeks and resolved with continued treatment. In the long-term EMERGENT-4 (NCT04659174) and EMERGENT-5 (NCT04820309) open-label trials, xanomeline/trospium was safe and generally well tolerated over 52 weeks. Here, we characterize the incidence, onset, and duration of the most common treatment-related AEs with xanomeline/trospium in EMERGENT-4.

Methods: EMERGENT-4 was a 52-week, open-label, extension trial in adults with schizophrenia who completed EMERGENT-2 or EMERGENT-3. At time of enrollment in the acute trials, participants were experiencing an acute exacerbation of psychosis warranting hospitalization, had a Positive and Negative Syndrome Scale total score 80-120, and had a Clinical Global Impression–Severity score ≥4. Participants initiated twice-daily oral xanomeline 50 mg/trospium 20 mg for the first 2 days, titrated to 100 mg/ 20 mg for the remainder of week 1, and then titrated to the maximum dose of 125 mg/ 30 mg unless they continued to experience AEs at the 100 mg/20 mg dose. Participants titrated to 125 mg/30 mg could return to 100 mg/20 mg for the remainder of the trial for clinical response or tolerability reasons. The safety population for analyses included all participants who received ≥1 dose of xanomeline/trospium (X/T) in the extension trial.

Results: A total of 152 participants (XT/XT, n=68; placebo/XT, n=84) were included in the safety population. Treatment with xanomeline/trospium over 52 weeks was safe and generally well tolerated in people with schizophrenia; no new safety or tolerability issues emerged. Overall, 35.5% of participants experienced ≥1 treatment-related AE. The incidence of treatment-related AEs was similar in participants with (35.3%) and without (35.7%) prior xanomeline/trospium exposure in the acute trials. The most common treatment-related AEs were nausea (9.2%), vomiting (7.9%), dyspepsia (5.9%), dry mouth (5.3%), hypertension (5.3%), constipation (3.3%), increased weight (3.3%), diarrhea (2.6%), gastroesophogeal reflux disease (2.6%), dizziness (2.6%), headache (2.0%), and somnolence (2.0%). Most participants did not require a dose reduction for tolerability reasons; the incidence of dose reduction was higher among participants who received placebo (11.9%) versus xanomeline/trospium (2.9%) in the acute trials. Among the participants with a dose reduction, 3.9% up-titrated again. Additional analyses evaluating the onset and duration of the most common treatment-related AEs will be presented.

Conclusion: In EMERGENT-4, long-term treatment with xanomeline/trospium for 52 weeks was safe and generally well tolerated. The most common treatment-related AEs were consistent with the known activity of xanomeline/trospium at muscarinic receptors and those reported in the acute trials. Most participants did not require a reduction in xanomeline/trospium dose for tolerability reasons.

W59. EFFICACY AND SAFETY OF STRATEGIES FOR SWITCHING TO XANOMELINE AND TROSPIUM CHLORIDE FROM STANDARD OF CARE ATYPICAL ANTIPSYCHOTICS: DESIGN OF A PLANNED OPEN-LABEL TRIAL IN PEOPLE WITH SCHIZOPHRENIA

David Walling[*1], *Pierre Nicolas*[2], *Naomi Marbot*[2], *Lauren White*[1], *Eliesha Daniels*[2]

[1]*CenExel - CNS,* [2]*Bristol-Myers Squibb*

Abstract Background: Switching between antipsychotics is common among people with schizophrenia. The dual M1/M4 preferring muscarinic receptor agonist xanomeline combined with the pan muscarinic receptor antagonist trospium chloride was recently approved by the U.S. Food and Drug Administration for the treatment of schizophrenia in adults. Data on safe and effective real-world strategies for switching from standard of care atypical antipsychotics (AAs) to xanomeline/trospium are needed to guide clinical decision-making. This will be the first study evaluating the naturalistic switching from AAs to an approved muscarinic compound.

Methods: The 8-week, open-label, multicenter, outpatient trial will assess the efficacy, safety, and tolerability of xanomeline/trospium in adults with schizophrenia who switch from AAs. The trial will enroll approximately 120 adults aged 18 to 65 years who have a primary diagnosis of schizophrenia, stable symptoms, and baseline scores of ≤80 on the Positive and Negative Syndrome Scale (PANSS) and ≤4 on the Clinical Global Impression–Severity (CGI-S) scale. Participants will be required to be on a stable dose of an oral AA for ≥6 weeks at the time of screening. Exclusion criteria include any primary diagnosis other than schizophrenia, a history of resistance to antipsychotic therapy, psychiatric hospitalization for > 30 days within 12 months of screening, and prior exposure to xanomeline or trospium. The trial design will employ de-escalation of current AA therapy after titrating xanomeline/trospium to a therapeutic dose deemed appropriate by the investigator. Following a screening period of ≤2 weeks, participants will be randomized to 1 of 2 treatment arms that utilize an accelerated or a slower switch from current AA treatment. All participants will initiate oral xanomeline/trospium at a dose of 50 mg/20 mg twice daily. People in the accelerated arm will begin treatment with xanomeline/trospium per package insert, similar to the dosing regimen used in the clinical trials. Participants must be switched off of their prior AA by week 2. In the slower treatment group, clinicians may cross-titrate AA and xanomeline/trospium treatment, with full switch to xanomeline/trospium by week 4. Participants in both groups will receive xanomeline/trospium for up to 8 weeks. A safety follow-up will take place the week following the end of treatment.

Results: The primary endpoint is all-cause discontinuation during the 8-week treatment period. Secondary outcome measures include incidence of adverse events and change from baseline at week 8 in PANSS total, CGI-S, and Personal and Social Performance scale scores.

Conclusion: While many trials conducted in support of regulatory approval are designed to answer questions from regulators, this will be the first trial to answer the real-world question of how participants can be cross-titrated from atypical antipsychotics to xanomeline/trospium. Results can provide clinicians with evidence-based guidance on how to safely and efficaciously make the switch to xanomeline/trospium.

W60. TRAUMA, MENTAL DISORDERS, AND SUICIDE: A RETROSPECTIVE CHART REVIEW IN AN URBAN EMERGENCY CENTER

Ynhi Thomas[1], Nidal Moukaddam[2], Syed Murtaza[2], Kelly Keene[3], Christopher Verrico[2], Nicholas Murphy[2], Sanjay Mathew[4], Thomas Kosten[4], Alan Swann[2]*

[1]Henry J.N. Taub; Center for Innovations in Quality, Effectiveness, and Safety (IQuESt), Michael E. DeBakey Veterans Affairs Medical Center, [2]Menninger, Baylor College of Medicine, [3]Henry J.N. Taub, Baylor College of Medicine, [4]Menninger, Baylor College of Medicine; Michael E. DeBakey Veterans Affairs Medical Center

Abstract: Background: Unintentional injuries and suicide are leading causes of death and disability in the United States. Among survivors of medically severe suicide attempts and non-suicidal traumatic injuries, subsequent accidents are a major source of premature mortality. Individuals who have survived non-suicidal injuries also face an elevated risk of recurrent severe physical trauma and possible suicide attempts. Notably, about 60% of suicide deaths occur during a first attempt without prior mental disorder diagnoses. Understanding how accident-proneness relates to suicide risk can inform prevention strategies.

Methods: This 18-month retrospective review examined 225 adult trauma patients (≥18 years) at an urban Emergency Center. All had psychiatric consults due to provider concern for mental health. We collected demographics, clinical history, and injury mechanisms, comparing those with versus without a past suicide attempt. We compared participants in 2x2 cells: a) current suicide attempt or self-harm versus b) no suicide attempt or self-harm, by c) past suicide attempt versus d) no past suicide attempt.

Results: All participants (N=225) were included in analyses, with mean age 38 years; 61% were male, 39% female; 49% White, 42% Black, 1% Asian, 7% other. Compared to those without a suicide attempt history, individuals with a past attempt had more overdoses (9% vs 4%), penetrating wounds (31% vs 14%), and fewer blunt traumas (44% vs 61%; $P < 0.004$). Among 88 participants with a past attempt, 64% re-presented with another suicide attempt, versus 21% with a non-suicidal accident ($P < 0.001$). Those with past attempts had higher rates of psychotic, affective, drug use, and post-traumatic stress disorders, as well as more medical and psychiatric hospitalizations, and more Emergency Center visits (all $P < 0.05$). Self-harm rates were comparable (20% vs 17%), but suicide attempt rates were approximately half (20% vs 50%) in those without (n=137) versus with (n=88) a prior attempt. Among 137 with no past attempt, 50 had a new attempt/self-harm at presentation, whereas 87 did not. Notably, the 87 with no previous or current attempt had more prior Emergency Center visits (4.61 vs 3.08, $P < 0.001$) and medical hospitalizations (0.74 vs 0.24, $P < 0.05$) than the 50 with both previous and current attempt/self-harm. No differences emerged in demographics, mental disorder rates, or psychiatric hospitalization.

Conclusions: Participants with a history of suicide attempts were more likely to present with another suicide attempt and to have mental health comorbidities. However, 37% (50/137) of those without a documented past attempt presented with new self-harm or suicidality, which may be part of the 60% of suicides occurring on a first attempt without prior diagnoses. Those without prior or current attempts had more Emergency Center visits and hospitalizations, suggesting underlying risk. These findings underscore the need for enhanced

screening and targeted interventions in acute-care settings. The similarity in demographics, mental disorder rates, and psychiatric hospitalizations between these groups suggests other factors, such as the context of physical trauma, may influence suicide risk. More research is needed to identify characteristics of suicide attempts or self-harm in trauma patients that could predict potentially lethal first attempts. Understanding these predictors may inform interventions and improve outcomes for high-risk individuals.

W61. DEVELOPING A NEUROECONOMICALLY INFORMED AND BIOLOGICALLY CONSTRAINED REGRET INVENTORY

Romain Durand de Cuttoli[1], Alexandra Fink[1], Austin Baggetta[1], Giorgio Coricelli[1], Helen Mayberg[1], A. David Redish[1], James Murrough[1], Xiaosi Gu[1], Ignacio Saez[1], Laurel Morris[1], Jonathan DePierro[1], Brian Sweis[1]*

[1]Icahn School of Medicine at Mount Sinai

Abstract: Regret is a poorly understood emotion that may contribute to nearly every mental illness. Regret describes a form of counterfactual thinking where one recognizes alternative decisions could have led to better outcomes. Despite being widely accepted that regret can be detrimental to emotional well-being, no description appears in the DSM nor is pathognomonic for any disorder. Further, little is known about what aspects of regret if any carry utility worth preserving to restore healthy emotional processing and adaptive coping, even if evoking cognitive dissonance. Although psychologists, economists, and neuroscientists have been working toward understanding regret, this has historically occurred outside of a unified framework without a shared lexicon rooted in underlying neurobiology. Currently, there are limited clinical tools that move beyond plain language to describe regret. We propose the concept of a Neuroeconomic Regret Inventory (NRI) inspired by cross-species research efforts to resolve attributes of regret into discretely measurable computational units. The NRI characterizes multiple, orthogonal dimensions of regret. Question items examine cognitive domains derived from neuroeconomic principles, including aspects of reinforcement learning, foraging theory, and temporal discounting. Here, we collected data from 350 subjects online via the Prolific platform. We found subjects could complete the 115-item NRI survey in approximately 15 min. We found that overall, subjects ranked regret related to relationships as the most important life category compared to finance, health, career, and legal decisions. Interestingly, relationship regret-related decisions was the only category that interacted with sex and age. Across the 115 NRI items, questions elicited a wide distribution of responses that scored with varying direction and magnitude. This included within each of the 6 major themes of question items: general questions, regret recognition and registration, feeling and affect, mental operations, reactions and responses, and lastly, anticipation avoidance and learning. Our vision is that this tool could provide improved neuroeconomic language to be leveraged in multiple settings, e.g., structured interviews to guide psychotherapy strategies and inform computational models of task-based behavior and physiology. By enhancing the diagnostic nosology of psychiatric disorders through a description of one's decision narrative, we can develop more effective treatments based on a richer understanding of the psychological mechanisms mediating the perception and influence of one's prior actions.

W62. SINGLE-DOSE COMP360 PSILOCYBIN FOR POST-TRAUMATIC STRESS DISORDER

Niall McGowan[1], James Rucker[2], Rachel Yehuda[3], Manish Agrawal[4], Hollie Simmons[1], Agata Tofil-Kaluza[1], Shriya Das[1], Guy Goodwin[1]*

[1]Compass Pathfinder Ltd., [2]King's College London, Institute of Psychiatry, Icahn School of Medicine at Mount Sinai, [4]Sunstone Therapies,

Abstract Purpose and content: Post-traumatic stress disorder (PTSD) is a severely debilitating psychiatric disorder for which there are few efficacious treatments. Results are presented from a phase 2 open-label clinical trial which examined the safety and tolerability of COMP360, Compass Pathfinder Limited's proprietary synthesized psilocybin formulation, in PTSD.

Methodology: This was a 12-week, open-label, nonrandomized trial. The primary outcome of this trial was the safety and tolerability of a single 25 mg dose of COMP360 psilocybin, administered with psychological support, in participants with PTSD. Secondary outcomes were change in PTSD symptoms (Clinician-Administered PTSD Scale for DSM-5 [CAPS-5]; and PTSD Checklist for DSM-5 [PCL-5]), functional impairment (Sheehan Disability Scale; SDS) and quality of life (EQ-5D-5L index score). Treatment-emergent adverse events (TEAEs), serious adverse events (TESAEs) and the PCL-5 were assessed at all visits. The CAPS-5, SDS and EQ-5D-5L were assessed at Baseline, Week 4 and Week 12. Spearman rank correlations (rs) between subjective psychedelic experience (5D-ASC) on Day 1, and CAPS-5 change from Baseline at Week 4 and Week 12 were also examined.

Results: Amongst the 22 participants enrolled (63.6% female; mean [SD] age, 39.0 [7.91] years), there was a total of 117 treatment-emergent adverse events (TEAEs); 70 (59.8%) were reported on administration day, of which 64/70 (91.4%) resolved by the end of the next day. TEAEs commonly included headache (n=11; 50.0%), nausea (n=8; 36.4%), crying (n=6; 27.3%), and fatigue (n=6; 27.3%). There were no TESAEs observed or TEAEs that led to study withdrawal. There were two TEAEs of suicidal ideation; both resolved during the study. Treatment was associated with a reduction in mean (standard deviation [SD]) CAPS-5 scores from Baseline to Week 4 (-29.9 [14.06]) and Week 12 (-29.5 [15.43]). This translated to an 81.8% response rate and a 63.6% remission rate at Week 4. Response and remission rates at Week 12 were 77.3% and 54.5%, respectively. Mean [SD] PCL-5 score reduction was rapid, notable by Day 2 (-33.5 [14.32]) and sustained until Week 12 (-34.3 [18.13]). Participants showed an improvement in functional impairment over the 12 weeks of the study; from a mean SDS total score of 22.7 [5.38] at Baseline, there was a -11.7 [8.41] point reduction at Week 4 and a -14.4 [8.21] reduction at Week 12. Quality of life scores improved throughout the study, indicated by an EQ-5D-5L index score of 0.51 [0.287] at Baseline increasing to 0.73 [0.272] at Week 4 and 0.78 [0.269] at Week 12. The 5D-ASC dimension Oceanic Boundlessness on Day 1 was associated with a greater change from Baseline on the CAPS-5 at Week 4 (rs=-0.442) and Week 12 (rs=-0.394).

Importance: Single-dose 25 mg COMP360 psilocybin, delivered with psychological support, was generally well-tolerated and was not associated with any TESAEs. Participants

experienced a clinically meaningful and durable reduction in clinician-rated PTSD symptoms, and rapid self-reported improvement by Day 2. Treatment was associated with improvements to functioning and quality of life across the 12-week study period. The intensity of participants' subjective positive psychedelic experience on dosing day was associated with better treatment response at Week 4 and Week 12, suggesting that this measure may be informative for predicting treatment response in PTSD. Results should be interpreted within the context of the modest sample size and the open-label design with no control comparator. Whilst the results are promising, larger well-controlled studies are required to inform the viability of COMP360 psilocybin as a potential efficacious treatment for PTSD.

W63. ROBUST ANTIDEPRESSANT EFFICACY OF THE NOVEL 5-HT2A RECEPTOR AGONIST GM-2505 IN A DOUBLE BLIND, RANDOMIZED, CONTROLLED PHASE 2A TRIAL IN PATIENTS WITH MDD

Gerard Marek[*1], Daniel Umbricht[2], Edward Christian[1], Jason Winters[1], Shane Raines[3], William Leong[1], Laszlo Kiss[1], Zoe Hughes[1], Robert Berman[4], Jorge Quiroz[1], Andrew Kruegel[1], Jonathan Sporn[1]*

[1]Gilgamesh Pharmaceuticals, Inc., [2]Xperimed GmbH, [3]2b Analytics, [4]Yale University School of Medicine

Abstract: GM-2505 is a novel 5-hydroxytryptamine2A (5-HT2A) receptor agonist and serotonin (5-HT) releaser with a short half-life and duration of psychotropic effects. It is currently being investigated for the treatment of major depressive disorder (MDD) and other neuropsychiatric disorders. Described here are the results of a randomized, double-blind, active-controlled Phase 2a trial of GM-2505 in 40 male and female patients with recurrent MDD. All participants were antidepressant-free for at least 6 weeks prior to screening and remained off antidepressant medication throughout the trial. All patients were administered two intravenous doses of GM-2505 with a 2-week interval between dosing. In Arm 1, half of the patients initially received a low dose on Day 1 as active control, which produced measurable, but minimal, psychotropic effects in healthy volunteers (HVs). In Arm 2, the other half received a moderate dose on Day 1, which exerted robust psychedelic effects in HVs. On Day 15, all patients received a high dose, which induced maximal psychedelic effects in HVs. The patients were monitored for safety and antidepressant responses through Day 29, with a priori timepoints for comparing MADRS change from baseline scores at Day 14 and Day 29. This allowed for initial examination of dose-response for efficacy, safety, PK, and PD. Statistically significant decreases in MADRS scores were observed in both study arms and decreases were always greater for Arm 2, which received two robustly psychedelic doses. At Day 14, there was an effect size of ~1.0 for a between-subjects comparison of the least square mean change from baseline in MADRS scores for Arm 2 treated with the moderate dose compared to Arm 1 treated with the active control low dose. At Day 29, two weeks following the high dose, MADRS scores further significantly decreased in both arms based on a within-subject comparison of Day 29 to Day 14 and the MADRS change from baseline in Arm 2 was significantly > in Arm 1 based on a between-subjects comparison. Further, there were robust categorical MADRS response and remission rates indicating that both the moderate and high doses were efficacious. The superior response in Arm 2 also suggests that a regimen of two robustly psychedelic doses, administered two weeks apart,

produces greater efficacy than a single robust psychedelic dose. There were no serious adverse events (SAEs) and the treatment emergent adverse events (TEAE) profile was similar to that in HVs. There were no patients with suicidal ideation and a plan/intent. GM-2505 induced expected transient increases in systolic and diastolic blood pressure and pulse rate. In conclusion, GM-2505 is a promising, best-in-class 5-HT2A receptor agonist with the potential to safely and effectively treat patients with MDD, offering a novel and transformative approach to depression treatment.

W64. ONCE-DAILY NBI-1117568, A HIGHLY SELECTIVE ORTHOSTERIC M4 MUSCARINIC RECEPTOR AGONIST, DEMONSTRATES MEANINGFUL IMPROVEMENTS IN PANSS TOTAL SCORE AND IS WELL TOLERATED IN ADULTS WITH SCHIZOPHRENIA: PHASE 2 STUDY RESULTS

Abigail Nash[*1], Elia E. Acevedo-Diaz[2], Kurt Olson[1], Satjit Brar[1], Ashley Whitcomb[1], Eiry Roberts[1], Samir Siddhanti[1], Jaskaran Singh[1]*

[1]Neurocrine Biosciences, Inc., [2]CenExel CBH

Abstract Background: Current therapies for the treatment of schizophrenia have limited efficacy and/or poor tolerability. Novel mechanisms that might improve efficacy and safety are urgently needed. Muscarinic receptor agonists represent a novel approach for treating schizophrenia. A phase 2 dose-finding study (NCT05545111) was conducted to assess the efficacy, safety, and tolerability of NBI-1117568, a highly selective orthosteric M4 muscarinic receptor agonist, in adults with schizophrenia.

Methods: Adults (18-55 years) with schizophrenia experiencing acute exacerbation or symptom relapse requiring hospitalization and a Positive and Negative Syndrome Scale (PANSS) total score ≥80 were randomized (2:1) to NBI-1117568 or placebo (PBO). Other antipsychotics were not allowed during the study. The adaptive dose-escalation design comprised double-blind placebo-controlled treatment (6 weeks) and safety follow-up (2 weeks). Based on results of 2 independent, unblinded, interim safety analyses, the final treatment arms were as follows: PBO, 20 mg QD, 40 mg QD, 60 mg QD, and 30 mg BID. Changes from baseline (BL) were analyzed for PANSS total score and Clinical Global Impression Scale-Severity (CGI-S), with results presented as least-squares mean (LSM) changes by treatment arm (±standard error [SE]) and the LSM difference (LSMD) between treatment arms.

Results: Demographics and BL characteristics were generally similar across treatment arms: placebo (n=70); 20 mg QD (n=40); 40 mg QD (n=39); 60 mg QD (n=34); 30 mg BID (n=27). Significant improvements in PANSS total score were observed with NBI-1117568 20 mg QD by Week 3 (-13.4 [±2.1] vs -7.7 [±1.5] for PBO, LSMD -5.7 [±2.6], P=0.0141) and at all post-BL visits to Week 6 (primary endpoint: -18.2 [±2.7] vs -10.8 [±1.9], LSMD -7.5 [±3.2], P=0.0113, Cohen's d effect size=0.61). A significant improvement in CGI-S was also observed at Week 6 with NBI-1117568 20 mg QD (-1.2 [±0.2] vs -0.5 [±0.1] for PBO, LSMD -0.7 [±0.2], P=0.0003). For other doses (40 mg QD, 60 mg QD, 30 mg BID), mean decreases from BL at Week 6 in PANSS total and CGI-S scores were greater with NBI-1117568 versus PBO, but not statistically significant. The percentage of participants reporting ≥1 treatment-emergent adverse event (TEAE) was similar between NBI-1117568

(56.4% [all doses]) and PBO (58.6%), as was the percentage who discontinued study drug due to a TEAE (5.0% vs 4.3%). TEAEs reported in ≥5% of all NBI-1117568–treated participants were somnolence (10.7% vs 2.9% for PBO), dizziness (9.3% vs 1.4%), headache (8.6% vs 20.0%), nausea (5.7% vs 2.9%), and constipation (5.0% vs 2.9%). Transient increases in heart rate (HR) were observed with NBI-1117568, which attenuated over the course of treatment (HR mean change from BL: +10.3 bpm [Week 1], +6.2 bpm [Week 6]). No weight gain was associated with NBI-1117568 relative to PBO.

Conclusions: Adults with schizophrenia experiencing acute exacerbation or relapse of symptoms had significant PANSS and CGI-S improvements after 6 weeks of treatment with NBI-1117568 20 mg QD. NBI-1117568 was well tolerated with low incidences of peripheral cholinergic-related TEAEs (e.g., nausea) and TEAEs common with other antipsychotic medications (e.g., constipation). NBI-1117568 was associated with transient increases in HR that attenuated over the course of treatment, and it was not associated with weight gain relative to PBO. These results support further investigation of NBI-1117568 as a novel therapeutic approach for schizophrenia.

W65. ORAL, ONCE-DAILY LB-102 (N-METHYL AMISULPRIDE): RECENT POSITIVE RESULTS FROM A PHASE 2 STUDY IN PATIENTS WITH ACUTE SCHIZOPHRENIA

Anna Eramo[1], Leslie Callahan[1], Niccolo Bassani[2], Baker P. Lee[1], Zachary Prensky[1], Andrew R Vaino[1], John Kane[6]*

[1]LB Pharmaceuticals Inc., [2]Worldwide Clinical Trials, [6]The Donald and Barbara Zucker School of Medicine at Hofstra/Northwell

Abstract Schizophrenia is a chronic and debilitating mental illness that affects ~1% of the population. The course of schizophrenia is highly variable, with periods of psychosis and stabilization of varying duration and intensity. Sustained remission of both positive and negative symptoms occurs in a minority of patients even with prolonged therapy. Compliance with long-term medication is a significant problem due to dissatisfaction with side effects or self-discontinuation of medication, contributing to relapse among schizophrenia patients. Patients with schizophrenia suffer a profoundly reduced quality of life, have a 3.5-times higher mortality rate, and are 10 times more likely to commit suicide than the general population. Half of all suicides occur within the first 2 years of disease onset, pointing to the urgency for behavioral and pharmaceutical intervention.

LB-102 (N-methyl amisulpride), a potential first-in-class benzamide antipsychotic was designed based on the safe and effective benzamide amisulpride with a goal of increasing its permeability across the blood-brain barrier, potentially decreasing plasma concentration needed to achieve efficacy (which could decrease the magnitude and frequency of adverse events typically observed with amisulpride). In vitro studies confirmed that LB-102 has similar activity and selectivity toward the D2, D3, and 5HT7 receptors as amisulpride. In vivo studies demonstrated LB-102 had a PK profile in rats and mice similar to amisulpride, and had similar/superior efficacy to amisulpride in animal schizophrenia models.

In a Phase 1 randomized, double-blind, placebo-controlled study designed to evaluate the safety and PK of LB-102 in healthy volunteers, LB-102 was well-tolerated; all TEAEs mild

or moderate, and there were no SAEs. The maximum tolerated dose in health volunteers was 150 mg/day.. This study achieved its objectives of identifying the safety, tolerability, and PK of single and multiple oral doses of LB-102 in healthy volunteers.

A Phase 1 open-label, positron emission tomography study was conducted to evaluate the dopamine receptor occupancy (RO) of orally dosed LB-102 in healthy volunteers. This study highlighted that LB-102 afforded dopamine RO in the desired range to treat schizophrenia under steady-state conditions, as doses as low as 50 mg/day with no SAEs.

A Phase 2 US-based, double-blind, placebo-controlled, 28-day inpatient trial of LB-102 (NCT06179108, NOVA1) was recently completed. Adults (18–55 yr) with schizophrenia (DSM-V) were randomized (3:3:3:1) to oral once-daily placebo, LB-102 50 mg, LB-102 75 mg, or LB-102 100 mg. The primary endpoint of this study was the change from baseline to week 4 in PANSS total score. Secondary endpoints included change from baseline in CGI-S score and PANSS responder rates. Safety was assessed through TEAEs and other assessments. LB-102 met the primary endpoint, with mean change from baseline to week 4 in PANSS total score of placebo, -9.3; 50 mg, -14.3; 75 mg, -14.0; and 100 mg, -16.1. Each treatment arm demonstrated a statistically significant (Hochberg multiplicity correction for 50 and 75 mg) reduction in PANSS score vs. placebo (50 mg: -5.0, p=0.0009, effect size=0.61; 75 mg: -4.7, p=0.0022, effect size=0.41; 100mg: -6.8, p=0.0017, effect size=0.83).

The phase 2 NOVA1 clinical trial provided robust evidence demonstrating the efficacy and safety of LB-102 in adults with acute schizophrenia, informing the continued clinical development of LB-102.

W66. A NOVEL COMBINATION PHARMACOTHERAPEUTIC PLATFORM FOR SUBSTANCE USE DISORDER TREATMENT

*Tong Lee**[1]

[1]*Generys Biopharmaceuticals Corp.*

Abstract: [MPh-IR + Ond-PR2], comprising an immediate-release (IR) formulation of methylphenidate (MPh) and a delayed pulsatile-release (PR) formulation of ondansetron (Ond) is a first-in-kind, disease-modifying Phase 2B/3-stage drug candidate being developed for the treatment of multiple substance use disorders and trauma and stressor-related disorders. The impetus for the development of this combination drug candidate derives from the concept of "pharmacologically-mediated reactivation and reconsolidation blockade" of "dysfunctional neural memory" that underlies the targeted neuropsychiatric disorder (see Lee et al., 2012, Drug and alcohol dependence 124: 11-18). Various neuropsychiatric disorders, including substance use disorders, may be considered as a consolidated form of maladaptive synaptic plasticity, and treatment-mediated normalization of these neuroplastic changes may lead to a successful therapeutic outcome (Centonze et al., 2005, Neuroscience 130: 559-565; Agren, 2014, Brain Res. Bull. 105: 70-82; Walsh et al., 2018, Psychopharmacology 235: 2507-2527; Bender and Torregrossa, 2020, Cell. Mol. Life Sci. 77: 3745-3768; Rout et al., 2022, Pharmacology and Therapeutics 239: 108195).
In a proof-of-concept Phase 2A, single-site, randomized, double-blind, placebo-controlled clinical trial, we determined the efficacy of [MPh-IR + Ond-PR2] in reducing cue-induced

craving and cue-reactivity deficits in psychostimulant (cocaine or methamphetamine) use disorder (PUD) patients residing in a local residential program, using standard behavioral rating scales and cue-reactivity and resting-state neuroimaging paradigms. Subjects were treated with either [MPh-IR + Ond-PR2] (20/10 mg methylphenidate/ondansetron hydrochloride) or identical-appearing placebo (qd x 2 weeks). Treatment outcome assessments were performed 2-7 days after the last dosing to ensure that observed changes represented true treatment-induced modifications, rather than effects of residual [MPh-IR+Ond-PR2].

A total of 30 qualifying subjects were randomized into either [MPh-IR + Ond-PR2] or placebo treatment group. Twenty-eight subjects completed the 2-week drug treatment and pre- and post-treatment behavioral rating and fMRI assessments. Compared to placebo, [MPh-IR + Ond-PR2] significantly reduces cue-induced craving scores with a "large" effect size (Henry's effect size d = 0.73) that also correlated with selected cue-reactivity and resting-stage neuroimaging changes induced by the study drug (d = 1.26 - 1.70).

There are currently no drugs approved by the FDA for PUD treatment. A follow-up combined Phase 2B/3 trial is scheduled to confirm the Phase 2A results that [MPh-IR + Ond-PR2] may provide for an effective option for the treatment of methamphetamine use disorder.

W67. EVALUATING THE CORRELATION BETWEEN THE EFFICACY OF MM120 (LYSERGIDE) IN GENERALIZED ANXIETY DISORDER AND SELF-REPORTED MYSTICAL EXPERIENCE

Todd Solomon, PhD[1], Sarah M. Karas, PsyD[1], Alexander Deschamps, MSW[1], Miguel A. Pinheiro, PhD[1], Daniel R. Karlin, MD, MA[2]*

[1]Mind Medicine Inc., [2]Mind Medicine Inc., Tufts University School of Medicine

Abstract Introduction: The administration of classic psychedelic drugs has been associated with improvements in overall mental health and psychological disorders such as major depressive disorder (MDD) and generalized anxiety disorder (GAD). In some individuals, these compounds cause transient subjective effects that include qualities described as "mystical." It has been hypothesized that such experiences have a causal role in producing therapeutic benefits. Some research suggests that these transient subjective effects are related to neurobiological, cognitive, and affective processes involved in recalling, engaging with, and making meaning of the psychedelic experience and might play a critical role in their potential efficacy. Conversely, other literature indicates that such effects are not necessary for efficacy. Notably, many studies examining the association of mystical experience with improvements in mental health have lacked methodological rigor and most involved co-administered psychotherapy or facilitation, thus making the interpretation of their results challenging. MM120 (lysergide D-tartrate), a formulation of LSD, is currently under development as a potential treatment for GAD and MDD. This analysis explored the correlation between mystical experience and subsequent improvement in GAD using data from a phase 2b dose-finding study of MM120.

Methods: The Mystical Experience Questionnaire (MEQ30), measuring self-reported mystical experience, was administered during a phase 2b (NCT05407064) multicenter, randomized, double-blind, placebo-controlled, dose-finding study of MM120 in adults

diagnosed with GAD and moderate-to-severe anxiety as defined by a Hamilton Anxiety Scale (HAM-A) of ≥20. The MEQ30 is a 30-question validated instrument used to measure the acute subjective effects of psychedelics, particularly focusing on mystical-type experiences. A score of > 60% suggests a full mystical experience. MEQ30 was completed by participants approximately 24 hours post-MM120 dosing. Correlation between MEQ30 and change in HAM-A at weeks 4 (primary endpoint) and 12 was assessed by calculation of Pearson's correlation coefficient, r.

Results: MEQ30 score increased with MM120 dosage (25, 50, 100, and 200 µg) compared with placebo. Mean MEQ30 scores were 36.7+26.8, 50.5+29.6, 65.6+25.6, 75.4+23.7, and 11.7+17.4, respectively. Median MEQ30 scores were 32.0, 61.3, 68.7, 82.7, and 4.70, respectively. Correlations between MEQ30 and change in HAM-A at weeks 4 and 12 were weak to moderate across all dosing groups, and most P values > .05. The strongest correlation was observed among the placebo and 25 µg groups at week 4. Among participants in the 100 and 200 µg groups who met criteria for HAM-A response, there was no correlation between total MEQ30 and change in HAM-A at week 4 (r=-0.03, P=.868). Among participants identified as having achieved remission, a weak correlation was observed at week 4 that was not statistically significant (r=0.23, P=.221).

Conclusion: Results suggest MEQ30 does not strongly predict reductions in HAM-A after a single MM120 treatment. However, for the placebo and 25 µg groups, MEQ30 demonstrated some predictive value for reduction in HAM-A at week 4, suggesting that the degree of mystical experience in these groups may have contributed to a placebo response. Across all groups, the correlation between MEQ30 and HAM-A reductions weakened over time, with no statistically significant associations observed at week 12. Despite the prevailing theory that MEQ30 predicts treatment response, these results suggest that MEQ30 scores do not predict sustained treatment response, or that a mystical experience is needed to achieve a drug effect.

W68. INITIAL FINDINGS FROM THE ASCP TASK FORCE DELPHI PANEL ON THE DEPRESCRIBING OF PSYCHIATRIC MEDICATIONS

Joseph Goldberg[*1], Roger McIntyre[2], Rajnish Mago[3], Holly Swartz[4], Joshua Rosenblat[2], Michael Ostacher[5], Marlene Freeman[6], Mauricio Tohen[7], Michael E. Thase[8], Leslie Citrome[9], Swapnil Gupta[1]*

[1]Icahn School of Medicine at Mount Sinai, [2]University of Toronto, [3]Simple and Practical Medical Education, LLC, [4]University of Pittsburgh School of Medicine, [5]Stanford University School of Medicine, [6]Massachusetts General Hospital, Ammon-Pinizzotto Center for Women's Mental Health, [7]University of New Mexico, [8]Perelman School of Medicine, University of Pennsylvania, and Corporal Michael J. Crescenz VAMC, [9]New York Medical College

Abstract: "Deprescribing" refers to the process of identifying, modifying, dose- tapering or discontinuing medications that are deemed ineffective, redundant, obsolete, detrimental, futile, or otherwise pharmacodynamically inappropriate for a given patient. Little is known

about the clinical parameters and dynamic principles, as well as the contextual psychosocial factors, that impact decisions to continue versus stop psychotropic medications of questionable value. To shed greater light on these issues, the ASCP Convened a task force of 49 international psychopharmacology experts who completed a 91-item Delphi survey of both general principles and disease-state scenarios in which deprescribing decisions bear relevance. Consensus (> 75% agreement) was reached among panelists on 38/91 recommendations. Key statements that achieved concordance with high confidence included:

- discontinue a medication that fails to produce at least 25% improvement in symptom severity or resolves at least 1 target symptom;
- deprescribing should not occur before an adequate trial has occurred, absent significant treatment intolerance;
- pharmacogenetic testing results in themselves should not prompt deprescribing;
- do not deprescribe a medication for perceived lack of efficacy without first ascertaining adequate adherence;
- strive to deprescribe only one medication at a time when feasible;
- complex polypharmacy regimens involving non-evidence based medications should be routinely evaluated for deprescribing if efficacy is not apparent;
- in patients taking > /=2 non-clozapine antipsychotics, switch to monotherapy should be attempted unless there is documentation of clear benefit from antipsychotic polypharmacy;
- patients who develop tolerance to stimulants not surmountable by dosage increases may warrant stimulant discontinuation;
- antidepressants should be tapered or deprescribed in patients with emerging signs of (hypo)mania
- adjunctive atypical antipsychotics should not be deprescribed sooner than 6 months after resolution of acute mania
- valproate should be deprescribed in sexually active women of child-bearing age
- anticholinergic drugs should be deprescribed whenever feasible

Most prominent areas where dissensus of opinion occurred included:

- favor discontinuing a medication that was used in an intentional overdose;
- stimulants should be deprescribed for ADHD patients who regularly use cannabis
- benzodiazepines should generally be deprescribed in patients > age 65
- benzodiazepines should not be prescribed long-term for patients with PTSD
- after an unequivocal initial response, antidepressants should be deprescribed as soon as feasible in bipolar depression
- lithium should routinely be deprescribed in the setting of a rising serum creatinine level
- prophylactic antimanic medications can be tapered off and stopped in single-episode mania patients after > 1 year of euthymia
- after even gradual lithium discontinuation, risk for nonresponse upon rechallenge is substantial in bipolar disorder

Diversity of opinion was also noted among experts about use of the term "deprescribing" (versus "drug discontinuation or tapering") as a psychopharmacological intervention.

These findings should directly inform both clinical practice and future research directions for managing and curating complex pharmacology regimens.

W69. AZETUKALNER, A NOVEL, POTENT KV7 POTASSIUM CHANNEL OPENER IN DEVELOPMENT FOR MAJOR DEPRESSIVE DISORDER AND BIPOLAR DEPRESSION: UPDATES FROM THE ONGOING CLINICAL PROGRAMS

Noam Butterfield[1], Celene Grayson[1], Danny Lee[1], Erin MacKenzie[1], Joe McIntosh[1], Rostam Namdari[1], Anna Osmukhina[1], Jenny Qian[1], Christopher Kenney[1], Aleksandar Skuban[1]*

[1]Xenon Pharmaceuticals Inc.

Abstract Background: Effective treatments for major depressive disorder (MDD) and depression in bipolar disorder (BPD) remain a major challenge. Therapies with a novel mechanism of action (MOA), improved efficacy and tolerability, and faster onset are needed. Voltage-gated KCNQ-type potassium channels (KV) regulate cell membrane excitability. Certain KV7 channel openers have demonstrated potential for reducing seizures and improving symptoms of depression, supported by preclinical and clinical data (Friedman, 2016; Costi, 2021), while preclinical research suggests a genetic association between KV7 and BPD, including altered gene expression of certain Kv7 subunits and potential Kv7 channel dysfunction (Smolin 2012, Kaminsky 2015, Judy 2013, Borsotto, 2007). Azetukalner is a novel, potent, selective KV7.2/7.3 potassium channel opener currently under development for epilepsy, MDD, and planned future development for bipolar depression. In addition to its novel MOA, azetukalner has shown early-onset efficacy at week 1 in Phase 2 studies for focal epilepsy (French et al., JAMA Neurology, 2023) and MDD (Butterfield et al., ASCP 2024). Results from the proof-of-concept X-NOVA phase 2 study also suggest that azetukalner may improve anhedonia in MDD, addressing a critical unmet medical need. Here, we report the design of the first of three planned Phase 3 trials to evaluate azetukalner as monotherapy for MDD.

Methods: X-NOVA2 (NCT06775379) is a Phase 3, multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy, safety, and tolerability of azetukalner as monotherapy in adults with MDD. An estimated 450 participants with moderate-to severe MDD will be randomized 1:1 to azetukalner 20 mg or placebo once daily with food with no titration period for 6 weeks. The primary endpoint is the change from the baseline in Hamilton Depression Rating Scale 17-Item (HAMD-17) at week 6. The secondary endpoints include a change from baseline in Snaith-Hamilton Pleasure Scale (SHAPS) and Clinical Global Impression of Severity (CGI-S) at week 6 and a change from baseline in HAMD-17 at week 1. Upon completion of the double-blind phase, eligible patients may enter an open-label extension study for up to 12 months.

Results: The X-NOVA results collectively highlighted azetukalner's potential to improve symptoms of depression and anhedonia. In X-NOVA, azetukalner was generally well tolerated, with no serious adverse events reported in the azetukalner treatment groups. Azetukalner was not associated with notable weight gain (mean [SD] change from baseline, 0.84 [2.3] kg) or patient reports of notable sexual dysfunction (1 participant [0.9%] reported

mild decreased libido). Building on the promising results of X-NOVA, the ongoing X-NOVA2 Phase 3 study will further evaluate the efficacy and safety of azetukalner in MDD.

Conclusions: Azetukalner has the potential to improve symptoms of depression in MDD with a rapid onset of efficacy and a potentially distinctive safety profile from currently marketed antidepressants. Its effects on anhedonia may further distinguish it within the treatment landscape. Additionally, a Phase 3 program, including two studies evaluating the efficacy and safety of azetukalner in both bipolar I and II depression, is expected to begin by mid-2025. Ongoing and planned azetukalner Phase 3 trials are expected to provide additional evidence of clinical benefit in MDD, anhedonia, and bipolar depression.

Funding: This study was funded by Xenon Pharmaceuticals Inc.

W70. PRE-TREATMENT BODY MASS INDEX AS A MARKER OF ANTIDEPRESSANT RESPONSE TO KETAMINE: PRELIMINARY FINDINGS OF A LARGE-SCALE META-ANALYSIS

Gustavo Medeiros[*1], Ian Qian[1], Darcy Curtis[1], Balwinder Singh[2], Brittany O'Brien[3], Sagar Parikh[4], Mark Kvarta[5], Lace Riggs[6], Annabelle Belcher[1], Eric Goldwaser[7], Mikael Tiger[8], Johan Lundberg[8], Bo Hu[9], Amit Anand[10], Gustavo Vazquez[11], Rebecca Price[12], Sanjay Mathew[3], Todd Gould[1], Carlos Zarate Jr[5], Fernando Goes[13]*

[1]University of Maryland School of Medicine, [2]Mayo Clinic, [3]Menninger, Baylor College of Medicine, [4]University of Michigan, [5]Experimental Therapeutics and Pathophysiology Branch, NIMH-NIH, [6]McGovern Institute for Brain Research at the Massachusetts Institute of Technology, [7]Interventional Psychiatry Program, Weill Cornell Medicine, [8] for Psychiatry Research, Karolinska Institute and Stockholm County Council, [9]Duke University, [10]Mass General Brigham, and Harvard Medical School, [11]Queen's University, [12]University of Pittsburgh, [13]Johns Hopkins School of Medicine

Abstract Introduction: Intravenous ketamine (KET) has revolutionized the treatment of major depressive disorder (MDD) and bipolar depression (BDep) as this medication overcomes some of the limitations of conventional antidepressants. However, there is significant variability in response and there are no well-established ways to identify individuals who are likely to benefit from KET. A clinical marker of response to KET that has been widely investigated is pre-treatment body mass index (BMI), which is an easily obtainable and reliably measured variable. Some studies have found an association between higher pre-treatment BMI and greater antidepressant response to KET, but results have been mixed. The sample size of the studies with KET have been increasing; however, most investigations have used relatively small samples, which are less likely to be replicable. The goal of this study is to conduct a large-scale meta-analysis to establish whether there is a relationship between pre-treatment BMI and antidepressant response to KET.

Methods: We conducted a systematic search of PubMed, Embase, and PsycINFO from inception until October 23, 2024, complemented by manual searches. We included manuscripts that (1) examined adult human individuals, (2) included individuals diagnosed with MDD or BDep, (3) were clinical trials or naturalistic studies that treated individuals with at least one dose of KET, (4) had a total sample of at least ten individuals, (5) reported changes in depressive symptoms with a standardized depression outcome, and (6) assessed

the association between pre-treatment BMI and antidepressant response to ketamine. We compared the mean and standard deviation (SD) between responders to KET (i.e., individuals with at least 50% of improvement in depressive symptoms) and non-responders using random-effects models with inverse-variance weighting. Heterogeneity was evaluated using the I^2 statistic and moderation analyses were conducted.

Results: We identified 332 citations (database searching: 305; manual searching: 17), of which 47 were identified as duplicates and removed prior to screening. The titles/abstracts of 258 were examined, and 60 manuscripts were identified as potentially eligible for inclusion and were reviewed in full. Ultimately, 38 manuscripts met criteria for inclusion. This preliminary report includes 21 articles (n = 910) for which we had available data compatible with the quantitative synthesis. There was no statistically significant association between pre-treatment BMI and antidepressant response to ketamine: SMD (95% CI) = .05 (-.09, .20), T = .74, df = 20, p = .47. Moderation analysis did not reveal a significant effect of number of infusions, mean BMI, age, or gender on the relationship between pre-treatment BMI and response to KET. Importantly, there was no heterogeneity among the studies included in this analysis ($I^2 = 0$).

Conclusion: We found no statistically significant association between pre-treatment BMI and response to KET. To the best of our knowledge, this preliminary analysis is the largest study analyzing the association between pre-treatment BMI and response to KET. Our findings address a longstanding debate in the literature and suggest that pre-treatment BMI likely does not predict response to KET.

W71. COMP005 AND COMP006: EXAMPLE APPROACHES TO CHALLENGES IN RANDOMIZED-CONTROLLED CLINICAL TRIALS WITH PSYCHEDELICS

Matt Young[1], *Caroline Hostetler**[1], *Claudia Sisa*[1], *Guy Goodwin*[1]

[1]*Compass Pathfinder Ltd.*

Abstract Background: There is great interest in the development of psychedelic treatments for a range of psychiatric conditions. Although many neuropsychiatric treatments have psychoactive effects, the acute effects of psychedelic compounds magnify challenges to the design and interpretation of clinical trials with these compounds. Recently completed and ongoing clinical studies with psychedelics and similar compounds can provide insight into these challenges and how they may be addressed in study design.

Methods: We describe some of the considerations in designing clinical trials with psilocybin and explore two ongoing Phase 3 registrational clinical trials with investigational COMP360 psilocybin for treatment-resistant depression (COMP 005 and COMP 006).

Results: Some of the considerations in the clinical development of psilocybin include: (1) potent psychoactive drug effects that could be functionally unblinding, (2) the inclusion of psychological support aimed at safeguarding patients during the drug administration, and (3) how to adequately inform a non-daily treatment regimen. Ongoing trials with investigational COMP360 psilocybin (COMP005 and COMP006) include several design elements to help address these considerations and align with FDA draft guidance on clinical trials with

psychedelics. COMP005 and COMP006 are double-blind RCTs designed to assess safety and efficacy. In addition to assessing efficacy, COMP005 provides key safety data by comparing 25 mg COMP360 to inert placebo. COMP006 addresses some of the functional unblinding risks of an inert placebo-control by comparing the safety and efficacy of 25 mg COMP360 to a low active control dose of COMP360 (1 mg), while also including a moderately psychoactive active treatment arm (10 mg COMP360 psilocybin). In contrast to psychedelic-assisted psychotherapy, COMP360 psilocybin is administered with non-directive psychological support rather than directive psychotherapy. The Compass Psychological Support Model (CPSM) has been designed as a manualized standard of care in clinical research with COMP360 psilocybin, not to support efficacy, but to safeguard study participants and ensure consistency across multi-site trials. Lastly, both COMP005 and COMP006 are 52-week trials that allow double-blind collection of data on the durability of effect as well as the safety and efficacy of repeat dosing over 26 weeks, longer than typical pivotal RCTs of antidepressants.

Conclusions: COMP005 and COMP006 take into consideration challenges confronted in the development of COMP360 psilocybin for treatment resistant depression. Outcomes from these trials may further inform future study design with psilocybin and other psychedelic treatments.

W72. SELTOREXANT, ADJUNCTIVE TO ANTIDEPRESSANTS, IN ADULTS WITH MAJOR DEPRESSIVE DISORDER IN THE ONE YEAR OPEN LABEL EXTENSION

Gahan Pandina[1], Michael E. Thase[2], Andrew D. Krystal[3], Ewa Wajs[4], Joseph M. Trombello[1], Ryan Kelly[1], Yun Zhan1[1], Haiyan Xu[1], John Thipphawong[1], Sandra Ruschel[5], Yanina Flossbach[6], Carla M. Canuso[1], Thomas Laughren[7], Wayne C. Drevets[1]*

[1]Johnson and Johnson, [2]Perelman School of Medicine, University of Pennsylvania, and Corporal Michael J. Crescenz VAMC, [3]UCSF School of Medicine, [4]Johnson and Johnson, Beerse, [5]Ruschel Medicine and Clinical Research, [6]Actelion Research and Development, Allschwil,[7]Laughren Psychopharm Consulting, LLC

Abstract Background: Seltorexant, a first-in-class, selective orexin-2 receptor antagonist that normalizes manifestations of hyperarousal and enhances physiological sleep, is being investigated as an adjunctive treatment for major depressive disorder (MDD). A phase 3, multicenter trial (NCT04533529) in participants with MDD on a background therapy with SSRI/SNRI consisted of two phases: a double-blind (DB), 6-week, placebo-controlled phase and a 52-week open label extension (OLE). Previously reported primary results in participants with MDD with insomnia symptoms (IS) from the DB phase with seltorexant treatment versus placebo showed statistically significant and clinically meaningful antidepressant effects, beyond improvement in sleep disturbance, and a similar safety profile to placebo. Here, we report the long-term safety and efficacy results of seltorexant in participants with MDD from the OLE.

Methods: Participants were 18-74 years old with a primary DSM 5 diagnosis of MDD without psychotic features, Hamilton Depression Rating Scale total scores ≥20 and ≥18 at first and second screening interviews, respectively, and an inadequate response to 1-2

antidepressants administered at an adequate stable dose for ≥6 weeks but ≤24 months in the current episode. In the DB phase, eligible participants were randomized 1:1 to receive seltorexant 20 mg or matching placebo for 6 weeks, while continuing their baseline SSRI/SNRI. In the OLE, eligible participants from the DB phase received open label 20 mg seltorexant for an additional 52 weeks while continuing their baseline SSRI/SNRI. Incidence of treatment-emergent adverse events (TEAEs) and change from OLE baseline over time in Montgomery-Åsberg Depression Rating Scale (MADRS) total score were assessed. Remission was defined as MADRS total score ≤12.

Results: 588 participants with MDD were randomized in the DB phase (284 [216 with IS] in the seltorexant group and 304 [228 with IS] in the placebo group), of which 586 received ≥1 dose of study drug. Of the 540 eligible participants from the DB phase, 522 (96.7%) continued in the OLE and 360 (69.0%) completed the OLE; the most common reasons for discontinuation included withdrawal by participant (12.3%), AE (6.3%), and lack of efficacy (4.2%). The mean duration of exposure was 42.3 weeks. TEAEs occurred in 330/522 (63.2%) participants; the most frequent (≥5%) were COVID (8.8%), nasopharyngitis (8.4%), headache (11.9%), and weight increase (6.5%). Serious TEAEs occurred in 29/522 (5.6%) participants; the most common being suicide attempts (n=7), depression (n=2), and suicidal ideation (n=2). AEs of special interest included falls (n=9) and road traffic accidents (n=2). The mean (SD) change in MADRS total score from OLE baseline to OLE week 52 was -11.0 (10.55). The proportion of participants in remission increased from 23.4% at OLE baseline (from DB baseline) to 59.9% (observed case) and 45.9% (imputed case) at OLE week 28, and further to 73.8% (observed case) and 51.2% (imputed case) by OLE week 52.

Conclusion: Seltorexant was well tolerated, and no new safety concerns were identified with long-term seltorexant treatment in OLE participants. Depressive symptoms continued to improve, including increases in remission rate.

W73. EFFICACY AND SAFETY OF ESKETAMINE NASAL SPRAY AS MONOTHERAPY IN ADULTS WITH TREATMENT-RESISTANT DEPRESSION BASED ON ORAL ANTIDEPRESSANT STATUS AT STUDY ENTRY: A POST HOC ANALYSIS

Andrew J. Cutler[1], Dong-Jing Fu[2], Ibrahim Turkoz[2], Patricia Cabrera[2], Oliver Lopena[2], Lisa Lim[2], Muhammad Ahmed[2], Dillon McGovern[2]*

[1]SUNY Upstate Medical University, Syracuse, NY, [2]Johnson and Johnson

Abstract Background: Esketamine nasal spray (ESK) is indicated for the treatment of treatment-resistant depression (TRD) in adults as monotherapy (recently approved) or in combination with an oral antidepressant (OAD). It is also indicated for the management of depressive symptoms in adults with major depressive disorder with acute suicidal ideation or behaviors, when used alongside an OAD. The objective of this post hoc analysis was to evaluate the efficacy and safety of ESK monotherapy in adults with TRD (history of nonresponse to ≥2 different OADs) based on their OAD status at study entry in a randomized, double-blind, placebo-controlled, 4-week, multicenter study (NCT04599855).

Methods: Patients were randomly assigned to receive fixed doses of ESK 56 mg, ESK 84 mg, or placebo (PBO) twice weekly for 4 weeks. Patients entered the screening phase either taking (on treatment) or not taking (off treatment) OADs. Prior to randomization, patients were required to discontinue OADs for at least 2 weeks. Efficacy during the 4-week double-blind treatment phase was assessed by changes in Montgomery-Åsberg Depression Rating Scale (MADRS). Least squares (LS) mean differences between ESK (56 mg or 84 mg) and PBO groups for change from baseline in MADRS total scores were assessed using a mixed model for repeated measures model, with fixed effects for treatment group, analysis center, day, and day-by-intervention interaction, and baseline MADRS total score as a covariate. Treatment-emergent adverse events (TEAEs) were monitored throughout the duration of the study.

Results: Of the 378 patients included in the study, 248 (65.6%) were on treatment and 130 (34.4%) were off treatment at study entry. For patients on treatment, the most common OADs received within 7 days of study entry were bupropion (35.9%), duloxetine (15.9%), trazodone (14.6%), sertraline (13.6%), fluoxetine (11.7%), and escitalopram (10.0%). At baseline, mean MADRS total scores were 37.2 and 37.5 for patients who were on treatment and off treatment, respectively. Regardless of OAD status at study entry, at day 28 MADRS total scores were significantly decreased in patients treated with ESK compared with PBO. The LS mean difference [95% CI] between PBO and ESK 56 mg or 84 mg treatment groups at day 28 was −4.8 [−8.2, −1.3] and −5.6 [−8.9, −2.2] for on-treatment patients, and −6.3 [−11.4, −1.2] and −9.5 [−14.5, −4.5] for off-treatment patients, respectively. At day 2, MADRS total scores were decreased numerically in patients treated with ESK compared with PBO in both on-treatment and off-treatment patients. The LS mean difference [95% CI] between PBO and ESK 56 mg or 84 mg treatment groups at day 2 was −4.4 [−7.6, −1.2] and −3.7 [−6.7, −0.6] for on-treatment patients, and −2.7 [−7.1, 1.7] and −3.0 [−7.3, 1.3] for off-treatment patients, respectively. TEAEs were similar between on-treatment and off-treatment groups and the most common TEAEs were nausea, dissociation, dizziness, and headache. The majority of TEAEs for ESK were transient and resolved on the same day as dosing.

Conclusion: Regardless of OAD status at study entry, treatment with ESK as monotherapy in adults with TRD is associated with clinically meaningful improvements in MADRS total score versus PBO at day 28, and as early as day 2.

W74. TSND-201 DEMONSTRATED RAPID, ROBUST, AND DURABLE THERAPEUTIC EFFICACY IN A RANDOMIZED, PLACEBO-CONTROLLED TRIAL (IMPACT-1) FOR THE TREATMENT OF POST-TRAUMATIC STRESS DISORDER

Amanda Jones[*1], Jennifer Warner-Schmidt[1], Martin Stogniew[1], Blake Mandell[1], Hannah Kwak[1], Terence Ching[2], Benjamin Kelmendi[2]*

[1]Transcend Therapeutics, [2]Yale School of Medicine

Abstract Post-Traumatic Stress Disorder (PTSD) is a serious psychiatric disorder that affects approximately 13 million adults in the US each year. There is an urgent need for rapid, durable, effective pharmacological interventions for PTSD, as currently available options

have slow onset, limited effectiveness, and lasting side effects. TSND-201 is a highly-selective, rapid-acting neuroplastogen in development for PTSD and other CNS conditions. TSND-201 acts at monoamine transporters, rapidly increasing neuroplasticity and neurotrophic factors in key brain areas associated with PTSD. No hallucinogenic activity has been reported in humans or animal models, likely due to its lack of direct activity at 5HT2A receptors. The current study explored the efficacy and safety of TSND-201 in a randomized, double-blind, placebo-controlled Phase 2 study of individuals with PTSD.
The IMPACT-1 study was a multi-center Phase 2 clinical trial. The study enrolled 65 adult participants with severe PTSD (Clinician-Administered PTSD Scale for DSM-5 [CAPS-5] ≥ 35) who had tried at least 1 prior treatment for PTSD. Participants received 4 weekly oral, in-clinic doses of TSND-201, then were followed for an additional 6 weeks. The primary endpoint was the change from baseline to Day 64 on the CAPS-5 total severity score compared to placebo. Secondary endpoints included response (≥ 50% improvement from baseline), remission (≤11 total severity score), and loss of PTSD diagnosis. Safety was assessed by monitoring adverse events, vital signs, and C-SSRS.

TSND-201 demonstrated rapid, robust, and durable improvements in PTSD symptoms. On the primary endpoint, change from baseline to Day 64, TSND-201 demonstrated a statistically significant placebo-adjusted CAPS-5 improvement of -9.64 points on Day 64 (-23.28 points vs. -13.64 points; p = 0.011). Treatment with TSND-201 led to rapid and durable improvements in PTSD symptoms, evidenced by a placebo-adjusted treatment difference of -8.00 on the CAPS-5 at Day 10 (p = 0.012); statistical separation from placebo was maintained through the end of study (Day 64). TSND-201 demonstrated statistically significant improvements compared to placebo on secondary endpoints, including response (57% vs. 19.2%; p = 0.002), remission (32.1% vs. 11.5%; p = 0.036), and loss of PTSD diagnosis (60.7% vs. 30.8%; p = 0.014).

Treatment with TSND-201 was generally safe and well tolerated. The majority of adverse events were transient, occurring on the day of dosing and resolving the same day. The most commonly occurring adverse events in the TSND-201 group were headache, decreased appetite, nausea, dizziness, blood pressure increase, dry mouth, insomnia, muscle tightness, and feeling abnormal. One serious adverse event of seizure occurred in the TSND-201 group; the event occurred 7 days after the last dose in a patient with a history of seizure and was considered unrelated to study drug.

These findings demonstrate the potential of TSND-201 as a rapid-acting and durable treatment for PTSD, and support further development of TSND-201 as a treatment for PTSD.

W75. RESULTS FROM A PHASE 2 RANDOMIZED CONTROLLED TRIAL OF LUVADAXISTAT IN COGNITIVE IMPAIRMENT ASSOCIATED WITH SCHIZOPHRENIA: THE ERUDITE STUDY

Ni Khin[*1], Reuben H. Fan[1], Tingting Ge[1], Hans S. Klein[2], Jacob Ballon[3], Satjit Brar[1], Philip D. Harvey[4], Joshua Kantrowitz[5], Richard S.E. Keefe[6], Eiry Roberts[1], Jaskaran B. Singh[1]*

[1]*Neurocrine Biosciences, Inc.*, [2]*WCG Clinical Endpoint Solutions*, [3]*Stanford University*, [4]*University of Miami Miller School of Medicine*, [5]*Columbia University Medical Center*, [6]*Duke University Medical Center*

Abstract Background: Cognitive impairment associated with schizophrenia is an unmet medical need. The glutamate hypothesis proposes that cognitive symptoms are due to hypofunction of NMDA receptors. Luvadaxistat, an inhibitor of D-amino acid oxidase, can modulate glutamatergic neurotransmission by elevating the levels of D-serine, one of the NMDA receptor co-agonists. In a prior study of luvadaxistat in negative symptoms of schizophrenia (INTERACT, NCT03382639), daily luvadaxistat 50 mg showed a nominally significant improvement in cognitive test performance in adults with schizophrenia. To find out if the INTERACT study results were replicable, a phase 2 study (ERUDITE, NCT05182476) was conducted.

Methods: ERUDITE was a randomized, double-blind, placebo-controlled, parallel group study in participants with schizophrenia who were receiving background antipsychotic therapy. The primary endpoint was the 14-week change from baseline (CFB) in the Brief Assessment of Cognition (BAC) in Schizophrenia composite score. Secondary endpoints included the CFB to Week 14 in the Schizophrenia Cognition Rating Scale (SCoRS) score and the Virtual Reality Functional Capacity Assessment Tool (VRFCAT). Safety endpoints included frequency of treatment-emergent adverse events (TEAEs).

Results: Of 203 participants randomized 2:1:1 to receive placebo, luvadaxistat 20 mg or 50 mg, respectively, 177 (87.2%) completed the double-blind treatment period. In the placebo, luvadaxistat 20 mg and 50 mg groups, the mean age was 36, 37 and 38 years, 58%, 71% and 70% were male, mean (SD) baseline BAC composite score was 32.8 (13.0), 34.1 (15.3) and 36.0 (12.2) and mean (SD) baseline SCoRS interviewer total score was 33.3 (8.7), 34.5 (9), 37 (9.7).

There were no significant improvements in CFB to Week 14 BAC composite score vs placebo with luvadaxistat 20 mg ($p = 0.75$) or 50 mg ($p = 0.69$). The least squares (LS) mean CFB to Week 14 in BAC were placebo: 2.6 (95% confidence interval [CI]: 1.4, 3.8), luvadaxistat 20 mg: 1.9 (0.1, 3.7) and luvadaxistat 50 mg: 2.1 (0.3, 3.8).

Similarly, there were no significant improvements in CFB to Week 14 SCoRS interviewer total score vs placebo with luvadaxistat 20 mg ($p = 0.52$) or 50 mg ($p = 0.2$) either. For the SCoRS interviewer total score, LS mean CFB to Week 14 were: placebo, –2.2 (CI: –3.3, –1.0); luvadaxistat 20mg, –2.1 (–3.8, –0.4) and luvadaxistat 50 mg, –3.0 (–4.6, –1.4).

Finally, there were also no significant improvements in CFB to Week 14 VRFCAT score vs placebo with luvadaxistat 20 mg ($p = 0.88$) or 50 mg ($p = 0.63$). For VRFCAT score, LS mean CFB to Week 14 were placebo: 1.92 (CI: –0.87, 4.71), luvadaxistat 20mg: 2.30 (–1.86, 6.45) and luvadaxistat 50 mg: 3.12 (–0.90, 7.13).

Overall, 32 (31.7%) participants receiving placebo and 29 (28.7%) receiving luvadaxistat had ≥1 TEAE. TEAEs occurred in ≥3 participants (headache, anxiety, back pain, infection) at similar frequencies with placebo and luvadaxistat. Four participants receiving placebo and one receiving luvadaxistat had TEAEs leading to drug discontinuation.

Discussion: ERUDITE did not meet its primary or secondary endpoints. Luvadaxistat did not significantly improve cognitive performance or cognitive functional test results vs placebo.

Results may be impacted by variability in cognition measures across the studied population and BAC baseline differences between arms.

Study funded by Neurocrine Biosciences, Inc.

W76. SWITCHING FROM ANTIPSYCHOTIC AGENTS TO ULOTARONT IN PARTICIPANTS WITH SCHIZOPHRENIA: A PHASE 3 OPEN-LABEL STUDY

David Crandall[1], Nicholas DeMartinis[2], Brian Rothman[3], Heather Dworak[2], Michael Tocco[2], Courtney Zeni[2]*

[1]Sunovion Pharmaceuticals, Inc., [2]Sumitomo Pharma America, Inc., [3]Otsuka Pharmaceutical Development and Commercialization, Inc.,

Abstract Introduction: Ulotaront is an investigational agent in development for schizophrenia and other psychiatric conditions. Unlike current antipsychotics, ulotaront is a trace amine-associated receptor 1 (TAAR1) agonist with 5-hydroxytryptamine 1A (5-HT1A) activity but no dopamine D2 receptor blockade. Phase 2 studies of ulotaront in patients with acute exacerbation of schizophrenia demonstrated acute efficacy versus placebo in a 4-week trial and continued improvement in a 6-month extension study, with a well-tolerated safety profile that is different from D2 blocking antipsychotics. Given the common practice of switching antipsychotic medications and ulotaront's novel mechanism of action, we conducted a study to evaluate the safety, tolerability, and effectiveness of switching clinically stable adults with schizophrenia from a typical or atypical antipsychotic to ulotaront.
Methods: This Phase 3 (NCT05628103), 8-week, outpatient, multicenter, open-label, single-group, flexible-dose study enrolled participants (18–65 years) with a diagnosis of schizophrenia, who required a change in antipsychotic(s) due to intolerability or lack of efficacy. Stability criteria required a Clinical Global Impression – Severity (CGI-S) score of ≤ 4 and a Positive and Negative Syndrome Scale (PANSS) score of ≤ 80 at screening and baseline, with no changes in antipsychotic medication(s) ≤ 6 weeks before screening. Treatment resistance and unstable medical conditions were exclusionary. Ulotaront was flexibly dosed (50–100 mg/day). Preswitch antipsychotic treatment was discontinued at investigator discretion by the end of Week 2, 3, 4, 5, or 6, while ulotaront was continued until study end (Week 8). The primary endpoint was percentage who discontinued for clinical reasons (adverse events [AEs] or lack of efficacy). The secondary endpoint was percentage who discontinued for any reason. Other endpoints included incidence of AEs and change from baseline to Week 8 in PANSS and CGI-S scores.

Results: The study included 101 adults (71.3% male; 63.4% Black or African American), with mean (standard deviation [SD]) age of 48.1 (12.0) years. In total, 83 (82.2%) completed the study. For the primary outcome, 8 (7.9%) discontinued due to clinical reasons. Of these, 7 (6.9%) discontinued due to AEs and 1 (1.0%) due to lack of efficacy, with median (range) time to discontinuation of 20.0 (3–54) days. Three had serious AEs of exacerbation/worsening of schizophrenia, and 4 had nonserious AEs (worsening of schizophrenia [n = 2], heart rate increase [n = 1], and muscle strain [n = 1]). For the secondary outcome, 18 (17.8%) discontinued study due to any reason. Overall, 42 (41.6%) participants experienced ≥ 1 AE; most were mild to moderate and unrelated to ulotaront.

Both PANSS and CGI-S scores generally remained stable during treatment, with a mean change (SD) from baseline to Week 8 of −2.6 (9.25) and −0.12 (0.59), respectively.

Conclusions: Ulotaront was well tolerated in clinically stable adults with schizophrenia switching from prior antipsychotic(s) over a 6-week period. Discontinuation rate due to clinical reasons was low and below the projected rate (15%), and was comparable to rates typically seen in similar studies. No new safety signals were identified. Treatment effectiveness remained stable during switch, further supporting the ability to switch clinically stable patients to ulotaront without concern for safety or efficacy.

W77. A PHASE 4, OPEN-LABEL, MULTICENTER, TWO-COHORT, TWO-PERIOD, SLOW-TITRATION AND FOOD EFFECT TRIAL TO ASSESS THE SAFETY AND EFFICACY OF XANOMELINE AND TROSPIUM CHLORIDE IN PARTICIPANTS WITH SCHIZOPHRENIA

Jenna Hoogerheyde[1], Rachel Dyme[1], Daniel Tatosian[1], Andrew Miller[1], David Walling[2], Elan Cohen[2], Kimball Johnson[2], Katrin Kupas[1], Ranjan Tiwari[1], Ken Kramer[1]*

[1]Bristol-Myers Squibb, [2]CenExel - Collaborative Neuroscience Research

Abstract Background: The dual M1/M4 preferring muscarinic receptor agonist xanomeline in combination with the peripherally restricted pan muscarinic antagonist trospium chloride was approved for the treatment of schizophrenia in adults by the U.S. Food and Drug Administration in 2024.1 Because dosing with food (high- or low-fat meals) has been shown to reduce trospium bioavailability, twice daily (BID) dosing of xanomeline/trospium on an empty stomach (≥1 hr before a meal or ≥2 hr after a meal) is directed to improve tolerability. The most common treatment-emergent adverse events (TEAEs) generally resolved with continued treatment in the 5-week EMERGENT clinical trials of xanomeline/trospium in adults with schizophrenia, suggesting that acclimation to xanomeline may occur, and this acclimation may mitigate the reductions in trospium bioavailability associated with food intake.2 Here, final data from Cohort 1 are presented from a 2-cohort trial examining xanomeline/trospium safety and efficacy after 4 weeks of treatment on an empty stomach with up-titration slower than used in the registrational trials, followed by 4 weeks of administration with food at a stable dose.

Methods: An inpatient, open-label, 2-period trial (NCT06572449) enrolled adults aged 18-65 years with a confirmed DSM-V diagnosis of schizophrenia, stable symptoms, and a Positive and Negative Syndrome Scale (PANSS) total score ≤80. In Period 1, Cohort 1 participants began BID treatment on an empty stomach for 4 weeks starting at a dose of 50 mg xanomeline/20 mg trospium chloride and up-titrated weekly to a maximum dose of 125 mg xanomeline/30 mg trospium chloride. Treatment continued for 4 more weeks in Period 2, during which participants continued on the same dose but received treatment within 30 minutes of a meal or snack. Participants could down-titrate to a dose of 100 mg xanomeline/20 mg trospium chloride in the event of intolerable side effects or at investigator discretion. Incidence of TEAEs and changes in PANSS total and Clinical Global Impression–Severity scores were assessed. Safety was examined in the Cohort 1–treated population, defined as all participants who received ≥1 dose of trial medication; efficacy analyses were performed in participants who also had ≥1 efficacy assessment.

Results: The Cohort 1–treated population consisted of 100 participants (Period 1, n=100; Period 2, n=90). A total of 62% and 38% of participants reported ≥1 TEAE in Period 1 and Period 2, respectively. The most common TEAEs (incidence of ≥5%) in Period 1 were nausea (24%), dyspepsia (14%), headache (12%), constipation (11%), vomiting (10%), gastroesophageal reflux disease (7%), abdominal discomfort (6%), dry mouth (6%), salivary hypersecretion (5%), and dizziness (5%). The most common TEAEs in Period 2 were vomiting (10%), nausea (7.8%), and dyspepsia (5.6%). The most common TEAEs were all mild or moderate in intensity. In Period 1, the mean±SD change from baseline to day 29 in PANSS total score was -2.3±6.8 points and in CGI-S was -0.2±0.67 points (n=100).

Conclusion: In Cohort 1 of an open-label trial of adults with schizophrenia, people who slowly titrated to the target dose of xanomeline/trospium during 4 weeks of treatment on an empty stomach did not experience an increase in the incidence of adverse events when switched to dosing with food. No new safety signals were identified when treatment was administered with food. Results suggest that taking xanomeline/trospium with food may be safe after a period of acclimation.

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W78. BRILAROXAZINE'S EFFECTS ON EFFICACY, SAFETY, ADHERENCE, AND BIOMARKERS IN THE PHASE 3 RECOVER 12-MONTH OPEN-LABEL TRIAL EXTENSION IN PATIENTS WITH STABLE SCHIZOPHRENIA

Laxminarayan Bhat[*1], Seema R Bhat[1], Arulprakash Ramakrishnan[1], Wasim Khan[1], Simeen Khan[1]*

[1]Reviva Pharmaceuticals, Inc.

Abstract Background: Brilaroxazine (RP5063), a multimodal, serotonin-dopamine neurotransmitter signaling modulator, possesses high affinity (Ki, < 6nM) and selectivity for key serotonin receptors 5-HT1A/2A/2B/7, partial agonist functional activities for serotonin 5-HT1A/2A and dopamine D2/4 receptors, and the ability to reduce proinflammatory cytokines contributing to neuroinflammation.

Phase 3 investigation (RECOVER, NCT05184335) demonstrated significant broad-spectrum efficacy at 50 mg and activity at 15 mg versus placebo for total PANSS and multiple symptom domains in acute schizophrenia, excellent tolerability, and low treatment-related discontinuation. The 52-week open-label follow-on evaluation reinforced the initial 28-day randomized trial initial efficacy and safety observations.

An exploratory analysis from this trial identified significant speech latency patterns in patients with high PANSS negative symptom scores. It also found significant treatment improvements from baseline versus placebo in vocal biomarker-positive patients, as compared with vocal biomarker-negative individuals, for primary and secondary endpoints. The most notable improvement was with negative symptoms at 1,017%.

Methods: The 12-month, global, multi-center open-label extension (OLE) evaluated brilaroxazine's longer-term effect on efficacy, safety, and speech latency. It involved 435 enrolled participants undergoing treatment at flexible doses (Dose: 139 [15 mg], 155 [30 mg], and 141 [50 mg]). Evaluation occurred at baseline and every four weeks thereafter until Week 52. Efficacy endpoints included total PANSS and subdomains. Safety comprised treatment-related adverse events and adherence rates. Exploratory endpoints included speech latency and blood biomarkers. Speech latency analysis, based on audio recordings from psychiatric interviews, compared clinical responses of vocal biomarker-positive versus vocal biomarker-negative patients. Blood biomarker data included brain-derived neurotrophic factor and proinflammatory cytokines (IL-6, IL-8) levels.

Results: Initial readout of OLE showed sustained dose-dependent efficacy for all completed patients (N=113). The 15, 30, and 50 mg doses produced total PANSS significant ($p < 0.0001$) reductions from baseline to Week 52 of -15.2, -18.6, and -20.8 points, respectively. PANSS total score decrease in double-blind rollover patients included > 30-point in 86.76%, > 40-point in 64.70%, and > 50-point in 33.82%. Pooled data (all doses) showed clinically meaningful, sustained, and significant ($p < 0.0001$) reductions across PANSS Total scores (-18.6), positive symptoms (-5.2), and negative symptoms (-4.5). This presentation will provide the final data set involving 300 and 150 patients completing six and 12 months of treatment, respectively, highlighting clinical response, safety, adherence, and speech and blood biomarker data.

Conclusion: Findings from the brilaroxazine phase 3 OLE part of the study reinforce the initial safety and efficacy results from the double-blind study. Brilaroxazine shows statistically significant and very encouraging findings involving multiple blood and speech biomarker data, further supporting the clinically assessed outcome of primary and secondary endpoints. These results highlighted the persistence of brilaroxazine's significant, broad-spectrum efficacy and provided a clinical biomarker reflective of improvement within a select enriched population.

W79. VALBENAZINE IMPROVES THE IMPACTS AND SYMPTOMS OF TARDIVE DYSKINESIA: TOPLINE RESULTS FROM THE PHASE 4 KINECT-PRO STUDY

Eduardo Dunayevich[1], M. Mercedes Perez-Rodriguez[2], Joseph McEvoy[3], Ashok Parameswaran[1], Morgan Bron[1], Ericha Franey[1], Donna Sparta[1], Cathy Zeng[1], Susan D. Mathias[4], Christoph U. Correll[5]*

[1]Neurocrine Biosciences, Inc., [2]Icahn School of Medicine at Mount Sinai, [3]Augusta University, Medical College of Georgia, [4]Health Outcomes Solutions, [5]The Zucker Hillside Hospital; The Donald and Barbara Zucker School of Medicine at Hofstra/Northwell; Charité Universitätsmedizin

Abstract Background: Once-daily valbenazine is a uniquely selective vesicular monoamine transporter 2 (VMAT2) inhibitor approved for the treatment of tardive dyskinesia (TD), a debilitating movement disorder associated with prolonged exposure to antipsychotics and other dopamine receptor blocking agents. TD is known to have negative impacts on social,

emotional, and physical functioning, even in patients with mild severity. However, the effects of a VMAT2 inhibitor on the impacts of TD, as assessed using multiple validated patient-reported outcomes (PROs), have not been reported.

Methods: This open-label study included screening (4 weeks), initial treatment with valbenazine 40 mg (4 weeks), continuation with 40 mg or increase to 60 or 80 mg (12 weeks), stable dosing with 40, 60, or 80 mg (8 weeks), and safety follow-up (2 weeks). Participants had at least mild TD severity (per item 8 of the Abnormal Involuntary Movement Scale [AIMS]) and were aware of their dyskinetic movements with mild or worse associated distress (per AIMS item 10). PROs included the Tardive Dyskinesia Impact Scale (TDIS), Sheehan Disability Scale (SDS), and EuroQoL's EQ-5D-5L visual analog scale (EQ-VAS). Mean changes from baseline for the PROs and AIMS total score (sum of items 1-7) were analyzed in participants overall, by TD severity (mild or moderate/severe based on AIMS item 8), and by psychiatric diagnosis (schizophrenia/schizoaffective disorder [SCHZ] or major depressive disorder/bipolar disorder [MOOD] per DSM-5 criteria).

Results: Of 59 enrolled participants (24 mild, 35 moderate/severe; 27 SCHZ, 32 MOOD), 52 (88%) completed the Week 24 visit; 45 were included for efficacy analyses. In the overall population, TDIS, SDS, EQ-VAS, and AIMS improvements were observed by Week 4 after initial treatment with the lowest clinically effective valbenazine dose (40 mg) and sustained through Week 24. In participants overall, the mild TD subgroup, and the moderate/severe TD subgroup, mean changes from baseline at Week 24 were: TDIS (-8.0, -6.8, -8.9, respectively); SDS social life (-2.3, -1.8, -2.8) and family life (-1.6, -1.3, -1.8); EQ-VAS (+13.1, +12.8, +13.3). In the SCHZ and MOOD subgroups, mean changes were: TDIS (-5.8, -9.7, respectively); SDS social life (-1.6, -2.9) and family life (-0.7, -2.3); EQ-VAS (+8.3, +17.0). Mean changes in AIMS total score were -6.8 (overall), -5.6 (mild), -7.8 (moderate/severe), -5.8 (SCHZ), and -7.6 (MOOD). Adverse events were consistent with the known safety and tolerability profile for valbenazine.

Conclusion: This study, the first to report the effects of a VMAT2 inhibitor on the impacts of TD using multiple validated PROs, presents a comprehensive assessment of the effectiveness of valbenazine treatment for TD. The study results demonstrate robust and sustained improvements in physical, social, and emotional functioning across multiple PROs with once-daily valbenazine, along with a substantial reduction in TD severity, regardless of TD severity at baseline or underlying psychiatric condition.

W80. A PHASE IB STUDY TO EVALUATE THE PHARMACODYNAMICS, SAFETY, AND TOLERABILITY OF THE NOVEL NEUROPLASTOGEN DLX-001 IN PARTICIPANTS WITH MAJOR DEPRESSIVE DISORDER: INTERIM FINDINGS

Aaron Koenig[*1], Renger Tiessen[2], Nicholas Pelletier[1], Daniel Gillie[1], Sydney DeCaro[1], Joi Dunbar[1], Kurt Rasmussen[1], David Olson[1], Eliseo Salinas[1]*

[1]Delix Therapeutics, [2]ICON

Abstract DLX-001 is a non-hallucinogenic, non-dissociative neuroplastogen being developed for the treatment of major depressive disorder (MDD). Here, we describe findings

from a phase Ib dose-blinded, single-center, multiple-dose study in participants with recurrent MDD. This ongoing study is designed to assess the effects of DLX-001 on translational biomarkers associated with neuroplasticity, as well as safety, tolerability, and preliminary efficacy. Participants in cohort A (n=9) received DLX-001 once daily for 7 days, with findings described in this report. Cohort B, in which participants will receive DLX-001 twice over 7 days, is ongoing.

Upon admission to a research unit (Groningen, NL), participants completed habituation and baseline assessments, including polysomnography (PSG), quantitative electroencephalography (qEEG), and clinical symptom scales. Beginning on day 1, participants received DLX-001 once daily for 7 days. On days 1, 4, and 7, qEEG was collected while awake; on the evenings of day 1 and day 7, PSG was collected overnight. Clinical measures were collected daily. After discharge from the unit on day 8, participants returned for assessments on Days 22 and 36.

Mean age at admission was 33 years (range 23 to 54), with 5/9 (55%) females. Mean HAM-D of 18.8 (SD= 2.4), and mean MADRS of 27.2 (SD=4.2) indicated moderate depression severity at baseline. Co-morbid anxiety measured by the HAM-A was low at baseline (Mean=12.0, SD=4.5). All 9 participants completed the 7-day treatment period. DLX-001 was well-tolerated, with no discontinuations due to adverse events (AEs) and only mild AEs reported. The most frequent DLX-001-related AEs were nausea (n=5), tiredness (n=4), and headache (n=4). Nausea was tracked using a daily Visual Analogue Scale and was mild, self-limited, and required no intervention. There were no changes in safety parameters, including vital signs, ECGs, laboratory measures, or physical exam findings. Consistent with the previous phase I healthy volunteer study, there was no evidence of psychotomimetic, hallucinatory, or dissociative effects, as measured by the MEQ-30, BPRS, and CADSS. Cognitive performance remained unchanged, as measured by a computerized Symbol Coding task. Plasma levels of DLX-001 were consistent with target exposures.

The primary endpoint—change from baseline to end of treatment on brain slow-wave activity (SWA)—is an emerging translational measure of cortical plasticity and synaptic strength (Duncan et al. 2013). Cohort A demonstrated a pharmacodynamic signal consistent with that previously observed in the phase I healthy volunteer study – namely, a consistent increase in slow-wave theta activity, with other non-specific qEEG changes also observed. Increases in theta activity were observed using both a traditional wet electrode 64-channel EEG acquisition system (Biotrial, Inc) and a novel 16-channel dry EEG headset (Cumulus NeuLogiq platform). From an efficacy perspective, rapid, meaningful, and sustained decreases in depression scores were observed across most participants. By day 8, 8/9 (88.9%) participants demonstrated an improvement on the MADRS, with 4/9 (44.4%) meeting criteria for MDD response (defined as 50% reduction in MADRS score from baseline). Follow-up assessments are ongoing, and most participants have continued to show improvement on the MADRS up to 4 weeks after completing a 7-day course of DLX-001. Together, these data suggest that DLX-001 may potentially address significant unmet needs in patients with MDD and reinforce the concept that promotion of neuroplasticity may play a critical role in the efficacy of DLX-001.

W81. ADVANCING TARDIVE DYSKINESIA MANAGEMENT THROUGH TARGETED EDUCATION: A SIX-MONTH REAL-WORLD EVALUATION

Soumya Staton[*1], Margaret Harris[1], Jovana Lubarda[1], Jordan Schwartz[1], Katie Lucero[1], Denise Vanacore Chase[2], Leslie Citrome[3], Christoph Correll[4]*

[1]Medscape Education, [2]Holy Family University, [3]New York Medical College, [4]The Donald and Barbara Zucker School of Medicine at Hofstra/Northwell

Abstract Introduction: Despite advances in Tardive Dyskinesia (TD) understanding, many clinicians are not diagnosing patients in a timely manner and are underutilizing available guideline-based treatment strategies (eg, VMAT-2 inhibitors). To address this gap, 2 accredited continuing medical education (CME) activities were developed. This study aimed to assess if CME education could improve TD diagnosis rates and selection of appropriate guideline-based treatment in real world clinical practice.

Methods and Sample

The educational intervention included 2 online CME activities that were distributed in September of 2023. This real world outcomes (RWO) study was designed to assess the impact of the CME series on the diagnosis of TD and treatment selection of guideline-based care by psychiatrists, neurologists, primary care providers (PCPs), and advanced practice providers (APPs) who manage the disease. A retrospective matched case-control study was conducted to examine the primary outcome of interest—the number of patients diagnosed with TD who also were managed according to guideline-based treatments.

Medical and pharmacy claims were aggregated by matching patients with the coding clinicians between May 2023 through June of 2024. Learners and non-learners were matched based upon specialty and geographic location. An analysis of covariance (ANCOVA) was conducted to assess the difference in number of patients diagnosed and treated by CME learners versus control. Data were pulled for 6 months pre and 6 months-post first CME activity participation date ("index date").

Results: The sample included 1,099 CME learners who participated in at least 1 of the 2 CME activities between September and December 2023, and 1,099 matched comparison non-participants. All data were time aligned 6 months pre-/post-index date. Learners who participated in 1 or more activity diagnosed more patients with TD vs. the control group ($P < .05$) and implemented evidence-based treatment for TD than the control group ($P < .05$). Patients of CME learners were 11.6% more likely to be diagnosed with TD versus the control group. Psychiatrists were the primary specialist driving new TD diagnoses. Existing and newly diagnosed patients of CME learners were 22% more likely to be treated with evidence-based treatment versus the control group. The largest increase in utilization of evidence-based treatment was among APP learners. Further, psychiatrists were found to be 1.5 to 2 times more confident in diagnosing TD compared to other specialists, respectively, illustrating that confidence in diagnosing new TD patients is related to practice change.

Conclusions: The results of this RWO study confirmed that participation in 1 or more activities within a CME series was associated with improved diagnosis and adoption of evidence-based treatment of TD amongst psychiatrists, neurologists, PCPs, and APPs, aiming to improve the management and outcomes of patients.

W82. IV KETAMINE VS. ESKETAMINE FOR DEPRESSION: A SYSTEMATIC REVIEW AND META-ANALYSIS

Ahmed Elmosalamy[*1], Idil Tarikogullari[1], Liliana Patarroyo Rodriguez[1], Gwen Wilson[2], Balwinder Singh[1]*

[1]Mayo Clinic, [2]Mayo Clinic Libraries

Abstract Background: Depression affects approximately 5% of adults globally, impacting over 280 million individuals. Approximately 35% of these cases result in treatment-resistant depression (TRD). Research indicates that both intravenous ketamine (KET) and intranasal (IN) esketamine (ESKET) are effective in treating TRD. While KET has demonstrated effectiveness, it lacks FDA approval, whereas ESKET has received FDA approval for major depression and TRD. Given the different administration methods and dosing protocols of these formulations, a comparative analysis of their efficacy can assist clinicians and patients in making informed decisions. We conducted a systematic review and meta-analysis to synthesize existing evidence and compare the efficacy of IV KET and ESKET for depression during the acute/induction phase.

Methods: A systematic search of MEDLINE, Embase, Cochrane, APA PsycInfo, and Scopus was conducted on March 19, 2025, following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, with no restrictions on date or language. Studies involving adult patients with unipolar or bipolar depression that directly compared IV-KET and ESKET and reported clinical outcomes of response and remission were included. Observational studies, randomized controlled trials (RCTs), and abstracts with available data were considered. Odds ratios (OR) were calculated using the Mantel-Haenszel random-effects model, and heterogeneity was assessed using the I2 and Tau statistics.

Results: A total of 1,090 papers were screened, 21 full-text articles were reviewed, and 8 studies were included for qualitative analysis (n = 924). Of these, 6 studies were included in the quantitative meta-analysis (n = 816). Only one study was an RCT, while the rest were observational studies. One study compared IV KET to IV ESKET, whereas seven studies (one on bipolar disorder and six on unipolar depression) compared IV KET to IN ESKET. When compared to IN ESKET, the pooled OR for remission across six studies was 1.35 (95% confidence interval [CI]: 0.92–1.98), showing a trend toward statistical significance ($Z = 1.65$, $p = 0.10$) in favor of IV KET. The heterogeneity was minimal ($tau^2 = 0.00$, $\chi^2 = 2.26$, degrees of freedom [df] = 5, $p = 0.81$, $I^2 = 0\%$), indicating consistent findings. For response rates, the combined OR for five studies was 1.32 (95% CI: 0.96–1.82), also trending toward significance ($Z = 1.73$, $p = 0.08$) in favor of IV KET, with low heterogeneity ($tau^2 = 0.00$, $\chi^2 = 2.71$, $df = 4$, $p = 0.61$, $I^2 = 0\%$). A major limitation is the lack of sufficient RCTs directly comparing IV KET to IN ESKET.

Conclusion: IV-KET exhibited a tendency towards greater efficacy compared to IN-ESKET in both response and remission; however, this difference did not reach statistical significance during the acute phase. Two RCTs are currently underway that will further investigate these findings. In the interim, this data indicates similar efficacy between the two treatments, with a trend suggesting a higher response with IV ketamine.

W83. MANAGEMENT OF FIRST EPISODE PSYCHOSIS: PSYCHOPHARMACOLOGY AND THERAPEUTIC INTERVENTIONS

Saba Saleem[1], Sukhpreet Badesha[2], Darakhshan Adam[1], Faisal Suba[1], Mujeeb Shad[3]*

[1]Valley Health System, [2]Idaho College of Osteopathic Medicine, [3]University of Nevada, Las Vegas

Abstract Purpose: To present a case-based review that discusses the psychopharmacology and therapeutic interventions applied in the management of a patient with first-episode psychosis. For psychopharmacology, we will address the use of Aripiprazole and the potential for developing Dopamine Supersensitivity Psychosis (DSP) in a medication-naïve patient. For therapeutic interventions, we will explore the impact of familial involvement and culturally competent care for this patient, who belongs to a refugee minority community.

Content: Aripiprazole is an atypical antipsychotic that is a partial agonist at the 5-HT1A and D2 receptors and an antagonist at the 5-HT2A receptor. DSP, or rebound psychosis, is thought to be induced by compensatory upregulation of dopamine D2 receptors. This can be provoked in medication-naïve patients or by administering an antipsychotic that is a complete D2 antagonist and then abruptly switching to the partial D2 agonist Aripiprazole without a proper taper. These mechanisms may ultimately enhance dopamine release leading to an acute psychotic worsening. Additionally, poor outcomes in first-episode psychosis are often seen in minority populations due to limited access to mental health services, particularly culturally competent care. Aside from medication management, providing proper therapeutic interventions and utilizing familial support plays a major role in long-term prognosis.

Methodology: Case-based review of a 19-year-old female patient from Afghanistan who presented with first-episode psychosis and anorexia in September 2024. The three main antipsychotic medications she was administered were Haldol, Abilify, and Zyprexa. She was also given culturally competent care by her providers and had strong family support from both immediate and extended relatives.

Results: The patient's initial mental status exam demonstrated erratic behavior, disorganized thinking, poor hygiene, underweight, paranoid ideation, persecutory delusions, and auditory and visual hallucinations (AVH). The first antipsychotic she was given was Haldol for two weeks. She did not improve, so she was abruptly switched to a second antipsychotic, Abilify, for one week. This led to an acute psychotic worsening, so it was discontinued and changed to the third antipsychotic, Zyprexa. Her symptoms then improved over the course of 1.5 weeks, so she was discharged on this medication. As of March 2025, she has been stable on Zyprexa for the past five months and is being seen in the outpatient clinic for follow-up.

Importance: This case highlights the potential mechanism for developing DSP in a patient started on Aripiprazole without a taper off the previous antipsychotic. Haloperidol is full D2 receptor antagonist and its long-term administration can upregulate D2 receptors to produce receptor supersensitivity. Thus, if a patient is first administered Haloperidol and then given a partial dopamine agonist like Aripiprazole it can lead to rebound psychosis. However, Aripiprazole, compared to Haldol and Zyprexa, has a lower incidence of EPS, metabolic syndrome, weight gain, cardiovascular abnormalities, and hyperprolactinemia. Yet, clinicians hesitate to administer it due to myths regarding its effectiveness in treating psychosis. These

claims should be closely investigated as this medication may be more beneficial to patients for long-term treatment due to a better side effect profile. Finally, for this patient, we saw the impact of culturally competent care and familial support in improving medication compliance, strengthening the therapeutic alliance, and ultimately helping the patient slowly return to normal life.

W84. LIPID AND GLYCEMIC PROFILE OF OLANZAPINE AND SAMIDORPHAN: A PATIENT SUBGROUP ANALYSIS OF A 4-YEAR OPEN-LABEL STUDY

Jacob S. Ballon[1], Christina Arevalo[2], Martin Dunbar[2], Alexandra Lovett[2], Christoph U. Correll[3]*

[1]Stanford University, [2]Alkermes, Inc., [3]The Zucker Hillside Hospital, Northwell Health, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, The Feinstein Institute for Medical Research, Northwell Health, Charité Universitätsmedizin Berlin, German Center for Mental Health

Abstract Objective: To analyze lipid/glycemic parameters across patient subgroups in a 4-year, open-label study of combined olanzapine and samidorphan (OLZ/SAM) in adults with schizophrenia, schizophreniform disorder, or bipolar I disorder.

Methods: Patients completing studies in the ENLIGHTEN clinical trial program were eligible to receive ≥2 and up to 4 years of additional treatment in a phase 3, open-label study assessing OLZ/SAM's safety, tolerability, and durability of treatment effect. Prespecified subgroup analyses were conducted by age (< 30 or ≥30 years), sex (male or female), race (Black/African American or non-Black/African American), baseline body mass index (< 25 or ≥25 kg/m2), and geographic region (US or non-US). Changes from baseline in lipid and glycemic parameters were assessed.

Results: Overall, 523 patients were included; 53.7% (242/451) and 32.5% (109/335) received 2 and 4 years of treatment, respectively. At 2 years, OLZ/SAM treatment was associated with minimal mean changes from baseline in lipid parameters across subgroups, including total cholesterol (range: −10.9 to −2.1 mg/dL) and triglycerides (range: −10.2 to 2.1 mg/dL). Mean changes from baseline in glycosylated hemoglobin (HbA1c; range: 0.04% to 0.09%) and fasting glucose (range: −2.7 to 3.3 mg/dL) were small. At 4 years, mean changes from baseline remained minimal and generally similar across subgroups for total cholesterol (range: –1.3 to –15.0 mg/dL), triglycerides (range: –7.7 to 3.4 mg/dL), HbA1c (range: 0.08 to 0.13%), and fasting glucose (range: –4.3 to –1.8 mg/dL).

Conclusions: Changes in lipid/glycemic parameters following up to 4 years of OLZ/SAM treatment were minimal and generally similar across demographic and geographic subgroups.

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W85. NON-CLINICAL EFFICACY AND SAFETY OF SUVN-L3307032, A MUSCARINIC M4 POSITIVE ALLOSTERIC MODULATOR (M4 PAM), FOR THE TREATMENT OF NEUROPSYCHIATRIC SYMPTOMS ASSOCIATED WITH SCHIZOPHRENIA AND ALZHEIMER'S DISEASE

Ramakrishna Nirogi[1], VIjay Benade[1], Renny Abraham[1], Venkatesh Goura[1], Rajesh Kallepalli[1], Rajesh Babu Medapati[1], Onamala Varalakshmi[1], Kumar Bojja[1], Aamer Shaikh[1], Rajesh Kumar Badange[1], Sravanthi Manchineella[1], Tirumala Narasimhula[1], Ankit Das[1], Naga Sai Soma Chandra Sekhar Guduru[1], Keerthi Sai Bitra[1], Anil Shinde[2]*

[1]Suven Life Sciences, [2]Suven Life Sciences Limited

Abstract Background: Neuropsychiatric symptoms (NPS) associated with schizophrenia and/or Alzheimer's disease (AD) are challenging for both patients and caregivers. Current therapies for managing these symptoms are often associated with limited effectiveness and significant side effects. Therefore, new treatment options are urgently needed to provide better symptom control. The combination of xanomeline and trospium (KarXT) has recently been approved for the treatment of schizophrenia and has been suggested as a potential treatment for NPS as well. Xanomeline, a muscarinic M1/M4 agonist, may lead to peripheral side effects. To mitigate these side effects, trospium, a peripheral anticholinergic agent, is used alongside xanomeline. Positive allosteric modulators (PAMs), which target the allosteric site rather than the orthosteric site, tend to produce fewer peripheral side effects. In this context, we evaluated the safety and pharmacodynamic properties of an M4 PAM, SUVN-L3307032.

Methods: The in-vitro properties of SUVN-L3307032 were characterized. Its effect on the allosteric site of the muscarinic M4 receptors was characterized using reporter gene assay. The efficacy of SUVN-L3307032 was assessed in an amphetamine induced hyperlocomotion test using an open field. Receptor occupancy of SUVN-L3307032 was assessed using non-radiolabeled based method. SUVN-L3307032 was assessed for its efficacy to reverse hallucinations induced by 2,5-dimethoxy-4-iodoamphetamine hydrochloride (DOI) by assessing head twitch responses. Efficacy of SUVN-L3307032 in reversing cognitive deficits associated with psychiatric symptoms was assessed in a fear conditioning task. Preliminary toxicity studies were conducted in rats and dogs to evaluate the safety of SUVN-L3307032.

Results: SUVN-L3307032 was found to be a selective M4-PAM. SUVN-L3307032 attenuated amphetamine induced hyperlocomotion in an open field test. In the fear conditioning task, SUVN-L3307032 reversed amphetamine induced cognitive deficits. SUVN-L3307032 attenuated head twitch responses induced by DOI. The observations from the amphetamine-induced hyperlocomotion assay correlated well with the occupancy at the allosteric site of muscarinic M4 receptors. Preliminary toxicity studies did not show any concerns for further development.

Discussion: SUVN-L3307032 has the potential to be a new therapeutic option for the treatment of NPS associated with schizophrenia and/or AD.

W86. PRECISION IN PSYCHIATRY TRIALS: A NOVEL MATHEMATICALLY-AUGMENTED MACHINE LEARNING APPROACH FOR IDENTIFYING PATIENT PERSONAS FOR TAILORED ANTIPSYCHOTIC THERAPY THE CATIE SCHIZOPHRENIA TRIAL

Joseph Geraci[1], Bessi Qorri[1], Paul Leonchyk[1], Adam Gogacz[1], Larry Alphs[1], Luca Pani[2], Larry Alphs[3]*

[1]NetraMark Holdings, [2]University of Miami, [3]Denovo Biopharma LLC

Abstract: The future of precision psychiatry relies on innovative methodologies that can unravel patient heterogeneity and enhance personalized treatment strategies. Schizophrenia, a disorder with diverse symptomatology and treatment responses, presents significant challenges for conventional machine learning (ML) approaches due to small, complex datasets and the difficult of identifying robust biomarkers. To address these challenges, we introduce NetraAI, a mathematically-augmented ML technology leveraging sub-insight learning to stratify patient populations into explainable and unexplainable subgroups to reveal high-effect-size "personas" linked to differential treatment responses.

We applied NetraAI to the 1600-patient CATIE schizophrenia trial, focusing on patients randomized to olanzapine and perphenazine (n=597). The primary outcome, time to all-cause treatment failure, was defined by medication discontinuation or change. Unlike traditional ML methods that are prone to overfitting, NetraAI identifies explainable subpopulations that lead to more robust models. The output consists of 2-4 variables which define a subpopulation or "persona", ensuring generalizability and reproducibility in hold-out validation sets.

Using clinical scale data, key findings include the following:

•Olanzapine Response Persona (n=206): Patients with PANSS Total Score between 38-81, PANSS Negative Score between 7-22, and PANSS Hostility score of 1 (verbal and non-verbal expression of anger and resentment) demonstrated a significant likelihood of responding to olanzapine (Cohen's D=0.399, p=0.00519). These criteria indicate mild negative symptoms and minimal hostility, correlate with a preferential olanzapine response.

•Perphenazine Response Persona (n=53): Patients with PANSS Difficulty in Abstract Thinking scores between 1-2 (better abstract thinking abilities), PANSS Total Score between 43-65, and PANSS General Score between 22-37 were more likely to benefit from perphenazine (Cohen's D=0.771, p=0.0081).

In an independent split-sample validation (training set n=304, testing set n=293), NetraAI confirmed:

•Olanzapine Persona (n=70; 44 Olanzapine, 26 Perphenazine): Defined by PANSS Total Score between 69-132 and PANSS Marder Factor Negative Symptoms score between 19-39 (Cohen's D=0.75, p=0.048), replicated in hold-out validation (Cohen's D=0.397, p=0.0381).

•Perphenazine Persona (n=13; 7 Perphenazine, 6 Olanzapine): Characterized by PANSS Total Score between 35-87, PANSS Unusual Thought Content score of 1, and PANSS Marder Factor Negative Symptoms score between 7-16 (Cohen's D=2.53, p=0.045), replicated in a hold-out validation (Cohen's D=0.273, p=0.038).

Additional personas containing physiological and blood markers were verified through multiple iterations and testing in the hold-out dataset emphasized the importance of baseline profiles in predicting treatment efficacy.

NetraAI provides a powerful approach for identifying explainable, treatment-responsive subpopulations in schizophrenia, leveraging early-stage clinical data (from screening or baseline) to optimize treatment assignment. Through its ability to learn from high-effect size subpopulations, this approach enhances clinical trial enrichment strategies and precision psychiatry applications, paving the way for a more individualized and effective approach to antipsychotic therapy. This sub-insight learning framework introduces a novel paradigm in ML-driven psychiatric research, demonstrating high clinical utility for navigating patient heterogeneity.

W87. CLOZAPINE AUGMENTATION WITH ANTIPSYCHOTICS AMONG PATIENTS IN THE FORENSIC PSYCHIATRY SYSTEM IN ONTARIO

Mark Kaggwa[1], Joan Abaatyo[2], John Bradford[1], Gary Chaimowitz[1], Andrew Olagunju[1]*

[1]McMaster University, [2]Uganda Christian University

Abstract: Background: Clozapine augmentation with antipsychotic is often employed to manage complex cases in forensic psychiatric settings, especially individuals with treatment-resistant schizophrenia and refractory illnesses, yet its prevalence and associated factors remain underexplored.

Objective: This study aims to investigate the prevalence and determinants of clozapine augmentation with antipsychotic (CAA) among patients in forensic psychiatry contexts diagnosed with schizophrenia spectrum disorders in the province of Ontario.

Methods: A retrospective analysis was conducted on 262 patients in forensic psychiatric settings prescribed clozapine during the 2014/15 reporting year (mean age = 41 years (SD = 11.8), male = 227(86.6%). For comparative analysis, patients were categorized into those on clozapine monotherapy versus patients on clozapine augmentation with another antipsychotic, and logistic regression analysis was applied to evaluate factors associated with clozapine augmentation with antipsychotic.

Results: The prevalence of CAA was 48.5%, and higher among inpatients and patients with a history of violence towards objects, absconsion, and poor treatment response. Individuals with reported adequate response to treatment had a significantly lower chance of clozapine augmentation with another antipsychotic, with an adjusted odds ratio (aOR) of 0.27 (95% Confidence Interval [CI]: 0.12–0.57, p=0.001). Similarly, patients with a history of self-harm showed a decreased likelihood (aOR 0.37, 95% CI: 0.14–0.93, p=0.035) of combining clozapine with another antipsychotic. In contrast, patients with a history of absconding (aOR 2.35, 95% CI: 1.09–5.05, p=0.028), and a violent offense at admission (aOR 4.76, 95% CI: 1.16–19.46, p=0.030) had an increased likelihood and a heightened risk of clozapine augmentation with antipsychotic, respectively.

Conclusion: Nearly half of the patients studied were on CAA, particularly those with more severe symptoms and significant risk profiles. These findings underscore the need for further research to better understand the unique attributes of patients on CAA in the forensic contexts and support an effective and safe clozapine therapy strategy.

W88. PHYSICAL ACTIVITY AND MENTAL HEALTH AMONG INDIVIDUALS IN INCARCERATION: A SYSTEMATIC REVIEW

Paige Harris[1], Sarah Lalji-Mawji[1], Kairavi Parikh[1], Britta Ostermeyer[2], Andrew Olagunju[1]*

[1]McMaster University, [2]University of Oklahoma

Abstract: Introduction: Incarcerated persons are disproportionately affected by mental and physical illness. Restrictions in prison can limit physical activity, which may affect wellbeing. The importance of exercise is well-demonstrated for the general population; however, few studies have focused on the population in incarceration. To address this gap in the literature, the present review aims to summarize existing literature on the impacts of physical activity on mental health, recovery, community re-integration, and recidivism among persons in incarceration. Perception of and engagement in exercise will also be explored.

Methods: This review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline. Major electronic databases (AMED, APA PsycInfo, Cochrane Trial Registry, Embase, CINAHL, and PubMed/MEDLINE) were searched. Screening and extraction were completed by at least two independent investigators. Conflicts were resolved through discussion, with senior authors consulted when necessary. Quality will be assessed using the Cochrane RoB-2 and ROBINS-I tools.

Results: Database searches identified 2306 articles for screening. Title and abstract screening yielded 91 articles for full-text screening. 37 articles were eligible for extraction. Preliminary findings from 12 articles, including 3 randomized control trials showed different types of exercise-based interventions, including yoga, cardiovascular and resistance training, sport, and unspecified activity. Outcomes assessed included psychiatric symptoms, perceived health, activity level, concentration, memory, decision making, and self-esteem. Findings from trials and observational studies suggest that exercise may improve mental health and overall wellbeing for incarcerated persons.

Conclusion: Overall, the results of this study support the benefits of exercise for the wellbeing of the population in incarceration. Further trials involving diverse populations and other forms of exercise in correctional settings are required to improve the generalizability of findings.

Thursday, May 29, 2025

Poster Session II with Lunch

T1. THE BRAIN CONNECTOME DURING REST SHOWS INTERACTION BETWEEN COCAINE USE DISORDER AND CHILDHOOD MALTREATMENT

Keren Bachi[*1], Tien T. Tong[2], Yasmin L. Hurd[1], Keren Bachi[1]*

[1]The Addiction Institute of Mount Sinai; Icahn School of Medicine at Mount Sinai, [2]Center for Traumatic Brain Injury Research, Kessler Foundation

Abstract Background: Childhood maltreatment is known to alter social stress- and reward-related brain regions, which are also highly implicated in addiction. Little is known regarding the social-neural effects of childhood maltreatment in addiction. We therefore studied the interaction between childhood maltreatment and cocaine use disorder (CUD) on neural function using resting-state functional connectivity (rsFC).

Methods: Individuals with CUD and healthy controls (HC) were grouped into those with low and high childhood trauma (-/+) using the Childhood Trauma Questionnaire: 20 HC-; 20 HC+; 12 CUD; and 17 CUD+. Network-based statistic, a group analysis method controlling for family-wise error rate, was run on rsFC estimated from 44 social brain regions clustered into 4 subnetworks.

Results: We observed a drug effect (CUD < HC, pcorrected=.06, trend) in a cluster of 54 connectivity edges with high-degree nodes (i.e., node with high number of significant edges) included limbic [nucleus accumbens (NAcc), ventromedial prefrontal cortex (vmPFC), amygdala], dorsomedial PFC (dmPFC), and precuneus nodes. Trauma effect (High < Low Trauma, 63 edges, pcorrected=.03) was most evident in limbic nodes (vmPFC, amygdala) and precuneus. Importantly, DrugxTrauma interaction (74 edges, pcorrected=.002) was most evident in nodes of the drug/trauma main effects (NAcc, amygdala, dmPFC), as well as insula, inferior frontal, and visuosensory nodes (V5, fusiform).

Conclusions: Social-neural function may hold key roles to understand CUD. While the main effects of drugs and trauma were most evident in limbic and executive subnetworks, all social subnetworks had high-degree nodes showing significant interaction. This suggests that addiction and childhood trauma might have widespread effects on the intrinsic connectivity of social regions.

T2. IMPACT OF INDIVIDUAL BASELINE FACTORS ON OPIOID-NEGATIVE URINE SAMPLES: COMPARING TREATMENT WITH WEEKLY/MONTHLY INJECTABLE BUPRENORPHINE VS DAILY SUBLINGUAL BUPRENORPHINE/NALOXONE IN PATIENTS WITH OPIOID USE DISORDER

Michael P. Frost[1], Sandra D. Comer[2], Michelle R. Lofwall[3], Sharon L. Walsh[3], Genie L. Bailey[4], Peter Almgren[5], Stefan Peterson[5], Elin Banke Nordbeck[5], Susanna Meyner[5], Adam Friedman[6], Natalie R. Budilovsky-Kelley[6]*

[1]The Frost Medical Group LLC, [2]Columbia University, [3]University of Kentucky College of Medicine, Center on Drug and Alcohol Research, [4]Brown University and Stanley Street Treatment and Resources (SSTAR), [5]Camurus AB, [6]Braeburn Inc

Abstract Background: Certain patient baseline characteristics such as injection drug use versus oral/intranasal drug use can be a poor prognostic factor for OUD treatment outcomes. The aim was to report subgroup efficacy analyses for people who inject opioids (PWIO; n = 209) from a phase 3 trial comparing weekly and monthly extended-release injectable buprenorphine (CAM2038) to sublingual buprenorphine/naloxone (SL BPN/NX) among treatment-seeking adults with moderate to severe Opioid Use Disorder (OUD) (n = 428).
Methods: This was a post-hoc analysis of an outpatient randomized double-blind, double-dummy 24-week trial comparing weekly and monthly CAM2038 to SL BPN/NX for OUD treatment. The efficacy outcomes urine drug test (UDT) opioid results, Clinical Opiate Withdrawal Scale (COWS) scores, Subjective Opiate Withdrawal Scale (SOWS) scores, and need- and desire-to-use opioid visual analogue scales (VAS) were compared between CAM2038 and SL BPN/NX for the treatment of patients with OUD. Data on the subgroup of patients who inject opioids at baseline are presented in this abstract. Further subgroup analysis is ongoing, and more results are planned to be included in the poster.

Results: Mean percentage of urine samples negative (with self-report) for illicit opioids was higher in the CAM2038 group (30.6%) vs. SL BPN/NX (14.3%) (p=0.0008). In both groups, total scores on the COWS and SOWS were suppressed from day 1 and throughout the study, without significant group differences. In both groups, opioid craving as evaluated by need- and desire-to-use VAS, was greatly reduced from day 1 and throughout the study, without significant group differences.

Conclusions: Treatment with CAM2038 increased the likelihood of no illicit opioid use vs. SL-BPN/NX in participants injecting opioids at baseline. Further analysis will show if there was an impact on other clinically meaningful outcomes such as treatment retention.

T3. NMDA-RECEPTOR PARTIAL AGONISTS AS A POTENTIAL APPROACH TO THE TREATMENT OF ETHANOL BINGE DRINKING BEHAVIOR IN A MOUSE MODEL

Hannah Campbell[1], Madeline Newlin[1], Caitlyn Magee[1], Cynthia Kuhn[1]*

[1]Duke University

Abstract: Alcohol use disorder is a prevalent and disabling condition with current medication therapies often ineffective in reducing alcohol consumption and preventing relapse. Chronic ethanol exposure has been linked to altered glutamatergic transmission that may contribute to maladaptive behaviors in alcohol use disorder. Rapastinel is an NMDA-receptor partial agonist that has previously been shown to be effective in reducing cravings for opiates in preclinical rodent models. We hypothesized that rapastinel may be effective in reducing alcohol binge drinking behaviors in alcohol exposed mice. We utilized the previously published drinking-in-the-dark (DID) paradigm, in which C57Bl6J mice were given access to 20% alcohol for 2 hours for 3 days/week and 4 hours for 1 day a week starting at 3 hours into the dark cycle. Using this method, we saw mice drink to intoxication with our data consistent with prior literature. Mice received intraperitoneal injections of

rapastinel at a dose of 30 mg/kg or saline 30 minutes prior to alcohol exposure with volume of alcohol consumed measured at the end of the drinking period. We found no effect of rapastinel on alcohol consumption in DID in alcohol naïve animals. However, rapastinel significantly reduced alcohol consumption in male mice that had previously experienced 6 weeks of DID. There were no treatment effects in female mice. Regardless of treatment, females drank more than male mice, consistent with prior literature. We conclude an NMDA-receptor partial agonist reduces binge drinking behaviors in male mice and that this reduction is likely dependent on chronic ethanol-induced changes in neural glutamatergic signaling. This preclinical data suggests that rapastinel and other NMDA receptor modulators, including the zelquistenel- a molecule with oral bioavailability, may serve as a novel approach to the treatment of alcohol use disorder. Future directions of this work include examining whether zelquistenel can reduce binge or relapse drinking behavior as well as anxiety-like behavior during withdrawal in dependent mice exposed to chronic ethanol containing liquid diet. We will also examine how zelquistenel affects region dependent neural activity as measured via c-Fos staining during alcohol intoxication and withdrawal states in alcohol dependent animals.

T4. THE ENTACTOGEN, EMP-01, REPRESENTS A NOVEL APPROACH TO THE TREATMENT OF SOCIAL ANXIETY DISORDER WITH ITS PHARMACOLOGICAL SELECTIVITY AND DISTINCT SUBJECTIVE EFFECTS SUPPORTIVE OF SAFETY AND THERAPEUTIC UTILITY

Sarah McEwen[1], Sarah McEwen[2], Carrie Bowen[2], Jonathon Holt[2], Holden Janssens[2], Glenn Short[2], Kevin Craig[2], Srinivas Rao[2]*

[1]atai Life Sciences, [2]EmpathBio Inc

Abstract Background: Social anxiety disorder (SAD) is among the most common psychiatric disorders, with an estimated lifetime prevalence of 12.1% and has one of the lowest remission rates in psychiatry (~35%) (Keller, 2006; Ruscio et al., 2008). Untreated SAD can be associated with debilitating avoidant behaviors due to fear-based beliefs and leads to chronic health problems and co-morbid psychiatric disorders (Vriends et al., 2014). Entactogens, including racemic MDMA, have been shown to be effective in treating SAD in autistic adults, post-traumatic stress disorder (PTSD), anxiety, and by facilitating improvements in affect, empathy, introspection, openness to new ideas and prosocial behaviors, while reducing social anxiety and increasing emotional disclosure and trust (Bedi et al., 2010; Danforth et al., 2018; Fluyau et al., 2024; Hysek et al. 2014; Mithoefer et al., 2011). EMP-01, the R-enantiomer of MDMA, is an entactogen with subjective effects indicative of therapeutic utility in SAD and has a favorable safety profile.
Methods: The pharmacology of EMP-01 was characterized using in vitro assays of receptor and transporter interactions and functional activity. SAD translational in vivo, disease-relevant effects of EMP-01 were determined in the mouse fear extinction assay. Following full characterization of the nonclinical safety and tolerability of EMP-01, a first-in-human (FiH) Phase 1 single-ascending dose study characterized the safety, tolerability, pharmacokinetic (PK), and PD effects of EMP-01 in healthy adult volunteers.

Results: EMP-01 selectively activates known targets of entactogen potential with selectivity toward beneficial serotonergic activity and low activity at catecholaminergic targets (receptors and reuptake transporters). In mice, EMP-01 facilitated fear extinction, an SAD-relevant translational assay. EMP-01 presented no significant concerns in rat and dog

absorption, distribution, metabolism, and excretion (ADME), safety pharmacology and toxicology studies, with the potential for a good therapeutic window across species. In the FiH study with EMP-01, 32 adults received a single dose of EMP-01 at a dose level of 75mg, 125mg, 175mg, 225mg or placebo. EMP-01 was found to be safe and well-tolerated at all dose levels up to 225 mg, with no serious adverse events (SAEs). There were no early study or drug discontinuations. No clinically significant abnormalities were found in vital signs, laboratory parameters, or ECG in any cohort. Treatment emergent AEs (TEAEs) were mild or moderate and generally dose-dependent; the most common were nausea and headache. EMP-01 was associated with dose-related increases in emotional breakthrough experiences, greater introspective awareness, increased self-compassion scores, and it produced subjective experiences and altered states that were more like those of classic serotonergic psychedelics.

Conclusions: There is substantial nonclinical and clinical data to support the development of an entactogen to treat SAD. The entactogen EMP-01 was found to be safe and well-tolerated in healthy adults. EMP-01 has a distinct pharmacology leading to differentiated subjective effects and a favorable safety profile and is being developed as a novel treatment for SAD. A Phase 2a, randomized, placebo-controlled trial of EMP-01 with SAD patients is currently underway.

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T5. A PLACEBO CONTROLLED TRIAL OF CARIPRAZINE IN SOCIAL ANXIETY DISORDER

Jason Careri[1], Rita Hanover[2], Elizabeth Ducat[1], Jenny Wallier[1], Skylar Scull[1], Julie Newcombe[1], Nichika Holdrum[1], Matt Turzilli[1], Ann Draine[1], Michael Liebowitz[1]*

[1]Medical Research Network, [2]Independent Statistical Consultant

Abstract Background: Social anxiety disorder is a prevalent, chronic and often disabling illness. New effective treatment for it are needed. Several lines of evidence suggested that a partial dopamine agonist like cariprazine could be effective for social anxiety disorder. To test this hypothesis a placebo controlled trial of cariprazine was conducted.

Methods: The study was a placebo controlled double blind 12 week trial of cariprazine 1.5-3mg/day conducted at a single site. 49 subjects subjects meeting DSM 5 criteria for social anxiety disorder were screened and 41 were randomized. The primary outcome measure was change from baseline to endpoint in total score on the Liebowitz Social Anxiety Scale (LSAS). The statistical comparison used was analysis of covariance (ANCOVA) using LOCF.

Results: Capriprazine was statistically and clinically superior to placebo on the primary outcome measure F (1,37) = 5.85; p=.021. Least square means were -21.74 for placebo and -37.81 for cariprazine. CGI-I responder rates were 65% for cariprazine vs 40% for placebo, p=.102. Changes in the CGI-S were -1.10 for placebo and -2.10 for cariprazine (p=.015). The difference at endpoint for change in total LSAS between cariprazine and placebo was as great or > what was seen in the registration trials of FDA approved treatments for social anxiety disorder such as sertraline,

paroxetine and venlafaxine ER.

Conclusions: Cariprazine may represent a new treatment for social anxiety disorder, a condition for which no new therapies have been approved in two decades. Cariprazine efficacy, if replicated by further trials, would also suggest that dopaminergically active drugs may have a place in treating social anxiety disorder.

T6. REGULATION OF THE KYNURENINE PATHWAY METABOLISM WITH THE GALANTAMINE-MEMANTINE COMBINATION IN THE TREATMENT OF AUTISM SPECTRUM DISORDERS

Phillip Bempong[1], Niyathi Vadlapalta[2], Aravind Menon[3], John Esposito[4], Maju Koola[5]*

[1]New Jersey Medical School [2]Rowan University, [3]Rutgers Health/Trinitas Regional Medical Center, [4]Cooper Medical School of Rowan University, [5]Mental Health and Behavioral Services, Veterans Affairs New Jersey Health Care System

Abstract: Autism spectrum disorder (ASD) is a neurodevelopmental disease characterized primarily by challenges in social interaction, communication, and repetitive behaviors. Per the Centers for Disease Control and Prevention, the prevalence of ASD in the United States is about 1 in 36 children, or 2.8%. There are currently no FDA-approved medications for the treatment of ASD. Cognitive impairments are prevalent in ASD. The cognitive impairments in ASD are the worst amongst all the psychiatric diseases, second only to schizophrenia. Galantamine and memantine are FDA-approved medications for the treatment of Alzheimer's disease. Galantamine works by inhibiting acetylcholinesterase and modulating alpha7 nicotinic receptors (α7nAChR) and improving cognition. Memantine modulates the N-methyl-D-aspartate (NMDA) receptor. NMDA and α7nAChR are core pathophysiologic mechanisms in ASD. The kynurenine pathway is also critically involved in ASD. Kynurenic acid (KYNA) inhibits NMDA and α7nAChR, resulting in cognitive impairments. Combining galantamine and memantine can counteract the effects of KYNA and improve the cognitive impairments found in ASD. KYNA modulates all the major pathophysiological mechanisms in ASD. Hence, stabilizing KYNA using the combination of galantamine and memantine is a novel approach that has not been undertaken before. A systematic review of clinical trials examining the use of Alzheimer's disease medications, including donepezil, rivastigmine, tacrine, galantamine, and memantine, concluded there was some efficacy with a single medication, but no clinical significance. Another review demonstrated that all clinical trials with a single medication in the treatment of Alzheimer's disease failed. This is the same scenario in all psychiatric diseases. Hence, we are proposing randomized controlled trials (RCTs) with two medications. All these findings underscore the potential of repurposing galantamine and memantine for ASD, offering a novel therapeutic strategy to address symptoms and improve patient outcomes. This can primarily be achieved through the concurrent modulation of NMDA and α7nAChR. Therefore, RCTs examining the efficacy of the galantamine-memantine combination treatment in ASD are warranted.

T7. IMPROVING TEST-RETEST RELIABILITY OF EEG-BASED CONNECTOMICS USING INDIVIDUALIZED STRUCTURAL MRI-BASED TEMPLATES: FINDINGS FROM ESTABLISHING MODERATORS AND BIOSIGNATURES OF ANTIDEPRESSANT RESPONSE IN CLINICAL CARE (EMBARC)

Nabila Haque[1], Russell Toll[1], Thomas Carmody[1], Manish Jha[1], Madhukar Trivedi[1], Amrita Ghose[1]*

[1]University of Texas Southwestern Medical Center

Abstract Background: Resting electroencephalogram (EEG) offers a powerful and easily implementable tool to understand neural circuit functioning. However, it remains unclear whether using an individual's structural MRI to compute these EEG-based biomarkers is advantageous over the current practice of using MNI template. Here, we used data from healthy controls who participated in the EMBARC Study.
Methods: Healthy individuals from the Establishing moderators and biosignatures of antidepressant response in clinical care (EMBARC) study (N=39) were tested in two sessions separated by one week. Resting state EEG (eyes-open (REO) and eyes-closed (REC)) was recorded and structural MRI was performed. Functional connectomes were computed using the Schaefer 100-parcel atlas for the following networks in alpha, beta and theta bands: default mode (DMN), visual (VIS), somatomotor (SMN), dorsal attention (DAN), salience (SN), limbic (LN), and frontoparietal (FPN) using two methods to construct the imaging

kernel: 1) the individual subject's structural (native) MRI scan or 2) a template brain based on the Montreal Neurological Institute (MNI) standard. Reliability of EEG metrics was calculated using concordance correlation coefficients (CCC) for the 336 pairs of network connections.

Results: Between baseline and week one, good test-retest reliability, defined as CCC more than 0.8, were shown for 25 pairs of connections. Out of these 25 pairs, 9 connections were calculated using the MNI template and 16 the native template, 23 were in the beta band, and 23 in resting eyes open (REO) paradigm. The LN was not represented in any of the pairs while the FPN and DAN were represented in about 50% of the pairs. When comparing the native with the MNI derived connections in these 25 pairs, all but one of the template-derived connections were also represented in the native connections; the FPN was represented 7 times in template and 6 times in native, while DMN was represented once in template and 7 times in native.

Discussion: The demonstration of good reliability for EEG connectome measures provides a template for future studies utilizing EEG and informs whether structural MRI must be performed in conjunction with EEG for specific connectivity-based EEG biomarkers and is an important step for evaluating EEG as a clinical biomarker. EEG biomarkers appear to have good test-retest reliability a week apart and using native MRI template appears to further enhance reliability in measuring certain network connections.

T8. OPEN BOARD

T9. COST-EFFECTIVENESS OF CARIPRAZINE VERSUS ARIPIPRAZOLE IN PATIENTS WITH BIPOLAR I DISORDER

Huiying Guo[1], Mousam Parikh[1], Robert Boer[1], Jamie Ta[1]*

[1]AbbVie

Abstract Introduction: Atypical antipsychotics (AAs) are a first-line treatment option for patients with bipolar I disorder (BP-I), which is characterized by recurring manic and depressive episodes. Many AAs such as aripiprazole are approved for only 1 pole of BP-I yet remain commonly used in the treatment of BP-I. Cariprazine is a dopamine D3-preferring D3/D2 and serotonin 5-HT1A receptor partial agonist approved for the treatment of BP-I manic/mixed and depressive episodes. While the efficacy and safety of cariprazine in BP-I manic/mixed and depressive episodes has been established in clinical trials, there is limited evidence on the cost-effectiveness of cariprazine relative to other AAs for the treatment of BP-I. Therefore, the objective of this analysis was to assess the cost-effectiveness of cariprazine vs aripiprazole for the treatment of BP-I.

Methods: An economic model was constructed in Microsoft Excel from the societal (base case) and US payer perspectives, which consisted of a 4-week acute phase as represented by a decision tree followed by a Markov model with 4-week cycles and up to a 5-year time horizon. Due to the longer duration spent in depressive episodes vs manic/mixed episodes in BP-I, it was assumed that 74% of patients entered the decision tree model in an acute BP-I depressive episode and 26% entered in an acute BP-I manic/mixed episode. Patients received first-line (1L) treatment with either cariprazine or aripiprazole and after the initial acute

phase, entered the Markov model, where patients who responded to initial treatment continued their 1L therapy, while non-responders switched to the next line of treatment. The model consisted of 2 lines of subsequent therapy: BP-I depression─lurasidone, quetiapine, and olanzapine with equal distribution; BP-I mania/mixed─quetiapine, olanzapine, and risperidone with equal distribution. Key model inputs included treatment-specific efficacy for BP-I manic/mixed and depressive episodes and adverse events (significant weight gain, akathisia, extrapyramidal symptoms, somnolence) from published network meta-analyses as well as discontinuation rates, affective switch rates from BP-I depression to mania/mixed and BP-I mania/mixed to depression, health state utilities, mortality risk, and costs. Outcomes included total costs expressed in 2022 US dollars (direct medical + pharmacy costs for payer perspective; + productivity losses for societal perspective), equal value life years (evLYs), and the incremental cost-effectiveness ratio (ICER; cost per equal value life year gained [evLYG]) for cariprazine vs aripiprazole. One-way and probabilistic sensitivity analyses were conducted to assess the robustness of the model results.

Results: From the societal perspective, cariprazine resulted in 0.024 evLY gains at an incremental cost of $2,313 vs aripiprazole, resulting in an ICER of $97,610/evLYG. From the US payer perspective, cariprazine resulted in the same evLY gains at an incremental cost of $2,771 vs aripiprazole, resulting in an ICER of $116,920/evLYG. In one-way sensitivity analyses, results were most sensitive to cariprazine and aripiprazole response rates, discontinuation rates, and health state utilities. Model results were robust to probabilistic sensitivity analyses.

Conclusions: The results of this economic evaluation suggest that cariprazine is a cost-effective strategy compared with aripiprazole for the treatment of BP-I from the societal and US payer perspectives.

T10. HEALTHCARE RESOURCE UTILIZATION FOLLOWING CARIPRAZINE INITIATION AMONG MEDICARE BENEFICIARIES WITH BIPOLAR I DISORDER

Mousam Parikh[1], Sally W. Wade[2], Nadia Nabulsi[1], Andrea Barthel[3], Andrew Rava[3], Haiyan Sun[3], Lakshmi Kandukuri[1], Zheng Wu[3], Yajin Zhao[3], Tracy Yee[3], Thomas Wasser[3], Jamie Ta[1]*

[1]AbbVie, [2]Wade Outcomes Research and Consulting, , [3]Genesis Research Group

Abstract Introduction: Cariprazine is a dopamine D3 preferring D3/D2 and serotonin 5-HT1A receptor partial agonist atypical antipsychotic that is approved by the US Food and Drug Administration for the treatment of schizophrenia, mania/mixed and depressive episodes associated with bipolar I disorder (BP-I), and for the adjunctive treatment of Major Depressive Disorder (MDD). Clinical trials and real-world studies have demonstrated the impact of cariprazine on clinical outcomes and healthcare resource utilization (HCRU) among patients with BP-I, yet there is limited real-world evidence on the impact of cariprazine initiation on HCRU in Medicare Fee-for-Service (FFS) beneficiaries with BP-I. The objective of this study was to compare all-cause HCRU before vs. after cariprazine initiation among Medicare FFS beneficiaries with BP-I.

Methods: A retrospective observational study was conducted using administrative claims data from the Centers for Medicare and Medicaid Services 100% Research Identifiable Files.

Medicare FFS beneficiaries ≥ 18 years with BP-I who newly initiated cariprazine (index date = first cariprazine claim) between January 1, 2019 and June 30, 2022 and had 6-months pre- and post-index continuous enrollment in Medicare Parts A, B, and D were included. The post-index period spanned the period of continuous cariprazine treatment from index date until the earliest of the following: discontinuation of cariprazine (≥45-day gap), exposure to a different oral atypical antipsychotic, exposure to a long-acting injectable antipsychotic, death, disenrollment from the database, or end of the study period. All patients were required to have 6 months of continuous cariprazine use during the post-index period. All-cause HCRU (inpatient, emergency room [ER], outpatient) was assessed during the 6-month pre- and post-index periods and compared using paired t-tests and McNemar tests for continuous and categorical variables, respectively. P-values < 0.05 were considered statistically significant.

Results: A total of 1,655 Medicare FFS beneficiaries with BP-I who initiated cariprazine were included in this study. The mean (standard deviation [SD]) age at index was 50.8 (13.7) years, 74.4% of patients were female, and 84.4% were White. Mean (SD) Charlson Comorbidity Index score was 1.1 (1.5) and 74.9% of beneficiaries were fully dual-eligible. The proportion of beneficiaries with ≥1 all-cause inpatient hospitalization during the 6-month post-index period was significantly lower versus pre-index (pre- vs. post-index: 15.4% vs. 10.3%, $p < 0.0001$). The mean number of all-cause hospitalizations was also significantly lower post- vs. pre-index (0.22 vs. 0.14, $p < 0.0001$). The proportion of beneficiaries with ≥1 all-cause ER visit and mean number of ER visits were significantly lower post- vs pre-index (41.3% vs. 33.9%; 1.01 vs. 0.77; all $p < 0.0001$). Mean number of all-cause outpatient visits was not significantly different post- vs. pre-index (22.62 vs. 22.07, $p > 0.05$).

Conclusions: This analysis demonstrates that all-cause HCRU was statistically significantly lower after cariprazine initiation than before. These **Results:** highlight the real-world economic value of cariprazine in reducing the HCRU burden among Medicare FFS beneficiaries with BP-I.

T11. REAL WORLD ASSESSMENT OF HEALTH CARE RESOURCE USE FOR MANIC EVENTS AMONG PATIENTS TREATED WITH CARIPRAZINE OR OTHER ATYPICAL ANTIPSYCHOTICS FOR BIPOLAR I DISORDER

Roger S. McIntyre[1], Mousam Parikh[2], Enrico Zanardo[3], François Laliberté[4], Huy-Binh Nguyen[2], Eric Christopher[2], Kaixin Zhang[4], Sophie Ma[4], Jamie Ta[2], Lauren Aronin[2]*

[1]University of Toronto, [2]AbbVie, [3]Analysis Group, Inc., [4]Groupe d'analyse, Ltée

Abstract Introduction: Antipsychotics, including atypical antipsychotics (AAs), are a first-line treatment for bipolar I disorder (BP-I). Cariprazine is a dopamine D3 preferring D3/D2 and serotonin 5-HT1A receptor partial agonist AA approved by the US Food and Drug Administration for treating BP-I manic/mixed and depressive episodes. Cariprazine's efficacy and tolerability are established in clinical trials; however, there is limited information about its real-world effectiveness compared to other commonly used agents. The objectives of this study were to compare rates of BP-I manic events among commercially insured patients treated with cariprazine versus quetiapine and lurasidone.

Methods: This retrospective observational study used claims data from the IQVIA PharMetrics® Plus database (September 17, 2014 to September 30, 2022). Adults with BP-I and ≥ 2 AA pharmacy claims for cariprazine, quetiapine, or lurasidone were included. Index date was the first claim for cariprazine, quetiapine, or lurasidone. The baseline period was the 12 months preceding the index date. The follow-up period (≥ 3 months) spanned from the index date to the earliest of the following: discontinuation of the index AA, exposure to a different AA or a long-acting injectable antipsychotic, diagnosis of schizophrenia, or end of data availability or eligibility. Inverse probability of treatment weighting was used to balance differences in baseline patient characteristics between AA cohorts. Manic events were identified using a claims algorithm based on place of service and frequency of claims with a mania diagnosis. Rates of manic events per patient-year (PPY) were compared between weighted cohorts of patients initiating cariprazine vs comparator AA (quetiapine and lurasidone, separately). Rate ratios (RRs) from Poisson regression models were calculated for each pairwise comparison, with 95% CIs and P values calculated from nonparametric bootstrapping.

Results: For the pairwise comparison of manic events between patients treated with cariprazine (n = 4,125) vs quetiapine (n = 12,177), the weighted cohorts were well-balanced across baseline characteristics, including mean age (39.1 vs 39.3 years) and sex (64.9% vs 63.2% female). For the cariprazine (n = 4,440) vs lurasidone (n = 8,134) comparison, the characteristics in the weighted cohorts were also balanced, including mean age (38.9 vs 38.8 years) and sex (70.3% vs 70.4% female). Patients using cariprazine had lower rates of manic events PPY compared with those using quetiapine (RR [95% CI] = 0.57 [0.44, 0.74], P < .001), driven by lower rates of inpatient (IP)-defined manic events (RR = 0.49 [0.30, 0.73], P < .001) and outpatient (OP)-defined manic events (RR = 0.57 [0.43, 0.75], P < .001). Similarly, patients using cariprazine had lower rates of manic events PPY compared with those using lurasidone (RR = 0.71 [0.55, 0.93], P < .05), due to lower rates of IP-defined manic events (RR = 0.64 [0.45, 0.87], P < .01) and OP-defined manic events (RR = 0.71 [0.53, 0.96], P < .05). Manic events in the emergency room setting were not significantly different between cariprazine and comparators.

Conclusions: Commercially insured patients with BP-I treated with cariprazine had significantly lower rates of overall, IP, and OP manic events compared with those treated with quetiapine or lurasidone. This study provides real-world evidence of the relative effectiveness of cariprazine on rates of BP-I mania events.

T12. EFFECTIVE TREATMENT OF HYPOMANIA WITH THE USE OF LURASIDONE IN A BIPOLAR 2 DISORDER PATIENT: A CASE REPORT AND A REVIEW OF THE LITERATURE

Majd Al-Soleiti[1], Jonathan Leung[1], John Powers[1], Abigail Tarasewicz[1]*

[1]Mayo Clinic

Abstract: Lurasidone has been one of the mainstay treatments for schizophrenia and bipolar depression (as both monotherapy and as adjunctive therapy with other mood stabilizers).

Clinical studies have explored efficacy of lurasidone for bipolar depression with mixed features, including subsyndromal hypomanic symptoms. However, no studies at all suggested its use for the treatment of mania or hypomania. In fact, Food and Drug Administration (FDA)-approved labeling for lurasidone notes that a small minority of patients treated with it for bipolar depression developed manic or hypomanic episodes.
In this case, we present a 69-year-old woman with history of bipolar 2 disorder and ovarian cancer with secondary metastasis, who developed a hypomanic episode, and was treated primarily by increasing the dose of her long-standing mood stabilizer, lurasidone, in addition to very low-dose short-term lorazepam. The patient presented with a 2-month period of elated mood, distractibility, flight of ideas, decreased sleep, and increased impulsive goal-directed activity (that is a historical highlight of her decompensation), with no coexistent depressive or anxiety symptoms. She was treated to full remission over the course of the following 4-6 weeks with increasing lurasidone dose (from 80 to 120 mg daily) and initiating low-dose short-term lorazepam (0.25-0.5 mg daily with inconsistent use).

We present a thorough timeline of the symptoms, confirmed by collateral information, as well as the coinciding medication changes and adjustments. We also explain why lurasidone was the most satisfactory explanation for her improvement, as opposed to other explanations; inconsistent low-dose short-term lorazepam, natural course of the illness, decreasing dexamethasone (which was used for chemotherapy-induced nausea with the decrease starting only after improvement in hypomanic symptoms), placebo effect, and spurious improvement.

We further review the literature on lurasidone indications, and the studies based on which they were established. We highlight the scarce data available about lurasidone efficacy in treating subsyndromal hypomanic and manic symptoms in these studies. We finally present some pharmacodynamic pathways that may explain lurasidone-responsive hypomania.

This case introduces the potential utility of lurasidone in managing hypomanic episodes, a use that is not currently supported by FDA or robust clinical studies. The observed resolution of hypomanic symptoms following an increase in lurasidone dosage highlights the need to reconsider its pharmacodynamic pathways and explore its broader therapeutic potential, with further research. Expanding our understanding of lurasidone's applications could lead to more tailored treatment approaches, particularly for complex cases where standard therapies may fall short. Additionally, this case emphasizes the importance of individualized care, careful symptom monitoring, and good knowledge of the patient’s psychiatric history (which may aid both diagnosis and treatment).

T13. HEALTHCARE RESOURCE UTILIZATION 12 MONTHS FOLLOWING INITIATION OF OLANZAPINE/SAMIDORPHAN: REAL-WORLD ASSESSMENT OF PATIENTS WITH BIPOLAR I DISORDER

Rakesh Jain[1], Hemangi Panchmatia[2], Alejandro G. Hughes[3], Michael J. Doane[2], Hara E. Oyedeji[4], Andrew J. Cutler[5]*

[1]Texas Tech University School of Medicine-Permian Basin, [2]Alkermes, Inc., [3]Optum, Inc., [4]Fortitude Behavioral Health, [5]SUNY Upstate Medical University, Syracuse; Neuroscience Education Institute

Abstract Objective: The combination of olanzapine and samidorphan (OLZ/SAM) provides the antipsychotic efficacy of olanzapine while mitigating olanzapine-associated weight gain. OLZ/SAM treatment was associated with significant reductions in acute healthcare resource utilization (HCRU) in a previous 6-month pre/post study. This study examined HCRU among patients with bipolar I disorder (BD-I) in the 12 months before and after OLZ/SAM initiation.
Methods: Administrative claims data from October 18, 2020, to December 31, 2023, from the Komodo Healthcare Map were analyzed retrospectively. Adults with BD-I and continuous enrollment ≥12 months before (baseline) and after (follow-up) OLZ/SAM initiation were eligible. Inpatient (IP) admissions, emergency department (ED) and outpatient (OP) visits, and average numbers of IP days/patient were compared between baseline and follow-up. A secondary analysis was conducted in patients receiving OLZ/SAM for the full 12 months of follow-up.

Results: Patients (n=1004; mean age: 39 years; female: 69%) were on average persistent for 173.7 days. Proportions of patients with ≥1 all-cause, mental health (MH)-related, and BD-I–related IP admissions and ED visits significantly decreased between baseline and follow-up (all $P < 0.001$). Mean numbers of all-cause, MH-related, and BD-I–related IP days/patient decreased significantly (all $P < 0.001$). Proportions of patients with OP visits were similar during baseline and follow-up. Larger reductions in IP admissions and ED visits were observed in patients receiving OLZ/SAM for the entire 12-month follow-up period (both $P < 0.001$; n=300).

Conclusions: Among patients with BD-I, OLZ/SAM initiation results in clinically meaningful reductions in disease burden, as evidenced by reductions in hospital-based HCRU. Longer OLZ/SAM treatment retention was associated with improved effectiveness.

T14. HEALTHCARE RESOURCE UTILIZATION 12 MONTHS FOLLOWING INITIATION OF OLANZAPINE/SAMIDORPHAN: REAL-WORLD ASSESSMENT OF PATIENTS WITH SCHIZOPHRENIA

Andrew J. Cutler[1], Hemangi Panchmatia[2], Alejandro G. Hughes[3], Michael J. Doane[2], Hara E. Oyedeji[4], Rakesh Jain[5]*

[1]SUNY Upstate Medical University; Neuroscience Education Institute, [2]Alkermes, Inc., [3]Optum, Inc., [4]Fortitude Behavioral Health, [5]Texas Tech University School of Medicine-Permian Basin

Abstract Objective: The combination of olanzapine and samidorphan (OLZ/SAM) provides the antipsychotic efficacy of olanzapine while mitigating olanzapine-associated weight gain. OLZ/SAM treatment was associated with significant reductions in healthcare resource utilization (HCRU) in a previous 6-month pre/post study. This study examined HCRU among patients with schizophrenia in the 12 months after OLZ/SAM initiation.
Methods: This retrospective analysis used administrative claims data from October 18, 2020, to December 31, 2023, from the Komodo Healthcare Map. Adults with schizophrenia and continuous enrollment ≥12 months before (baseline) and after (follow-up) OLZ/SAM initiation were eligible. Inpatient (IP) admissions, emergency department (ED) and outpatient (OP) visits, and average numbers of inpatient days/patient were compared between baseline

and follow-up. A secondary analysis was conducted in patients who received OLZ/SAM treatment for the full 12 months of follow-up.

Results: Patients (n=1287; mean age: 39 years; female: 46%) were on average persistent for 196.6 days. Proportions of patients with ≥1 all-cause, mental health (MH)-related, and schizophrenia-related IP admissions and ED visits significantly decreased between baseline and follow-up (all $P < 0.001$). Mean numbers of all-cause, MH-related, and schizophrenia-related inpatient days/patient decreased significantly (all $P < 0.001$). Proportions of patients with OP visits were similar during baseline and follow-up. Larger reductions in IP admissions and ED visits were observed in the population receiving OLZ/SAM treatment for the entire 12-month follow-up period (both $P < 0.001$; n=481).

Conclusions: Among patients with schizophrenia, OLZ/SAM initiation may result in clinically meaningful reductions in real-world disease burden, as evidenced by reductions in hospital-based HCRU. Longer treatment retention was associated with improved effectiveness.

T15. SOLRIAMFETOL FOR EXCESSIVE DAYTIME SLEEPINESS IN PATIENTS WITH NARCOLEPSY AND OSA REPORTING ANXIETY AND DEPRESSION IN THE REAL-WORLD SURWEY STUDY

Ulf Kallweit[1], Heike Benes[2], Lothar Burghaus[3], Graham M.L. Eglit[4], Samantha Floam[4], Gregory Parks[4], Hasib Bhojwani[4], Yaroslav Winter[5]*

[1]Center for Biomedical Education and Research, University Witten/Herdecke, [2]Somni bene GmbH Institutfür Medizinische Forschungund Schlafmedizin Schwerin GmbH, [3]Heilig Geist-Hospital, [4]Axsome Therapeutics, Inc., [5]Mainz Comprehensive Epilepsy and Sleep Medicine Center, Johannes Gutenberg-University

Abstract Introduction: Psychiatric comorbidities are common in patients with excessive daytime sleepiness (EDS) from narcolepsy or obstructive sleep apnea (OSA). Solriamfetol (Sunosi®), a dopamine/norepinephrine reuptake inhibitor and TAAR1/5HT1a agonist approved for treating EDS in narcolepsy or OSA, has limited data in patients with psychiatric comorbidities. We describe the real-world use of solriamfetol in German patients with narcolepsy or OSA who self-reported depression/anxiety at baseline.
Methods: A retrospective chart review (SURWEY) was performed using data from German physicians prescribing solriamfetol to patients with EDS associated with narcolepsy or OSA, treated at a stable dose for ≥6 weeks. Comorbidities, including anxiety/depression, were documented at baseline.

Results: Of 154 patients, n=48 (31.2%) reported anxiety and/or depression (OSA, n=23/83 [27.7%], narcolepsy, n=25/71 [35.2%]). Baseline mean±SD Epworth Sleepiness Scale (ESS) scores were similar in patients with (OSA, 16.1±2.8; narcolepsy, 17.9±3.6) and without (OSA, 16.0±3.3; narcolepsy, 17.5±2.9) anxiety/depression. Mean±SD ESS score decreases were 4.6±3.2 and 5.2±3.6 with and without anxiety/depression, respectively. Most patients (≥88%) and physicians (≥88%) reported improvements in EDS, which were similar across sleep etiologies and anxiety/depression presence. Common adverse events were headache, insomnia, and decreased appetite, occurring at similar rates regardless of anxiety/depression.

Conclusion: These real-world data describe solriamfetol treatment outcomes in patients with narcolepsy or OSA by self-reported anxiety/depression. Regardless of anxiety/depression, ESS scores improved, and most patients and physicians reported improved EDS. Our findings are consistent with clinical trial results and suggest solriamfetol is effective in managing EDS symptoms in these populations regardless of common psychiatric comorbidities.

T16. EFFICACY AND SAFETY OF AXS-05 IN ALZHEIMER'S DISEASE AGITATION: A PHASE 3 RANDOMIZED-WITHDRAWAL DOUBLE-BLIND PLACEBO-CONTROLLED STUDY

Jeffery Cummings[1], George Grossberg[2], Caroline Streicher[3], Courtney Zeni[3], Herriot Tabuteau[3]*

[1]University of Nevada, Las Vegas, [2]Saint Louis University Hospital, [3]Axsome Therapeutics Inc.

Abstract Background: Alzheimer's disease (AD) agitation is present in ~70% of individuals with AD. Current pharmacologic therapies are limited, leaving a need for additional rationally-designed treatments. Here, we report results from ACCORD-2, a Phase-3, multicenter, double-blind, placebo-controlled, randomized withdrawal study of AXS-05 (dextromethorphan-bupropion), an oral NMDA receptor antagonist/sigma-1 receptor agonist, in AD agitation.

Methods: ACCORD-2 was a randomized withdrawal study comprised of an AXS-05 open-label period (OLP; ≤12 months, n=295) followed by a 26-week, double-blind, randomized withdrawal period (DBP). Participants had a diagnosis of probable AD (National Institute on Aging-Alzheimer's Association, 2011) and clinically-significant associated agitation. Of patients treated for at least 8 weeks, there were 167 that achieved sustained clinical response in the OLP and were randomized 1:1 into the DBP (AXS-05: n=83, placebo: n=84). Mean CMAI total scores at randomization were 44.3 and 45.4 for AXS-05 and placebo, respectively.

Result: AXS-05 statistically significantly delayed time to AD agitation relapse (hazard ratio=0.276, P=0.001, 3.6-fold lower risk), meeting the primary endpoint. AXS-05 statistically significantly prevented AD agitation relapse (key secondary endpoint; relapse rates: AXS-05=8.4%, placebo=28.6%, P=0.001). AXS-05 statistically significantly prevented worsening of severity of AD overall (CGI-S AD overall clinical status; proportion with worsening: AXS-05=13.3%, placebo=39.3%, $P < 0.001$), and statistically significantly prevented worsening of severity of AD agitation (CGI-S agitation; proportion with worsening: AXS-05=20.5%, placebo=41.7%, P=0.004). Adverse event (AE) rates in the DBP: AXS-05=29.3%, placebo=32.1%; none occurred in > 3.7% of patients. Two (2.4%) AXS-05 patients reported falls; one treatment-related. DBP discontinuations from AEs were low (AXS-05=0%, placebo=1.2%). AXS-05 was not associated with sedation or cognitive decline; no deaths were reported.

Conclusion: AXS-05 achieved primary and key secondary endpoints by statistically significantly delaying and preventing AD agitation relapse versus placebo, respectively.

AXS-05 prevented worsening of severity of AD agitation and AD overall compared to placebo. AXS-05 was well tolerated, with no new safety signals.

T17. IMPACT OF SCREENING CALL DURATION ON INITIAL EVALUATION ATTENDANCE RATE FOR ALZHEIMER'S DISEASE DRUG TRIALS

Ralph Lee[*1], Yu-Jay Huoh[1], Brenda Martinez[1], Elizabeth Sosa[1], Tara Parnitvithikul[1], Elly Lee[1]*

[1]Irvine Clinical Research

Abstract Objective: Recruitment of participants for Alzheimer's Disease (AD) drug trials is typically more difficult than recruitment for traditional clinical trials. The target population is typically older, which lowers the effectiveness of traditional recruitment channels and methods. With the bulk of potential participants identified primarily through online advertising, these challenges often lead to high recruitment costs.
In this study, we examine the relationship between screening call duration and the attendance rate of downstream initial screening visit appointments that are scheduled as a result of these screening calls.

Methods: From August 2023 to March 2024, 2,267 potential participants had appointments scheduled for an in-person initial screening. These potential participants were identified primarily through online advertising campaigns.

Of these 2,267 potential participants, 1,258 attended their scheduled appointment, 586 modified (canceled or rescheduled) their scheduled appointment, and the remaining 423 did not show up or modify their scheduled appointment.

A multinomial logistic regression analysis was conducted to evaluate the impact of the screening call duration on the different outcomes while controlling for how many days out the appointment was scheduled.

Findings: A multinomial regression of the appointment outcomes for the initial screening appointment against screening call duration while controlling for appointment scheduling lag showed the impact of screening call duration to be statistically significant. Inclusion of screening call duration into the regression improved the model deviance by 7.136 on two degrees of freedom, yielding a p-value of 0.028.

A separate logistic regression of no-show rates (the outcome with the largest screening call duration effect size in the multinomial regression) against screening call duration while controlling for scheduling lag also revealed a clearly significant effect ($\beta = -0.0051$, $p = 0.026$).

Conclusion: Based on the outcomes of the analysis, it is clear that there is a negative relationship between screening call duration and no-show rates for initial screening appointments for Alzheimer's Disease drug trials; potential participants who spend more time on the phone are less likely to outright not attend a scheduled initial screening appointment.

The analyses conducted in this study are merely correlative and not enough to conclusively infer a causal relationship between phone screen duration and no show rates; additional investigation is necessary to determine causality of the relationship.

T18. DOES TREATMENT FOR INSOMNIA IMPROVE SLEEP STATE MISPERCEPTION?

Dinesh Kumar[1], Jocelyn Y. Cheng[1], Margaret Moline[1]*

[1]Eisai Inc.

Abstract Objective: In insomnia patients, a discrepancy often exists between patient-reported (subjective) durations and objective sleep data determined by polysomnography (PSG), yet few studies have examined the effects of hypnotics when patients present with different degrees of sleep state misperception. The objective of this analysis was to determine whether discrepancies between objective PSG data and subjective assessments for sleep onset and sleep maintenance were impacted by treatment. Data were derived from a Phase 3 study of lemborexant (LEM), a dual orexin receptor antagonist approved in > 20 countries to treat adult patients with insomnia.

Methods: E2006-G000-304 was a 1-month, randomized, double-blind study of LEM 5 mg (LEM5), LEM 10 mg (LEM10), placebo (PBO), and zolpidem extended-release (ZOL) 6.25 mg in participants with insomnia disorder aged ≥55 years. Participants were classified into misperception index quartiles (Qs) based on differences between baseline (BL) PSG and sleep diary values (1 week during PBO run-in). Participants in Q1 had the largest differences between PSG and sleep diary, meaning they were the least accurate in estimating how long it took to fall asleep or how long they were awake, always with values longer than the PSG. The Q2 and Q3 participants had smaller differences between PSG and sleep diary, whereas participants in Q4 reported falling asleep faster or had less wakefulness during sleep than the PSG. Changes from BL (CFBs) in latency to persistent sleep (LPS) and wake-after-sleep-onset (WASO) averaged values at Day 1/2 and Day 29/30 were compared for LEM5, LEM10, and ZOL versus PBO. For subjective sleep onset latency (sSOL) and subjective WASO (sWASO), CFBs were compared with the first and last 7 days of treatment. Comparisons were then made between posttreatment values for PSG- and diary-based parameters at the beginning and end of treatment.

Results: In total, 1006 participants were randomized to treatment (LEM5, n=266; LEM10, n=269; ZOL, n=263; PBO, n=208) and divided into Q1-4 by treatment based on the degree of misperception at BL. BL values for LPS and WASO in the 4 treatment groups did not differ substantively in Q1-Q3; however, BL values in Q4 were significantly larger than the other groups. Whereas BL values for sSOL and sWASO in the 4 treatment groups did not differ substantively in Q2-Q4, Q1 values were larger than the other groups. As reported previously, LEM5 and LEM10 led to larger, statistically significant decreases from BL in LPS and WASO compared with ZOL and PBO. LEM5 and LEM10 led to larger, statistically significant decreases from BL in sSOL and sWASO versus PBO but not versus ZOL. Regardless of treatment group, differences between LPS and sSOL and WASO and sWASO became closer over time relative to BL. There was little change in discrepancy with any treatment in Q2 and Q3. Differences between PSG and sleep diary became closest in Q4, whereas a large difference remained in Q1.

Conclusion: Treatment tended to decrease the discrepancy between PSG and diary values in most older participants with insomnia disorder regardless of the assigned treatment group. While many participants with insomnia become more accurate in reporting their sleep parameters with treatment, sleep state misperception persisted in many individuals despite improvement in sleep. Future studies evaluating additional reasons for these discrepancies will be helpful toward elucidating the role of insomnia medication in the over- or underestimation of actual sleep.

T19. PHARMACOKINETIC RESULTS: OF SINGLE-DOSE AND MULTIPLE-DOSE BIOEQUIVALENCE STUDIES OF MILSAPERIDONE AND ILOPERIDONE IMMEDIATE-RELEASE ORAL TABLETS

Sean Chadwick[*1], Rosarelis Torres[1], Changfu Xiao[1], Christos Polymeropoulos[1], Gunther Birznieks[1], Mihael Polymeropoulos[1]*

[1]*Vanda Pharmaceuticals, Inc.*

Abstract Objectives: Evaluate the pharmacokinetics and comparative bioavailability of milsaperidone as compared to iloperidone, as measured by the metabolites iloperidone and milsaperidone under fasted conditions.

Methods: Two (2) randomized, open-label, two-way crossover pharmacokinetic studies were conducted comparing milsaperidone and iloperidone oral immediate release tablets: 1) a single-dose study in healthy volunteers with washout, and 2) a multiple-dose study in stable psychiatric participants treated to steady-state without a washout period. In both studies, the milsaperidone and iloperidone profiles were evaluated using standard PK parameters (e.g., AUC0–t or AUC0-inf, Cmax), and pharmacokinetic equivalence between the formulations was defined as containment of the 90% confidence intervals (CIs) of the milsaperidone/iloperidone geometric least-squares mean ratios (LSGMRs) within the equivalence limits of 80–125%.

Results: 1) In healthy volunteers given 3mg milsaperidone and 3mg iloperidone, geometric mean plasma concentrations of iloperidone and milsaperidone metabolites were similar and visually superimposable and LSGMRs for Cmax, AUC0-t, and AUC0-inf were similar for the two formulations.

2) In stable psychiatric patients treated to reach steady state conditions at the highest FDA approved dose level for iloperidone (12mg twice daily or BID), after administration of 12mg BID milsaperidone or iloperidone, the LSGMR plasma concentrations of iloperidone and milsaperidone metabolites were comparable and Cmax and AUC0-12 were similar for the two formulations. In both studies, associated 90% CIs of the LSGMRs were contained within 80% to 125%, demonstrating bioequivalence.

Conclusions: Remarkably, the results demonstrate that iloperidone and milsaperidone tablets have equivalent exposure across the entire therapeutic range of iloperidone, and that both moieties efficiently interconvert to reach equilibrium in vivo.

Trial registration: ClinicalTrials.gov No.: NCT04969211 and NCT06494397

Key Words: iloperidone, milsaperidone, pharmacokinetics, bioequivalence

T20. DEVELOPMENT OF THE SUBJECT-RATED COMPREHENSIVE DRUG WITHDRAWAL SCALE (CDWS) TO EVALUATE THE PHYSICAL DEPENDENCE POTENTIAL OF INVESTIGATIONAL DRUGS

Beatrice Setnik[1], Denise Milovan[1]*

[1]*Altasciences*

Abstract Introduction: Novel drugs with abuse potential are assessed for physical dependency as part of the approval process under the Controlled Substances Act. Several drug class-specific withdrawal scales are available; however, these are mostly clinician-rated, challenging to administer frequently in late-stage clinical trials, and contain questions irrelevant to non-drug abusing populations. A novel, comprehensive, subject-rated scale that can be frequently administered in a clinical investigational drug trial to identify potential signs and symptoms of physical dependence and withdrawal is under development.
Methods: A review of the published literature and scales of withdrawal were evaluated for presentation of symptoms and intensity ratings related to drug withdrawal syndrome resulting from various classes of drugs. A collective list of symptoms was identified, and each term was evaluated for comprehension and ease of administration using SMOG and Flesch Kincaid Readability scoring. Questions were drafted to include comprehensive language and past tense suitable to evaluate symptoms (current and past 24 hours). Validation of the scale for content, comprehension, and appropriateness of recall period is ongoing.

Results: Following a thorough literature review, 62 drug withdrawal symptoms associated with scheduled and unscheduled drug classes were identified. A standard Likert 0–3-point rating scale was selected where 0= no symptoms and 1-3 range from mild, moderate to severe, respectively. The SMOG Readability measure to ensure comprehension at no > a 6th grade reading level (easy to read). The Flesch Kincaid Readability scoring identified some terms (e.g., diarrhea, constipation) were deemed more than a grade 8 level. Validity testing is ongoing, and results will be presented.

Conclusion: A reliable subject-reported withdrawal scale is needed to effectively identify potential sings and symptoms of drug discontinuation in clinical trials evaluating new drugs in development. A novel CDWS tool, currently in development to address the pragmatic and validity concerns of existing scales.

T21. NAVIGATING THE UNCHARTERED TERRITORY OF ASSESSING PSYCHEDELICS IN HUMAN ABUSE POTENTIAL STUDIES

Beatrice Setnik[1], Jadwiga Martynowicz[2], Anthony Coulson[3], John Carlos Diaz[4], Amir Inamdar[5], Shishuka Malhotra[6], Denise Milovan[1], Collin Price[7], Claire Roberts[8], Joyce Tsai[9], Berra Yazar-Klosinski[10]*

[1]*Altasciences,* [2]*Neokee Pharma Consulting LLC,* [3]*NTH Consulting Inc.,* [4]*GeoSera,* [5]*Cybin,* [6]*Neuro-Behavioral Clinical Research Inc,* [7]*UCLA; West LA VA Medical Center,* [8]*Beckley Psytech Ltd.,* [9]*Independent,* [10]*Lykos Therapeutics*

Abstract Introduction: Psychedelics' unique pharmacological properties necessitate adaptations in Human Abuse Potential (HAP) study methodology to assess their pleasurable and reinforcing effects. To date, no formal HAP study has been conducted for FDA drug approval purposes. These studies, typically double-blind, randomized, crossover single-dose, placebo- and active-drug controlled, are designed to evaluate abuse potential in non-dependent recreational drug users. They assess subjective effects using various endpoints, including the maximum Drug Liking score on a bipolar visual analog scale (VAS), with secondary measures such as overall drug liking, desire to take the drug again, and adverse events (AEs), including abuse-related AEs.
Psychedelics present challenges in HAP studies due to their mixed positive and negative effects, which can increase endpoint variability, compromise validity, and complicate data interpretation. Functional unblinding, resulting from the perceptual distortions often induced by psychedelics, further complicates these studies. Consequently, HAP methods must be adapted for psychedelic substances.

Methods: A working group of clinical trial experts reviewed the 2017 FDA guidance on HAP studies and explored its application to psychedelics. Meetings focused on identifying limitations in current methods and proposing revisions to study endpoints, dose selection, identification of active controls, blinding, and safety oversight.

Results: The working group proposed several adaptations to better evaluate novel psychedelics in HAP studies. Dose selection should prioritize safety, with an emphasis on avoiding supratherapeutic levels if their inclusion is deemed unnecessary or unsafe. Including a minimally effective dose in the qualification phase may reduce expectancy effects and functional unblinding. During treatment, a range of therapeutic doses, from minimal to maximum, could further mitigate these issues and help establish dose-response relationships. Until other psychedelics are FDA-approved, positive controls may be limited to ketamine or dextromethorphan. While the bipolar VAS for Drug Liking has not been used with psychedelics, it may also have limited predictive validity; instead the Take Drug Again VAS may be a suitable primary endpoint substitute. Statistical adaptations may be needed to ensure validity, including considering a lower margin for primary endpoint differences between the positive control and placebo. Monitoring participants should focus on safety, given the healthy volunteer population without neuropsychiatric conditions, to minimize bias and promote consistency.

Conclusions: HAP studies for psychedelics require methodological modifications to address their unique pharmacological properties. Study endpoints, analysis, and data interpretation must account for the variability in subjective responses. Dose selection, positive controls, blinding, and monitoring interventions will also need to be carefully tailored to ensure valid results.

T22. EFFECTS OF SGLT2 INHIBITORS ON LITHIUM-ASSOCIATED KIDNEY DYSFUNCTION IN PATIENTS WITH MOOD DISORDERS: A HISTORICAL COHORT PROOF-OF-CONCEPT STUDY

Mete Ercis[1], Idil Tarikogullari[1], Vanessa Pazdernik[1], Maria L Gonzalez Suarez[1], Raman Baweja[2], Osama A. Abulseoud[3], Jonathan Leung[3], Ashok Seshadri[1], Susan McElroy[3], Alfredo Cuellar-Barboza[4], Michael Gitlin[5], Aysegul Ozerdem[1], Mark A. Frye[1], Balwinder Singh[1]*

[1]Mayo Clinic, [2]Penn State College of Medicine, [3]Lindner Center of HOPE/University of Cincinnati College of Medicine, [4]Universidad Autónoma de Nuevo León, Monterrey, [5]Geffen School of Medicine at UCLA

Abstract Background: Nearly one in five individuals in the U.S. will be diagnosed with a mood disorder in their lifetime. Lithium remains a cornerstone treatment for bipolar disorder and a key augmentation strategy for major depression, yet its prescription rates remain low due to concerns about its association with chronic kidney disease (CKD) with long-term use. Sodium-glucose cotransporter-2 inhibitors (SGLT2i), initially developed for type 2 diabetes, have demonstrated efficacy in slowing CKD progression in both diabetic and non-diabetic patients. However, their effectiveness in patients with mood disorders and their impact on lithium-associated CKD remain unknown. Clinicians often discontinue lithium in patients who develop CKD (prevalence: 10-15%) due to concerns about kidney function decline, which can lead to mood destabilization. This is the first study to examine the impact of SGLT2i therapy on estimated glomerular filtration rate (eGFR) trajectory in patients with mood disorders who had received long-term lithium therapy.

Methods: This historical cohort study included patients with mood disorders receiving care at Mayo Clinic, Rochester, between 2001 and 2023 who had been on long-term lithium therapy (≥6 months of lithium exposure before SGLT2i initiation) and had at least one month of SGLT2i treatment. Data on SGLT2i initiation, duration of SGLT2i use, and lithium use were individually abstracted from electronic health records, while all available serum creatinine values were extracted using automated queries. eGFR was calculated using the 2021 CKD-EPI creatinine equation from all available serum creatinine measurements. eGFR trajectory analysis was limited to the 10 years before SGLT2i initiation, with no restriction on follow-up duration thereafter. Linear mixed-effects models with a piecewise linear spline (knot set at SGLT2i initiation date) were used to estimate eGFR slopes before and after SGLT2i initiation, adjusting for age and sex, with random effects for intercepts and slopes.

Results: A total of 56 patients (46.4% female, mean age 57.38 ± 12.67 years) with mood disorders, primarily bipolar disorder (85.7%), were included. The mean eGFR prior to SGLT2i initiation was 77.87 ± 25.98 mL/min/1.73 m². Most of the patients had a diagnosis of type 2 diabetes (89.3%) and hypertension (78.6%). Older age at SGLT2i initiation was associated with uniformly lower eGFR trajectory (β = -1.22, 95% CI: -1.60 to -0.84, $p < 0.001$). Prior to SGLT2i initiation, patients exhibited a significant decline in eGFR, with a mean slope of -1.43 mL/min/1.73 m² per year (95% CI: -2.01 to -0.86, $p < 0.001$). Following SGLT2i initiation, the eGFR trajectory significantly improved, with a change of +1.93 mL/min/1.73 m² per year (95% CI: 0.01 to 3.84, $p = 0.049$). The post-SGLT2i mean slope was +0.49 mL/min/1.73 m² per year (95% CI: -1.15 to 2.16, $p = 0.56$). Sensitivity analyses restricted to patients on lithium at the time of SGLT2i initiation (n = 22) or those with > 1 year of SGLT2i use (n = 30) showed similar improvements in eGFR trajectory, though these findings were not statistically significant.

Conclusions: In this novel proof-of-concept study, SGLT2i initiation was associated with a significant improvement in eGFR trajectory among patients with mood disorders who

received long-term lithium therapy. These findings suggest that SGLT2is may be a potential strategy for mitigating lithium-associated CKD. Urgent randomized controlled trials are warranted to validate these findings and determine the long-term efficacy and safety of SGLT2is in this population.

T23. EVIDENCE-BASED DOSING OF BREXPIPRAZOLE IN PATIENTS WITH AGITATION ASSOCIATED WITH DEMENTIA DUE TO ALZHEIMER'S DISEASE: AN EXPOSURE–RESPONSE ANALYSIS

Christoph Correll[1], Yanlin Wang[2], Sanjeda Chumki[2], David Wang[3], Arash Raoufinia[2], Jogarao Gobburu[4], Pedro Such[5], Amita Patel[6]*

[1]The Zucker Hillside Hospital, The Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Charité Universitätsmedizin, Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, [2]Otsuka Pharmaceutical Development and Commercialization, Inc., [3]Lundbeck LLC, [4]Pumas-AI Inc., [5]H. Lundbeck A/S, Valby, [6]Joint Township District Memorial Hospital; Private Practice

Abstract Background: Agitation is a common and treatable neuropsychiatric symptom associated with dementia due to Alzheimer's disease, which substantially impacts patients' quality of life and burden on caregivers. Achieving the right treatment at the right dose is critical to ensuring meaningful improvement, while minimizing risks associated with suboptimal treatment, particularly in this vulnerable population. In the US, brexpiprazole is approved for the treatment of agitation associated with dementia due to Alzheimer's disease, at doses of 2 or 3 mg/day. However, in practice, there may be hesitancy to dose brexpiprazole above 1 mg/day. The present analysis aimed to support evidence-based dosing of brexpiprazole in this patient population, through an exposure–response analysis.

Methods: Data were analyzed from Trial 283 (NCT01862640) and Trial 213 (NCT03548584) – two Phase 3, 12-week, placebo-controlled trials, conducted in the US, Europe, and Russia. In Trial 283, patients were randomized 1:1:1 to brexpiprazole 1 mg/day, brexpiprazole 2 mg/day, or placebo (a fourth arm [brexpiprazole 0.5 mg/day] was removed in a protocol amendment). In Trial 213, patients were randomized 2:1 to brexpiprazole (further randomized 1:2 to 2 mg/day or 3 mg/day), or placebo. In the trials, improvement in the frequency of agitated behaviors was observed for brexpiprazole 2 mg/day and 3 mg/day versus placebo, but not for 1 mg/day versus placebo. Patients were included in the present exposure–response analysis if they had evaluable pharmacokinetic (PK) data (for brexpiprazole-treated patients), and baseline and Week 12 Cohen-Mansfield Agitation Inventory (CMAI) data (primary outcome measure). The average blood concentration at steady state was predicted for each patient using a population PK model. Efficacy was evaluated by percentage change from baseline in CMAI Total score at Week 12. An exposure–response analysis using a sigmoid Emax model characterized the relationship between average blood concentration and percentage change from baseline in CMAI Total score.

Results: A total of 608 patients were included in the exposure–response analysis. The model adequately demonstrated the effect of brexpiprazole exposure on percentage change from baseline in CMAI Total score at Week 12. For the brexpiprazole 1 mg dose, the resulting

blood concentration was lower than the level required to achieve the half-maximal effect on the CMAI Total score. For brexpiprazole 2 mg and 3 mg, the resulting blood concentration exceeded the level required to achieve the half-maximal effect on the CMAI Total score. Model-predicted percentage change from baseline in CMAI Total score plateaued beyond the 3 mg dose, indicating no further increase in efficacy beyond this dose.

Conclusion: Supportive of clinical trial results, the exposure–efficacy analysis demonstrated a dose–response relationship for brexpiprazole in patients with agitation associated with dementia due to Alzheimer's disease. Brexpiprazole dosed at 2–3 mg/day is expected to achieve meaningful reduction in agitation frequency, while brexpiprazole 1 mg/day is unlikely to be effective in reducing frequency of agitation. These findings should be considered when selecting appropriate treatment for individual patients.

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T24. DEVELOPMENT OF DEUTERATED ANALOGUES OF PSYCHEDELICS FOR THE TREATMENT OF MENTAL HEALTH CONDITIONS

*Amir Inamdar**[1]

[1]*Cybin Inc*

Abstract: At Cybin, we are developing differentiated, next-generation therapeutics with the potential to improve clinical outcomes and address key unmet needs for people with mental health conditions. We are developing intermittent treatments with potential rapid-onset, long-lasting clinical efficacy in treating depression and anxiety. Unlike current treatments that only address symptoms, our therapies target underlying causes in neural circuitry that lead to mental health disorders.
The two clinical programs (CYB003 and CYB004) are currently being developed at Cybin.

CYB003 is a synthetic, deuterated isotopomer of psilocin, the active metabolite of psilocybin which is a natural product produced by numerous species of Psilocybe mushrooms. In humans, psilocin is an agonist of a variety of serotonin receptors, most importantly the 5-HT2A receptor, through which it is believed to exert it's therapeutic effects. CYB003 is being developed as an adjunctive to antidepressants in the treatment of patients suffering from major depressive disorder who are inadequately responding to their ongoing treatment. A seamless Phase 1/2 study (CYB003-001) was designed to evaluate safety, tolerability, and therapeutic efficacy of ascending doses of CYB003. In this study patients suffering from moderate to severe MDD (scoring ≥21 on the Montgomery-Åsberg Depression Rating Scale (MADRS)) who were inadequately responding to their ongoing antidepressant treatment, were enrolled in a double-blind, randomized, placebo-controlled manner across three cohorts with 12 patients per cohort. 36 MDD patients were randomized to placebo or CYB003 at a 1:3 ratio for the first dose, with all patients receiving CYB003 as the second dose. Doses

were administered 3 weeks apart. MADRS scores were collected at baseline and up to 16 weeks after the first dose to assess acute and medium-term (Day 126) efficacy. To further evaluate the durability of effect of two doses of CYB003 up to 12 months, a follow-up study (CYB003-001b) was initiated for patients who had completed the CYB003-001 study.

The primary endpoint for the efficacy assessment was the change from baseline in MADRS total score. A responder analysis (improvement of at least 50%) and the number of subjects going into remission (MADRS scores of 10 or below) was performed after unblinding at Days 21, 42, and 126., 270 and 364.

CYB003 demonstrated a favorable safety profile. Adverse effects were mild or moderate and mostly self-limiting, and no severe or serious AEs occurred.

CYB003 showed a rapid improvement with a difference of 14 points on the MADRS total score compared to the placebo-group, leading to a clinically meaningful effect size of 2.15 (P=0.0005) at the end of the double-blind phase (Day 21) for the 12 mg dose. Similar results were obtained in the 16 mg dose group with a difference of 13-point improvement over placebo (Effect size 2.54, P=0.008).

This resulted in a response rate of 53.3% and 44.4% and a remission rate of 20% and 22.2%, compared to 0% response and remission in the placebo group for the 12 mg and 16 mg groups, respectively, at the end of the double-blind phase (Day 21).

A second dose of CYB003 on Day 22 led to further improvement of the response and remission rates for the 12 mg (78.6% and 78.6%) and 16 mg (75% and 50%) groups, respectively, 3 weeks after a 2nd dose (Day 42).

Based on these data, the FDA granted CYB003 a breakthrough therapy status.

Long term efficacy was assessed in the follow-up study (CYB003-001b) with clinical and safety assessments at Days 270 and 364. Of the 36 eligible participants, 21 provided informed consent and were followed up to 12 months from the time of initial dosing. Participants who had received 2 doses of 12 mg CYB003 demonstrated a reduction in total MADRS scores of 18 points at 12 months and those administered 16 mg CYB003 had a reduction of 23 points. Response rates were 60% and 100% at 12 months and remission rates were 50% and 71% for those receiving 2 doses of 12 mg and 16 mg, respectively. There were no AEs reported, nor any instances of suicidal ideation or behavior as assessed by the Columbia Suicide Severity Rating Scale in the long term follow up.

A phase 3 development program for CYB003 has been initiated and is underway.

Our second program, CYB004, is a deuterated analog of dimethyl tryptamine (DMT) and we have conducted a series of clinical studies that have explored the PK, PD, and safety of DMT and CYB004 in healthy participants and patients with MDD.

CYB004E (Parts A, B, and C) explored the PK, PD, and safety of DMT and CYB004 in a series of studies.

CYB004E Part A evaluated safety, PK and PD of a 90-minute infusion of DMT in healthy smokers at dose levels of 0.12 mg/kg, 18.2, 36.4, and 72.8 mg DMT hemifumarate and recruited 38 participants across 4 cohorts. DMT was well tolerated; all adverse events (AEs) were mild and self-limiting. Statistically significant effects ($p < 0.0001$) were observed at

72.8 mg on the Mystical Experiences Questionnaire-30 (MEQ-30) total score, visual analogue scale (VAS) feeling high, hallucinogen rating scale (HRS) subscales cognition, intensity, perception and somaesthesia. We concluded that the rate at which Cmax is attained contributes to the psychedelic effects.

CYB004E Part B evaluated DMT IV as a bolus over 5 min followed by an infusion over 55 min, in an open label, fixed order, 2-way crossover rising dose design in healthy participants. An infusion rate of 18.2 mg in 5 min + 44.5 mg in 55 min IV was selected to provide a mean steady state DMT concentration of approximately 40 ng/mL, a concentration level that was reported previously in the literature to be associated with robust psychedelic effects. Doses for the second treatment period (18.2 mg in 5 min + 71.2 mg in 55 min IV) were selected based on safety, PK and PD data from the first dosing period. 10 healthy non-smokers were enrolled in Part B. Intense psychedelic effects were reported by subjects during the 5-minute bolus and were sustained during the infusion, with effects in Part B being more intense compared to Part A.

Part C was a first-in-human dosing of deuterated DMT (CYB004) in healthy volunteers (n=12) evaluating IV dosing regimens (5 min bolus ± 30 min infusion). Intense psychedelic effects were reported by subjects for about 40 min after the stop of the infusion and these effects correlated with the plasma concentrations of CYB004.

Based on these data, CYB004 is being evaluated in patients with generalized anxiety disorder.

These data, the phase 3 plan for CYB003 and the development pipeline will be presented at the conference.

T25. TARGETING THE KCNQ (A.K.A., KV7) POTASSIUM CHANNEL AS A NOVEL TREATMENT FOR DEPRESSION AND ANHEDONIA: INITIAL RESULTS: FROM A RANDOMIZED, CONTROLLED TRIAL OF XEN1101 VS. PLACEBO IN ADULTS WITH MAJOR DEPRESSIVE DISORDER

James Murrough[*1], Rachel Freemont[1], Jessica Ables[1], Philipp Neukam[1], Usha Govindarajulu[1], Helena Chang[1], Sara Hameed[1], Marcella Corwin[1], Mackenzie Hargrove[1], Laurel Morris[1], Sanjay Mathew[2]*

[1]Icahn School of Medicine at Mount Sinai, [2]Baylor College of Medicine

Abstract Background: Basic research suggests that enhancing signaling at KCNQ (a.k.a., Kv7) type potassium channels in the brain may represent a promising new strategy for drug discovery for depression and related conditions. Our group previously conducted a randomized, controlled trial (RCT) of the KCNQ2/3-preferring positive allosteric modulator (PAM) ezogabine in adults with major depressive disorder (MDD) and elevated levels of anhedonia. In that study, individuals randomized to ezogabine showed improvements in depression and anhedonia compared to placebo. Herein, we report the first clinical results from a new RCT comparing the novel selective Kv7 PAM XEN1101 to placebo in adults with MDD.

Methods: Adults with MDD in a current major depressive episode with elevated levels of anhedonia who met all eligibility criteria were randomized 1:1 under double-blind conditions

to XEN1101 20 mg or matching placebo daily for eight weeks. Change over time in response to reward during functional magnetic resonance imaging compared between XEN1101 and placebo represents the primary outcome. Change over time compared between XEN1101 and placebo on depression severity measured every two weeks by the Montgomery-Åsberg Depression Rating Scale (MADRS) and anhedonia measured by the Snaith-Hamilton Pleasure Scale (SHAPS) represent the key secondary outcomes. A two-sided alpha level was set at 0.10 for each specified test.

Results: Of 60 participants, 29 were randomly assigned to XEN1101 and 31 to placebo.

T26. REDUCED DEPRESSIVE SYMPTOMS AFTER A SINGLE TREATMENT WITH MM120 (LYSERGIDE) IN PATIENTS WITH GENERALIZED ANXIETY DISORDER PRESENTING WITH COMORBID DEPRESSIVE SYMPTOMS

Todd Solomon, PhD[1], Paula L. Jacobsen, PhD[1], Sarah M. Karas, PsyD[1], Jamie M. Freedman, BS[1], Daniel R. Karlin, MD, MA[2]*

[1]Mind Medicine Inc., [2]Mind Medicine Inc., Tufts University of Medicine

Abstract Introduction: Generalized anxiety disorder (GAD) and major depressive disorder (MDD) are serious, chronic conditions and leading causes of disease burden worldwide. Both GAD and MDD are also associated with significantly reduced psychosocial functioning and quality of life and increased risk of suicidality. Symptoms of GAD and MDD clinically overlap.1 Current GAD and MDD treatments often have limited efficacy and struggle to balance quality of life decisions with treatment related side effects. Effective and well-tolerated pharmacotherapies are needed for both disorders. A phase 2b study of the dose-response to a single treatment MM120 (lysergide D-tartrate) suggests a safe, rapid, and durable dose-dependent response in participants with moderate-to-severe GAD.2 In this post hoc analysis, MM120 treatment-related outcomes were explored for participants with high depressive symptom scoring at baseline screening.

Methods: This phase 2b (NCT05407064) multicenter, randomized, double-blind, placebo-controlled study enrolled adults aged 18 to 74 years with moderate-to-severe GAD.2 The Montgomery-Åsberg Depression Rating Scale (MADRS) was collected as a secondary endpoint. Post hoc analyses examining MADRS change from baseline were performed using a subset of participants with moderate-to-severe GAD receiving 100µg MM120 and with a baseline MADRS > 26 and at least one post-baseline MADRS. Definitionally, these participants had comorbid depressive symptoms in the upper range of moderate to severe.

Results: In total, 198 participants were enrolled in the study, and 115 of these had a baseline MADRS > 26. Prespecified analysis of the 40 total participants who were randomized to receive 100µg MM120, with a mean baseline MADRS of 26.5 ± 8.0, showed placebo-adjusted reductions in MADRS of 5.7 ($P < 0.05$) and 6.4 ($P \leq 0.05$) and mean change from baseline scores of -18.1 ± 12.0 and -18.7 ± 11.5 at weeks 4 and 12. Twenty-two participants, who were randomized to the 100µg group, had a baseline MADRS score of 32.5 ± 4.6 and a mean change from baseline of -23.3 ± 11.3 and -25.0 ± 9.2 at weeks 4 and 12. A mixed method model with repeated measures analysis demonstrated least square mean changes in baseline MADRS of -23.6 (95% CI: -28.5 to -18.7, $P < 0.001$) and -25.4 (95% CI: -30.2 to -

20.6, P < 0.001) at weeks 4 and 12, respectively. Within the full safety set, treatment-emergent adverse events (TEAEs) occurred in 97.5% of participants in the MM120 100μg group versus 56.4% in the placebo group. Most events were mild to moderate, occurred on dosing day, and were consistent with the expected acute effects of MM120. One serious AE occurred, and no deaths were reported in the study.

Conclusion: MDD and GAD have overlapping symptoms. A single treatment of MM120, provided without psychotherapy, demonstrated efficacy in reducing depressive symptoms in participants diagnosed with moderate to severe GAD with no identified safety concerns. Increased reduction in depressive symptoms was shown in participants with higher baseline symptom burden. These analyses suggest efficacy for the reduction of depressive symptoms and support the initiation of a phase 3 development program for MM120 in MDD.

T27. KETAMINE FOR DEPRESSION, BUT AT WHAT COST? A REVIEW OF KETAMINE'S NEUROTOXIC EFFECTS FROM PRECLINICAL AND HUMAN STUDIES

Kristina Kumpf[*1], S. William Li[2], Julian Urrutia Ripoll[2], John Krystal[2], Gerard Sanacora[2], Samuel Wilkinson[2]*

[1]Yale University, Child Study Center, [2]Yale University School of Medicine

Abstract Importance: Ketamine, an N-methyl-D-aspartate antagonist, has emerged as an effective, off-label interventional treatment for a range of psychiatric conditions including treatment resistant depression. Despite robust evidence for efficacy, regulatory entities remain concerned about the neurotoxic risk of exposures in excess of 8 lifetime doses of 60mg for research studies in adults. However, as ketamine is used off-label for psychiatric applications, there is a high degree of variability in the dose and frequency of ketamine treatment in clinical settings, raising questions regarding the risk of neurotoxicity.
Objective: Here we examine ketamine's neurotoxic potential across preclinical and clinical studies to inform clinicians and advise researchers of where critical knowledge gaps exist.

Evidence Review/Results: We synthesized data from preclinical models, then integrated findings from human clinical trials of esketamine and observational studies in recreational users. Animal studies indicate that repeated or high dose subanesthetic ketamine resulted in consistent excitotoxic neuronal damage and lasting cognitive deficits, especially in younger subjects. Moderate, infrequent subanesthetic doses do not yield overt histopathology in animal models. In humans, observational studies in frequent high-dose (> 1g/day) ketamine users show memory and executive-function impairments. In contrast, a large clinical trial of intranasal esketamine at doses up to 84mg, administered weekly or biweekly for several years, is associated with maintained or slightly improved higher cognitive function. Lower cognitive function (attention, processing speed) showed some worsening, especially in elderly patients; the significance of this finding is unknown. Direct comparisons of esketamine and off-label racemic ketamine at higher doses have not been done.

Conclusions: These evidence underscores the potential for neurotoxic effects when ketamine is used at doses or frequencies beyond those utilized in clinical trials, highlighting a critical need for robust, longitudinal research. Clinicians are advised to exercise caution, particularly

when prescribing racemic ketamine off-label at doses significantly higher than those used in clinical trials. When deviating from this in clinical practice, strong consideration should be given to conducting repeated cognitive assessments. Funding agencies should incentivize preclinical researchers to conduct studies that further elucidate the threshold of ketamine's neurotoxicity.

T28. A PHASE 1 DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED, SINGLE AND MULTIPLE ASCENDING DOSE STUDY OF THE SAFETY, PHARMACOKINETICS, AND PHARMACODYNAMICS OF THE NOVEL THYROMIMETIC ABX-002 IN HEALTHY ADULT PARTICIPANTS

Bridgette Franey[*1], Ashlee Heldreth[1], Heather Smith[1], Jason Everett[1], Alida Barry[1], Jason Harris[1], Jihao Zhou[1], Tom Scanlan[2], Jeffrey Vivian[1], Gudarz Davar[1]*

[1]Autobahn Therapeutics, [2]Oregon Health and Science University

Abstract: Major depressive disorder (MDD) is one of the leading causes of disability, impacting 280 million people around the world. The current pharmacological standard of care for MDD is the use of selective serotonin and serotonin-norepinephrine reuptake inhibitors (SSRI/SNRIs). However, more than 50% of patients receiving SSRI/SNRIs will have an inadequate response to their first and second antidepressant monotherapies and continue to experience clinically significant symptoms, resulting in the need to switch treatments or augment current treatment with additional pharmaceutical agents. Two such augmentation agents are the thyroid hormones (TH) triiodothyronine (T3) and thyroxine (T4). While T3 and T4 have demonstrated efficacy as adjunctive treatments for MDD, these hormones have a very narrow therapeutic range limited by tolerability and safety concerns. ABX-002 is a novel CNS-targeted prodrug exerting its effects through the active metabolite and thyroid hormone partially beta-receptor (TRβ) preferring agonist, LL-340001. With its preferential CNS distribution, ABX-002 may augment the clinical response of patients with MDD who have had an inadequate response to their antidepressant treatment. ABX-002 and its active metabolite, LL-340001, were studied for safety, tolerability, plasma pharmacokinetics (PK) and pharmacodynamics (PD) in a Phase 1, first-in-human (FIH), randomized, double-blind, placebo-controlled study in healthy adult participants. For both single ascending dose (SAD) and multiple ascending dose (MAD) portions of the study, ABX-002 was safe and well-tolerated up to the highest doses tested of 150 and 5.6 µg, respectively. No participants discontinued related to safety or adverse events. No serious adverse events (SAEs) or deaths were reported. There were no changes of clinical relevance observed in clinical laboratory tests, vital signs, physical examinations, electrocardiogram (ECG) and electroencephalogram (EEG) parameters, or in ophthalmic monitoring. Specific to TH class-related effects, thyroid stimulating hormone (TSH) was transiently reduced at the 150 µg single dose. Clinical evidence of CNS target-engagement after administration of ABX-002 was demonstrated in the MAD; specifically, there were modest (Grade 2 TEAEs), tolerable and reversible mood-altering effects at 5.6 µg, consistent with effects described for overtreatment with thyroid hormone medication. ABX-002 is being developed as an adjunctive treatment of mood disorders including MDD and depressive episodes associated with bipolar disorder (BD). With its tolerability profile observed to date, and preferential CNS distribution and partial TRβ selectivity, ABX-002 has the potential to differentiate from TH and standard of care

(e.g., atypical antipsychotics), while augmenting the clinical response of patients with MDD or BD who have failed to respond adequately to their current therapies. Data from this FIH study revealed ABX-002 to be well-tolerated up to and including single oral doses of 150 µg and support further development of ABX-002 in the treatment of depressive illness.

T29. DEVELOPMENT OF A MACHINE LEARNING MODEL FOR ESTIMATING CGI-I SCORES USING ELECTRONIC MEDICAL RECORDS FROM REAL-WORLD DATA SOURCES

Stevan Severtson[1], Pedro Alves[1], Costas Boussios[1], Carl Marci[1]*

[1]OM1, Inc.

Abstract Background and Rationale: The Clinical Global Impression Scale - Improvement (CGI-I) is a widely used clinician-reported measure of change in a patient's symptoms over time. The CGI-I is used in both clinical trials and real-world settings to evaluate treatments for patients with major psychiatric disorders. Consistent capture of the CGI-I over time is useful for evaluating treatment effectiveness. However, documentation of the CGI-I is inconsistent in real-world data (RWD) sources such as electronic medical records (EMRs). This limits the potential role of these RWD sources for supporting large, heterogeneous effectiveness studies. This study applied machine learning methods to fill in missing data in three RWD cohorts.

Methods: A machine learning model was developed to generate estimated CGI-I (eCGI-I) scores for clinical encounters. Training data were drawn from the OM1 Mental Health Specialty Network, an EMR data source from mental health specialists across the United States. Patient encounters with both recorded CGI-I scores and clinical notes from mental health specialists were identified and randomly assigned to a training cohort (n=1,971,155) using an extreme gradient boosting (XGBoost) model. Information from each encounter and the previous encounter was used to estimate each CGI-I score. Encounters used to generate an estimated score were filtered to eliminate those with low levels of clinically relevant features. A validation cohort (n=29,921) was drawn from patient encounters from three condition specific datasets (OM1, Boston, MA) – they include major depressive disorder, bipolar I disorder, and schizophrenia. These datasets are continuously updated subsets of patients within the OM1 Mental Health Specialty Network who have linked claims and EMR data. To assess model performance, the area under the receiver-operating-characteristic curve (AUC) was calculated using a binarized version of the outcome. The binary outcome was a score of > =4 (unchanged or worsening) compared to scores < 4 (improving). Continuous eCGI-I scores were evaluated using Spearman's and Pearson's correlation coefficients.

Results: The model had an AUC of 0.71 when evaluating performance using the binarized version of the outcome in the validation cohort, a Spearman's r value of 0.40 and a Pearson's r value of 0.38 when evaluating performance using continuous scores. When applied to the encounters among patients with conditions of interest, there were 2.5x the number of CGI-I scores and 3.9x the number of patients with scores or 3,061,625 additional scores added (for a total of 5,164,898 encounters with recorded or estimated CGI-I scores).

Conclusions: A machine learning model can estimate CGI-I scores using information routinely recorded in EMR clinical notes from mental health professionals. Use of the model could provide a more complete view of changes in a patient's symptoms over time across multiple diagnoses. At the population level, application of the model to RWD sources increases the number of patient encounters with outcomes and expands available RWD patients for psychiatric research.

T30. ADJUNCTIVE LUMATEPERONE IN PATIENTS WITH MAJOR DEPRESSIVE DISORDER: RESULTS: FROM AN ADDITIONAL RANDOMIZED, DOUBLE-BLIND, PHASE 3 TRIAL

Willie Earley[*1], Suresh Durgam[1], Susan G. Kozauer[1], Yifan Mo[1], Hassan Lakkis[1], Renee Rotolo[1], Susan G. Kornstein[2], Maurizio Fava[3]*

[1]Intra-Cellular Therapies, Inc., [2]Virginia Commonwealth University School of Medicine, [3]Massachusetts General Hospital and Harvard Medical School

Abstract Background: Lumateperone is an FDA-approved antipsychotic for schizophrenia and bipolar depression. This Phase 3, randomized, double-blind, placebo-controlled, multicenter trial (NCT05061706) investigated adjunctive lumateperone 42mg in patients with major depressive disorder (MDD) with inadequate antidepressant therapy (ADT) response.
Methods: Eligible adult outpatients (18-65 years) met DSM-5 criteria for MDD with inadequate response to 1-2 ADT in the current depressive episode (< 50% improvement on the Antidepressant Treatment Response Questionnaire) and Montgomery-Asberg Depression Rating Scale (MADRS) Total score ≥24, Clinical Global Impression Scale-Severity (CGI-S) score ≥4, and Quick Inventory of Depressive Symptomatology-Self Report-16 item (QIDS-SR-16) score ≥14. Patients were randomized to 6-week placebo or lumateperone 42mg adjunctive treatment to ADT. Primary and key secondary endpoints were change from baseline to Day 43 in MADRS Total score and CGI-S score, analyzed using a mixed-effects model for repeated measures. Additional measures included response (≥50% MADRS Total score decrease), remission (MADRS Total score ≤10), and change from baseline in QIDS-SR-16 Total score. Safety assessments included adverse events (AEs), vital signs, laboratory parameters, and extrapyramidal symptoms.

Results: Of 480 patients (placebo, 238; lumateperone, 242), 89% completed treatment. Mean age was 46 years, 70% were women, and 95% were White. Primary and key secondary endpoints were met with significant improvement for adjunctive lumateperone vs placebo from baseline to Day 43 in MADRS Total score (least squares mean difference vs placebo [LSMD]=−4.5; effect size [ES]=−0. 56; P < .0001) and CGI-S (LSMD=−0.5; ES=−0.51; P < .0001). Rates of MADRS Total score response (placebo, 25%; lumateperone, 40%; P < .01) and remission (placebo, 14%; lumateperone, 25%; P < .01) were significantly greater with lumateperone vs placebo at Day 43. Adjunctive lumateperone significantly improved self-reported depressive symptoms at Day 43 vs placebo, as measured by QIDS-SR-16 Total score (LSMD=−2.2; P < .0001). Adjunctive lumateperone was relatively well-tolerated, consistent with prior studies. The most common treatment-emergent AEs with lumateperone

(≥5% and twice placebo) were dizziness, somnolence, dry mouth, nausea, diarrhea, and fatigue. AEs were mostly mild or moderate.

Conclusion: Lumateperone 42mg adjunctive to ADT demonstrated robust, clinically meaningful efficacy over adjunctive placebo to ADT and was generally safe and well-tolerated, indicating lumateperone is a promising treatment as adjunctive therapy to ADT to treat MDD in adults.

T31. CHARACTERISTICS OF AKATHISIA WITH LONG-TERM ADJUNCTIVE CARIPRAZINE TREATMENT IN PATIENTS WITH MAJOR DEPRESSIVE DISORDER: POST HOC ANALYSES OF A PHASE 3 OPEN-LABEL TRIAL

Rakesh Jain[1], Jun Yu[2], Simranpreet Waraich[2]*

[1]Texas Tech University School of Medicine -- Permian Basin, [2]AbbVie,

Abstract Introduction: Akathisia is among the most common adverse events associated with dopamine receptor blocking agents, often leading to discontinuation of treatment. Cariprazine is a dopamine D3-preferring D3/D2 receptor partial agonist and serotonin 5-HT1A receptor partial agonist approved to treat schizophrenia and acute manic, mixed, and depressive episodes of bipolar I disorder; it is also approved as an adjunctive treatment for major depressive disorder (MDD). In an 8-week, double-blind, placebo-controlled, phase 2 study that demonstrated efficacy and safety of adjunctive cariprazine in adult patients with MDD, akathisia was the most frequently reported treatment-emergent adverse event (TEAE), though discontinuation rates due to the TEAE were low (< 5.0% in any treatment group). A subsequent open-label, phase 3 study was conducted to evaluate the long-term safety and tolerability of cariprazine in patients with MDD. Post hoc analyses of data from this long-term study aimed to characterize akathisia associated with long-term use of adjunctive cariprazine in patients with MDD.

Methods: A 26-week, phase 3, multi-center, open-label, flexible-dose (1.5 – 4.5 mg/day) study (NCT01838876) assessed the long-term safety and tolerability of cariprazine treatment used adjunctively with antidepressant therapy (ADT) in adult patients with MDD who completed an 8-week lead-in study (NCT01715805) or were newly recruited. These analyses evaluated the incidence, severity, time to onset, and time to resolution of akathisia. The discontinuation rate due to a TEAE of akathisia and rate of rescue medication use for akathisia were also determined.

Results: Of the 345 patients who received cariprazine + ADT in the phase 3 open-label study, 15.9% experienced akathisia; most of these patients experienced mild or moderate symptoms (98.2%). The mean (standard deviation [SD]) time to onset of akathisia was 24.2 (27.7) days. For patients whose akathisia resolved during adjunctive cariprazine treatment, the mean (SD) time to resolution was 31.6 (27.3) days. The discontinuation rate due to a TEAE of akathisia was 2.9%. Of the patients with akathisia, 16.4% initiated rescue medications for akathisia within the open-label treatment period.

Conclusions: In a 26-week, phase 3, open-label study, incidences of akathisia with adjunctive cariprazine use were generally mild or moderate in severity and infrequently resulted in discontinuation of treatment, suggesting that this adverse event could be managed with rescue medication. Time to resolution was on average approximately one month for

patients in whom akathisia resolved during treatment. Overall, data suggest that akathisia associated with long-term adjunctive cariprazine treatment was tolerated by patients, further supporting the favorable long-term safety profile of adjunctive cariprazine in patients with MDD.

T32. PSILOCYBIN THERAPY FOR CHRONIC SUICIDAL IDEATION: AN OPEN-LABEL STUDY

Andrew van der Vaart[*1], Audrey Shoultz[2], Bryce Lund[2], Tammy Miller[2], Jeffrey LaPratt[2], Scott Aaronson[1]*

[1]Sheppard Pratt Health System and University of Maryland School of Medicine, [2]Sheppard Pratt Health System

Abstract Background: Chronic suicidal ideation is a challenging symptom to treat with conventional approaches, often persisting despite adequate therapeutic interventions. Emerging evidence suggests that psychedelics, such as psilocybin, may provide rapid and sustained improvements in mood and related symptoms. This study explores the safety and efficacy of psilocybin therapy in individuals with chronic suicidal ideation.

Methods: Nineteen adults (11 male, 8 female; mean age 36.5 ± 11.4) with chronic suicidal ideation were recruited for this open-label pilot study. Participants received a single 25 mg dose of psilocybin (COMP360) following three preparatory therapy sessions. Post-treatment support included three integration sessions. Key efficacy measures included the Modified Scale for Suicidal Ideation (MSSI) and the Montgomery-Åsberg Depression Rating Scale (MADRS), assessed at baseline and across a 12-week follow-up period. Treatment effects were evaluated using linear mixed-effects models, with post-hoc comparisons employing Bonferroni correction.

Results: Significant reductions in MSSI and MADRS scores were observed at all post-treatment timepoints. At Week 12, 14 participants demonstrated complete or near-complete remission of suicidal ideation (MSSI ≤ 2). The effect sizes were robust (Cohen's $d \geq 1.75$ across timepoints). Improvements in depressive symptoms were strongly correlated with reductions in suicidal ideation ($r = 0.70$, $p = 0.001$). Adverse events were mild and transient, with no severe events reported.

Conclusions: In this open-label study, psilocybin therapy was associated with significant reductions in chronic suicidal ideation and depressive symptoms, with durable effects observed over 12 weeks. These findings highlight the potential of psilocybin as a novel therapeutic option for individuals with refractory suicidal ideation, warranting further investigation in controlled trials.

T33. LUMATEPERONE AS ADJUNCTIVE THERAPY IN PATIENTS WITH MAJOR DEPRESSIVE DISORDER AND ANXIOUS DISTRESS

Suresh Durgam[1], Willie R Earley[1], Susan G Kozauer[1], Changzheng Chen[1], Dennis Sholler[1], Gary S. Sachs[2]*

[1]*Intra-Cellular Therapies, Inc.*, [2]*Massachusetts General Hospital and Signant Health*

Abstract Background: Most patients with major depressive disorder (MDD; 54%-78%) have comorbid anxiety according to the DSM-5 anxious distress specifier. Patients with MDD and anxious distress have impaired psychosocial functioning, reduced quality of life, and poorer treatment response vs those without the specifier.
Lumateperone is an FDA-approved antipsychotic to treat schizophrenia and depressive episodes associated with bipolar I or II disorder. In a Phase 3, randomized, double-blind, placebo-controlled trial (Study 501; NCT04985942), adjunctive lumateperone 42mg was efficacious over placebo with a favorable safety profile in patients with MDD with inadequate antidepressant therapy (ADT) response. This analysis of Study 501 investigated efficacy of adjunctive lumateperone 42mg in patients who met DSM-5 criteria for anxious distress.

Methods: Eligible adults (18-65 years) met DSM-5 criteria for MDD with inadequate response to 1-2 ADT in the current major depressive episode and Montgomery-Asberg Depression Rating Scale (MADRS) Total score ≥24, Clinical Global Impression Scale-Severity (CGI-S) score ≥4, and Quick Inventory of Depressive Symptomatology-Self Report-16 item (QIDS-SR-16) score ≥14. Patients were randomized 1:1 to 6-week oral lumateperone 42mg or placebo adjunctive to ADT. Anxiety was assessed using Generalized Anxiety Disorder-7 (GAD-7) Total score. This analysis included patients meeting DSM-5 criteria for anxious distress. Change from baseline in MADRS Total score, CGI-S score, and patient-reported depression (QIDS-SR-16 Total score) were evaluated.

Results: Of 481 patients in the modified intent-to-treat population (mITT; lumateperone, 239; placebo, 242), 207 (43.0%) had anxious distress (lumateperone, 109; placebo, 98) at baseline. Lumateperone+ADT improved MADRS Total score from baseline to Day 43 vs placebo+ADT in patients with anxious distress (least squares mean difference vs placebo [LSMD]=−6.8; effect size [ES]=−0.85; $P < .0001$). Significantly greater ($P < .05$) MADRS Total score reductions occurred by Day 15 and persisted throughout the study with lumateperone+ADT. Lumateperone+ADT also significantly improved CGI-S score at Day 43 vs placebo+ADT (LSMD=−0.9; ES=−0.91; $P < .0001$), with significant ($P < .05$) reductions occurring by Day 22 and continuing throughout the study. Lumateperone+ADT significantly improved self-reported depression (QIDS-SR-16 Total score; LSMD=−3.7; ES=−0.80; $P < .0001$) at Day 43 vs placebo+ADT in patients with anxious distress. Patient-reported anxiety (GAD-7 Total score) improved at Day 43 vs placebo+ADT in the ITT (baseline mean: lumateperone+ADT, 9.9; placebo+ADT, 9.6; LSMD=−1.6; ES=−0.43; $P < .0001$) and subgroup with anxious distress (LSMD=−3.24; ES=−0.88; $P < .0001$).

Conclusions: Lumateperone 42mg adjunctive to ADT demonstrated efficacy in improving symptoms of depression and anxiety vs placebo adjunctive to ADT, indicating lumateperone as a promising adjunctive therapy to ADT in patients with MDD and anxious distress.

T34. EXAMINING THE IMPACT OF CHILDHOOD TRAUMA ON KETAMINE'S REAL-WORLD EFFECTIVENESS IN TREATMENT-RESISTANT DEPRESSION

Danica Johnson[1], Nelson Rodrigues[2], Rodrigo Mansur[1], Roger McIntyre[1], Joshua Rosenblat[1]*

[1]*University of Toronto,* [2]*University of Windsor*

Abstract Background: Childhood trauma is a well-established risk factor for the development and persistence of major depressive disorder (MDD), contributing to increased illness severity, chronicity, and resistance to standard antidepressant treatments. Intravenous (IV) ketamine has emerged as a rapid-acting and efficacious intervention for treatment-resistant depression (TRD), but the impact of childhood trauma on its effectiveness remains unclear. This study aimed to examine the impact of trauma load, type, and severity on the antidepressant effectiveness of ketamine in individuals with TRD, addressing a critical gap in the existing literature.

Methods: We conducted a retrospective analysis on adults (n = 83) who received four ketamine infusions at a community clinic to examine whether childhood trauma influences ketamine's antidepressant effectiveness in TRD. Trauma load (high vs. low) and specific trauma types were assessed using the Childhood Trauma Questionnaire (CTQ). Trauma severity was also rated on a 7-point Likert scale. Depressive symptoms were evaluated using the Quick Inventory of Depressive Symptomatology Self-Report 16-item (QIDS-SR16) at baseline and after each infusion. Linear mixed models (LMMs) assessed the effects of trauma load and specific trauma types on depressive symptom trajectories, while chi-square tests examined response (=50% reduction in QIDS-SR16) and remission rates (QIDS-SR16 =5). Pearson correlation analyses explored the relationship between trauma severity and antidepressant response.

Results: Depressive symptoms decreased significantly across participants over time (mean QIDS-SR16 reduction: 5.7 points, $p < .001$). High trauma load was reported by 55% of participants. Response rates were 25% in the high trauma group and 19% in the low trauma group, while remission rates were 14% and 11%, respectively. LMMs revealed no significant differences in depressive symptom trajectories between high and low trauma load groups ($p = .572$) or between individuals with specific trauma types and those without (all $p > .05$). Similarly, chi-square tests found no significant associations between trauma load and response ($p = .230$) or remission ($p = .397$). Trauma severity, assessed via Likert ratings, was not significantly correlated with antidepressant response ($r= .124$, $p= .266$).

Conclusion: These preliminary findings suggest that ketamine is an effective treatment for TRD, regardless of childhood trauma load, type, or severity. This highlights ketamine's potential utility in addressing depressive symptoms in populations burdened by significant trauma. Future research should focus on replicating these findings and identifying specific mechanisms that mediate ketamine's antidepressant effects in trauma-affected populations to further optimize its therapeutic potential.

T35. A NOVEL ARTIFICIAL INTELLIGENCE-BASED METHODOLOGY FOR PREDICTING NON-SPECIFIC RESPONSE TO TREATMENT IN MAJOR DEPRESSIVE DISORDER CLINICAL TRIALS

Clotilde Guidetti[1], Maurizio Fava[2], Paolo Manfredi[3], Marco Pappagallo[3], Roberto Gomeni[4]*

[1]*Massachusetts General Hospital, and Harvard Medical School,* [2]*Massachusetts General Hospital,* [3]*Relmada Therapeutics,* [4]*Pharmacometrica*

Abstract: Non-specific response to treatment (NSRT) is the primary contributor to the failure of randomized clinical trials in major depressive disorder (MDD). The objective of this study is to develop artificial neural network (ANN) models to predict the individual probability for NSRT. Pre-randomization data from a failed antidepressant trial were considered as potential predictors of the NSRT probability (prob-NSRT) using the response endpoint in subjects randomized to placebo. The inverse of the individual prob-NSRT (NSRT propensity score) was used as a weight in the mixed-effects model applied to assess treatment effect (TE). The comparison of the results obtained with and without the NSRT propensity score indicated that the weighted analyses provided an estimate of TE significantly larger than the conventional analyses. The propensity score weighted (PSW) analysis, adjusting for inter-individual variability in prob-NSRT, enhanced signal detection of TE. These findings support the potential role of PSW methodology for analyzing RCTs and determining TE.

T36. CHANGES IN SYMPTOMS OF ANHEDONIA WITH PSILOCYBIN-ASSISTED PSYCHOTHERAPY: A SECONDARY ANALYSIS OF A RANDOMIZED CLINICAL TRIAL FOR TREATMENT-RESISTANT DEPRESSION

Erica Kaczmarek[1], Nelson Rodrigues[2], Noah Chisamore[1], Zoe Doyle[3], Shakila Meshkat[1], Marc G Blainey[3], Ryan Brudner[1], Shaun Ali[3], Kayla M Teopiz[4], Roger S McIntyre[1], Joshua D Rosenblat[1]*

[1]*University of Toronto,* [2]*University of Windsor,* [3]*Independent Practice,* [4]*Brain and Cognition Discovery Foundation*

Abstract Background: Across all psychiatric disorders, anhedonia is associated with poorer outcomes, higher levels of functional impairment, impaired quality of life, and treatment non-response. Psilocybin assisted psychotherapy (PAP) has shown promising results for treatment resistant depression (TRD), however, specific effects on anhedonia have been minimally studied.

Methods: Participants (n=30) with a primary diagnosis of Major Depressive Disorder or Bipolar II Disorder received at least one 25 mg oral dose of synthetic psilocybin with accompanying psychotherapy as part of a randomized, waitlist controlled, clinical trial. The primary outcome of this analysis examined changes in anhedonia, measured through the Snaith-Hamilton Pleasure Scale (SHAPS). A linear regression was conducted to examine whether high baseline anhedonia (SHAPS) was correlated with antidepressant efficacy (changes in Montgomery-Asberg Depression Rating Scale (MADRS) scores at Week 2 primary endpoint).

Results: A significant reduction in SHAPS scores over time was observed, $t(28) = 4.088$, $p = < 0.001$, 95% confidence interval [1.548, 4.667], with a mean difference of 3.107 (standard deviation = 4.022); however, symptoms of anhedonia returned 6-10 weeks after the first

psilocybin dose. Repeated doses of psilocybin reproduced improvements in anhedonia over the course of 6 months. No correlation between baseline anhedonia and antidepressant efficacy was observed.

Conclusions: The present analysis provides preliminary results in support of potential benefits with PAP for symptoms of anhedonia in TRD. Unlike conventional antidepressants, higher baseline anhedonia was not associated with reduced antidepressant efficacy. Future research is needed and merited to evaluate the effects of PAP on anhedonia in rigorously designed clinical trials.

T37. SAFETY AND EFFICACY OF GH001 IN TREATMENT-RESISTANT DEPRESSION: RESULTS: FROM A PHASE 2B, DOUBLE-BLIND, RANDOMIZED, CONTROLLED TRIAL

Michael E. Thase[*1], Bernhard T. Baune[2], Narcís Cardoner[3], Rosa Maria Dueñas Herrero[4], Luboš Janů[5], John R. Kelly[6], Shane McInerney[7], Alexander Nawka[8], Tomáš Páleníček[9], Andreas Reif[10], Víctor Pérez Sola[11], Madhukar H. Trivedi[12], Velichka Valcheva[13], Eduard Vieta[14], Wiesław J. Cubała[15]*

[1]Perelman School of Medicine, University of Pennsylvania, and Corporal Michael J. Crescenz VAMC, [2]University of Muenster, Muenster, Germany, [3]Hospital Santa Creu i Sant Pau, Mental Health Research Group, Institut de Recerca Sant Pau, Universitat Autònoma de Barcelona, CIBERSAM, [4]Parc Sanitari Sant Joan de Deu Hospital de Dia de Numancia, [5]A-Shine SRO, [6]Tallaght University Hospital, [7]University of Galway, [8]Institut Neuropsychiatrické Péče, [9]Psyon s.r.o., [10]Goethe University Frankfurt, University Hospital, [11]Centre for Biomedical Research in Mental Health, (CIBERSAM ISCIII), Spain; Institute of Mental Health, Hospital del Mar; Pompeu Fabra University, [12]University of Texas Southwestern Medical Center, [13]GH Research, [14]Hospital Clinic de Barcelona, Institute of Neuroscience, University of Barcelona, IDIBAPS, CIBERSAM, [15]Faculty of Medicine, Medical University of Gdańsk,

Abstract Background: Treatment-resistant depression (TRD) affects approximately 30% of patients treated for major depressive disorder (MDD) and is associated with higher rates of comorbidity, hospitalization, mortality, suicide, and poorer quality of life compared to MDD patients who are more responsive to treatment. Current therapies for TRD are limited and there is a great unmet need for treatments that offer rapid and sustained effects. Mebufotenin acts as a non-selective serotonin (5-HT) agonist with highest affinity for the 5-HT1A receptor subtype. Early phase trials in patients with TRD suggest that GH001, which is a synthetic form of mebufotenin for pulmonary inhalation, may have the potential to induce ultra-rapid improvement in depressive symptoms. The aim of this placebo-controlled trial was to investigate the safety and efficacy of GH001 in patients with TRD.

Methods: This Phase 2b multicenter trial planned to assess the efficacy and safety of GH001 in 80 patients with TRD. The trial consisted of two parts: Part 1, fully described here, was a randomized, double-blind (DB), placebo-controlled trial with follow up to 7 days post-dose. Patients were randomized in a 1:1 ratio to receive GH001 or placebo. Part 2 is an ongoing 6-month open-label extension (OLE), where up to five GH001 retreatments may be administered, depending on the patient's clinical status.

In Part 1, patients were randomized to receive an individualized dosing regimen (IDR) of up to three escalating doses of GH001 (6, 12, and 18 mg) or placebo on a single day. There was a 1-hour interval between doses. Administration of subsequent doses was based on the patient's subjectively reported psychoactive effects and the safety and tolerability of the previous dose. As in previously conducted GH001 trials, this trial was conducted under the supervision of physicians, nurses, and other qualified healthcare professionals, but without any planned psychotherapeutic intervention before, during, or after dosing. The primary endpoint of Part 1 of this trial was mean change in Montgomery–Åsberg Depression Rating Scale (MADRS) from baseline to Day 8, assessed by a rater without knowledge of the treatment condition.

Results: A total of 81 patients with TRD were enrolled in Part 1 with 40 patients randomized to receive GH001 IDR and 41 patients to receive placebo IDR. Change in MADRS total score from baseline to Day 8 was significantly greater with GH001 than with placebo (difference of least square means=-15.5; SE=1.7); likewise, statistically significant reductions were observed in the GH001 group at 2 hours postdose and on Day 2. Remission (MADRS total score ≤10) was achieved in 57.5% of patients treated with GH001 on Day 8 compared with 0% in the placebo group ($P < 0.0001$). Inhalation of GH001 was well tolerated and no serious adverse events were reported. All treatment-emergent adverse events were mild or moderate with no severe adverse events. Preliminary results from 54 patients who have completed the ongoing OLE indicate that GH001 can maintain long-term remission from TRD with 77.8% of patients (n=42) in remission at 6 months. This is achieved with relatively infrequent treatment visits and rapid reduction in MADRS after each GH001 re-treatment. No serious adverse events have been reported in the OLE to date.

Conclusion: In this randomized trial, GH001 demonstrated significant improvements in depressive symptoms with an acceptable safety profile, supporting the potential of GH001 as a novel, rapid-acting treatment for TRD.

T38. SAFETY AND TOLERABILITY OF GH001 IN TREATMENT-RESISTANT DEPRESSION: RESULTS: FROM A PHASE 2B, DOUBLE-BLIND, RANDOMIZED, CONTROLLED TRIAL

Wiesław J. Cubała[*1], Bernhard T. Baune[2], Narcís Cardoner[3], Rosa Maria Dueñas Herrero[4], Luboš Janů[5], John R. Kelly[6], Shane J. McInerney[7], Alexander Nawka[8], Tomáš Páleníček[9], Andreas Reif[10], Victor Perez Sola[11], Madhukar H. Trivedi[12], Velichka Valcheva[13], Eduard Vieta[14], Michael E. Thase[15]*

[1]Faculty of Medicine, Medical University of Gdańsk, [2]University of Muenster, [3]Hospital Santa Creu i Sant Pau, Mental Health Research Group, Institut de Recerca Sant Pau, Universitat Autònoma de Barcelona, CIBERSAM, [4]Parc Sanitari Sant Joan de Deu Hospital de Dia de Numancia, [5]A-Shine SRO, [6]Tallaght University Hospital, [7]University of Galway, [8]Institut Neuropsychiatrické Péče, [9]Psyon s.r.o., [10]Goethe University Frankfurt, University Hospital, [11]Centre for Biomedical Research in Mental Health (CIBERSAM ISCIII); Institute of Mental Health, Hospital del Mar; Pompeu Fabra University, [12]University of Texas

Southwestern Medical Center, [13]GH Research, [14]Hospital Clinic de Barcelona, Institute of Neuroscience, University of Barcelona, IDIBAPS, CIBERSAM, [15]University of Pennsylvania, Corporal Michael J Crescenz Veterans Affairs Medical Center

Abstract Background: Treatment-resistant depression (TRD) is a chronic condition affecting approximately 30% of patients with major depressive disorder and is associated with a significant human and economic burden to healthcare systems, patients, and their families. At present, only two pharmacotherapies have been approved for the treatment of TRD, highlighting the unmet need for additional safe and effective treatments. Early-phase clinical trials of GH001 suggest it is well tolerated in healthy volunteers and in patients with TRD, postpartum depression, and bipolar II disorder with a current major depressive episode. This trial evaluates the safety and tolerability of GH001 in patients with TRD in a randomized, placebo (PBO)-controlled setting.

Methods: This was a two-part, Phase 2b trial that assessed the efficacy and safety of GH001 in patients with TRD. Part 1, presented here, was a 7-day, double-blind (DB), randomized, PBO-controlled part where patients were randomized in a 1:1 ratio to receive GH001 or PBO. Part 2 is an ongoing, 6-month, open-label extension (OLE) with up to five GH001 retreatments depending on the patient's clinical status.

In Part 1, patients were randomized to receive an individualized dosing regimen of up to three escalating doses of GH001 (6, 12, and 18 mg) or PBO on a single day with a 1-hour interval between doses. Administration of subsequent doses was based on the patient's subjectively reported psychoactive effects and the safety and tolerability of the previous dose. As in previously conducted GH001 trials, this trial was conducted under the supervision of physicians, nurses, and other qualified healthcare professionals, but without any planned psychotherapeutic intervention before, during, or after dosing. Safety and tolerability of GH001 were assessed up to Day 8 by incidence of treatment-emergent adverse events (TEAEs), vital signs and weight, electrocardiogram (ECG), physical examinations, laboratory assessments, spirometry, and safety assessment tools (Modified Observer's Alertness/Sedation scale, Clinician-Administered Dissociative States Scale [CADSS], Brief Psychiatric Rating Scale positive symptoms subscale [BPRS+], and Columbia-Suicide Severity Rating Scale [C-SSRS]).

Results: In the DB part, GH001 was well tolerated in patients with TRD with no serious adverse events reported in either group. TEAEs were observed in 29/40 (72.5%) patients who received GH001 and 3/41 (7.3%) patients who received PBO. All TEAEs in patients who received GH001 were mild (14/29) or moderate (15/29); none were severe. The most commonly reported TEAEs in patients in the GH001 group were nausea (42.5%), salivary hypersecretion (20%), paresthesia (20%), headache (7.5%), and dysgeusia (7.5%). No TEAEs resulted in study drug withdrawal or early withdrawal from the trial in either group. There were no clinically significant changes or adverse events related to vital signs, ECG, or laboratory safety assessments in either group. Similarly, there was no evidence of treatment-emergent effects on suicidal ideation (assessed by the C-SSRS), psychotic symptoms (assessed by the BPRS+), or dissociation at discharge (assessed by the CADSS). By 1-hour postdose, no sedation was observed and 97.4% of patients were discharge-ready.

Conclusion: The results of the DB part of this trial indicate that GH001 is well tolerated in patients with TRD and has an acceptable safety profile up to 7 days postdose.

T39. RESULTS: OF A PHASE 2A CLINICAL TRIAL OF INHALED MEBUFOTENIN (GH001) IN PATIENTS WITH POSTPARTUM DEPRESSION

Claus Bo Svendsen[1], Emilio Arbe[2], Sem E. Cohen[3], Kristina M. Deligiannidis[4], William Gann[5], Sarah Keady[1], Rachael MacIsaac[1], Stuart Ratcliffe[2], David R. Rubinow[6], Dan Tully[5], Velichka Valcheva[1], Jasper B. Zantvoord[3], Martin Johnson[2]*

[1]GH Research, [2]St. Pancras Clinical Research, [3]Amsterdam UMC, University of Amsterdam, [4]Institute of Behavioral Science; Feinstein Institutes for Medical Research, [5]Sheffield Health and Social Care NHS Foundation Trust, [6]University of North Carolina

Abstract Background: Postpartum depression (PPD) is a debilitating mood disorder occurring during pregnancy or within four weeks of delivery. PPD represents a substantial perinatal complication that can have serious consequences for both the mother's well-being and the long-term development of the child. Current treatment options are limited, particularly for patients with more severe disease. GH001 is an inhalation formulation of synthetic mebufotenin (5-MeO-DMT) that has been shown to exert ultra-rapid antidepressant effects in patients with treatment-resistant depression. This study investigated the safety and potential antidepressant effects of GH001 in adult patients with PPD.

Methods: This Phase 2a, proof-of-concept, open-label trial enrolled women aged 18-45 years who met the Mini-International Neuropsychiatric Interview diagnostic criteria for major depressive disorder with peripartum onset. Patients were required to have received no other antidepressant therapy for 14 days prior to dosing and have a Montgomery–Åsberg Depression Rating Scale (MADRS) score of ≥28 at pre-dose. GH001 was administered as an individualized dosing regimen (IDR) of at least one and up to three escalating doses (6, 12, and 18 mg) on a single day (Day 1). This trial was conducted under the supervision of a psychiatrist who provided a standard psychiatric assessment during the screening window but did not provide any planned psychotherapeutic intervention intended to enhance the efficacy of GH001 treatment before, during, or after administration. The primary endpoint was the change in MADRS from baseline to Day 8, and MADRS remission (MADRS total score ≤10) was also assessed. The safety and tolerability of GH001 were evaluated up to Day 8.

Results: A total of 10 patients were enrolled in this trial. Mean MADRS total score at baseline was 36.7 (standard deviation [SD]=4.8). Mean change from baseline to Day 8 in the MADRS total score was -35.4 points (SD=5.5; $P < 0.0001$). All patients were in remission 2 hours after their final dose on Day 1, and this was sustained up to Day 2 and Day 8. Inhalation of GH001 was well tolerated and no serious adverse events were reported. All treatment-emergent adverse events were mild or moderate in severity, with the most commonly reported event being headache (n=5), and all other events were only reported once.

Conclusion: In this trial, GH001 demonstrated rapid and significant improvements in depressive symptoms with an acceptable safety profile and remission of PPD.

T40. A CIRCUIT-BASED APPROACH TO TARGET VALIDATION USING OPTOGENETICS

Kimberly R Thompson[1], Zane C Norville[1], Alice Shi On Hong[1], Susmita Chatterjee[1], James Lillie[1], Michael W. Wood[1], Anatol C Kreitzer[1]*

[1]MapLight Therapeutics

Abstract: Optogenetics refers to the use of light-sensitive opsins to control the activity of genetically defined neuronal populations. Over the last 20 years, optogenetic technology has transformed basic neuroscience research by providing an unprecedented level of experimental control in awake, behaving animals, which makes it possible to establish causal relationships between brain activity and behavior. We leverage optogenetics to generate novel, circuit-based models of psychiatric symptoms. Here we describe how this approach has been applied to the validation of muscarinic M1 and M4 receptors for psychosis. M1 and M4 receptors localize to brain regions that have been implicated in psychosis. In particular, the striatum is a well-known site of modulation by typical and atypical antipsychotics primarily through D2 antagonism. We used cell-type specific mouse transgenic Cre lines to limit the expression of the excitatory opsin, channelrhodopsin, to either dopamine D1 receptor direct-pathway or D2 receptor indirect-pathway medium spiny neurons (D1 or D2 MSNs) using viral-mediated gene delivery in Drd1a-Cre or A2A-Cre lines, respectively. We first tested the efficacy of striatal circuitry in a standard preclinical assay used to model psychosis, amphetamine-induced hyperlocomotion (AIH), which induces a transient hyperdopaminergic state throughout the brain. Selective optogenetic stimulation of D2 MSNs was found to reduce AIH, pointing to the therapeutic potential of D2 MSNs to restore balance within dysregulated circuitry. We then generated a circuit-based model of basal ganglia dysfunction to examine the effect of a novel investigational M1/M4 agonist, ML-007. Direct optogenetic stimulation of D1 MSNs resulted in a hyperlocomotion phenotype similar to that produced by amphetamine, which was significantly decreased by ML-007 administration through its effects on striatal circuitry without blocking D2 receptors. Using optogenetics, our results validate that ML-007 is effective at reducing hyperlocomotion resulting from aberrant basal ganglia activity, and further localizes a key site of action to the striatum. Thus, this circuit-based approach to drug discovery provides new models for target validation and drug testing under in vivo conditions where there is a clear circuit-to-symptom understanding of mechanism.

T41. NON-SULFONAMIDE DUAL OREXIN RECEPTOR AGONISTS: PRELIMINARY RESULTS: OF AEX-41 AND AEX-2 IN A MOUSE MODEL OF NARCOLEPSY

Leila Langbour[1], Sebastien Arthaud[1], Christelle Peyron[1], Anh-Tuan Lormier[2], Maxime Robin[3], Eric Konofal[4]*

[1]Centre de Recherche en Neurosciences de Lyon (CRNL), Equipe SLEEP, UMR5292 CNRS / INSERM U1028 Université Claude Bernard Lyon1 CH Le Vinatier, NeuroCampus Michel Jouvet, 69675 Bron, [2]CayLab, 13800 Istres, [3]Aix-Marseille Université Institut de Chimie Radicalaire ICR UMR 7273, 13397 Marseille, [4]University of Paris, Robert-Debré Hospital, France

Abstract: Narcolepsy type 1 (NT1) is a neurological disorder caused by the autoimmune-mediated destruction of orexin-producing neurons in the hypothalamus, resulting in symptoms such as excessive daytime sleepiness, cataplexy, and REM sleep abnormalities.

Current treatments primarily focus on symptom management, targeting only OX2R or downstream mechanisms, leaving significant unmet needs in addressing the full spectrum of narcolepsy's pathophysiology. AEX-41, developed by Aexon Labs, represents a novel class of non-sulfonamide dual orexin receptor agonists (DOXA) that target both OX1R and OX2R. This dual mechanism aims to restore orexin signaling more comprehensively, offering significant therapeutic potential for narcolepsy and other central hypersomnolence disorders. Additionally, AEX-41 is designed to modulate neuroinflammation through Cathepsin H (CTSH) inhibition, providing a multitarget approach beyond sleep-wake regulation.
AEX-41 is tested in OXR KO mice, a validated NT1 model, as well as wild-type (WT) mice. Animals are treated with vehicle or AEX-41 at doses of 5 mg/kg, 40 mg/kg, and 80 mg/kg administered orally (per os) at ZT2, when sleep is maximal in mice. The study assesses wake and REM sleep duration and sleep latency, using EEG/EMG recordings and efficacy comparison in changes in sleep-wake architecture between treated and control groups.

Preliminary results show an improvement in the maintenance of wakefulness with AEX-41 at the dose of 40 mg/kg wake bouts duration for 2-hour post-administration compared to baseline, at the expense of non-REM sleep. At the dose of 80 mg/kg, AEX-41 had no additional effect, while 5mg/kg showed no effect, suggesting that 40 mg/kg as the optimal therapeutic dose in mice.

In conclusion, AEX-41 has a significant therapeutic potential as a first-in-class non-sulfonamide DOXA for narcolepsy, offering improved wakefulness, reduced REM sleep, and potentially long-term stability of sleep-wake cycles. Unlike sulfonamide-based compounds, with its non-sulfonamide structure, AEX-41 should minimize the risk of receptor desensitization, ensuring sustained efficacy. The inclusion of CTSH inhibition offers additional neuroprotective benefits by mitigating neuroinflammation, which plays a role in disease progression. Further studies will expand on these findings with AEX-2, which is anticipated to have enhanced pharmacokinetics and receptor selectivity, supporting broader applications in CNS disorders.

T42. TREATMENT PATTERNS FOR SLEEP DISORDERS IN THE UNITED STATES VETERANS AFFAIRS HEALTH SYSTEM

Karla Brandao-Viruet[1], Ying Wang[2], Joel Reisman[3], Shibei Zhao[4], Brant Mittler[5], Dan Berlowitz[3], Peter Morin[6], Amir Abbas Tahami Monfared[7], Margaret Moline[7], Quanwu Zhang[7], Weiming Xia[8]*

[1]Tufts Medical Center, [2]Wentworth Institute of Technology, [3]University of Massachusetts, [4]Bedford VA Healthcare System, [5]South Texas VA Healthcare System, [6]Boston University, [7]Eisai, Inc, [8]Boston University School of Medicine

Abstract Objective: This study evaluated treatment patterns for select sleep medications in the Veterans Affairs Health System (VAHS) and the Centers for Medicare and Medicaid Services (CMS).
Methods: We identified all patients aged ≥50 years with select sleep medication prescriptions in the merged VAHS and CMS databases (2020–2022). Clinical Practice Guidelines for pharmacological treatment of insomnia define nonbenzodiazepines such as z-

drugs as first-line. Other treatments may include the melatonin receptor agonist (ramelteon) or sedating antidepressants (trazodone, off label). The FDA has also approved three dual orexin receptor antagonists (DORAs), suvorexant, lemborexant, and daridorexant. Frequency distributions of the select sleep drugs were examined.

Results: Among Veterans using VA outpatient services (N=6,761,233), we identified 906,519 patients with ≥1 sleep drug prescribed during the 2020-2022 study period. Patients had a mean (SD) age of 65.2 (13.1) years at first prescription; 9.4% were women, 17.8% were Black/African American vs 71.1% White, and 6.7% were Hispanic vs 87.5% non-Hispanic. Overall, an estimated 2.6% were prescribed zolpidem, 0.7% temazepam, 0.28% eszopiclone, 0.12% ramelteon, 0.6% zaleplon, 0.5% suvorexant, 0.4% triazolam, 0.006 lemborexant, 0.005% estazolam, and 0.0001% daridorexant. Use of sedative antidepressants was prevalent (trazadone 10.4%; doxepin 0.9%). Over the 3-year period, most patients (89%) used a single sleep medication and 9.6% used 2 drugs. Melatonin supplements were prescribed in 46.2% of patients in conjunction with the other sleep medications.

Conclusion: The Z-drug zolpidem was the most commonly prescribed medication indicated for insomnia. Sedative antidepressants were also frequently utilized, likely due to their affordability and the lack of widely accepted, cost-effective alternatives for managing insomnia. Lemborexant and daridorexant, more recently approved for insomnia, were prescribed less frequently and have not yet become mainstream frontline treatments. However, their novel dual orexin receptor antagonist mechanism provides a viable alternative therapeutic option for new users seeking effective insomnia management.

T43. OPEN BOARD

T44. SPEECH-BASED QUALITY ANALYSIS IN COA ADMINISTRATION: PROFILING CLINICIAN BEHAVIORS IN MADRS INTERVIEWS

Georgios Efstathiadis[1], Michelle Worthington[2], Anzar Abbas[1]*

[1]Brooklyn Health, [2]Brooklyn Health, Yale University

Abstract Introduction: CNS clinical trials often rely on clinician-administered scales like the Montgomery–Åsberg Depression Rating Scale (MADRS). Secondary review of these clinical interviews are necessary to ensure standardized administration. The current process to do this is manual and time-consuming. Here, we propose a supplement to manual secondary review through quantification of clinician behavior in an automatic, scalable, and objective manner.

Methods: Data: Four MADRS interviews were conducted by a trained rater on a healthy volunteer. The rater intentionally used a different interview style in each administration:

Structured Profile: The reference profile, a well-structured approach with close adherence to the interview guide for MADRS (SIGMA).

Disorganized Profile: Less engaged and less familiar with the protocol, missing parts of the interview, and struggling to maintain the conversation flow.

Rushed Profile: More forceful approach, speaking quickly, often cutting off the patient, creating an intense and hostile environment.

Therapeutic Profile: Overly positive, providing positive reinforcement rather than maintaining closer adherence to the interview structure.

These profiles were chosen to simulate a range of ways in which raters could stray from protocol.

Rater Behavior Measures: We analyzed the clinician's speech using measures indicative of behavior. These included measures of speech behavior (pace, pauses, overlapping speech), linguistic/emotional expression (reading ease, filler words, sentiment) and scale administration (script adherence, followup questions, order of administration).

Qualitative feedback: We implemented retrieval-augmented generation (RAG) on a large language model (LLM), leveraging typical rater training materials. The model was provided with the transcript of each interview along with rater behavior measures, and it generated feedback on the quality of the interview.

Results: Measurement of behavior

We compared the rater behavior measures from the three irregular clinician profiles to the reference profile. P-values are extracted from t-tests on the turn-level measures, if available.

The disorganized profile had more filler words (13.5% vs. 2.4%; p-value: 2e-11), more out-of-order sections (10% vs. 0%), and lower adherence to follow-up questions (0.14 vs. 0.74; p-value: 0.01).

The rushed profile showed a higher word rate (226 vs. 189; p-value: 0.01), more interruptions (11.1% vs. 0%; p-value: 0.01), shorter pre-turn pauses (0.96 sec vs. 1.99 sec; p-value: 2e-5), and increased positive sentiment (0.19 vs. 0.114; p-value: 0.01) and negative reinforcement (22.2% vs. 7.4%).

The therapeutic profile had higher positive sentiment (0.176 vs. 0.114; p-value: 0.01), more positive reinforcement (28.6% vs. 1.9%), and no negative reinforcement (0% vs. 7.4%), but lower item adherence (0.637 vs. 0.839; p-value: 1e-3) due to excessive validation.

Qualitative feedback

We extracted highlights from the feedback provided by the LLM. These included “high standard of interview quality” for the reference profile, “occasionally seem to overlook or underexplore follow-up prompts on key symptoms” for the disorganized profile, “appears impatient and skips over certain questions” for the rushed profile and “occasionally risks over-empathizing” for the therapeutic profile.

Conclusions: This experiment demonstrates that measures derived from rater speech during MADRS interviews can be used to detect deviations from expected clinician behavior. Importantly, this approach enables us to monitor all interviews and detect anomalies earlier. As a result, data quality is enhanced, improving the detection of meaningful treatment effects.

T45. PERSONALIZED ACCELERATED INTERMITTENT THETA BURST STIMULATION FOR POST-ACUTE SUICIDAL IDEATION: A PILOT STUDY PROPOSAL

Se Ri Bae[*1], *Manpreet Singh*[2]

[1] *University of California, Davis* [2]*University of California, Davis, School of Medicine*

Abstract Background and Research Aims: The majority of patients who present with suicidal ideation (SI) in the emergency department (ED) are admitted or transferred to an inpatient psychiatric unit. However, a substantial proportion of patients are discharged without hospitalization, yet may remain at high risk for persistent suicidal ideation and/or suicidal behaviors. This pilot study aims to assess the feasibility and efficacy of 5-day fMRI-guided intermittent theta burst stimulation (iTBS), an accelerated form of repetitive transcranial magnetic stimulation (rTMS), within 1 week of discharge from the ED for SI. Given the high risk of suicide during the immediate post-discharge period, this prospective study investigates whether personalized accelerated iTBS (paiTBS) guided by neuroimaging can provide stabilization of depressive symptoms and SI. We hypothesize that this intervention will be feasible and effective in reducing depressive symptoms, SI, ED readmissions, and psychosocial dysfunction in patients with depression. Lastly, we aim to explore the neural mechanisms underlying the antidepressant and anti-suicidal benefits of paiTBS utilizing neuroimaging data.

Sample: The proposed pilot study will enroll 25 participants > 18 years-old who present to the ED with SI and are discharged home without psychiatric hospitalization. Participants must have a Montgomery-Åsberg Depression Rating Scale (MADRS) score > 20 to be eligible.

Measures: Primary outcome is change in MADRS scores from baseline to 1 week follow-up. Secondary outcomes include SI as measured by Columbia Suicide Severity Rating Scale (C-SSRS) at 1-week follow-up, and ED readmission rates for SI and psychosocial function as measured by Functioning Assessment Short Test (FAST) at 1 month follow-up. Longitudinal mixed-effects model will be performed on a modified intention-to-treat sample.

Procedures: Participants will undergo a 5-day paiTBS treatment protocol which involves an initial MRI scan to individually target the left dorsolateral prefrontal cortex (DLPFC). The treatment will involve sessions of intermittent theta burst stimulation (iTBS) of 60 cycles of 10 bursts of three pulses at 50 Hz delivered in 2-second trains (5 Hz) with an 8-second intertrain interval. Ten sessions of iTBS will be delivered daily, for a total of 18,000 pulses per day, on 5 consecutive days. Stimulation will be delivered at 90% of resting motor threshold, adjusting for depth of the identified MRI target. After completion of rTMS treatment, participants will complete another MRI scan to study changes in functional connectivity between brain regions associated with depression and SI.

Potential Impact: This study addresses a critical period of high suicide risk immediately following ED discharge. By demonstrating the feasibility and potential efficacy of paiTBS treatment in this context, the research aims to establish paiTBS as a rapid intervention to stabilize depressive symptoms and SI and reduce ED readmissions and overall psychosocial dysfunction. This could lead to broader adoption of paiTBS for high-risk patients and potentially decrease overall healthcare costs related to recurrent ED visits and

hospitalizations. This pilot study aims to fill a significant gap in the current suicide prevention strategies by offering a novel, rapid treatment option for high suicide risk patients. Future research should include randomized controlled trials and explore additional outcomes such as long-term remission rates, accessibility, and overall efficacy of paiTBS in other acute settings.

T46. EXAMINING WITHIN-PERSON LONGITUDINAL CHANGE ON A MOBILE VERBAL LEARNING TEST IN ADULTS WITH AND WITHOUT HIV

Alena Stasenko[1], Laura M. Campbell[1], Anne Heaton[1], Jonathan L. Helm[2], David J. Moore[1], Robert K. Heaton[1], Colin A. Depp[1], Amy E. Pinkham[3], Robert A. Ackerman[3], Philip D. Harvey[4], Raeanne Moore[1]*

[1]University of California, San Diego, [2]San Diego State University, [3]The University of Texas at Dallas, [4]University of Miami

Abstract: Remote cognitive testing is gaining momentum due to its scalability and ability to assess cognitive function repeatedly in real-world settings. However, there is limited evidence as to whether remote cognitive tests are sensitive to within-person change, which is critical for longitudinal studies and clinical trials. We previously validated the mobile verbal learning test (mVLT) for assessing learning in adults with and without HIV. Here, we examined whether the mVLT is sensitive to within-person longitudinal change in these two groups.

Twenty-four persons with HIV (PWH) and 13 persons without HIV (aged 51-74) completed remote administrations of the mVLT at baseline and 26.7 (± 9.5) months later. At each timepoint, participants completed a standardized neuropsychological battery and three recall trials of the mVLT following presentation of a different word list on a smartphone once daily for 14 days. The primary outcome was the mVLT total score (i.e., sum of three recall trials aggregated across 14 days). Mixed-effects models, controlling for age and testing interval, revealed significant group-by-timepoint interactions for mean and median mVLT total scores (ps $< .01$; partial eta squared = .19-.21). Whereas persons without HIV exhibited significant improvement across timepoints (ps $< .05$), PWH showed a trend toward decline. Interactions for other mVLT metrics (e.g., intra-individual variability, maximum score, learning curve) did not reach significance. The pattern of results was similar but less robust when classifying individuals by Mild Cognitive Impairment status. Notably, the group-by-timepoint interaction was not significant for a standard in-person measure of verbal learning (HVLT-R). Among PWH, older age, lower global learning performance, lower social function, and greater comorbidities (i.e., cardiovascular risk, liver function) at baseline were associated with greater decline in total mVLT scores (ps $< .05$; rs = .40-.56). In contrast, subjective cognitive complaints, functional status, and other clinical factors (e.g., mood, substance use) were not associated with decline (ps $> .05$).

Aggregate metrics from a 14-day remote verbal learning test demonstrated differential sensitivity to within-person longitudinal change in adults with and without HIV. Unlike individuals without HIV, who exhibited significant practice effects, PWH showed a lack of expected learning effects. The lack of improvement relative to controls may reflect early cognitive vulnerability, highlighting the sensitivity of mobile cognitive testing tools like the mVLT in detecting subtle cognitive changes in at-risk populations. In addition, longitudinal change was associated with known risk factors for cognitive decline in PWH, such as age and comorbidities. With further validation in larger samples, the mVLT holds promise as a scalable, fully remote tool for tracking subtle memory changes over time.

T47. REMISSION OF TARDIVE DYSKINESIA IN PATIENTS RECEIVING LONG-TERM VALBENAZINE TREATMENT

Andrew J. Cutler[1], Laxman Bahroo[2], Kira Aldrich[3], Elaine Liu[3], Cathy Zeng[3], Khody Farahmand[3]*

[1]Norton College of Medicine, State University of New York Upstate Medical University, [2]Georgetown University, [3]Neurocrine Biosciences, Inc.

Abstract Background: Once-daily valbenazine is approved for tardive dyskinesia (TD) and chorea associated with Huntington's disease. In a long-term, open-label study of TD (KINECT® 4 [NCT02405091]), treatment with valbenazine resulted in substantial mean improvements from baseline to Week 48 (end of treatment) in the Abnormal Involuntary Movement Scale (AIMS) total score (40 mg, -10.2; 80 mg, -11.0). These findings warrant further investigation, including the potential remission of TD symptoms when patients are being treated with valbenazine.
Objective: To assess a potential threshold for remission of TD during valbenazine treatment.

Methods: Derived from the Schooler-Kane criteria for TD, a potential threshold for remission was defined as an AIMS item score of ≤1 (rating of "none" or "minimal") in each of the 7 body regions (items 1-7). Among participants who reached the Week 48 visit ("completers"), the percentage who met the threshold for remission was analyzed by dose (40 mg, 80 mg) and by psychiatric diagnosis (schizophrenia or schizoaffective disorder [SCHZ], mood disorder [MOOD]). Participants who had a dose reduction from 80 to 40 mg during the study were categorized as 40 mg. AIMS total score (sum of items 1-7) was also analyzed by dose at baseline and Week 48 in participants who met the remission threshold.

Results: Valbenazine dosing and psychiatric diagnoses in the completer population (N=103) were as follows: 80 mg (71.8% [n=74]), 40 mg (28.2% [n=29]), SCHZ (68.9% [n=71]), MOOD (31.1% [n=32]). Among the 103 completers, 61 (59.2%) met the threshold for remission (score ≤1 in all 7 AIMS items) at Week 48: 40 mg, 58.6% (17/29); 80 mg, 59.5% (44/74). Mean values for AIMS total score at baseline (80 mg, 15.1 [range: 6-23]; 40 mg, 12.4 [6-22]) and Week 48 (80 mg, 2.5 [range: 0-7]; 40 mg, 2.1 [0-6]) indicated substantial TD improvements with both valbenazine doses. Among the 71 completers who had a SCHZ diagnosis, 41 (57.7%) met the threshold for remission; among 32 completers with a MOOD diagnosis, 20 (62.5%) achieved remission.

Conclusions: A majority of participants who received 48 weeks of once-daily valbenazine reached a potential threshold for remission of TD while on treatment, regardless of dose or underlying psychiatric diagnosis. The threshold for remission used in this analysis could be applied to clinical settings and/or used in future research as a potential treatment goal for TD.

T48. INDIRECT TREATMENT COMPARISON OF SOMNOLENCE OR SEDATION WITH DOPAMINE PARTIAL AGONISTS VERSUS D2 RECEPTOR ANTAGONISTS IN MAJOR DEPRESSIVE DISORDER AND SCHIZOPHRENIA

Nadia Nabulsi[*1], Jamie Ta[1], Filmon Haile[1], Mousam Parikh[1], Ning Cheng[1], Nahida Mirza[1], Kateryna Onishchenko[1], Nika Adham[1], Shane Varughese[1], Julie Adams[1]*

[1]*AbbVie*

Abstract: Introduction: Major depressive disorder (MDD) and schizophrenia (SCZ) are often treated with atypical antipsychotics (AAs), either as adjunctive therapy in MDD or as monotherapy in SCZ. AAs can be categorized as either dopamine D2 receptor partial agonists (eg, cariprazine), which act as functional agonists or antagonists depending on the surrounding levels of endogenous dopamine, or dopamine D2 receptor antagonists (eg, quetiapine), which act as pure antagonists at these receptors. Some AAs are associated with somnolence and sedation; these side effects can cause a strong desire for sleep, drowsiness, slower reaction times, and impaired performance. The objective of this indirect treatment comparison was to evaluate the rates of somnolence/sedation associated with dopamine D2 receptor partial agonists vs D2 receptor antagonists in the adjunctive treatment of MDD and the treatment of acute SCZ.

Methods: Two separate systematic literature reviews were performed to identify relevant clinical trials in MDD and SCZ. The adjunctive MDD analysis included randomized, double-blind, placebo-controlled, phase II/III trials ≥6 weeks long evaluating AAs approved by the US Food and Drug Administration for the adjunctive treatment of MDD in adults; somnolence was a required outcome. The SCZ analysis included double-blind, randomized controlled trials with a randomized phase ≥4 weeks long evaluating AAs for the treatment of acute SCZ in adults (excluding patients with first episode SCZ, predominantly negative symptoms or refractory disease); somnolence/sedation was a required outcome. For both indications, a Bayesian network meta-analysis was performed to evaluate the absolute effect of each treatment on somnolence (MDD) and somnolence/sedation (SCZ) and conduct an indirect treatment comparison of dopamine D2 receptor partial agonists vs D2 receptor antagonists. Relative treatment effects of dopamine D2 receptor partial agonists vs D2 receptor antagonists on rates of somnolence or somnolence/sedation were estimated using a binomial likelihood model with a logit link function, with relative effects expressed as Odds ratios (OR) with 95% credible intervals (CrI).

Results: A total of 10 studies were included in the adjunctive MDD analysis (8 evaluating dopamine D2 receptor partial agonists and 2 evaluating D2 receptor antagonists). The odds of

experiencing somnolence were 72% less for patients taking dopamine D2 receptor partial agonists compared with those taking D2 receptor antagonists (OR [95% CrI]: 0.28 [0.13, 0.59]). In the analysis of acute SCZ randomized controlled trials, a total of 50 studies were included (5 studies of dopamine D2 receptor partial agonists, 43 of D2 receptor antagonists, and 2 of dopamine D2 receptor partial agonists vs D2 receptor antagonists vs placebo). The odds of somnolence/sedation were 56% less for patients taking dopamine D2 receptor partial agonists compared with those taking D2 receptor antagonists (OR [95% CrI]: 0.44 [0.27, 0.77]). Limitations include a disparity in dopamine D2 receptor partial agonist vs antagonist studies in the MDD analysis.

Conclusions: The results of this indirect treatment comparison suggest that in patients treated with AAs either adjunctively for MDD or for the acute treatment of SCZ, dopamine D2 receptor partial agonists may be less likely to cause somnolence (MDD) or somnolence/sedation (SCZ) relative to D2 receptor antagonists.

T49. MEDICATION ADHERENCE FOLLOWING PHARMACOGENOMIC TESTING IN INSURANCE CLAIMS DATA FROM PATIENTS WITH MAJOR DEPRESSIVE DISORDER

Andria Del Tredici[*1], Holly Johnson[1], Brady DeHart[2], Alexander Gutin[1], Katie Johansen Taber[1], Pamela Morin[2], Laura Becker[2], Julia Certa[2], Boadie Dunlop[3], Devika Chawla[1], Andrew Nierenberg[4]*

[1]Myriad Genetics, [2]Optum, [3]Emory University School of Medicine, [4]Massachusetts General Hospital, Harvard Medical School

Abstract Background: Approximately 50% of patients with major depressive disorder (MDD) discontinue
their antidepressant medication within 6 months, which increases risk of relapse. Clinical application of pharmacogenomic (PGx) testing has been associated with improved medication adherence in some studies, and we hypothesized that it could improve adherence to antidepressants in patients with MDD.

Methods: We assessed medication adherence and discontinuation in patients with MDD who received a weighted multi-gene PGx test between 5 January 2015 and 30 September 2021 and had a medication switch. PGx test results from adult patients with MDD were de-identified and linked with de-identified administrative claims data from Optum Labs Data Warehouse. Diagnosis codes were used to identify patients with MDD without specific psychiatric comorbidities. All medications on the PGx test, including antidepressants, were evaluated. The PGx test report organized psychiatric medications into three categories: no known gene-drug interactions (congruent), moderate gene-drug interactions (congruent), and significant gene-drug interactions (incongruent). Patients were considered as taking incongruent medications if any of their filled medications were incongruent. Using medication claims data, patients were assigned to the following groups based on medication congruency 90 days pre- and post-PGx testing: incongruent-to-congruent, congruent-to-incongruent, and no change in congruency. Medication adherence (defined as the proportion of days covered

[PDC]) and discontinuation (defined as a ≥45-day gap in medication fills after medication calendar-date runout) were assessed for the new medication fill during the 180 days following the medication switch. A patient with PDC ≥0.8 was considered highly adherent. Adherence and discontinuation were statistically compared across the medication congruency groups.

Results: A total of 6,224 patients with PGx testing (72.9% female, mean age 44.8 years, SD 18.3) were identified. Patients in the incongruent-to-congruent group had the most adherence (mean PDC 0.65, SD 0.33), which was significantly greater ($p < 0.05$) compared to the congruent-to-incongruent (mean PDC 0.58, SD 0.34) and no-change-in-congruency groups (mean PDC 0.61, SD 0.34). The proportion of highly adherent patients was highest in the incongruent-to-congruent group (49%), followed by the no-change-in-congruency (44%) and congruent-to-incongruent groups (40%) ($p < 0.05$). The incongruent-to-congruent group also had the lowest proportion of discontinuation events (46%), followed by the no-change-in-congruency (50%) and congruent-to-incongruent groups (55%) ($p < 0.05$).

Conclusions: MDD patients with PGx testing who were switched to psychiatric medications with no/moderate gene-drug interactions showed higher medication adherence and lower discontinuation compared to patients who were switched to psychiatric medications with significant gene-drug interactions.

T50. COMPARISON OF PHARMACOLOGICAL MANAGEMENT IN THE TREATMENT OF PERINATAL DEPRESSION: EFFICACY, TOLERABILITY, TERATOGENICITY, AND ETHICAL CONSIDERATIONS

Abdul Khan[*1], Saba Saleem[1], Mohammad Memon[1], Faisal Suba[1], Mujeeb Shad[1]*

[1]*Valley Health System*

Abstract Background: Perinatal depression is a threat to both maternal and infant health. In this comprehensive review, we evaluate the efficacy, tolerability, and teratogenicity of various pharmacological treatment options available for perinatal depression, including selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), bupropion, mirtazapine, tricyclic antidepressants (TCAs), and gamma-aminobutyric acid-A (GABA) modulators.

Methods: We conducted a systematic literature search on PubMed, utilizing the following keywords: ("Perinatal Depression" AND ("Pharmacological Treatment" OR "Antidepressants" OR "Drug Therapy") with a filter of the last ten years to include all original studies (i.e., diagnostic, interventional trials, cohort, and cross-sectional studies) and meta-analysis. The search yielded 21 results. The data from all reviewed studies were delineated to answer pertinent clinical, diagnostic, and management questions related to the pharmacological management of perinatal depression.

Results: The first line of treatment is often SSRIs, which are also the most extensively studied and have more safety data available. Studies have shown some concern for neonatal adaptation syndrome and persistent pulmonary hypertension with SSRIs. SNRIs are also effective but may require monitoring for gestational hypertension. Bupropion and mirtazapine present fewer studies but show promise with minimal teratogenic risks. The

novel GABA receptor modulator drug, brexanolone, was approved for postpartum depression. The drug shows rapid efficacy and response but requires inpatient administration due to the risks of sedation.

Conclusion: With all the psychotherapeutic agents available to manage perinatal depression, a balance between maternal mental health and potential fetal complications is critical to be achieved through an interdisciplinary approach. Open discussions with patient-centered care and autonomy should be carried out at all stages of pregnancy, including the postpartum period, to ensure the health and safety of the mother and infant.

T51. SAFETY, TOLERABILITY, AND DURABILITY OF TREATMENT EFFECT OF OLANZAPINE AND SAMIDORPHAN: A PATIENT SUBGROUP ANALYSIS OF A 4-YEAR OPEN-LABEL STUDY

Jacob Ballon[*1], Christina Arevalo[2], Martin Dunbar[2], Alexandra Lovett[2], David McDonnell[2], Christoph U. Correll[3]*

[1]Stanford University, [2]Alkermes, Inc., [3]Donald and Barbara Zucker School of Medicine at Hofstra/Northwell; Charité Universitätsmedizin

Abstract Objective: To analyze subgroup data from a 4-year, open-label study of combined olanzapine and samidorphan (OLZ/SAM) in adults with schizophrenia, schizophreniform disorder, or bipolar I disorder.

Methods: Patients completing studies in the ENLIGHTEN clinical trial program were eligible to receive ≥2–4 years of additional treatment in a phase 3, open-label study assessing OLZ/SAM's safety, tolerability, and durability of treatment effect. Prespecified subgroup analyses were conducted by age (18–29 or ≥30 years), sex (male or female), race (Black/African American or non-Black/African American), baseline body mass index (BMI; < 25 or ≥25 kg/m2), and geographic region (US or non-US). Safety assessments included changes from baseline in body weight and waist circumference and adverse event (AE) incidences. Durability of treatment effect was assessed using the Clinical Global Impressions–Severity (CGI-S) scale.

Results: Overall, 523 patients were included; 53.7% (242/451) and 32.5% (109/335) received 2 and 4 years of treatment, respectively. At 2 years, OLZ/SAM treatment was associated with small mean changes from baseline in body weight (range: 0–2.15 kg) and minimal mean changes from baseline in waist circumference (range: −1.13–0.15 cm) across subgroups. Mean changes in body weight (range: 1.51–5.49 kg) and waist circumference (range: 0.67–3.85 cm) were generally similar across subgroups at 4 years. No clinically meaningful subgroup differences in AEs were observed. Mean CGI-S scale scores were stable across subgroups at 2 and 4 years.

Conclusions: Outcomes following up to 4 years of OLZ/SAM treatment were generally similar across age, sex, race, BMI, and geographic subgroups.

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T52. WHAT'S IN A WORD: CAN DISCOURSE ANALYSIS OF THE LINGUISTIC CHOICES MADE BY PATIENTS PROVIDE CLINICIANS WITH DEEPER INSIGHTS INTO PATIENTS' PERSPECTIVES?

John Adeniji[1], Anyinke Atabong[2], Craig Chepke[3], Michael Ingram[4], Amber Hoberg[5], Shalina Omar[6], Maurcio Tohen[7], Joseph Goldberg[8]*

[1]Inland Psychiatric Medical Group, [2]Capital Multi Health Group, [3]Excel Psychiatric Associates, [4]Great Lakes Bay Healthcare, [5]Baptist Health System and Morning Star Family Medicine PLLC, [6]Guidehouse, [7]University of New Mexico Health Sciences Center, [8]Icahn School of Medicine at Mount Sinai

Abstract Background: Bipolar I disorder (BP-I) is a chronic disorder characterized by episodes of mania and depression. Adherence to oral medication for BP-I is often poor, but long-acting injectable (LAI) formulations of antipsychotic medications can improve treatment adherence and patient outcomes. To optimize BP-I management and shared decision-making, it is important that healthcare providers (HCPs) understand patients' experiences and needs regarding treatment information and communication with their HCPs. In this study, patient perspectives were gathered and reviewed by a sociolinguistic expert and a panel of eight psychiatrists and psychiatric nurse practitioners. The study objective was to compare how the panel of HCPs and the sociolinguistic expert interpreted the patient perspectives and to evaluate the similarities and differences in their analyses.

Methods: Using a discussion guide, a moderator asked a small group of patients (n=5) and a caregiver (n=1) about their experiences and preferences for BP-I treatment, their awareness of LAIs as a treatment option for BP-I, and recommendations for HCP communication on treatment options. The discussion was silently observed by HCPs, who then reconvened to discuss their observations. In parallel, a transcript of the moderated discussion was provided to a sociolinguistic expert, who carried out thematic and discourse analyses. The discourse analysis focused on examining linguistic choices made by the patients/caregiver, to provide additional insights into patient/caregiver perspectives.

Results: All patients and the caregiver were female; patients were Caucasian (n=3), Hispanic or Latino (n=1) or Caucasian, Hispanic or Latino (n=1), and aged 23–50 years old, with an average of 21.4 years since diagnosis. One patient was receiving LAI treatment; three others had heard of LAIs previously.

The observations of the HCPs and the sociolinguistic expert largely overlapped in terms of key themes identified from the patient/caregiver discussion. These themes included participants wishing for more open communication with their HCPs and to be more involved in treatment decisions. Key barriers to patients considering LAIs included previous negative experiences with injectable treatments, a perceived loss of control with LAIs versus oral formulations, and logistical challenges. Factors likely to increase patients' willingness to try LAIs included feeling involved in treatment decisions, trust in their HCP, and prior experience with oral versions of LAI formulations. Patients wished for easy-to-understand information about their BP-I treatments, and highlighted experiences from other patients with similar backgrounds as helpful for their decision-making.

The discourse analysis provided additional insights. Linguistic choices noted in the discourse analysis included patient use of humor, hedging, justification or qualifiers when discussing topics perceived as difficult. Use of constructed dialogue was a common technique to distill their experiences of interactions with HCPs. Patients also employed distancing or softening language when discussing negative experiences and used shifts in pronouns from the first person to the impersonal 'you' to place their struggles in the field of common experience, to build camaraderie with their audience and seek reassurance.

Conclusion: Analysis of the linguistic techniques used by patients may provide deeper insights into patients' perspectives.

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T53. BLACK ADULTS WHO STOPPED ENGAGING IN CARE PRIOR TO FIREARM SUICIDE DEATH: A PRELIMINARY ANALYSIS OF NATIONAL VIOLENT DEATH REPORTING SYSTEM DATA, 2013-2021

Evan Goldstein[*1], Aryanna Sanger[2]*

[1]*University of Utah School of Medicine,* [2]*University of Utah College of Social Work*

Abstract Background: Firearm suicide rates increased by 47.9%, from 3.53 to 5.22 deaths per 100,000 persons, among Black adults from 2010 to 2020 nationally.(1) Healthcare is often crucial for preventing suicide if at-risk adults can be offered effective interventions, e.g., psychopharmacology, psychotherapy, and lethal means counseling when firearms are accessible.(2) Critically, many Black Americans experience stigma and barriers to addressing mental health conditions, e.g., barriers to accessing psychiatric care. Even among those who access necessary services, continuing treatment can be challenging.

Objective: To identify common circumstances preceding firearm suicide among Black adults who were known to have a health condition but stopped engaging in psychopharmacology, psychotherapy, or other healthcare services before death.

Methods: We examined incident narratives from the National Violent Death Reporting System (NVDRS) abstracted from coroner/medical examiner and law enforcement investigative reports. The narratives provided information on the circumstances preceding each death. This analysis included incident narratives for 42 Black firearm suicide decedents (ages ≥18) from 2013-2021 who were known to have an ongoing health condition but stopped taking a prescribed medication or going to appointments, as documented in the narratives. The 42 decedents emerged from a larger study of 843 decedents who were demographically representative of all Black adult firearm suicide decedents in the NVDRS from 2013-2021. (3) We used quantitative content analysis to identify common circumstances before death. First-cycle coded narratives were reviewed a second time and re-coded deductively for this analysis.

Results: Of the decedents who stopped engaging in care before firearm suicide death, 81% (N=34) had a known/documented mental health condition. Thirty-eight percent (N=16) of the decedents were known to have experienced either suicidal ideation or nonfatal suicide attempts previously. Recreational or illicit substances (e.g., alcohol/cannabis) were involved

in 26% (N=11) of the deaths. Additional recurring circumstances included general medical conditions, legal distress, and employment or financial difficulties but occurred for < 10 decedents, so the frequencies cannot be reported per NVDRS policy.

Conclusions and Implications for Healthcare Delivery: Treatment disruptions may be a matter of life or death, preventing opportunities to uncover new warning signs, identify firearm accessibility, and conduct interventions such as lethal means counseling, which incorporates strategies for healthcare professionals to counsel individuals on securely storing or voluntarily limiting firearm access in times of crisis.(4, 5) Especially in cases where patients experience preexisting mental conditions, grief or loss, and past attempts, intensive outreach and follow-up care could interrupt individuals' preparation for firearm-involved suicide. This analysis serves as a critical call for new research on care disruptions and barriers to follow-up care prior to firearm suicide among Black adults, including wrap-around services such as legal support, financial and employment assistance, insurance enrollment, and care management not commonly offered to individuals who have disengaged in care across different healthcare contexts. Stigma, generational traumas, oppressive systems, and a history of unethical healthcare treatment likely also play a role in the access to and reception of effective psychiatric/medical care within Black communities.

T54. EFFECT OF DOSE ON XANOMELINE AND TROSPIUM CHLORIDE EFFICACY AND SAFETY: POST HOC ANALYSIS OF DATA FROM THE THREE 5-WEEK EMERGENT TRIALS

Inder Kaul[1], Soumya A Charturvedi[1], Tejendra R Patel[1], Nichole Neugebauer[1], Eliesha Daniels[1], Pierre Nicolas[1], Amy Claxton[1]*

[1]Bristol-Myers Squibb

Abstract Background: The muscarinic agent xanomeline and trospium chloride (X/T), which was recently approved by the U.S. Food and Drug Administration for the treatment of schizophrenia in adults, exhibits no direct D2 dopamine receptor binding. The efficacy and safety of X/T at different doses were characterized using data pooled from the phase 2 EMERGENT-1 (NCT03697252) and phase 3 EMERGENT-2 (NCT04659161) and EMERGENT-3 (NCT04738123) acute trials.

Methods: The acute EMERGENT trials were 5-week, randomized, double-blind, placebo-controlled, inpatient trials of adults with schizophrenia experiencing acute psychosis. EMERGENT-1 and EMERGENT-2 were conducted in the United States, and EMERGENT-3 was conducted in the United States and Ukraine. Key inclusion criteria were age of 18-65 years, a recent worsening of positive symptoms warranting hospitalization, Positive and Negative Syndrome Scale (PANSS) total score of 80-120, and a Clinical Global Impression–Severity scale score ≥4. Participants were randomized 1:1 to X/T or placebo. Twice-daily X/T dosing started at 50 mg/20 mg and increased after 2 days to 100 mg/20 mg for 5 days, followed by a maximum of 125 mg/30 mg based on tolerability. In each trial, the primary efficacy endpoint was change from baseline in PANSS total score compared to placebo at week 5. Data from the 3 acute EMERGENT trials were pooled, and safety and efficacy were examined among participants who completed trial participation at the two highest dose levels.

Efficacy analyses were conducted in the modified intent-to-treat population, defined as randomized participants who received ≥1 trial medication dose and had a baseline and ≥1 postbaseline PANSS assessment. The safety population included participants who received ≥1 trial medication dose.

Results: Among participants in the modified intent-to-treat population, 308 received X/T (100 mg/20 mg, n=49; 125 mg/30 mg, n=259) and 323 received placebo. The safety population included 331 people treated with X/T (100 mg/20 mg, n=60; 125 mg/30 mg, n=271) and 333 people who received placebo. Data from 9 participants who achieved a final dose of X/T 50 mg/20 mg and remained on treatment for a maximum of 3 days are not included in safety or efficacy analyses. Both X/T doses demonstrated a greater reduction from baseline to week 5 in PANSS total score compared with placebo (least squares mean [LSM] difference for X/T 100 mg/20 mg=-19.3; 95% confidence interval [CI], -25.4, -13.2; P < 0.0001; Cohen's d, 1.28; LSM difference for X/T 125 mg/30 mg=-8.8; 95% CI, -11.4, -6.2; P < 0.0001; Cohen's d, 0.58).The proportions of participants reporting ≥1 treatment-emergent adverse event (TEAE) were 81.7% (100 mg/20 mg), 65.7% (125 mg/30 mg), and 52.0% (placebo) and reporting ≥1 treatment-related AE were 68.3% (100 mg/20 mg), 49.1% (125 mg/30 mg), and 30.0% (placebo). Fewer than 2% of individuals in any of the treatment groups experienced ≥1 serious TEAE. TEAEs leading to dose reduction occurred in 13.3% and 0.3% of participants in the X/T 100 mg/20 mg and placebo groups, respectively, and none were recorded in the X/T 125 mg/30 mg group.

Conclusion: In post hoc analyses of data pooled from the three 5-week EMERGENT trials, individuals completing trial participation at doses of X/T 100 mg/20 mg or 125 mg/30 mg achieved greater reductions in PANSS total score compared with placebo. Participants treated and maintained at the highest dose of X/T experienced few serious TEAEs and required no dose reductions.

T55. POOLED ANALYSIS OF EXTRAPYRAMIDAL SYMPTOMS IN ADULTS WITH SCHIZOPHRENIA IN THE LONG-TERM, OPEN-LABEL TRIALS OF XANOMELINE AND TROSPIUM CHLORIDE

Inder Kaul[1], Tejendra R Patel[1], Soumya A Charturvedi[1], Wei-Chih Lin[1], Amy Claxton[1]*

[1]Bristol-Myers Squibb

Abstract Background: Use of antipsychotics approved for the treatment of schizophrenia that directly block D2 dopamine receptors can lead to notable safety and tolerability problems, including extrapyramidal symptoms (EPS). The M1/M4 preferring muscarinic receptor agonist xanomeline combined with the peripherally restricted muscarinic receptor antagonist trospium chloride was recently approved by the U.S. Food and Drug Administration for the treatment of schizophrenia in adults. In a pooled analysis of the 5-week, randomized, double-blind, placebo-controlled EMERGENT-1 (NCT03697252), EMERGENT-2 (NCT04659161), and EMERGENT-3 (NCT04738123) trials, xanomeline/trospium demonstrated low risk of EPS. This pooled analysis assessed the occurrence of EPS adverse events in the 52-week, open-label EMERGENT-4 (NCT04659174) and EMERGENT-5 (NCT04820309) trials with xanomeline/trospium.

Methods: EMERGENT-4 and EMERGENT-5 were 52-week, open-label trials in adults with schizophrenia. EMERGENT-4 was an open-label extension that enrolled participants who completed the treatment period of EMERGENT-2 or EMERGENT-3. EMERGENT-5 was an open-label trial in adults with a confirmed diagnosis of schizophrenia who had no prior exposure to xanomeline/trospium; participants with a Positive and Negative Syndrome Scale total score ≤80 and a Clinical Global Impression–Severity score ≤4 were eligible. All participants initiated twice-daily oral doses of xanomeline/trospium at xanomeline 50 mg/trospium 20 mg and titrated to a maximum dose of xanomeline 125 mg/trospium 30 mg for 52 weeks. Analyses were conducted in the safety population, defined as all participants who received ≥1 dose of trial medication. EPS were broadly defined as any treatment-emergent adverse event (TEAE) with a preferred term of dystonia, dyskinesia, akathisia, or extrapyramidal disorder. EPS were also evaluated using the Simpson-Angus Scale (SAS), Barnes Akathisia Rating Scale (BARS), and the Abnormal Involuntary Movement Scale (AIMS) in both trials.

Results: A total of 718 participants (all xanomeline/trospium) were included in the safety population for analysis. Across the long-term EMERGENT trials, xanomeline/trospium was generally well tolerated in people with schizophrenia. A total of 76.5% of participants experienced ≥1 TEAE, most of which were mild or moderate; 14.5% discontinued due to a TEAE. The most common TEAES were nausea (20.2%), vomiting (17.8%), constipation (15.2%), dry mouth (8.5%), diarrhea (8.4%), and dyspepsia (7.5%). Based on an interim analysis, the overall rate of EPS TEAEs with xanomeline/trospium during 52 weeks of treatment was 3.5%; the most commonly reported EPS TEAE was akathisia (1.3%). The incidence of EPS TEAEs (dystonia, dyskinesia, akathisia, or extrapyramidal disorder) deemed to be treatment related was 0.7%; the most commonly reported treatment-related EPS AE was akathisia (0.6%). The incidence of dose reduction and treatment discontinuation due to EPS TEAEs was < 0.3%. Xanomeline/trospium was associated with no clinically meaningful changes from baseline to week 52 in SAS, BARS, or AIMS scores.

Conclusion: The incidence of EPS TEAEs with xanomeline/trospium was low and not associated with increased scores on EPS scales in the long-term trials. These **Results:** suggest that xanomeline/trospium is effective and well tolerated in schizophrenia with a low EPS risk.

T56. TREATMENT EFFECTS OF OLANZAPINE/SAMIDORPHAN ON NEGATIVE SYMPTOMS IN PATIENTS WITH SCHIZOPHRENIA: A POST HOC ANALYSIS

Roger S. McIntyre[1], Desiree M. Matthews[2], Marni Harris[3], Christina Arevalo[3], Martin Dunbar[3], David McDonnell[4], Christoph U. Correll[5]*

[1]University of Toronto, [2]Different Mental Health, [3]Alkermes, Inc., [4]Alkermes Pharma Ireland Ltd., [5]Donald and Barbara Zucker School of Medicine at Hofstra/Northwell

Abstract Objective: Addressing negative symptoms of schizophrenia can be a treatment challenge. This post hoc analysis examined the long-term effect of the combination of olanzapine and samidorphan (OLZ/SAM) on negative symptoms.

Methods: All adults who completed a 4-week OLZ/SAM study (olanzapine- and placebo-controlled) for the treatment of acute schizophrenia and who had ≥1 postbaseline visit in a 52-week open-label extension study were analyzed. The 4-week study OLZ/SAM, olanzapine, and placebo arms were combined for this analysis, and all patients received OLZ/SAM during the extension. Negative symptoms were assessed with the Positive and Negative Syndrome Scale (PANSS) Marder Negative Symptoms Factor score (Marder, 1997). Changes from the 4-week study baseline were evaluated overall, in a high baseline negative symptoms (Marder Negative Symptoms Factor score ≥24) subgroup, and in a high negative/low positive symptoms subgroup (Marder Negative Symptoms Factor score ≥24, PANSS Mohr [2004] positive symptoms factor score ≤19, and score of ≥4 on 2 of 3 PANSS blunted affect, passive/apathetic social withdrawal, or lack of spontaneity/flow of conversation items).

Results: Patients (n=281) had a mean (SD) PANSS Total score of 101.7 (11.1) and Marder Negative Symptoms Factor score of 25.2 (4.6) at baseline. The mean (SE) change from baseline in Marder Negative Symptoms Factor score at week 56 was (–8.5 [0.41], n=183). Among patients with a Marder Negative Symptoms Factor score ≥24 at baseline (mean, 27.7), the mean (SE) change in Marder Negative Symptoms Factor Score was –9.8 (0.50) at week 56 (n=124). A similar pattern of change was observed for the high negative symptoms/low positive symptoms subgroup (mean [SE] change at week 56, –8.9 [0.90], n=37).

Conclusions: Results of this post hoc analysis suggest that OLZ/SAM provides a treatment benefit for negative symptoms of schizophrenia that is observable over long-term therapy.

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T57. STUDY RETENTION RATES IN THE OLANZAPINE/SAMIDORPHAN PHASE 3 CLINICAL PROGRAM

René S. Kahn[1], Christina Arevalo[2], Marni Harris[2], David McDonnell[3]*

[1]Icahn School of Medicine at Mount Sinai, [2]Alkermes, Inc., [3]Alkermes Pharma Ireland Ltd.

Abstract Objective: Efficacy and safety of the combination of olanzapine and samidorphan (OLZ/SAM) were assessed in 6 phase 3 studies of adults with schizophrenia or bipolar I disorder. We reviewed retention rates across these studies.

Methods: Patients in 3 randomized controlled trials (RCTs) of 1, 3, or 6 months' duration had the option to continue into two 1-year open-label extensions and one 4-year open-label study. Demographics and clinical characteristics were summarized. Proportions of patients completing the treatment period and reasons for study discontinuation were assessed descriptively for each study.

Results: In the RCTs, 134, 211, and 274 patients received ≥1 dose of OLZ/SAM, whereas 277 and 265 in the 1-year extensions and 523 in the 3-month study or the 1-year extensions

who continued into the 4-year open-label study did so. Proportions of patients who completed the OLZ/SAM treatment period were 91.0% (122/134, 1-month trial), 78.2% (165/211, 3-month trial), 64.2% (176/274, 6-month trial), 66.1% (183/277, 1-year extension), and 63.0% (167/265, 1-year extension). In the 4-year open-label study, retention rates were 53.7% (242/451) at 2 years and 32.5% (109/335) at 4 years. Withdrawal by subject was the most common reason for discontinuation from each study (6.0% [8/134, 1-month trial]; 9.5% [20/211, 3-month trial]; 15.5% [43/277, 1-year extension]; 13.6% [36/265, 1-year extension]; 25.4% [133/523, 4-year open-label study]) except the 6-month trial (adverse event, 12.0% [33/274]).

Conclusions: Across the OLZ/SAM phase 3 clinical program, retention rates were high. Overall, 70% of dosed patients completed studies ≤1 year in duration, whereas retention rates were 54% at 2 years and 33% at 4 years in the 4-year open-label study.

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T58. BASELINE SEVERITY OF ILLNESS AND RESPONSE TO TREATMENT WITH ARIPIPRAZOLE LAUROXIL EVERY 2 MONTHS: A POST HOC ANALYSIS OF PHASE 3 ALPINE CLINICAL TRIAL DATA

John Kane[1], Martin Dunbar[2], James A. McGrory[2]*

[1]*The Donald and Barbara Zucker School of Medicine at Hofstra/Northwell,* [2]*Alkermes, Inc.*

Abstract Objective: This post hoc analysis examined the efficacy and safety of aripiprazole lauroxil (AL) by baseline severity of illness in the double-blind ALPINE study (NCT03345979) in patients with schizophrenia treated with AL every 2 months.
Methods: Adults with acute schizophrenia were randomized to AL 1064 mg every 2 months initiated with a NanoCrystal Dispersion formulation of AL (ALNCD) 675 mg or active control (paliperidone palmitate [PP] 156 mg monthly). Based on Clinical Global Impression–Severity scores, baseline severity of illness was categorized as moderate, marked, or severe. Changes from baseline in Positive and Negative Syndrome Scale (PANSS) Total score were assessed at week 25, along with PANSS items related to hostility/excitement. Numbers of patients with activation adverse events (AEs; anxiety, agitation, and insomnia) were also evaluated.

Results: Of 96 AL patients assessed, 31 (32%) were moderately ill at baseline, 52 (54%) were markedly ill, and 13 (14%) were severely ill (PP: moderate, 26/99 [26%]; marked, 57 [58%]; severe, 16 [16%]). With AL treatment, mean ± SE changes from baseline in PANSS Total score at week 25 for each subgroup were −21.1 ± 2.5 (moderately ill; baseline mean, 87.1), −24.1 ± 1.8 (markedly ill; baseline mean, 95.3), and −25.6 ± 6.4 (severely ill, baseline mean, 106.1). With AL treatment, improvements from baseline in PANSS scores related to hostility/excitement items were similar among severity subgroups; a similar pattern was found for PANSS Total scores and those related to hostility/excitement in the PP subgroups. Activation AEs occurred in 7 AL-treated patients (moderate, 3/31 [10%]; marked, 3/52 [6%];

severe 1/13 [8%]) and 10 PP-treated patients (moderate, 5/26 [19%]; marked, 2/57 [4%]; severe, 3/16 [19%]).

Conclusions: In this post hoc analysis, AL efficacy and safety were comparable across baseline severity-of-illness subgroups of patients with schizophrenia.

T59. OPEN BOARD

T60. COMBINED KETAMINE AND DIALECTICAL BEHAVIOURAL THERAPY FOR SUICIDALITY IN COMORBID TREATMENT-RESISTANT DEPRESSION AND BORDERLINE PERSONALITY DISORDER: A PHASE II RANDOMIZED, MIDAZOLAM-CONTROLLED CLINICAL TRIAL PROTOCOL

Orly Lipsitz[*1], *Shelley McMain*[2], *Amer Burhan*[3], *Joshua D Rosenblat*[1]

[1]*University of Toronto,* [2]*Centre for Addiction and Mental Health,* [3]*Ontario Shores Centre for Mental Health Sciences*

Abstract Introduction: Borderline personality disorder (BPD) is a serious mental health condition characterized by significant impairment in areas of affect, identity, interpersonal relationships, and behavioural dysregulation, causing significant distress and functional difficulties. BPD is also strongly associated with death by suicide; up to 10% of individuals with BPD will die by suicide, and an estimated 60-80% of individuals with BPD engage in non-suicidal self-injury. Furthermore, BPD is highly comorbid with major depressive disorder, and an estimated 75% of individuals with comorbid MDD and BPD experience treatment-resistant depression (TRD), which is also associated with an increased risk of suicidality. Despite this elevated risk of suicide in this population, there has been minimal research to date on specialized pharmacotherapy interventions to target suicidality in individuals with both BPD and TRD. While dialectical behaviour therapy (DBT) is a gold-standard treatment for BPD, traditional DBT involves one year of therapy. Pilot studies have shown that intravenous (IV) ketamine effectively reduces suicidal ideation and depression symptom severity in comorbid BPD and TRD, however repeated infusions are required to maintain the effects over time. This clinical trial aims to address whether combining DBT with IV ketamine will result in a greater reduction in SI severity compared to DBT combined with midazolam (active-placebo) infusions in individuals with baseline suicidality and moderate-to-severe comorbid TRD and BPD (TRD-BPD).

Method: This is a phase II randomized, midazolam-controlled clinical trial evaluating safety, tolerability, and efficacy of combining an acute course of IV ketamine with six months of DBT for reducing SI severity in TRD-BPD. Participants will be stratified 1:1 by sex and past year suicide attempt to receive either ketamine or midazolam, with six infusions per week over four weeks; both arms will receive six months of comprehensive DBT. After completing six months of DBT, participants will enter a three-month observational period. The primary endpoint will be Day 35, with month six (i.e., end of DBT) and month nine serving as secondary endpoints. The primary outcome measure will be changes in SI severity as measured using the Modified Scale for Suicidal Ideation (MSSI). Symptoms of suicidal behaviour, depression and personality psychopathology will also be evaluated. Blinding integrity of both participants and research assessors will be measured. Other symptoms and

potential mechanisms will be measured as exploratory outcomes. 120 participants will be recruited to reach a target sample of 48 completers per treatment arm.

Analysis Plan: Primary analyses will be performed on the modified intention-to-treat (ITT) population, including all participants who were randomized and received at least one infusion. The primary analysis will estimate the between group difference in change from baseline to Day 35 in the MSSI, using analysis of covariance (recommended best practice for phase II randomized controlled trials), with Day 35 MSSI as the outcome and baseline MSSI and sex as covariates. Secondary analyses of the primary outcome will use a linear mixed effects model to estimate between-group differences at each assessment point, with particular interest in durability of potential benefits after final infusion (e.g., differences in MSSI and other clinical outcome scores beyond Day 35).

Significance: This study will be the first to evaluate combining IV ketamine with DBT, and the largest clinical trial of ketamine for BPD; findings have significant implications for improving quality of life in individuals with BPD-TRD and reducing suicide-related mortality.

T61. A THEORETICAL EXPLORATION OF THE EFFECT OF PSILOCYBIN ON INSIGHT FROM A NEUROBIOLOGICAL PERSPECTIVE AND ITS CLINICAL IMPLICATIONS

Misbah Alam[1], Mustafa Alam[2], Mujeeb Shad[1]*

[1]*The Valley Health System,* [2]*Alam Medical Research*

Abstract Introduction: Psychedelics have long been utilized as expanders of consciousness in multiple cultures. The reason for the diversity of the individual therapeutic experience and the possible relationship with insight as a metacognitive phenomenon involving multiple internally-oriented processes is unknown. Insight encompasses the ability to recognize the presence of mental illness and correctly identify and reinterpret signs and symptoms as disease pathology. In addition, it helps recognize the importance of treatment as well as the social consequences of psychiatric illness, thus signifying its clinical relevance. However, insight is an understudied phenomenon in mental health, especially in terms of the potential role of psychopharmacology in improving insight. This narrative summary aims to review the findings from the neuroimaging studies with psilocybin and those investigating insight to explain whether there is a connection between the two.
Aim: Our main objective is to explore whether there is any relationship between the impact of psilocybin functional changes and those reported with neuroimaging studies examining the neurobiological substrates of insight.

Methods: No studies have examined the effect of psilocybin directly on insight. However, neuroimaging studies using psilocybin have reported altered activity in the Default Mode Network (DMN). The DMN has also been implicated in studies examining insight as observed in severe mental illness. We reviewed studies showing the effect of psychedelics on DMN and studies analyzing the correlation between insight and DMN on PubMed using the following search string: insight, Neuroscience, Resting State Network, DMN, Psilocybin.

Results: Insight has been linked to altered resting state potentials in the Default Mode Network (DMN), which is an intrinsic network playing a key role in internally directed cognition, self-referential thinking, and creativity. Various neuropsychiatric disorders, including depression, OCD, PTSD, schizophrenia, ADHD, and anxiety, have shown altered functional connectivity (FC) in the DMN, which has also been reported in functional neuroimaging studies with insight. Poor insight may also lower expectations of treatment and although the patient may take medication, the response may be sub-optimal. Psilocybin was shown to decrease FC within the DMN but increase global connectivity. Reduced FC within DMN is also associated with positive states of ego dissolution, a known action of psilocybin, contributing to empathy and self-awareness i.e. recognition of illness, a core component of metacognition. Psilocybin has also been shown to enhance psychological functions that have been associated with insight. For example, sensory alteration associated with psilocybin plays a role in therapeutic outcomes by integrating the somatic and psychological processes and may contribute to somesthetic insight through its action on the DMN.

Conclusion: The findings from the reviewed studies revealed that the neurobiological correlates of insight appear to have similarities with psilocybin-induced brain changes, suggesting a potential for psilocybin to enhance insight. However, this warrants formal neuroimaging and clinical studies to examine our hypothesis; if proven, this research can yield valuable information to improve insight in a patient population known to have a high rate of medication nonadherence. In other words, only a couple of psilocybin microdoses can have an impact on long-term medication adherence in patients using other psychotropic medications. Utilizing psilocybin to improve insight may provide a novel therapeutic approach and improve our treatment efforts.

T62. MATERNAL MENTAL HEALTH OUTCOME AFTER STILLBIRTH DELIVERIES: A SECONDARY ANALYSIS STUDY

Rana Jawish[*1], Rana Jawish[1], Robert Silver[1], Mark Rapaport[2]*

[1]University of Utah School of Medicine, [2]University of Utah Huntsman Mental Health Institute

Abstract Objective: Stillbirth has a significant impact on maternal mental health. The decision to pursue autopsy following stillbirth can yield knowledge about cause of death (COD), however, both the decision to autopsy and receiving information about the COD may impact subsequent maternal mental health outcomes. Our objectives were to examine associations between the decision to autopsy and known COD with subsequent maternal mental health outcomes after stillbirth, and secondarily to determine characteristics and factors associated with poor maternal mental health outcome after stillbirth.

Methods: This was a secondary analysis of singleton stillbirth cases in the Stillbirth Collaborative Research Network case-control study. Primary exposures were decision to perform autopsy (none, partial, full) and autopsy results (known COD, otherwise.) The primary outcome was a composite mental health score derived from the Edinburgh depressive scale, elevated grief, elevated distress, low post-traumatic growth, or self-reported increase in drinking or smoking, assessed 1-3 years after the index pregnancy

Results: Of 620 birthing parents, 272 (44%) participated in the follow-up interviews. Out of 272 participant in follow up study N= 148(54%) had poor mental health at follow-up including depression (26%), elevated distress (25%), grief (18%), increased smoking or drinking (15%), and low resilience (11%). Neither autopsy decision nor knowledge of COD from autopsy were associated with mental health at follow-up (Table 1). Factors associated with poor mental health after stillbirth included childhood physical/emotional abuse/trauma, internalization of anger, chronic autoimmune conditions, prior mental health conditions, low income, and feeling blamed for stillbirth (Table 2). When modeled jointly, only childhood trauma (OR: 4.1 (1.6-10.7)) and low income (2.3 (1.3-4.0)) remained significantly associated with poor maternal mental health at follow-up.

Conclusions: Adverse mental health outcomes were remarkably high 1-3 years after stillbirth and were associated with low income, and prior trauma. Additional follow-up and screening tools could optimize maternal mental health after stillbirth.

T63. ZURANOLONE FOR POSTPARTUM DEPRESSION: WHAT IS THE NUMBER NEEDED TO TREAT, NUMBER NEEDED TO HARM, AND LIKELIHOOD TO BE HELPED OR HARMED?

Leslie Citrome[1], Derek Louie[2], Boyang Bian[3], Xiaotong Jiang[3], Theresa M. Vera[2], Veronica Nguyen[3], Melanie Young[2]*

[1]*New York Medical College,* [2]*Sage Therapeutics, Inc.,* [3]*Biogen Inc.*

Abstract Background: Zuranolone is a positive allosteric modulator of synaptic and extrasynaptic gamma-aminobutyric acid (GABA) type A receptors and a neuroactive steroid approved as an oral, once-daily, 14-day treatment course for adults with postpartum depression (PPD) in the US. The phase 3, double-blind, randomized, placebo-controlled ROBIN (NCT02978326) and SKYLARK (NCT04442503) Studies evaluated the efficacy and safety of zuranolone 30 mg (formulation equivalent to 40 mg of the SKYLARK Study dose) and 50 mg, respectively, for adults with PPD. This post hoc analysis assessed the potential treatment benefit of zuranolone by calculating the number needed to treat (NNT), and number needed to harm (NNH) for the clinically relevant outcomes observed in these studies.
Methods: The 2 studies enrolled females aged 18 to 45 years with a baseline 17-item Hamilton Rating Scale for Depression (HAMD-17) total score ≥26. Zuranolone NNT (i.e., the average number of patients who need to be treated to achieve a positive outcome, such as response/remission) was calculated as the inverse of the absolute risk reduction for achieving HAMD-17 response (≥50% improvement from baseline in HAMD-17 total score) and remission (HAMD-17 total score ≤7) at Days 15 and 45 when patients were off treatment. Zuranolone NNH (i.e., the average number of patients who are treated before an adverse outcome is experienced, such as a treatment-emergent adverse event [TEAE]) was calculated as the inverse of the absolute risk increase for treatment discontinuation due to TEAEs at Days 15 and 45. NNT and NNH were estimated with 95% confidence intervals (CI); conventional values (NNT < 10 and NNH ≥10) were considered to contextualize the clinical relevance of the treatment effects calculated. Likelihood to be Helped or Harmed (LHH) was calculated by dividing NNH by NNT.

Results: Across the SKYLARK and ROBIN Studies, 347 patients (safety analysis sets) received ≥1 dose of zuranolone (n=176) or placebo (n=171), of which 345 patients (zuranolone [n=174] vs placebo [n=171]) were included in efficacy analyses. In a pooled analysis of both studies, a higher proportion of patients achieved response at Day 15 with zuranolone (62.1%) vs placebo (43.9%), with a NNT (95% CI) of 6 (4–13). The NNT (95% CI) for remission at Day 15 (zuranolone, 33.3%; placebo, 19.3%) was 8 (5–21). The NNT (95% CI) for response at Day 45 (zuranolone, 66.1%; placebo, 53.8%) was 9 (5–50), and the NNT (95% CI) for remission at Day 45 (zuranolone, 45.4%; placebo, 27.5%) was 6 (4–13). The NNH (95% CI) for treatment discontinuation due to TEAEs through Day 15 (zuranolone, 2.8%; placebo, 1.2%) was 60 (−80 to −∞, +22 to +∞). At Day 15, the LHH for zuranolone for response and remission versus treatment discontinuation due to a TEAE was 10 and 7.5, respectively.

Conclusions: The low NNT values are consistent with the depressive symptom improvements observed with zuranolone treatment in clinical trials. The high NNH value supports the favorable benefit-risk profile of zuranolone for the treatment of PPD in adults. Zuranolone was 10 or 7.5 times more likely to result in response or remission than treatment discontinuation due to a TEAE, respectively, in this pooled analysis.

T64. TSND-201 (METHYLONE) AS A TREATMENT FOR PTSD: RAPID, ROBUST AND LONG-LASTING ACTIVITY IN PHASE 2

Jennifer Warner-Schmidt[1], Amanda Jones[1], Martin Stogniew[1], Blake Mandell[1], Benjamin Kelmendi[2]*

[1]*Transcend Therapeutics,* [2]*Yale School of Medicine*

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%. Compounds with rapid and long-lasting therapeutic benefit may offer significant advantages over currently available treatments (e.g. SSRIs) that show limited effectiveness. 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. Dysregulated monoamine neurotransmission and deficits in structural and functional neuroplasticity have been observed in PTSD. TSND-201 is a highly selective serotonin, norepinephrine, and dopamine releaser and rapid-acting neuroplastogen. TSND-201 increases neuroplasticity-related gene expression in brain areas associated with PTSD and depression and stimulates neurite outgrowth. Rapid and long-lasting changes in neuroplasticity may help to explain how a drug with a short half-life (~6h in humans) maintains long-lasting beneficial effects. Unlike classic psychedelics, TSND-201 shows no agonist/antagonist activity at the 5HT2A receptor and no hallucinogenic effects in humans or animal models. In preclinical models of PTSD, depression, and anxiety, methylone has demonstrated rapid, robust, and long-lasting antidepressant-like and anxiolytic activity. In clinical studies, TSND-201 has been well-tolerated. Here we present results from IMPACT-1, a multi-center two-part phase 2 clinical trial in participants with PTSD.

Methods: IMPACT-1 Part A was an open-label evaluation of 14 participants, completed in late 2023, and IMPACT-1 Part B is a randomized, placebo-controlled study in approximately 64 participants with PTSD. The study included patients with severe PTSD (CAPS-5 ≥ 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: Results from the open-label portion of the study demonstrated rapid and durable effects on PTSD symptoms. On the CAPS-5, the mean change from baseline after the first dose was -8.4 points and -36.2 points at the end of study (6-weeks after the last dose). Significant improvements in functioning, CGI-I, and sleep were also observed. In patients with comorbid depression, TSND-201 significantly reduced depression symptoms. On the MADRS, the mean change from baseline after the first dose was -8.2 points and -21.4 pts at the end of study. TSND-201 was generally safe and well-tolerated. The results from the placebo-controlled portion of the study are expected in Q2 2025 and will be presented.

Conclusions: TSND-201 has shown 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 and supports potential use for other CNS disorders.

T65. DEVELOPMENT OF GATE-251, AN ORALLY BIOAVAILABLE POSITIVE ALLOSTERIC MODULATOR OF THE NMDA RECEPTOR, TO TREAT MAJOR DEPRESSIVE DISORDER IN SUBJECTS WITH COMORBID INSOMNIA AND ANXIETY

*Anantha Shekhar**[1], *Ronald Burch*[2], *John Donello*[2]

[1]*University of Pittsburgh,* [2]*Gate Neurosciences, Inc*

Abstract: GATE-251 (zelquistinel) is a positive allosteric modulator of the N-methyl-D-aspartate (NMDA) receptor being developed for the treatment of major depressive disorder (MDD). To date, a single ascending dose study and a multiple ascending dose study have defined the pharmacokinetics in plasma and cerebrospinal fluid, and studied the dose-dependence of qEEG alpha power, a biomarker of target activation. An initial phase 2a dose-ranging study has also been completed and a phase 2b study is ongoing in MDD subjects. Safety. GATE-251 has been generally well-tolerated. A total of 493 subjects have received GATE-251. Of these, 133 healthy subjects received 1-10 doses of GATE-251, at doses up to 100 mg orally, and 360 subjects with MDD received 1-14 doses of GATE-251, ranging from 0.25–25 mg per dose. Among 120 healthy subjects, TEAES of > 2% incidence, have been headache, 5.8%, constipation, 3.3%, somnolence, 2.5%, and insomnia, 2.5%. Headache and constipation were of greater incidence in subjects who received GATE-251 compared to placebo (0% of subjects). Post-lumbar puncture syndrome was also prominent in healthy

subjects, with incidence of 7.5% of subjects who received GATE-251 and 6.7% of subjects who received placebo. Among subjects who received GATE-251, the most common treatment-emergent adverse events have been headache and abnormal dreams, both with incidence somewhat greater than in subjects who received placebo.

Pharmacokinetics. Following oral administration (tablet) GATE-251 is rapidly absorbed, with plasma Tmax of 0.5-1.0 hr and terminal t1/2 of 3-4 hr. Tmax in CSF is reached in 4 hr, with absorption from the plasma compartment into the CSF compartment of 20-25%.

Phamacodynamics. qEEG in healthy subjects and subjects with MDD found that alpha power increased in a dose-dependent fashion from 0.1 – 10 mg oral dose within 1 hr. Alpha power increased less at 25 mg compared to 10 mg and was not apparent at 50 mg.

Efficacy in phase 2a dose-ranging study. Following once-weekly oral doses (tablet), reduction in MADRS scores occurred in dose-dependent fashion with little difference compared to placebo noted follow 1 mg doses, some statistically significant time points following 3 mg doses, and maximum efficacy following 10 mg doses, consistent with the dose-response observed for increased qEEG alpha power.

Currently, GATE-251 is being investigated in a double-blind, placebo-controlled, parallel group study of 10 mg tablet administered orally one time each week for 6 weeks. The primary efficacy endpoint is change in the Hamilton Depression Rating Scale-17 (HDRS-17) compared to placebo at the end of Week 6. The main secondary endpoint is change in Clinical Global Impression-Severity compared to placebo at the end of Week 6. In this study screening and baseline HDRS-17 must be > 22, any subject taking another antidepressant at screening must be washed out for at least 14 days prior to randomization and dosing, subjects may not have treatment-resistant MDD, subjects may not have comorbid psychiatric diagnoses, except that subjects must have baseline scores > 15 in the Hamilton Anxiety Rating Scale and the Insomnia Severity Index.

Conclusions: To date, GATE-251 has been generally well-tolerated in healthy subjects and subjects with MDD. GATE-251 has been shown to enhance qEEG alpha power within 1 hr of dosing following oral administration in a dose-dependent fashion. Reduction of HDRS-17 score has demonstrated a similar dose-response to the qEEG alpha biomarker of NMDA receptor activation.

T66. EXPANDED ANALYSIS OF MM120 (LYSERGIDE) FOR GENERALIZED ANXIETY DISORDER: UPDATED FINDINGS ON QUALITY OF LIFE AND DEPRESSIVE SYMPTOMS

Daniel Karlin, MD, MA[1], Todd M. Solomon, PhD[2], Paula L. Jacobsen, PhD[2], Sarah M. Karas, PsyD[2], Jamie M. Freedman, BS[2]*

[1]Mind Medicine Inc., Tufts University School of Medicine, [2]Mind Medicine Inc.

Abstract Introduction: Generalized anxiety disorder (GAD) and major depressive disorder (MDD) are common, highly morbid conditions and manifest as a range of chronic and episodic psychiatric and somatic symptoms. Patients with a primary diagnosis of GAD often exhibit comorbid depressive symptoms, underscoring the 80% construct overlap of GAD and

MDD diagnostic criteria. For both disorders, management is limited by the inefficacy of available treatments and treatment-associated adverse events (AEs). Contemporary drug development for GAD should place increased priority on quality-of-life (QoL), well-being, and depressive symptoms. Primary and key secondary outcomes from a phase 2b (NCT05407064) dose-finding study of a single treatment with MM120 (lysergide D-tartrate) suggest a rapid, safe, and durable dose-dependent response in participants with a primary GAD diagnosis and moderate-to-severe-anxiety. Prespecified secondary analyses showed improvements in co-morbid depressive symptoms.2 Herein, we provide additional results from analyses of functional and QoL assessments and a post hoc analysis of depressive symptoms.

Methods: This phase 2b multicenter, randomized, double-blind, placebo-controlled study of a single dose of 25, 50, 100, or 200µg MM120 (freebase equivalent) vs placebo has previously been described. The effects of MM120 on functional disability, QoL, and sexual dysfunction were assessed throughout the trial by the Sheehan Disability Scale (SDS); the EQ-5D-5L and the Pittsburgh Sleep Quality Index (PSQI); and the Arizona Sexual Experiences Questionnaire (ASEX), respectively. Changes from baseline for each of these measures were analyzed descriptively. Montgomery-Åsberg Depression Rating Scale (MADRS) was collected as a key secondary endpoint. Post hoc analyses examining MADRS change from baseline were performed using a subset of participants with a baseline MADRS of > 26 and at least 1 post-baseline MADRS. Definitionally, these participants had comorbid depressive symptoms in the upper range of moderate to severe. Results for the dose with optimal level of clinical activity on the HAM-A are reported.

Results: The phase 2b study enrolled 198 participants. Placebo-adjusted improvements in functional outcome scales were observed with MM120 100µg at weeks 4 (primary endpoint) and persisted through weeks 12 across the SDS (-6.0 and -6.9), EQ-5D-5L (0.111 and 0.116), EQ VAS of the EQ5 (4.0 and 6.0), and PSQI (-1.6 and -1.6). Most measures showed improvements as early as week 1. At week 12, there was a considerable decrease from baseline in the proportion of male participants who reported sexual dysfunction with MM120 100µg (29.2% at baseline vs 10% at week 12) compared with placebo (15.4 at baseline vs 12.5% at week 12). Similar decreases from baseline were observed in the proportion of female participants who reported sexual dysfunction (75% at baseline vs 46.2% at week 12) compared with placebo (50% at baseline vs 33.3% at week 12). At post hoc analysis, 22 participants of the 40 randomized to receive MM120 100µg had baseline MADRS > 26 (mean baseline MADRS of 32.5 ± 4.6) and a mean change from baseline of -23.3 ± 11.3 and -25.0 ± 9.2 at weeks 4 and 12.

Conclusion: Single treatment with MM120 represents a promising new potential treatment option that demonstrated anxiety reduction and improvement of functional outcome measures in patients with moderate-to-severe GAD, regardless of the presence of comorbid depressive symptoms. Efficacy is also being explored in patients with a primary diagnosis of MDD in a planned Phase 3 program.

T67. DEVELOPMENT AND COGNITIVE DEBRIEFING OF THE ANHEDONIA INTERVIEW RATING SCALE CLINICIAN (AIRS) AND SELF-REPORT VERSION (AIRS-SR)

Jenicka Engler[1], Chris Kelly[2], Miriam Evans[3], Dyanna Domilici[3], Marian Acquino[1], Sean Madden[2], Cynthia McNamara[1], Janet Williams[4], James Murrough[2]*

[1]Cronos, an IQVIA Business, [2]Icahn School of Medicine at Mount Sinai, [3]Adams Clinical, [4]Columbia University

Abstract Introduction: Anhedonia, or a significant loss of interest or inability to experience pleasure, is a core symptom of Major Depressive Disorder (MDD) and a common transdiagnostic feature in other DSM-5-TR disorders. Current anhedonia assessments (e.g., Snaith-Hamilton Pleasure Scale (SHAPS), Dimensional Anhedonia Rating Scale (DARS)) are associated with a number of trial failures, and critiques (e.g., not measuring all anhedonia constructs, including items with little clinical or personal importance, double-barreled items combining severity and frequency, self-report only). The authors developed a clinician Anhedonia Interview Rating Scale (AIRS) to be paired with a self-report (AIRS-SR), that could address these concerns and meet FDA's draft guidance on Patient-Focused Drug Development for Clinical Outcome Assessments.

Methods: The AIRS and AIRS-SR assessments were created by 3 doctoral level expert MDD clinical trial raters (2 psychologists, one psychiatrist) and iteratively revised over 3 years along with an expert psychology scale developer and feedback from anhedonia key opinion leaders from academia and industry. Concepts of interest were based upon feedback from relevant clinical, academic, and industry stakeholders, and patients. A pilot validation study for the AIRS and AIRS-SR along with initial cognitive debriefing (N=10) for both scales was conducted at an academic medical center via an IRB-approved screening study (STUDY-10-00606).

Results: N=10 participants completed the AIRS, AIRS-SR, and cognitive debriefing for each scale. Sample identified as 60% female, 70% white, and mean age was 30.9 years (med=30, std dev=9.8). Primary diagnoses included MDD/Persistent Depressive Disorder (N=5), Generalized/Social Anxiety Disorder (N=2), Posttraumatic Stress Disorder (N=3). AIRS total severity scores ranged from 6 to 68 (mean = 40.8, med=44, std dev=17.1) and frequency scores ranged from 6 to 75 (mean =52.2, med=59, std dev=21.5). Total AIRS Anhedonia Composite scores (severity x frequency) ranged from 12 to 399 (mean=218.7, med=254, std dev=111.6). The AIRS-SR total severity scores ranged from 8 to 50 (mean= 31, med=32, std dev=10.9) and frequency scores ranged from 15 to 52 (mean =34.4, med=35, std dev=9.8). Total AIRS-SR Anhedonia Composite scores ranged from 18 to 200 (mean=86.3, med=95.3, std dev=20.1).

During cognitive debriefing 100% of the sample perceived the AIRS and AIRS-SR assessments to be relevant to their experience of anhedonia and 70% deemed it to be of appropriate duration for such an assessment. Majority of participants felt all of the items should be included, with suggestions to add items to assess hypersomnia, fatigue/energy level, and substance use to cope with emotional numbness. Participants' top 3 relevant and least 3 relevant AIRS and AIRS-SR items were ranked, as well as their perceptions of meaningful change, indicated to be symptoms of only mild severity and occasional frequency (although even a 1-point reduction on severity and frequency on items was noted to be considered a significant improvement). Overall, the introduction, lookback period, and each

of the items on both assessments were generally well understood per qualitative cognitive debriefing.

Conclusion: Our findings support the feasibility and relevance of the novel AIRS and AIRS-SR assessments for transdiagnostic assessment of anhedonia. Future work is needed for scale psychometric validation, and findings from the initial cognitive debriefing will be incorporated to update the scale based upon feedback from participants.

T68. ROBUST ANTIDEPRESSANT EFFICACY OF THE NOVEL 5-HT2A RECEPTOR AGONIST GM-2505 IN A DOUBLE-BLIND, RANDOMIZED, CONTROLLED PHASE 2A TRIAL IN PATIENTS WITH MDD

Gerard Marek[*1], Daniel Umbricht[2], Edward Christian[1], Jason Winters[1], Shane Raines[3], William Leong[1], Laszlo Kiss[1], Zoe Hughes[1], Robert Berman[4], Jorge Quiroz[1], Andrew Kruegel[1], Jonathan Sporn[1]*

[1]Gilgamesh Pharmaceuticals, Inc., [2]Xperimed GmbH, [3]2b Analytics, [4]Yale University School of Medicine

Abstract: GM-2505 is a novel 5-hydroxytryptamine2A (5-HT2A) receptor agonist and serotonin (5-HT) releaser with a short half-life and duration of psychotropic effects. It is currently being investigated for the treatment of major depressive disorder (MDD) and other neuropsychiatric disorders. Described here are the results of a randomized, double-blind, active-controlled Phase 2a trial of GM-2505 in 40 male and female patients with recurrent MDD. All participants were antidepressant-free for at least 6 weeks prior to screening and remained off antidepressant medication throughout the trial. All patients were administered two intravenous doses of GM-2505 with a 2-week interval between dosing. In Arm 1, half of the patients initially received a low dose on Day 1 as active control, which produced measurable, but minimal, psychotropic effects in healthy volunteers (HVs). In Arm 2, the other half received a moderate dose on Day 1, which exerted robust psychedelic effects in HVs. On Day 15, all patients received a high dose, which induced maximal psychedelic effects in HVs. The patients were monitored for safety and antidepressant responses through Day 29, with a priori timepoints for comparing MADRS change from baseline scores at Day 14 and Day 29. This allowed for initial examination of dose-response for efficacy, safety, PK, and PD. Statistically significant decreases in MADRS scores were observed in both study arms and decreases were always greater for Arm 2, which received two robustly psychedelic doses. At Day 14, there was an effect size of ~1.0 for a between-subjects comparison of the least square mean change from baseline in MADRS scores for Arm 2 treated with the moderate dose compared to Arm 1 treated with the active control low dose. At Day 29, two weeks following the high dose, MADRS scores further significantly decreased in both arms based on a within-subject comparison of Day 29 to Day 14 and the MADRS change from baseline in Arm 2 was significantly > in Arm 1 based on a between-subjects comparison. Further, there were robust categorical MADRS response and remission rates indicating that both the moderate and high doses were efficacious. The superior response in Arm 2 also suggests that a regimen of two robustly psychedelic doses, administered two weeks apart, produces greater efficacy than a single robust psychedelic dose. There were no serious

adverse events (SAEs) and the treatment emergent adverse events (TEAE) profile was similar to that in HVs. There were no patients with suicidal ideation and a plan/intent. GM-2505 induced expected transient increases in systolic and diastolic blood pressure and pulse rate. In conclusion, GM-2505 is a promising, best-in-class 5-HT2A receptor agonist with the potential to safely and effectively treat patients with MDD, offering a novel and transformative approach to depression treatment.

T69. EVALUATING THE ASSOCIATION BETWEEN ANTIDEPRESSANT EFFICACY AND DISSOCIATION WITH KETAMINE IN TREATMENT-RESISTANT BIPOLAR DEPRESSION (TRBD)

Sara Di Luch[*1], Diana Orsini[2], Tayyeba Shaikh[1], Rodrigo Mansur[2], Roger McIntyre[2], Joshua Rosenblat[2]*

[1]University Health Network, [2]University of Toronto

Abstract: Introduction: Intravenous (IV) ketamine has demonstrated rapid and robust antidepressant effects at sub-anesthetic doses for treatment-resistant depression. Ketamine induces variable dissociative effects, creating a wide spectrum of "psychedelic experience" intensity between patients. However, whether this mind-altering experience is required for clinical benefits in bipolar depression remains largely understudied.

Methods: We conducted a linear regression on adults (n = 14) with treatment-resistant bipolar depression (TRBD) who received four acute ketamine infusions in an ongoing single-arm, open-label study (NCT05339074) to examine the correlation between the intensity of dissociation and antidepressant efficacy. Antidepressant efficacy was evaluated as a change in depression severity between baseline and after four infusions using the Montgomery-Åsberg Depression Rating Scale (MADRS). Dissociation was assessed after the first infusion using the Clinician-Administered Dissociative States Scale (CADSS).

Results: Depression severity decreased over time, with a mean MADRS score reduction of 10.9 points (± 8.7) from a baseline mean of 24.4 (± 5.7). The mean CADSS score following the first infusion was 22.6 (± 13.1). Linear regression analysis showed no significant correlation between peak CADSS scores and change in MADRS scores ($R^2 = 0.01$), indicating that the intensity of dissociative effects did not predict antidepressant response.

Conclusion: As one of the first studies to evaluate ketamine's dissociative symptoms in TRBD, these findings can significantly challenge existing paradigms surrounding ketamine and related psychedelic therapies, suggesting that ketamine's clinical benefits may not depend on a meaningful psychedelic experience. Further research can lead to the engineering of ketamine-like treatments that minimize psychoactive side effects for improved tolerability.

T70. PREDICTING DIFFICULT-TO-TREAT DEPRESSION BEFORE IT BECOMES TREATMENT RESISTANT

Mark Zimmerman[*1], Daniel Mackin[2]*

[1]*Brown University,* [2]*Dartmouth University*

Abstract Background: There has been longstanding interest in defining and investigating treatment resistant depression (TRD). It is common to classify depressed patients who have not responded to multiple pharmacologic treatment efforts as treatment resistant. Recently, it has been recommended that the TRD be reconceptualized as difficult to treat depression (DTD). This shift emphasizes the importance of a broader conceptualization that requires a more comprehensive assessment and shifts the focus of treatment from a curative/remission model to a disease management model emphasizing functioning and quality of life rather than symptom elimination. It also makes identification of DTD possible prior to failed medication trials. The current study validates of the first self-report scale of DTD, the Difficult to Treat Depression Questionnaire (DTDQ), and assesses its ability to predict DTD prior to treatment failure.

Methods: Patients from a partial hospital program (N = 920) completed the DTDQ, including one item assessing the number of prior failed treatment episodes, prior to treatment. Patients also completed the Remission from Depression Questionnaire (RDQ) at admission and discharge from a partial hospital program as a measure of overall symptoms/functioning, depressive symptoms, non-depressive symptoms, coping ability, positive mental health, functional impairment, and quality of life. Analyses examined psychometric characteristics of the DTDQ, concurrent and predictive validity of the DTDQ, and compared the predictive validity of the DTDQ and multiple failed treatment episodes. These analyses were then replicated using a smaller subsample (n = 211) who did not have multiple prior episodes of treatment failure to examine the predictive validity of the DTDQ in characterizing treatment resistance prior to meeting criteria for TRD.

Results: The DTDQ demonstrated excellent internal consistency and test-retest reliability. Greater scores on the DTDQ were associated with greater symptomatology and worse functioning on all RDQ subscales at admission, discharge, and discharge after controlling for scores at admission. The DTDQ was significantly associated with outcomes after controlling for the number of failed trials, but the number of failed trials did not predict outcome after controlling for DTDQ scores. Patients with DTD according to the DTDQ (highest 25% of sample) demonstrated greater symptomatology and functioning on all RDQ scores at admission, discharge, and discharge controlling for admission RDQ. In the subsample who did not fail multiple treatment trials admission DTDQ scores predicted greater levels of depressive and non-depressive symptoms, and worse coping ability at baseline when controlling for scores at admission.

Conclusions: The DTDQ is a reliable and valid measure of the recently introduced construct of DTD and has good predictive validity. The DTDQ captures important prognostic information related to DTD beyond that accounted for by the number of medication trial failures. Critically, the DTDQ can be used to prospectively identify depressed patients who meet criteria for DTD before they fail multiple treatment trials.

T71. LACK OF GENERALIZABILITY OF PTSD TREATMENT TRIALS: THE RECENT BREXPIPRAZOLE-SERTRALINE TRIALS AS AN EXAMPLE

Mark Zimmerman[1], Matthew Snyder[1]*

[1]*Brown University*

Abstract Background: Two recent studies demonstrated that brexpiprazole combined with sertraline was effective in reducing posttraumatic stress disorder (PTSD) symptoms, and an application has been submitted to the FDA for the combination treatment. When reading the inclusion and exclusion criteria of these studies, we suspected that many patients that we treat in our clinical practice would not have been eligible for the studies establishing the efficacy of the brexpiprazole-sertraline combination. In the present report from the Rhode Island methods to Improve Diagnostic Assessment and Services (MIDAS) project, we determined how many patients with PTSD in our practice would have qualified for the brexpiprazole-sertraline trials.

Methods: The sample was derived from the 3,800 psychiatric outpatients evaluated with semi-structured diagnostic interviews, 417 of whom met DSM-IV criteria for PTSD upon presentation. The clinical protocol of the brexpiprazole-sertraline study listed the exclusion criteria. There were 11 exclusion criteria related to the patients' trauma history or psychiatric condition, almost all of which we assessed and applied to the sample.

Results: Three exclusion criteria were met by the majority of the patients: current major depressive disorder, PTSD age of onset before age 16, and the interval between the onset of PTSD and patients' current age was 10 years or greater. Nearly 95% of patients met at least 1 of the exclusion criteria used in the brexpiprazole-sertraline studies.

Conclusions: While the effectiveness of the brexpiprazole-sertraline combination offers hope for addressing a significant unmet need in the treatment of PTSD, it is concerning that so few of our patients would have qualified for the clinical trials. As a result, we remain uncertain about the medications' effectiveness for most patients treated in clinical practice. We urge regulatory agencies to require industry to conduct studies that better reflect the patient populations seen in clinical practice.

T72. CONVERGING PATHWAYS: SHARED BRAIN ACTIVITY ENGAGED BY MONOAMINERGIC ANTIDEPRESSANTS, KETAMINE AND PSILOCYBIN

*Pavel Osten**[1], *Kadeem Joseph*[1], *Janelle Collins*[1], *Thomas Genovese*[1], *Myran Maxwel*[1], *Jeffrey Lieberman*[2]

[1]*Theracast,* [2]*Columbia University*

Abstract: The discovery of ketamine's therapeutic effects in depression represents the most significant advancement in antidepressant treatment since the development of tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs). Its rapid efficacy in treatment-resistant patients has marked a major therapeutic breakthrough. Unlike conventional monoaminergic antidepressants, which require several weeks to take effect, ketamine can provide clinical relief within a single day—a critical advantage in managing severe depression. To elucidate ketamine's mechanism of action and facilitate the development of related therapeutics, we conducted a whole-brain screen comparing drug-evoked c-fos expression—a marker of neuronal activity associated with synaptic plasticity—following treatment with monoaminergic antidepressants, ketamine, and psilocybin. Our analysis revealed a shared brain circuit comprising interconnected frontocortical and subcortical regions, with a critical difference: c-fos-based activity in the prelimbic and infralimbic frontocortical areas—regions implicated in depression—emerged acutely with

ketamine and psilocybin but only after chronic dosing with the SSRI fluoxetine. Interestingly, a non-hallucinogenic dose of psilocybin failed to evoke frontocortical activity, but retained subcortical monoaminergic antidepressant-like activity. These findings suggest a core subcortico-cortical circuit underlying antidepressant efficacy, provide mechanistic insights into the delayed therapeutic effects of monoaminergic antidepressants, and highlight a potential overlap between monoaminergic antidepressants and psilocybin microdosing.

T73. ANTIDEPRESSANT ITRUVONE NASAL SPRAY DEPOLARIZES NASAL CHEMOSENSORY RECEPTORS FOLLOWED BY INCREASED GAMMA POWER SPECTRAL DENSITY OF THE OLFACTORY BULB IN HEALTHY SUBJECTS

Louis Monti[*1], Danajane Katz[1], Ester Salmán[1], Weiping Zhang[1], Ross Baker[1], Rita Hanover[1]*

[1]*VistaGen Therapeutics, Inc.*

Abstract Introduction: Itruvone nasal spray is a non-systemic rapid-onset neurocircuitry focused investigational pherine in Phase 2 development for the treatment of major depressive disorder (MDD). Within milliseconds of intranasal administration at low microgram-level doses, itruvone activates specific receptors in nasal chemosensory neurons that regulate olfactory-amygdala neural circuits to increase limbic-hypothalamic sympathetic nervous system activity and induce rapid antidepressant effect (1). We studied the pharmacodynamic response of placebo and itruvone on the electrogram recorded from the nasal chemosensory epithelium (EGNR) and the gamma power spectral density (gamma-PSD) of the olfactory bulb electrogram (EBG).

Methods: This was a single-center, randomized, single-blind, placebo-controlled Phase 1 study in clinically healthy male and female volunteers aged 18–60 years to compare the effect of administration of placebo, single spray itruvone (1.6µg/100µL) and double spray itruvone (1.6µg/100µL x 2) on the amplitude and duration of the EGNR, and the gamma-PSD of the EBG. Double nasal spray administration was used to assess the possible cumulative effect of itruvone on the EGNR and the EBG. EGNRs recorded with a non-polarizable silver electrode (0.5mm diam sphere) positioned on the surface nasal chemosensory epithelium and EBGs recorded with EEG electrodes on the skin of the internal eye canthus were continuously monitored and computer stored for offline processing and statistical analysis.

Results: Single spray itruvone increased mean EGNR amplitude (-mV 14.4; P itr/pl $<$ 0.0005) and mean EGNR duration (190.1 msec; P itr/pl= 0.021). Double spray itruvone also increased mean EGNR amplitude (-mV 11.5; P itr/pl =0.02) and mean duration (308.3 msec; P itr/pl $<$ 0.001) from placebo. EGNR duration increased significantly from single to double sopray administration (p= 0.008). Single spray and double spray itruvone showed trend of increased gamma-PSD from placebo (0.032 vs. 0.003 µV2/Hz; P itr/pl= 0.18, t= 1.4; and 0.025 vs 0.003 µV2/Hz; P itr/pl= 0.06, t= 2.1). Mean EGNR latency was 237 msec, and mean EBG latency was 198.9 msec. EBG activation lasted up to 20 seconds after itruvone nasal administration. Insomnia and dizziness were reported by 1 subject and were considered unrelated to study drug. Tolerability was similar for single and double spray itruvone and placebo.

Discussion: Our results show for the first time a correlation between itruvone induced stimulation of nasal chemosensory neurons (EGNR) and rapid activation of the olfactory bulb

gamma-PSD after single and double spray itruvone. Double spray itruvone administration further increased EGNR vs. single spray, and gamma-PSD remained sustained after both, suggesting significant recruitment and sensory integration in olfactory bulb neurons, the first CNS synaptic relay of the itruvone neurocircuits. Olfactory bulb gamma-PSD seems to be a physiologic marker of nasal-amygdala neurocircuit activation to be used in future trials and further supports a near-maximal amplitude effect of the 1.6 µg itruvone dose. As demonstrated in Phase 2A, low microgram dose of non-systemic, neurocircuitry-focused itruvone produced rapid-onset antidepressant effect that will be further tested in a planned Phase 2B study in MDD subjects (2).

T74. PRESCRIBER AND PATIENT-LEVEL CHARACTERISTICS ASSOCIATED WITH ADHERENCE TO ANTIPSYCHOTICS AMONG PATIENTS WITH SCHIZOPHRENIA IN THE UNITED STATES

Arthur Voegel[1], Charmi Patel[2], Lilian Diaz[1], Claire Vanden Eynde[1], Yuxi Wang[1], Ronaldo R Naranjo Jr[2], Dominic Pilon[1], Carmela Benson[2], Leslie Citrome[3]*

[1]Analysis Group, Inc., [2]Johnson and Johnson, [3]New York Medical College,

Abstract Purpose: Adherence to antipsychotics (AP) is an important part of schizophrenia management, which many patients struggle with. While existing real-world studies have evaluated patient level factors associated with adherence, the association between prescriber characteristics and adherence to APs remains unclear. This study aims to address that gap by examining characteristics of patients and prescribers, use of long-acting injectable (LAI) APs, and how these factors are associated with adherence to APs.

Methods: Closed claims from Komodo Research Data (01/01/2016-06/30/2023) were used to identify adult patients with schizophrenia in the US who were newly initiated on an oral or LAI AP (index date) during the intake period (07/01/2021-06/30/2022), by a prescriber who prescribed APs to ≥6 patients with schizophrenia over the intake period (index prescriber). Patients were required to have ≥12 months of continuous insurance eligibility or Medicare Advantage/Medicaid enrollment prior to (i.e., baseline/washout period) and after the index date. Patients with a baseline diagnosis for bipolar disorder or pregnancy were excluded. Patient characteristics were evaluated over the baseline period, and prescriber characteristics were evaluated over the study intake period. Providers were characterized as high, intermediate, and low LAI prescribers based on quartiles of the proportion of LAIs over all APs prescribed during the intake period (low [Q1; ≤8.5% LAIs], intermediate [Q2–Q3; > 8.5% and < 27% LAIs], high [Q4; ≥27% LAIs], with non-LAI prescribers accounted for separately). Adherence to any AP was reported over the fixed 12-month follow-up period and defined as a proportion of days covered ≥80%. multivariate logistic regression was used to evaluate prescriber and patient-level factors associated with adherence.

Results: Of the 22,255 patients included in the study, the mean age was 41 years, 34% were female, and racial/ethnic distribution was 31% White, 31% Black/African American, 17% Hispanic/Latino, 5% Asian, and 15% other/unknown. Most patients were covered by Medicaid (76%), followed by Medicare Advantage (14%), commercial insurance (7%), and unknown coverage (2%). At index, 82% of patients were initiated on an oral AP and 18% on

LAI, with 10% being prescribed by non-LAI prescribers, 21% by low LAI prescribers, 47% by intermediate LAI prescribers, and 22% by high LAI prescribers.

Holding all else equal, patients whose index AP was prescribed by an intermediate and high LAI prescriber had 39% (odds ratio [OR]=1.39; $p < 0.001$) and 63% (OR=1.63; $p < 0.001$) higher odds of adherence, respectively, relative to non-LAI prescribers. Patients with an LAI as the index agent were 25% more likely to be adherent (OR=1.25; $p < 0.001$) relative to those with an index oral AP. Each additional 10 years of patient age was associated with 14% higher odds of adherence (OR=1.14; $p < 0.001$). Relative to White patients, all racial/ethnic minorities were less likely to be adherent (ORs ranging from 0.64 to 0.87; $p < 0.05$).

Conclusion: Irrespective of the mode of administration, this study found higher rates of adherence among patients treated by high LAI prescribers, suggesting that prescriber awareness of challenges with adherence and of the value of LAIs may play a role in improving adherence in patients with schizophrenia. These findings also underscore the importance of improving access to care for ethnic minorities and support the use of LAIs over oral APs to achieve higher adherence.

SPONSORSHIP: Johnson and Johnson

T75. AN OPEN-LABEL STUDY OF SINGLE-DOSE COMP360 PSILOCYBIN FOR POST-TRAUMATIC STRESS DISORDER: SAFETY, TOLERABILITY, AND SECONDARY EFFICACY OUTCOMES

Niall McGowan[1], James Rucker[2], Rachel Yehuda[3], Manish Agrawal[4], Hollie Simmons[1], Shriya Das[1], Guy Goodwin[1]*

[1]Compass Pathfinder Ltd. (a subsidiary of Compass Pathways plc), [2]King's College London, Institute of Psychiatry, [3]Icahn School of Medicine at Mount Sinai, [4]Sunstone Therapies

Abstract Background: Post-traumatic stress disorder (PTSD) is a debilitating condition for which there are few efficacious treatments. Psilocybin is being studied for use in treatment-resistant depression but has not yet been investigated in PTSD.

Methods: A 12-week, phase 2, multicenter, open-label trial conducted at sites in the UK and US investigated the safety and tolerability of a single dose of 25 mg COMP360 psilocybin with psychological support in adult outpatients with moderate-to-severe PTSD (ClinicalTrials.gov ID: NCT05312151). Participants were recruited from the community and referring healthcare providers. Participants taking antidepressant or antipsychotic medications at Screening completed medication washout at least two weeks before Baseline. The primary outcome of the trial was the safety and tolerability of treatment. Safety measures comprised adverse events, electrocardiogram, clinical laboratory tests, vital signs, the Columbia-Suicide Severity Rating Scale and the Brief Psychiatric Rating Scale (Positive Symptom Subscale). Secondary outcomes were change in PTSD symptoms (Clinician-Administered PTSD Scale for DSM-5 [CAPS-5]; and PTSD Checklist for DSM-5 [PCL-5]), functional impairment (Sheehan Disability Scale; SDS) and quality of life (EQ-5D-5L index score).

Results: Twenty-two participants (63.6% female) were enrolled in total, and all completed the 12-week trial. The mean and median [standard deviation (SD)] CAPS-5 score at Baseline

was 47.5 [9.78] indicating that most participants had severe symptoms of PTSD; and the mean duration of PTSD amongst participants was 88.2 [68.65] months. There were no reported treatment-emergent serious adverse events. The most common treatment-emergent adverse events (TEAEs) included headache (n=11; 50.0%), nausea (n=8; 36.4%), crying (n=6; 27.3%), and fatigue (n=6; 27.3%). There were two TEAEs of suicidal ideation that resolved during the study, details of which are described in the poster. Treatment was associated with a clinically meaningful reduction in CAPS-5 score from Baseline at Week 4 (-29.9 [14.06]) and Week 12 (-29.5 [15.43]). This translated to an 81.8% response rate and a 63.6% remission rate at Week 4. Response and remission rates at Week 12 were 77.3% and 54.5%, respectively. PTSD symptom reduction was rapid, and durable indicated by a change from Baseline PCL 5 score (52.1 [13.68]) at Day 2 (-33.5 [14.32]) which was sustained to Week 12 (-34.3 [18.13]). Participants showed an improvement in functional impairment over the 12 weeks of the study; from a mean SDS total score of 22.7 [5.38] at Baseline, there was a -11.7 [8.41] point reduction at Week 4 and a -14.4 [8.21] reduction at Week 12. Quality of life scores improved throughout the study, indicated by an EQ-5D-5L index score of 0.51 [0.287] at Baseline increasing to 0.73 [0.272] at Week 4 and 0.78 [0.269] at Week 12.

Conclusion: Treatment with 25 mg COMP360 was generally well-tolerated and no serious safety concerns were observed. Participants experienced a clinically meaningful and durable reduction in clinician-rated PTSD symptoms, and rapid self-reported improvement by Day 2. Response and remission rates were high and sustained at the end of the trial. Functional impairment was reduced and quality of life scores improved across the 12-week study period.
Results: should be interpreted within the context of the modest sample size and the open-label design with no control comparator. Whilst the results are promising, larger well-controlled studies are required to inform the viability of COMP360 psilocybin as a potential efficacious treatment for PTSD.

T76. EFFECT OF LONG-TERM TREATMENT WITH ADJUNCTIVE CARIPRAZINE ON ANHEDONIA IN PATIENTS WITH MAJOR DEPRESSIVE DISORDER: POST HOC ANALYSIS OF A 26-WEEK OPEN-LABEL STUDY

Andrew J. Cutler[1], Craig Chepke[2], Andrea C. Wilson[3], Jun Yu[3], Ajarvis Cobb[3], Simranpreet Waraich[3]*

[1]SUNY Upstate Medical University, [2]Medical Director, Excel Psychiatric Associates, [3]AbbVie

Abstract Background: Anhedonia is a core symptom of major depressive disorder (MDD) and is associated with the severity of MDD and prolonged disease course in patients. Cariprazine, a dopamine D3-preferring D3/D2 receptor partial agonist, is an approved adjunctive therapy for MDD in adults. A post hoc analysis of pivotal short-term 6- and 8-week, double-blind, placebo-controlled trials showed that cariprazine plus antidepressant therapy (ADT) improves anhedonia symptoms in patients with MDD as assessed by the Montgomery Åsberg Depression Rating Scale (MADRS) anhedonia subscale. However, the durability of adjunctive cariprazine treatment of anhedonia is not known. Here, we describe the results of a post hoc analysis that evaluated the effect of long-term treatment with

adjunctive cariprazine on anhedonia during a 26-week, open-label (OL), flexible-dose phase 3 safety study in patients with MDD.

Methods: Patients with MDD and an inadequate response to ADT who completed an 8-week, phase 3 lead-in study or who were newly recruited into the OL study were treated with flexible-dose cariprazine (1.5–4.5 mg/day) plus ADT for 26 weeks. Anhedonia was assessed using the MADRS anhedonia subscale, which is comprised of 5 item scores (apparent sadness, reported sadness, concentration difficulties, lassitude, and inability to feel). Outcomes included mean (SE) change from baseline at week 26 using observed cases. In addition, the mean change from baseline at the end of the OL treatment period was assessed using the last available observation for all patients. Analyses were based on the intent-to-treat (ITT) population, which included all patients who received ≥1 dose of cariprazine and had baseline and ≥1 postbaseline efficacy assessments.

Results: The ITT population included 336 patients. At baseline, the mean (SE) MADRS anhedonia subscale score was 13.71 (0.31). Adjunctive treatment with cariprazine was associated with reductions from baseline in anhedonia subscale scores at all study visits. Mean (SE) changes from baseline in anhedonia subscale score at week 26 (n=210) and using the last available observation for all patients (N=336) were –6.73 (0.45) and –5.42 (0.37), respectively. Consistent with these results, decreases from baseline in the 5 anhedonia component item scores were observed at all visits. Mean (SE) baseline scores for apparent sadness, reported sadness, concentration difficulties, lassitude, and inability to feel were 2.69 (0.07), 2.93 (0.07), 2.64 (0.08), 2.69 (0.07), and 2.76 (0.07), respectively; at week 26 (n=210), mean (SE) changes from baseline were –1.45 (0.11), –1.48 (0.11), –1.29 (0.10), –1.13 (0.11), and –1.38 (0.12), respectively. Using the last available observation for all patients (N=336), the mean (SE) changes from baseline on the anhedonia-related items ranged from –0.93 (0.09) to –1.23 (0.09).

Conclusions: In this post hoc analysis, long-term open-label treatment with adjunctive cariprazine was associated with improvements in anhedonia for up to 26 weeks. Taken together with previous safety findings from this study, results suggest that long-term treatment with adjunctive cariprazine is safe and well tolerated with potentially durable effects on anhedonia in patients with MDD.

T77. STUDY DESIGN OF BALANCE-AAD-1, A PHASE 2, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL OF THE FAAH/MAGL INHIBITOR BMS-986368 FOR TREATMENT OF AGITATION IN PATIENTS WITH ALZHEIMER DISEASE

Walter Heine[*1], Rachel Heimall[1], Rosa Miceli[1], Brielle Carramusa[1], Yue Zhang[1], Rui Zhao[1], Jennifer Reardon[1], Richard Leigh-Pemberton[1]*

[1]*Bristol Myers Squibb*

Abstract Background: Agitation in patients with Alzheimer disease (AD) is common, disruptive, and associated with disease progression. Brexpiprazole is the only treatment approved for AD-related agitation, highlighting the need for alternative treatment options with improved side effect profiles. While exogenous cannabinoids show promise for

treatment of AD-related agitation, selective enhancement of endogenous endocannabinoid neurotransmission may offer a safer alternative. BMS-986368 is a first-in-class inhibitor of fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL), enzymes that degrade the endocannabinoids anandamide (AEA) and 2-arachidonoylglycerol (2-AG). FAAH and MAGL have been found in excess in postmortem studies of AD. By inhibiting FAAH and MAGL, BMS-986368 increases levels of AEA and 2-AG, which activate cannabinoid receptors CB1 and CB2. CB1 receptors are prevalent in the limbic system, which regulates emotions. Their activation helps reduce neurotransmitter release at presynaptic terminals, generating an anti-excitatory effect that could be beneficial in AD-associated agitation. Phase 1 studies have shown BMS-986368 administration to be safe and well tolerated, with rapid FAAH inhibition and long duration of MAGL inhibition. Objectives: Evaluate efficacy and safety of BMS-986368 vs placebo in treating AD-related agitation as well as pharmacokinetics and effect on caregiver/staff burden.

Methods: BALANCE-AAD-1 is a phase 2, double-blind trial in which participants are randomized (1:1:1) to 1 of 2 doses of BMS-986368 or placebo once daily for 8 wk followed by BMS-986368 at doses up to the higher of the 2 doses for 6 wk in an optional extension. Safety follow-up is 4 wk from last dose. To enroll, participants must have a biomarker-confirmed AD diagnosis meeting Alzheimer's Association criteria and agitation meeting International Psychogeriatric Association criteria, Mini-Mental State Examination-1 score $<$ 21, Neuropsychiatric Inventory Nursing Home Version (NPI-NH) agitation/aggression subscore $\geq$4, a stable living environment (nursing home, assisted living facility, or home) for $\geq$8 wk, and an identified caregiver, and be capable of self-locomotion ($\pm$ assistive device). The primary endpoint is score change from baseline in Cohen-Mansfield Agitation Inventory (CMAI) up to wk 8 completed by the caregiver. Secondary endpoints include Clinical Global Impression of Severity, CMAI domain scores, NPI-NH total and agitation/aggression domain scores, NPI-NH occupational disruptiveness rating for agitation/aggression domain score, plasma concentrations at pre- and post-dose time points, and safety/tolerability. In addition to treatment-emergent adverse events and laboratory abnormalities, safety assessments will include the Sheehan-Suicidality Tracking Scale and the Cannabis Withdrawal Score. Treatment-group comparisons will be assessed using mixed models for repeated measures with baseline, treatment, visit, living environment (nursing home or assisted living facility/home), treatment-by-visit, and baseline-by-visit as covariates.

Results: BALANCE-AAD-1 will enroll approximately 120 participants globally beginning in April 2025.

Conclusions: The endocannabinoid pathway is a promising target for treatment of agitation in patients with AD. Pending efficacy and safety results, BMS-986368 could provide a novel and important new treatment option for AD-associated agitation.

T78. REVISITING LONG-TERM LITHIUM THERAPY AND CHRONIC KIDNEY DISEASE IN BIPOLAR DISORDER: AN UPDATED COHORT STUDY

Idil Tarikogullari[*1], Mete Ercis[1], Vanessa Pazdernik[1], Maria L Gonzalez Suarez[1], Marin Veldic[1], Katherine Moore[1], Hannah Betcher[1], Osama A. Abulseoud[1], Aysegul Ozerdem[1],*

Alfredo Cuellar-Barboza[2], Francisco Romo-Nava[3], Susan McElroy[3], Joanna Biernacka[1], Mark Frye[1], Balwinder Singh[1]

[1]Mayo Clinic, [2]Universidad Autónoma de Nuevo León, [3]Lindner Center of HOPE/University of Cincinnati College of Medicine

Abstract Introduction: Bipolar disorder is a chronic severe psychiatric disorder with significant morbidity. Lithium, the gold-standard therapy for bipolar disorder, is complicated by its narrow therapeutic window and concerns about kidney dysfunction, contributing to its underutilization. Both patient-related and lithium-treatment-related factors are associated with chronic kidney disease (CKD), however, the extent of their impact on CKD progression remains an area of investigation. In our previous analysis, we reported that CKD was observed in one-quarter of patients with BD who had undergone long-term lithium therapy and progression of CKD may be influenced by coexisting comorbidities. In this 5-year extension of our original analysis, we aimed to re-examine the CKD rates and investigate the independent and combined effects of patient-related and lithium-treatment-related factors on CKD progression within the same cohort.

Methods: This study included patients with BD with long-term lithium therapy (> 1 year) who were enrolled in the Mayo Clinic BD Biobank. Data on potential risk factors and CKD diagnosis were extracted from electronic health records. Exposure variables included patient-related factors (age at lithium start, baseline creatinine, comorbidities and nephrotoxic medications) and lithium-treatment-related factors (duration of lithium use, median serum lithium level, history of lithium toxicity, and nephrogenic diabetes insipidus [nDI]). The primary outcome was CKD diagnosis based on the clinical assessment documented in the chart by clinicians and review of renal laboratories. Univariable (adjusted for age and gender) and multivariable Cox proportional hazards regression models were used to estimate the risk of individual patient and treatment-related factors in the progression to CKD.

Results: Among 152 patients (58.6% female, median follow-up of 12.1 years), 36.4% developed CKD (60.7% female). Patients with CKD were older than patients who did not develop CKD at BD diagnosis (35.9±14.7 vs. 29.1±12.3 years, $p < 0.001$) and had higher rates of hypertension (73.2% vs. 36.7%, $p < 0.001$), diabetes mellitus (DM) (33.9% vs. 16.3%, p=0.012), and nDI (28.6% vs. 2.0%, $p < 0.001$). Median lithium levels and duration did not significantly differ between patients who developed CKD and those who did not. Baseline DM (HR=2.13, %95 CI=1.19-3.81, p=0.011), antidepressant use (HR=2.03, %95 CI=1.08-3.81, p=0.028), NSAID use (HR=2.90, %95 CI=1.28-6.55, p=0.010), and development of nDI (HR=10.80, %95 CI=4.13-28.23, $p < 0.001$) were linked to earlier CKD onset. Age at lithium initiation (HR=1.06, 95% CI=1.04-1.09, $p < 0.001$) and nDI (HR=10.57, 95%CI=4.04-27.65, $p < 0.001$) were the only predictors of time-to-CKD.

Conclusion: Among patients with bipolar disorder who received long-term lithium therapy and at least one year of follow-up at an academic medical center, 36% developed CKD. Diabetes mellitus was linked to a higher risk of developing CKD, while nephrogenic diabetes insipidus was the only treatment-related factor associated with CKD. Monitoring patients with these comorbidities and managing their conditions effectively may help reduce CKD risk and progression. Further research is needed to determine if treating nDI can prevent or delay the onset of CKD.

T79. IMPROVEMENT TO QUALITY OF LIFE AND DEPRESSION SHOW INDEPENDENT PATHWAYS IN PSILOCYBIN RESPONSE

Audrey Shoultz[1], Andrew Van der Vaart[2], Scott Aaronson[1]*

[1]Sheppard Pratt Health System, [2]University of Maryland School of Medicine

Abstract Introduction: Psychedelics continue to show efficacy as a potential treatment for depressive disorders. It is still unclear what mechanism could be responsible for changes in functioning after a psychedelic intervention. Two small open-label studies by Aaronson ST, et al. demonstrate the efficacy of psilocybin in improvement of depression and quality of life (QoL) in patients with difficult-to-treat depressive disorders. To explain this finding, we examined whether improvements in depression mediate sustained improvement in QoL or if improvements in QoL mediate sustained improvement in depression.

Methods: N = 20 adults (n = 7 P-TRD, n = 13, BPII) received a single 25mg dose of COMP360 with therapeutic support. The Montgomery Asberg Depression Rating Scale (MADRS) was used to measure depression symptomology. The Quality of Life Enjoyment and Satisfaction Questionnaire Short Form (Q-LES-Q-SF) was used as a proxy for satisfaction with QoL. The scales were administered pre-dose at Baseline and post-dose at Week 3, and Week 12.

Results: Two regressions established the stability, or sustained improvement, within subjects through MADRS and Q-LES-Q scores at two timepoints (Week 3 to Week 12 $\beta = 0.553$ $p = .001$, $\beta = 0.679$ $p < .001$, respectively) Two distinct mediation analyses were performed. Mediation 1 tested whether early improvement in QoL scores (Baseline to Week 3) mediates sustained improvement in depression. In Mediation 1, there was no evidence that QoL improvement had an indirect effect on increasing the stability of depression improvement from Week 3 to Week 12 ($\beta = 0.076$, $p = .419$). Mediation 2 tested whether early improvement in depression scores (Baseline to Week 3) mediates sustained improvement in QoL. In Mediation 2, there was no evidence that depression improvement had an indirect effect on increasing the stability of QoL improvement from Week 3 to Week 12 ($\beta = -0.007$, $p = 0.905$).

Conclusions: Lack of a bidirectional relationship between QoL and depression suggests one or more independent extraneous mediators are aiding symptom improvement. A significant limitation of this conclusion is a low sample size which contributed to underpowered analyses. Additionally, the Q-LES-Q-SF may not capture the entire spectrum of QoL symptom change and individual perceptions. It is crucial to continue exploring possible mediators of psilocybin response to develop effective interventions for these underserved populations.

T80. LONG-TERM SAFETY AND TOLERABILITY OF XANOMELINE AND TROSPIUM CHLORIDE: POOLED RESULTS: FROM THE 52-WEEK, OPEN-LABEL EMERGENT-4 AND EMERGENT-5 TRIALS

Inder Kaul[1], Stephen K. Brannan[1], Sharon Sawchak[1], Tejendra R Patel[1], Soumya Chaturvedi[1], Ayesha Pavithran[1], Amy Claxton[1]*

[1]*Bristol-Myers Squibb*

Abstract Background: Xanomeline/trospium combines the dual M1/M4 muscarinic agonist xanomeline with the peripherally restricted muscarinic receptor antagonist trospium chloride. The combination was recently approved for the treatment of adults with schizophrenia by the U.S. Food and Drug Administration. Xanomeline/trospium was well tolerated and associated with significant improvement in symptoms of psychosis in the 5-week, randomized, double-blind, placebo-controlled EMERGENT-1 (NCT03697252), EMERGENT-2 (NCT04659161), and EMERGENT-3 (NCT04738123) trials of adults with schizophrenia. Here we report a pooled analysis of long-term safety from the 52-week EMERGENT-4 (NCT04659174) and EMERGENT-5 (NCT04820309) trials.

Methods: The acute EMERGENT trials enrolled participants with a confirmed diagnosis of schizophrenia, worsening psychosis symptoms requiring hospitalization, Positive and Negative Syndrome Scale (PANSS) score of 80-120, and Clinical Global Impression–Severity (CGI-S) score ≥4. EMERGENT-4 was an open-label extension trial of participants who completed the treatment period in EMERGENT-2 or EMERGENT-3. EMERGENT-5 employed a similar trial design but enrolled de novo participants with stable schizophrenia symptoms, no prior exposure to xanomeline/trospium, a PANSS score of ≤80, and a CGI-S score ≤4. All participants initiated twice-daily oral doses of xanomeline 50 mg/trospium 20 mg and titrated to a maximum dose of xanomeline 125 mg/trospium 30 mg for 52 weeks. Incidences of spontaneous adverse events were monitored from the time of first trial medication dose during the open-label treatment period until the end of treatment at week 52. Safety analyses were performed in the pooled EMERGENT-4/EMERGENT-5 safety population, defined as all participants who received ≥1 dose of trial medication.

Results: The pooled population included a total of 718 participants treated with xanomeline/trospium. Xanomeline/trospium was generally well tolerated, with no new safety issues compared with the acute trials. Across long-term trials, 549 (76.5%) of people reported ≥1 adverse event (AE). Treatment-emergent AEs (TEAEs) reported by ≥5% of people were nausea (20.2%), vomiting (17.8%), constipation (15.2%), hypertension (9.3%), dry mouth (8.5%), diarrhea (8.4%), dizziness (7.8%), dyspepsia (7.5%), headache (7.2%), and somnolence (5.4%). Treatment-related TEAEs reported by ≥5% of people were nausea (18.8%), vomiting (15.7%), constipation (13.9%), dry mouth (8.2%), dizziness (6.7%), dyspepsia (6.4%), hypertension (6.3%), diarrhea (5.8%), and somnolence (5.0%). Incidences of treatment-related weight decreases (2.5%), weight increases (2.1%), and increases in blood prolactin (0.6%) were low. Further analyses of these investigations are underway and will be presented at the meeting.

Discussion: Pooled analysis of these long-term, open-label trials found that xanomeline/trospium was generally well tolerated in individuals with schizophrenia in an outpatient setting across 52 weeks. In combination with positive efficacy data from the acute and long-term EMERGENT trials, the present results provide additional support for xanomeline/trospium as a new therapeutic option for people living with schizophrenia.

T81. RESULTS: FROM THE PHASE 3, DOUBLE-BLIND, PLACEBO-CONTROLLED VENTURA-1 AND -2 STUDIES OF ATICAPRANT, ADJUNCTIVE

TO ANTIDEPRESSANTS, IN ADULTS WITH MAJOR DEPRESSIVE DISORDER WITH MODERATE-TO-SEVERE ANHEDONIA

Vanina Popova[*1], Maha Ahmad[1], Alexandre Lemle[1], Naim Zaki[1], Filip Delaei[1], Li Nancy Chen[1], Xin Qiu[1], Rama Melkote[1], Michael E. Thase[2], Richard C. Shelton[3], Maurizio Fava[4], Andrew D. Krystal[5], Magali Arons[1], Carla M. Canuso[2], Wayne C. Drevets[1]*

[1]Johnson and Johnson, [2]Perelman School of Medicine, University of Pennsylvania, and Corporal Michael J. Crescenz VAMC,[3]Heersink School of Medicine, University of Alabama at Birmingham, [4]Harvard Medical School, [5]University of California, San Fransisco School of Medicine

Abstract Background: Major depressive disorder (MDD) is complex and heterogeneous with many patients experiencing partial response to standard of care antidepressants (ADs). There is a need for an individualized approach targeting the underlying disease biology known to be associated with specific symptom profiles. Anhedonia, 1 of 2 core MDD symptoms, results from dysregulation in multiple facets of brain reward processing and is associated with a worse MDD prognosis. Aticaprant, a novel, highly selective, kappa opioid receptor (KOR) antagonist, interrupts dynorphin-KOR activation and restores dopamine and serotonin signaling during reward processing. Positive Phase 2 data of adjunctive aticaprant warranted further evaluation in MDD with prominent anhedonia (ANH+).

Methods: The efficacy and safety of adjunctive aticaprant in MDD was evaluated in 2 global, identically designed, 6-week, randomized, double-blind, multicenter, placebo-controlled Phase 3 studies (VENTURA-1 [NCT05455684], VENTURA-2 [NCT05550532]). The studies enrolled adult and elderly participants (pts) with moderate-to-severe, non-psychotic, recurrent or persistent depression with or without prominent anhedonia and inadequate response to current AD. Anhedonia symptoms were assessed by clinical evaluation (DSM-5) and self-report (Snaith-Hamilton Pleasure Scale). Pts were randomized 1:1 to receive oral aticaprant 10 mg or placebo once daily for 42 days, adjunctive to their ongoing AD (SSRI/SNRI). Change from baseline to Day 43 in total scores of Montgomery-Åsberg Depression Rating Scale (MADRS; primary endpoint) and Dimensional Anhedonia Rating Scale (DARS; key secondary endpoint), a novel patient-reported outcome (PRO), were analyzed via a mixed-effect model for repeated measures. Adverse events (AEs) were evaluated.

Results: In VENTURA-1 and -2, respectively, 513 and 444 pts with MDD were randomized, and 511 (aticaprant+AD=253; placebo+AD=258) and 440 (aticaprant+AD=217; placebo+AD=223) received ≥1 dose of study drug and were included in the safety analyses. Of randomized pts with MDD ANH+ in VENTURA-1 and -2, respectively, 337 (aticaprant+AD=170; placebo+AD=167) and 331 (aticaprant+AD=165; placebo+AD=166) received ≥1 dose of study drug and were included in the efficacy analyses. The least squares (LS) mean (SE) of change from baseline to Day 43 in MADRS total score for aticaprant+AD and placebo+AD, respectively, was -12.3 (0.95) and -11.4 (0.98) in VENTURA-1, and -10.0 (0.96) and -9.4 (0.96) in VENTURA-2. MADRS total score improvement with aticaprant+AD vs placebo+AD did not reach statistical significance in either study (2-sided p=0.467 VENTURA-1 and 0.670 VENTURA-2). The LS mean (SE) of change from baseline to Day 43 in DARS total score for aticaprant+AD and placebo+AD, respectively, was 12.0

(1.43) and 10.5 (1.50) in VENTURA-1, and 8.8 (1.39) and 8.2 (1.39) in VENTURA-2. Pts with ≥1 AE totaled 116/253 (45.8%; aticaprant+AD) and 102/258 (39.5%; placebo+AD) in VENTURA-1, and 96/217 (44.2%; aticaprant+AD) and 85/223 (38.1%; placebo+AD) in VENTURA-2. Pruritus and diarrhea were the most common AEs in both studies.

Conclusion: Depressive symptoms improved in both aticaprant+AD and placebo+AD groups with no statistically significant separation demonstrated. The key secondary endpoint based on a novel anhedonia PRO could not be formally tested due to the pre-specified testing hierarchy. The safety profile was consistent with previous experience with no new findings.

T82. RESULTS: FROM EARLY-STAGE TRIALS OF INHALED MEBUFOTENIN (GH001) IN HEALTHY VOLUNTEERS AND PATIENTS WITH TREATMENT-RESISTANT DEPRESSION

Kelly Doolin[1], Velichka Valcheva[1], Claus Bo Svendsen[1], Padraig O'Grady[1], Michael E. Thase[2], Johannes T. Reckweg[3], Johannes G. Ramaekers[3]*

[1]GH Research, [2]University of Pennsylvania, Philadelphia, Corporal Michael J Crescenz Veterans Affairs Medical Center, [3]Faculty of Psychology and Neuroscience, Maastricht University

Abstract Background: Treatment-resistant depression (TRD) affects approximately 30% of patients with major depressive disorder (MDD) and is associated with higher rates of comorbidity, hospitalization, mortality, suicide and a reduced quality of life compared to patients with non-treatment-resistant depression. Only two pharmacotherapies are approved for TRD, highlighting the need for fast-acting, effective, and safe treatments. Mebufotenin (5-methoxy-N,N-dimethyltryptamine [5-MeO-DMT]) is a highly potent natural psychoactive substance from the tryptamine class. GH001 is a synthetic form of mebufotenin for pulmonary inhalation that has been evaluated in Phase 1 and Phase 2 clinical trials in healthy volunteers and patients with TRD, postpartum depression, and bipolar II disorder with a current major depressive episode. Results are presented herein for three early-stage clinical trials in healthy volunteers and patients with TRD.

Methods: Completed early-stage trials include two Phase 1 trials in 68 healthy volunteers (HVs; GH001: N=62; placebo: N=6]) and one Phase 1/2 trial in 16 patients with TRD (GH001: N=16). GH001 was administered via inhalation as single doses (2, 6, 12, 18 mg) or as an individualized dosing regimen (IDR) whereby up to three escalating doses (6, 12, 18 mg) were administered within a single day at intervals of 1-3 hours. Administration of subsequent doses was based on the patient's subjectively reported psychoactive effects and the safety and tolerability at the previous dose. Psychotherapeutic intervention was not a component in these trials, but psychological support per standard of care was available to participants. These trials evaluated the safety, pharmacokinetic, and pharmacodynamic profile of GH001 in HVs, and the safety and antidepressant effects in patients with TRD.

Results: Data from three completed early-stage trials demonstrated that GH001 induces psychoactive effects with an ultra-rapid onset (commonly within seconds) and short duration (commonly 5-30 minutes). Inhalation of GH001 was well tolerated across trials with no severe or serious adverse events reported. Among the 78 patients who received GH001, one or more treatment-emergent adverse events (TEAEs) were observed in 50 patients (64.1%)

with a similar incidence in the single dose and IDR groups. The most frequently reported TEAEs across the trials included headache, anxiety, and nausea. No noteworthy changes in vital signs were observed; transient increases in heart rate and blood pressure immediately after GH001 administration were not clinically significant. Safety assessments, including laboratory analyses, psychiatric scales, electrocardiogram, and cognitive function tests, showed no clinically meaningful changes. The safety profile of GH001 broadly aligns with that observed for other serotonergic psychedelic drugs.

In patients with TRD, remission (Montgomery-Åsberg Depression Rating Scale [MADRS] total score of ≤10) was achieved in 7/8 (87.5%) of patients in the IDR group at Day 8, compared to 3/8 (37.5%) patients in the single-dose group. This suggests that intraindividual dose escalation within a single day may increase the MADRS remission rate compared to single doses of GH001, whilst avoiding exposing the patient to unnecessarily high doses.

Conclusion: GH001 may represent an ultra-rapid, convenient, effective treatment for TRD and other depressive disorders without requirements for psychotherapeutic intervention before or after dosing.

T83. POPULATION-LEVEL CHANGES IN SUBSTANCE USE TRENDS BASED ON CRIMINAL JUSTICE SYSTEM INVOLVEMENT: FINDINGS FROM THE 2023 NATIONAL SURVEY ON DRUG USE AND HEALTH

Shruti Patil[*1], Manish Jha[1], Abu Minhajuddin[1]*

[1]*University of Texas Southwestern Medical Center*

Abstract: The American Criminal Legal System incarcerates over 5 million people in prisons, jails, and community supervision (i.e., parole, probation), and this population faces a heavier burden of substance use disorders (SUD), mental illness, and infectious and chronic diseases than compared to the general population. Presence of SUDs is often a barrier to addressing other health needs and may perpetuate continued involvement with legal system and contribute to recidivism. Therefore, understanding changes in substance use trends within this population, which may be differ from those observed in the general population, will inform development of targeted outreach and SUD treatment approaches for these individuals.

Using publicly available data from the 2023 National Survey on Drug Use and Health (NSDUH) that is conducted by the Substance Abuse and Mental Health Services Administration (SAMHSA) that included data on past-month substance use in years 2022 and 2023. We used descriptive statistics as well as chi square test to compare the substance use rates between probation and non-probation populations in years 2022 and 2023. We used a conservative statistical significance threshold of $p < 0.001$ to account for multiple comparisons.

Several trends were noted in the 2023 NSDUH survey. The probation population grew from 3.045 to 3.264 million people between 2022 and 2023, and the non-probationary group grew from 250.459 to 251.544 million people. Within the probation subpopulation, rates of methamphetamine use significantly increased between 2022 and 2023 from 6.1% to 7.9% ($p < 0.001$), while rates of marijuana use significantly dropped from 39.4% to 32.8% ($p <$

0.001), cocaine use significantly dropped from 5.3% to 3.4% ($p < 0.001$), and alcohol use dropped from 47.2% to 43.5% ($p < 0.003$). Within the non-probation subgroup, between 2022 and 2023, rates of marijuana use significantly increased from 15.5% to 16.1% ($p < 0.001$). In the same period, rates of cocaine use decreased from 0.7% to 0.6% ($p < 0.007$), methamphetamine use decreased from 0.6% to 0.5% ($p < 0.02$), opioids use significantly decreased from 1% to 0.8% ($p < 0.001$), and alcohol use significantly decreased from 53.1% to 51.8% ($p < 0.001$). Although generally rates of substance use have declined between 2022-2023, probationary populations are still significantly more likely to have past-month substance use for the following substances as compared with non-probationary populations: marijuana ($p < 0.001$), cocaine ($p < 0.001$), methamphetamines ($p < 0.001$), and opioids ($p < 0.001$). Alcohol was a notable exception to this trend with non-probationary populations being more likely to report past-month use as compared with probationary populations ($p < 0.001$).

These trends should be contextualized within probationary drug testing limitations and the complex forces driving substance use. However, these trends underscore the need for developing targeted outreach and treatment approaches for individuals with substance use disorders who have criminal justice system involvement.

T84. DO CENTRAL RATERS REMAIN BLINDED IN A LARGE PSYCHEDELIC CLINICAL TRIAL?

Javier Muniz, MD[1], Sarah M. Karas, PsyD[1], Adam Kolar, PhD[1], Todd M. Solomon, PhD[1], Daniel R. Karlin, MD, MA[2]*

[1]Mind Medicine Inc., [2]Mind Medicine Inc., Tufts University of Medicine

Abstract Introduction: Maintaining rater blinding is a critical methodological consideration in clinical trials of psychoactive drugs, particularly for psychedelic compounds.1-2 While many psychiatric drugs face some degree of participant unblinding due to perceivable drug effects, whether adverse or intended, psychedelic drugs at therapeutic doses reliably produce profound, transient perceptual effects. This inherent characteristic of the drug category significantly increases the risk of participant and site functional unblinding, potentially undermining the interpretability of clinical trial outcomes. Although central raters (CRs) are not exposed to participants' transient drug experience, their blinding could still be compromised through spontaneous participant responses or by rating evaluations that show minimal or no indication burden. This study assessed whether CRs administering key endpoint assessments in a clinical trial of lysergide D-tartrate (LSD or MM120) remained blinded to participant treatment allocation.

Methods: Data were collected during a phase 2b multicenter, randomized, double-blind, placebo-controlled, dose-finding study (NCT05407064) evaluating MM120 in adults diagnosed with generalized anxiety disorder (GAD) and moderate-to-severe anxiety as defined by a Hamilton Anxiety Scale (HAM-A) of ≥20. Participants were randomized equally across 5 arms to receive a single dose of MM120 (25µg, 50µg, 100µg, 200µg) or placebo. At each study visit (Screening, Baseline, Weeks 1, 2, 4, 8, and 12), CRs were randomly assigned to participants to administer the HAM-A and Montgomery-Åsberg Depression Rating Scale (MADRS). CRs conducted evaluations via audio calls and were

blinded to study information, including visit number, participant details, and treatment allocation. After completing both assessments during each visit, CRs completed the Rater Blinding Questionnaire (RBQ), a 5-point Likert scale: 1) I am certain the subject received the active drug; 2) I believe that the subject received the active drug; 3) I am unable to discern whether the subject received the active drug or placebo; 4) I believe the subject received placebo; or 5) I am certain the subject received placebo.

Results: The study screened 554 and randomized 198 participants. CRs completed 1586 unique RBQs. In over 80% of RBQs collected from the Screening Visit to Week 12, CRs selected item 3, indicating that they were unable to determine treatment allocation. At Week 4, the study's primary endpoint, 71% of RBQs reported item 3, confirming CRs' inability to discern treatment allocation. Only 12% of assessments at Week 4 indicated that CRs were certain a participant had received active drug. This trend remained largely consistent as the dose of active drug increased, suggesting that the use of CRs effectively mitigated bias throughout the study.

Conclusion: This is the first large randomized controlled trial of a psychedelic drug to collect data on CR unblinding. Analysis of RBQs indicates most CRs were unable to distinguish active drug from placebo at the primary endpoint and throughout the trial. These findings support the use of CRs as a viable strategy to maintain blinding when assessing key endpoints in clinical trials of drugs with pronounced subjective effects. Future research should further explore the effectiveness of CR blinding, including interplay with participant and site staff potential unblinding, and the impact of maintaining blinding on CR and site rater outcome assessments, and potential impact on data interpretability.

T85. ROPANICANT (SUVN-911), AN α4β2 NACHR ANTAGONIST: OUTCOME OF A PHASE-2A CLINICAL TRIAL EVALUATING THE SAFETY AND EFFICACY IN PARTICIPANTS WITH MODERATE TO SEVERE MAJOR DEPRESSIVE DISORDER

Ramakrishna Nirogi[1], Abdul Rasheed Mohammed[1], Veera Raghava Chowdary Palacharla[1], VIjay Benade[1], Jyothsna Ravula[1], Satish Jetta[1], Vinod Kumar Goyal[1], Ramkumar Subramanian[1], Santosh Kumar Pandey[1], Pradeep Jayarajan[1], Anil Shinde[1]*

[1]Suven Life Sciences

Abstract Background: Ropanicant (SUVN-911) is a potent and selective α4β2 nicotinic acetylcholine receptor (nAChR) antagonist. In animal models, Ropanicant was orally bioavailable in rats, mice, and dogs with good brain exposures in rats and dose-dependent brain α4β2 receptor occupancy. Ropanicant demonstrated antidepressant like effects in diverse animal models of depression. Safety pharmacology, genotoxicity, and general toxicity profile support for therapeutic development of Ropanicant. Further, Ropanicant was found to be safe and well tolerated following single and multiple oral administrations in healthy subjects in Phase 1 study.

Methods: An open-label parallel-group study evaluated the safety and efficacy of Ropanicant in patients with moderate to severe major depressive disorder (MDD) at several study centers in the USA (NCT06126497). The primary objective of the study was to assess the safety of

Ropanicant in patients with MDD. The secondary objectives included evaluation of Ropanicant for efficacy and pharmacokinetics in MDD patients. Following a screening period of up to 4 weeks, patients were treated for 2 weeks. A total of 41 patients were randomized to receive Ropanicant either 45 mg once a day (QD), 30 mg twice a day (BID), or 45 mg BID in a ratio of 1:1:1. Safety assessments included 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 included change from baseline in Montgomery–Asberg Depression Rating Scale (MADRS) and Clinical Global Impression of severity (CGI-S). Pharmacokinetics was assessed on day 1 and day 14 in patients receiving BID treatment.

Results: Of the 41 randomized patients, 14 patients received Ropanicant 45 mg QD, 14 received Ropanicant 30 mg BID, and 13 received Ropanicant 45 mg BID. The absolute values of MADRS total score for each treatment arm were analyzed using an analysis of variance (ANOVA) model (with SAS Proc Mixed procedure), with the main effects as randomized treatment, visit, treatment-by-visit interaction, and stratification factor gender as fixed effects and participant as random effect. On Day 14, the MADRS total score had changed significantly from baseline for the Ropanicant 30 mg bid group (-12.7), followed by the Ropanicant 45 mg qd (-10.5), and Ropanicant 45 mg bid (-10.4) groups. Day 14 MADRS total score showed a highly statistically significant improvement from baseline ($p < 0.0001$) across Ropanicant treatment arms. No statistically significant differences were observed between the Ropanicant treatment arms. On Day 14, the mean (standard deviation) CGI-S score had changed notably from baseline for the Ropanicant 30 mg bid group (-1.3 [1.06]), followed by the Ropanicant 45 mg bid (-1.0 [0.91]) and Ropanicant 45 mg qd (-0.8 [0.93]) groups. Ropanicant administered at 45 mg qd, 30 mg bid, or 45 mg bid was safe and well tolerated in patients with moderate to severe MDD.

Discussion: The highly statistically significant improvement in the MADRS total score suggested potential treatment benefits of Ropanicant in MDD patients. As a follow-up, Phase 2b, randomized, double-blind, placebo-controlled, parallel-group, multicenter trial to evaluate efficacy and safety of Ropanicant in patients with major depressive disorder has been initiated.

T86. PHARMACOKINETIC AND SAFETY COMPARISON OF MM120 (LYSERGIDE) CAPSULES AND ORALLY DISINTEGRATING TABLETS IN HEALTHY ADULTS

Ezekiel Powdar, MS[1], Nithya Srinivas, PhD[1], Todd M. Solomon, PhD[1], Sarah Karas[1], Jamileh Jemison, MD, MA[1], Amy Engel, MS[1], Daniel R. Karlin, MD, MA[2]*

[1]Mind Medicine Inc., [2]Mind Medicine Inc., Tufts University School of Medicine

Abstract Introduction: Generalized anxiety disorder (GAD) and major depressive disorder (MDD) represent leading causes of disease burden, possess overlapping symptomatic and diagnostic profiles, and often exist as comorbid conditions. A phase 2b dose-finding study of a single treatment with MM120 (lysergide D-tartrate) suggests a rapid, safe, and durable dose-dependent response in participants with moderate-to-severe GAD. Considering the

efficacy and safety profile observed in the phase 2b study, MM120 100µg (freebase-equivalent) is considered an acceptable therapeutic dose. This phase 1 study compared the pharmacokinetic (PK), subjective effect, and safety profiles of the phase 2b capsule formulation at 100µg with a new 100µg orally disintegrating tablet (ODT) formulation that was subsequently included in the phase 3 program.

Methods: This was a phase 1, multicenter (two sites), open-label, randomized, 2-period, 2-sequence, cross-over, within-subject study designed to compare the plasma PK profile of 2 MM120 formulations in healthy adults aged 18 to 55 years. All participants received a single dose of each formulation (capsules or ODT) in separate evaluation periods, separated by a 2-week washout period between dosing. Participants were randomized equally to receive either four 25-µg MM120 capsules followed by 100µg MM120 ODT or ODT followed by capsules. Plasma concentrations of MM120 were determined by validated bioanalytical method. The PK and analysis of relative bioavailability between the 2 formulations were performed using Phoenix WinNonlin. Subjective effects were assessed using the Visual Analogue Scales (VAS) and 5-Dimensional Altered States of Consciousness (5D-ASC) scale, and descriptive statistics were presented for each category. Adverse events (AEs) were summarized for each treatment group by system organ class and preferred term. Terms used to identify AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA v26.0).

Results: A total of 29 participants were randomized, and 24 participants received each MM120 formulation as a single dose. MM120 ODT showed a faster onset of plasma concentrations than MM120 capsules, retaining similar relative bioavailability for Cmax. For AUC, the GMR for MM120 ODT was 16% higher compared with MM120 capsules. Similar to PK profiles, the VAS scores showed an earlier onset of effects for MM120 ODT compared with capsules. Maximum drug effect VAS scores were reported at 3 and 4 hours post-dose for participants receiving MM120 ODT or capsules, respectively. In both formulations, the most frequently reported treatment-emergent adverse events (TEAEs) were from the system organ class of psychiatric disorders. Twenty-three (79.3%) and 22 (75.9%) participants reported 69 and 65 TEAEs after receiving MM120 ODT and capsules, respectively. Of these, participants receiving MM120 ODT compared with capsules reported similar rates of visual hallucinations (58.6 vs 51.7%), euphoric mood (48.3 vs 41.4%), and illusion (20.7 vs 17.2%).

Conclusion: This is the first study to characterize the PK of 100µg MM120 in both capsules and ODT formulations. The ODT formulation had bioavailability similar to that of the capsule. ODT absorption occurred faster compared with capsules and there was a more rapid onset of acute drug effects in the ODT formulation. Most TEAEs were mild to moderate after a single dose of both formulations and were consistent with the expected acute effects of MM120. This study demonstrated that 100µg MM120 ODT was an acceptable formulation to take forward in clinical development. Phase 3 programs are underway to investigate MM120 100µg ODT as a potential treatment for GAD and are planned for MDD.