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ANNUAL MEETING

ABSTRACTBOOK

PSYCHIATRY AND AI: PROMISES, PERILS, AND PATHWAYS FORWARD

LOEWS MIAMI BEACH HOTEL | MIAMI, FLORIDA

MAY 26-29, 2026

Tuesday, May 26, 2026

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

Panel Sessions

***NOVEL TARGETS AND TREATMENTS FOR STIMULANT USE DISORDERS AND DEPRESSION**

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

Overall Abstract: There are no US Food and Drug Administration (FDA)-approved pharmacotherapy options for the treatment of cocaine or methamphetamine use disorder (often referred to together as stimulant use disorder). Individuals with stimulant use disorders have often co-occurring and/or lifetime depression. There is thus an urgent need to identify other novel treatments, given that over 2 million adults in the United States suffer from these disorders, and overdose deaths involving these substances have increased exponentially over the past decade. The most recent wave of the opioid overdose epidemic has been driven, in part, by an increase in illicit stimulant use and fentanyl contamination. Challenges in treatment of stimulant disorders is also expected to worsen with the recently increasing trend of individuals receiving stimulant prescriptions accompanied by increases in prescription stimulant use disorders. To address these concerns, we propose a panel presentation comprised of individuals across the career span which will include presentations ranging from groundbreaking clinical trials, to neuroimaging with novel social-dynamic paradigm, and interventional experiments with intermittent theta burst stimulation (iTBS) and integration of CBT and TMS. Presentations include a neuroimaging study of circuit-level dysfunctions associated with social-neurobehavioral phenotype in individuals with cocaine use disorder as a foundation for advancement of social-related treatment targets (Bachi); the very first clinical trial of a glucagon-like peptide 1 (GLP-1) receptor agonist (tirzepatide, a dual GLP-1/glucose-dependent insulintropic peptide agonist) for methamphetamine use disorder (Jha); a feasibility trial of an accelerated course of intermittent theta burst for methamphetamine use disorder (Haque); and the first pilot study of augmenting perinatal rumination-focused cognitive-behavioral therapy with repetitive transcranial magnetic stimulation to enhance antidepressant response and modulate neurocircuitry in moderate–severe MDD (Jawish). Together, these presentations will provide an overview of cutting-edge research that may further our understanding of the circuitry-mechanisms underpinning stimulant use disorders and depression and outcomes of innovative trials to provide foundation for the development of novel and effective treatments.

Learning Objective 1: Learn about mechanisms of novel potential targets for treatments of stimulant use disorders and prenatal depression.

Learning Objective 2: Learn about outcomes of recent pilot and clinical trials that examine new potential targets for treatments of stimulant use disorders and prenatal depression.

Literary References:

1. Sahani, V., Hurd, Y.L., Bachi, K. (2022). "Neural Underpinnings of Social Stress in Substance Use Disorders." *Curr Top Behav Neurosci*.

2. Henney AE, Riley DR, Heague M, Roberts CA, Hydes TJ, Anson M, Hughes DM, Alam U, Cuthbertson DJ. (2025). Relative efficacy of GLP-1 and GLP-1/GIP receptor agonists in the prevention of alcohol-use disorders using a target trial emulation approach. *Diabetes Obes Metab*.
3. Li Y, Yang B, Ma J, et al. (2024). Assessment of rTMS treatment effects for methamphetamine addiction based on EEG functional connectivity. *Cogn Neurodyn*, 18(5):2373–2386.
4. Jawish, R., M. Smid, A. Gordon, K. Shangraw and B. J. Mickey (2024). "Prolonged transcranial magnetic stimulation in a pregnant patient with treatment-resistant depression: a case report." *J Med Case Rep* 18(1): 512.

SOCIAL-NEUROBEHAVIORAL PHENOTYPES FOR ADVANCEMENT OF SOCIAL-TARGET INTERVENTION IN COCAINE USE DISORDER

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

Individual Abstract Background: Cocaine use disorder (CUD) and childhood trauma, commonly co-occurring, feature concurrent social dysfunction that profoundly impact treatment outcomes. Yet, social dysfunction is understudied and has limited recognition as a treatment target in this population.

Methods: Participants [CUD n=32; healthy controls (HC) n=38] completed a naturalistic social navigation functional magnetic resonance imaging (fMRI) task. To probe the neural correlates of social decision-making, we used representational similarity analysis, with region-of-interest approach to test two predictions: 1) the social trajectory effect for CUD participants would be reduced in prefrontal cortex, specifically in right inferior frontal gyrus (rIFG), a region involved in processing navigational demands 2) individuals with higher childhood trauma would have a reduced social trajectory representation in left hippocampus, given the region's sensitivity to stress.

Results: We observed a smaller pattern similarity effect in CUD than HC in the rIFG ($t = -2.16$, right-tailed $p < 0.05$), suggesting altered engagement of this region during social navigation in CUD. Independent of CUD status, childhood trauma negatively correlated with the pattern similarity effect in the left hippocampus ($t = -2.88$, right-tailed $p < 0.01$), a region previously shown to track abstract social locations.

Conclusions: CUD-related prefrontal dysfunction and childhood trauma-related hippocampal dysfunction extend to the neural tracking of social relationships. Childhood trauma had similar reductions in left hippocampal effects in both CUD and HC participants, suggesting that the effect of trauma on representing social relationships is separable from the effects of cocaine addiction. Social-neurobehavioral phenotypes may inform the development of novel social-target interventions in substance use disorders.

Literature References:

1. Sahani, V., Hurd, Y.L., Bachi, K. (2022). "Neural Underpinnings of Social Stress in Substance Use Disorders." *Curr Top Behav Neurosci*.
2. Schafer, M., Kamilar-Britt, P., Sahani, V., Bachi, K., Schiller, D. (2024). "Neural Trajectories of Conceptually Related Events." *eLife* DOI 10.7554/elife.96895.1.

FEASIBILITY AND PRELIMINARY EFFICACY OF TIRZEPATIDE FOR INDIVIDUALS WITH MODERATE/SEVERE METHAMPHETAMINE USE DISORDER

Manish Jha, University of Texas Southwestern Medical Center

Individual Abstract: Glucagon-like peptide-1 (GLP-1) agonists have gained recent attention for drug repurposing to treat substance use disorder. Yet, tirzepatide, a dual agonist of GLP-1/glucose-dependent insulinotropic polypeptide, has not been studied systematically, especially for methamphetamine use disorder (MtUD).

Methods: This interim analysis included participants with moderate/severe MUD who received eight weeks of treatment with tirzepatide (2.5 mg/week for 4 weeks, then 5.0 mg/week for 4 weeks) for a weight-related indication (NCT06745128). Craving over the past week was assessed using Visual Analog Scale (VAS; 0=did not crave methamphetamine at all, 100=had the most intense craving possible). Current craving was assessed using 10-item Stimulant Craving Questionnaire (STCQ). Depression, anxiety, anhedonia, activity impairment and gastrointestinal symptoms were assessed weekly using Quick Inventory of Depressive Symptomatology Self-Report (QIDS-SR), 7-item Generalized Anxiety Disorder (GAD-7) scale, Snaith Hamilton Pleasure Scale (SHAPS), Work Productivity and Activity Impairment (WPAI) scale, and Gastrointestinal Symptom Rating Scale (GSRS), respectively.

Results: Of the 42 individuals screened, 35 were enrolled [20 females/15 males; mean (standard deviation, SD) age = 46.1 (8.3) years]. Two individuals dropped out after the first dose due to gastrointestinal side effects. Overall adherence to weekly injection visits was 95.0%. Mean (SD) of BMI, weight (in pounds), VAS, STCQ, QIDS-SR, GAD-7, SHAPS, WPAI activity impairment and GSRS at baseline were 35.9 (7.5), 224.8 (50.7), 57.0 (24.8), 41.6 (12.4), 8.2 (4.4), 8.7 (6.7), 2.4 (2.9), 29.4 (31.7), and 25.4 (11.2), respectively. After eight weeks of treatment with tirzepatide, there were significant reductions in BMI [estimate(β)= -2.3, standard error(SE)= 0.2, $p < 0.001$], weight (β = -14.5, SE= 1.0, $p < 0.001$), VAS (β = -20.4, SE= 5.2, $p < 0.001$), STCQ (β = -9.8, SE= 2.6, $p < 0.001$), QIDS-SR (β = -2.6, SE= 0.7, $p < 0.001$), GAD-7 (β = -3.5, SE= 1.0, $p=0.001$), and WPAI-activity impairment (β = -14.7, SE= 5.1, $p=0.004$) but no changes in SHAPS ($p=0.72$) and GSRS ($p=0.98$).

Conclusions: This study supports the feasibility of using tirzepatide for MUD and provides preliminary evidence for its efficacy in MUD by reducing craving for methamphetamine, depression, anxiety, and daily activity impairment.

Literature References: Hendershot CS, Bremner MP, Paladino MB, Kostantinis G, Gilmore TA, Sullivan NR, Tow AC, Dermody SS, Prince MA, Jordan R, McKee SA, Fletcher PJ, Claus ED, Klein KR. Once-Weekly Semaglutide in Adults With Alcohol Use Disorder: A Randomized Clinical Trial. *JAMA Psychiatry*. 2025 Apr 1;82(4):395-405.

Henney AE, Riley DR, Heague M, Roberts CA, Hydes TJ, Anson M, Hughes DM, Alam U, Cuthbertson DJ. Relative efficacy of GLP-1 and GLP-1/GIP receptor agonists in the prevention of alcohol-use disorders using a target trial emulation approach. *Diabetes Obes Metab*. 2025 Oct 7.

ACCELERATED COURSE OF INTERMITTENT THETA BURST FOR METHAMPHETAMINE USE DISORDER: FEASIBILITY AND EEG-DERIVED FUNCTIONAL CONNECTIVITY CORRELATES OF TREATMENT RESPONSE

Nabila Haque, University of Texas Southwestern Medical Center

Individual Abstract Background: Intermittent theta burst stimulation (iTBS) has been shown to reduce craving in individuals with methamphetamine use disorder (MUD). Low retention rates, due in part to housing and transportation challenges, is a common barrier which may be overcome using accelerated iTBS protocols. Concurrent electroencephalography (EEG) offers the potential to measure brain network-level effects of iTBS in MUD. Here, we evaluated the feasibility of an accelerated iTBS protocol in MUD and explored EEG-derived connectivity changes with iTBS.

Methods: Participants received 50 sessions of open-label iTBS of left dorsolateral prefrontal cortex (L-DLPFC) over a three-week-period (NCT06424184). Resting state EEG (eyes-closed) was recorded before and after the first iTBS session. EEG-derived power envelope source space connectivity was computed using the Schaefer 100-parcel atlas for default mode (DMN), visual (VIS), somatomotor (SMN), dorsal attention (DAN), salience (SN), limbic (LN), and frontoparietal (FPN) networks. Craving was assessed using a visual analog scale (VAS) before treatment and self-rated ability to control use (11-point Likert scale, 0= no ability and 10=complete ability) was assessed after first treatment each day. Depression severity was assessed with the 16-item Quick Inventory of Depressive Symptomatology Self-Report version.

Results: Of the 14 participants [4 females/ 10 males; mean (standard deviation, SD) age: 44.5 (8.6)], 12 completed at least 45 sessions. After three weeks of accelerated iTBS, there was significant reduction in craving [est. (95% CI): -18.79 (-34.20, -3.37)] and QIDS-SR [est. (95% CI): -3.36 (-4.74, -1.97)] and significant improvement in self-rated ability to control methamphetamine use [est. (95% CI): 1.36 (0.28, 2.43)]. A single iTBS session was associated with increased DMN-FPN connectivity (FDR-adjusted $p < 0.05$). Greater SMN connectivity with LN (rspearman = 0.71, $p=0.015$), SN (rspearman = 0.72, $p=0.012$) and DMN (rspearman = 0.69, $p=0.018$) after the first session was associated with higher self-reported ability to control use.

Conclusions: These findings suggest accelerated protocols enable delivery of therapeutic doses of iTBS to individuals with MUD. iTBS targeting L-DLPFC may increase DMN-FPN connectivity, reduce craving and improve ability to control methamphetamine use.

Literature References: Su H, Chen T, Jiang H, et al. Intermittent theta burst transcranial magnetic stimulation for methamphetamine addiction: A randomized clinical trial. *Eur Neuropsychopharmacol.* 2020;31:158–161.

Li Y, Yang B, Ma J, et al. Assessment of rTMS treatment effects for methamphetamine addiction based on EEG functional connectivity. *Cogn Neurodyn.* 2024;18(5):2373–2386.

INTEGRATING COGNITIVE-BEHAVIORAL THERAPY WITH REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION (CBT/TMS): A NOVEL COMBINED NEUROMODULATION-PSYCHOTHERAPY MODEL FOR PRENATAL DEPRESSION

Rana Jawish, University of Utah School of Medicine

Individual Abstract Background: Perinatal depression affects approximately 11.5% of pregnant individuals, with up to 1 in 7 women experiencing depressive symptoms during pregnancy. Despite its prevalence, 50–70% of cases go undiagnosed and nearly 85% untreated in the United States. Untreated prenatal depression is associated with preterm birth, low birth weight, congenital anomalies, and increased maternal risk of hypertension, preeclampsia, and gestational diabetes. A key transdiagnostic process within perinatal depression is repetitive negative thinking (RNT)/rumination, which predicts impaired maternal–fetal attachment, greater late-pregnancy depression and anxiety, and increased postpartum psychopathology. Rumination is linked to dysregulated activity in the default mode network (DMN)—particularly the PCC and vmPFC—as well as altered cognitive control network (CCN) functioning. Disrupted DMN–CCN connectivity is associated with impaired inhibitory control and heightened negative affect. Both rTMS and rumination-focused CBT (RF-CBT) independently modulate these neural networks: rTMS alters DLPFC–ACC connectivity, while RF-CBT changes medial PFC–ACC and fronto-limbic circuitry. Prior adult studies combining CBT with TMS demonstrate 66% response and 56% remission with sustained effect at follow-up. Emerging data support the safety and efficacy of TMS in pregnancy, with clinical trials, open-label studies, and case series—including Jawish et al. (2024)—demonstrating symptom improvement without major maternal or fetal adverse outcomes.

Objective: This pilot study is the first to evaluate whether augmenting perinatal TMS with RF-CBT enhances antidepressant response and modulates neurocircuitry underlying rumination. We hypothesize synergistic effects on depressive symptoms, rumination severity, DMN–CCN connectivity, and functional outcomes.

Methods: Pregnant individuals with moderate–severe MDD receive protocolized left-DLPFC rTMS combined with weekly RF-CBT. Outcomes include QIDS/EPDS change, WHODAS functioning, rumination indices, and exploratory fMRI.

Conclusion: Integrating TMS with RF-CBT may represent a novel, mechanism-informed, multimodal treatment for perinatal depression—targeting both symptoms and

Literature References:

1. Van Niel MS, Payne JL. Perinatal depression: A review. *Cleve Clin J Med*. May 2020;87(5):273-277. doi:10.3949/ccjm.87a.19054
2. Dagher RK, Bruckheim HE, Colpe LJ, Edwards E, White DB. Perinatal Depression: Challenges and Opportunities. *J Womens Health (Larchmt)*. Feb 2021;30(2):154-159. doi:10.1089/jwh.2020.8862
3. Becker M, Weinberger T, Chandy A, Schmukler S. Depression During Pregnancy and Postpartum. *Curr Psychiatry Rep*. Mar 2016;18(3):32. doi:10.1007/s11920-016-0664-7
4. Stein A, Lehtonen A, Harvey AG, Nicol-Harper R, Craske M. The influence of postnatal psychiatric disorder on child development. Is maternal preoccupation one of the key underlying processes? *Psychopathology*. 2009;42(1):11-21. doi:10.1159/000173699
5. McNamara J, Townsend ML, Herbert JS. A systemic review of maternal wellbeing and its relationship with maternal fetal attachment and early postpartum bonding. *PLoS One*. 2019;14(7):e0220032. doi:10.1371/journal.pone.0220032
6. Hamilton JP, Farmer M, Fogelman P, Gotlib IH. Depressive Rumination, the Default-Mode Network, and the Dark Matter of Clinical Neuroscience. *Biol Psychiatry*. Aug 15 2015;78(4):224-30. doi:10.1016/j.biopsych.2015.02.020

7. Hvenegaard M, Watkins ER, Poulsen S, et al. Rumination-focused cognitive behaviour therapy vs. cognitive behaviour therapy for depression: study protocol for a randomised controlled superiority trial. *Trials*. Aug 11 2015;16doi:ARTN 344
10.1186/s13063-015-0875-y
8. Donse L, Padberg F, Sack AT, Rush AJ, Arns M. Simultaneous rTMS and psychotherapy in major depressive disorder: Clinical outcomes and predictors from a large naturalistic study. *Brain Stimul*. Mar-Apr 2018;11(2):337-345. doi:10.1016/j.brs.2017.11.004
9. Cohen SL, Bikson M, Badran BW, George MS. A visual and narrative timeline of US FDA milestones for Transcranial Magnetic Stimulation (TMS) devices. *Brain Stimul*. Jan-Feb 2022;15(1):73-75. doi:10.1016/j.brs.2021.11.010
10. Pettman D, O'Mahen H, Blomberg O, Svanberg AS, von Essen L, Woodford J. Effectiveness of cognitive behavioural therapy-based interventions for maternal perinatal depression: a systematic review and meta-analysis. *BMC Psychiatry*. Mar 29 2023;23(1):208. doi:10.1186/s12888-023-04547-9
11. Sockol LE. A systematic review of the efficacy of cognitive behavioral therapy for treating and preventing perinatal depression. *J Affect Disord*. May 15 2015;177:7-21. doi:10.1016/j.jad.2015.01.052
12. Gatta G, Di Grezia G, Cuccurullo V, et al. MRI in Pregnancy and Precision Medicine: A Review from Literature. *J Pers Med*. Dec 23 2021;12(1)doi:10.3390/jpm12010009
13. Jacobs RH, Watkins ER, Peters AT, et al. Targeting Ruminative Thinking in Adolescents at Risk for Depressive Relapse: Rumination-Focused Cognitive Behavior Therapy in a Pilot Randomized Controlled Trial with Resting State fMRI. *PLoS One*. 2016;11(11):e0163952. doi:10.1371/journal.pone.0163952
14. Hizli Sayar, G., E. Ozten, E. Tufan, C. Cerit, G. Kagan, N. Dilbaz and N. Tarhan (2014). "Transcranial magnetic stimulation during pregnancy." *Arch Womens Ment Health* 17(4): 311-315.
15. Jawish, R., M. Smid, A. Gordon, K. Shangraw and B. J. Mickey (2024). "Prolonged transcranial magnetic stimulation in a pregnant patient with treatment-resistant depression: a case report." *J Med Case Rep* 18(1): 512.
16. Kim, D. R., E. Wang, B. McGeehan, J. Snell, G. Ewing, C. Iannelli, J. P. O'Reardon, M. D. Sammel and C. N. Epperson (2019). "Randomized controlled trial of transcranial magnetic stimulation in pregnant women with major depressive disorder." *Brain Stimul* 12(1): 96-102.
17. Lawson McLean, A. and R. Jawish (2025). "Transcranial magnetic stimulation for major depressive disorder during pregnancy." *Clin Neurophysiol* 178: 2110939.

***CONDUCTING CLINICAL TRIALS USING COMBINED TREATMENT MODALITIES: CHALLENGES, OPPORTUNITIES, AND INSIGHTS FOR FUTURE REGULATORY CONSIDERATION**

Samuel Wilkinson, Yale School of Medicine

Overall Abstract: Advances in interventional psychiatry have created new opportunities to combine therapeutic modalities in clinical trials to improve outcomes for patients with treatment-resistant psychiatric disorders. This panel presents the work of three labs (Pittsburgh, Yale, Calgary) that have developed lines of research of trial evaluating the feasibility and efficacy of combined treatment modalities. Here, we outline methodological

principles and insights from these efforts. The principles employed by the approach of these three labs include: (1) interventional techniques capable of rapidly altering dysfunctional neural circuits; (2) psychological or behavioral interventions that capitalize on periods of enhanced neuroplasticity; or (3) pharmacologic or biologic treatments with rapid onset or synergistic mechanisms. Early trials suggest that coordinating treatments within windows of enhanced plasticity may amplify therapeutic effects, though definitive efficacy data require larger controlled trials. The panel will discuss challenges and opportunities of these trial designs, as well as recent feasibility and efficacy data. The discussant (Yaseen from FDA) will converse ways that regulatory authorities consider combined modality treatment trials. The insights from this panel are highly applicable to ongoing discussions about how best to move forward in multimodality treatment design, including in the nascent psychedelic space, which often combines powerful biological therapies with a psychotherapeutic approach.

Learning Objective 1: To understand the challenges and opportunities of designing and conducting trials of combined treatment modalities

Learning Objective 2: To understand the challenges and limitations of the regulatory aspects of these trial designs

Literary References:

1. Beyond magic bullets: true innovation in health care. Narayan VA, Mohwinckel M, Pisano G, Yang M, Manji HK. *Nat Rev Drug Discov*. 2013 Feb;12(2):85-6.
2. A Novel, Brief, Fully Automated Intervention to Extend the Antidepressant Effect of a Single Ketamine Infusion: A Randomized Clinical Trial. Price RB, Spotts C, Panny B, Griffo A, Degutis M, Cruz N, Bell E, Do-Nguyen K, Wallace ML, Mathew SJ, Howland RH. *Am J Psychiatry*. 2022 Dec 1;179(12):959-968.

COGNITIVE BEHAVIORAL THERAPY FOLLOWING ESKETAMINE FOR MAJOR DEPRESSION AND SUICIDAL IDEATION FOR RELAPSE PREVENTION: THE CBT-ENDURE STUDY

Samuel Wilkinson, Yale School of Medicine

Individual Abstract: Objective: Suicide is a public health crisis in the US, with limited evidence demonstrating efficacy of treatments for high-risk patients due in part to their exclusion from most clinical trials. This study evaluates the feasibility of the adjunctive use of cognitive behavioral therapy (CBT) to esketamine in patients with major depression and suicidal ideation (MDSI).

Methods: Treatment-seeking patients (57 inpatients; 36 outpatients) with MDSI were randomized to receive esketamine plus a 16-week course of CBT or esketamine plus treatment as usual alone (TAU). The primary outcome was feasibility, with a key secondary outcome being improvement in suicidal ideation.

Results: 93 subjects were randomized with a 72% study completion rate, demonstrating feasibility (primary outcome) by meeting recruitment goals of 80% of targeted enrollment and 70% of retention through study endpoint. Change in suicidal ideation from baseline through week 26 (a key secondary outcome), based on the Beck Scale for Suicidal Ideation (BSSI), Clinician Global Improvement Scale for Suicide Severity (CGI-S), Montgomery-Asberg Depression Rating Scale, Suicidal Ideation item (MADRS) favored the CBT group over the TAU group (BSSI mean difference of -1.91, 95% CI -3.57 to -0.24, $p=0.025$; CGI-S mean difference of -0.33, 95% CI -0.58 to -0.08, $p=0.011$; MADRS mean difference of -3.77,

95% CI -6.62 to -0.93, $p=0.009$). No difference between groups was observed in the CSSRS score, MADRS-SI score, or suicide-related events.

Conclusions: This study demonstrates the feasibility and potential effectiveness of combining CBT with esketamine to reduce suicidal ideation and prevent relapse in patients with MDSI.

Literature References:

1. Cognitive behavioral therapy following esketamine for major depression and suicidal ideation for relapse prevention: The CBT-ENDURE randomized clinical trial study protocol. 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. *Psychiatry Res.* 2023 Dec;330:115585.
2. Beyond magic bullets: true innovation in health care. Narayan VA, Mohwinckel M, Pisano G, Yang M, Manji HK. *Nat Rev Drug Discov.* 2013 Feb;12(2):85-6.

INTERIM DATA FROM A RANDOMIZED PLACEBO-CONTROLLED TRIAL OF ACCELERATED TRANSCRANIAL MAGNETIC INTERMITTENT THETA-BURST STIMULATION AND ADJUNCTIVE D-CYCLOSERINE FOR SUICIDAL IDEATION

Alexander McGirr, University of Calgary

Individual Abstract Background: Suicide is a major public health problem and one of the most tragic outcomes in psychiatry. Individuals with a history of suicidal behavior are at elevated risk for reattempting suicide. Our preliminary data suggests that pharmacologically enhancing transcranial magnetic intermittent theta-burst stimulation (iTBS) with the partial NMDA receptor agonist, D-Cycloserine, leads to rapid resolution of suicidal ideation and reductions in implicit suicide risk as measured by the Death/Suicide Implicit Association Test. Here, among individuals with a past history of suicidal behavior and a recurrence of suicidal ideation, we test the anti-suicidal effects of D-Cycloserine pharmacological enhancement of twice-daily iTBS.

Methods: A sample of $n=54$ adults are planned for this 2-week, single-site, randomized placebo-controlled trial. Eligibility is based previous at least one previous suicide attempt based on the Columbia Suicide Severity Rating Scale, current moderate severity depressive symptoms ($HRDS-17 \geq 15$), and current suicidal ideation (MADRS suicide item $10 \geq 4$). Participants are randomized in a 1:1 ratio to daily placebo or D-Cycloserine (100mg) before receiving iTBS treatments. These consist of twice-daily iTBS separated by 60 minutes to the left dorsolateral prefrontal cortex using the BeamF3 method, for a total of 20 treatments over 10 days. The primary outcome is change in performance on the D/S-IAT from baseline to post-treatment. Secondary outcomes include change in suicidal ideation, change in depressive symptoms, and change in suicidal behaviors over a 6-month follow up period.

Results: Interim analyses with prespecified stopping and unblinding criteria are scheduled for $n=39$ of a planned sample of $n=54$ adults. Current enrollment stands at $n=25$.

Conclusion: This clinical trial tests the anti-suicidal efficacy of pharmacologically enhanced accelerated iTBS. Superiority of iTBS+D-Cycloserine over iTBS+Placebo would inform a novel treatment strategy for a population uniquely deserving of treatment options.

Literature References: Cole J, Sohn MN, Harris AD, et al. Efficacy of adjunctive D-Cycloserine to intermittent theta-burst stimulation for major depressive disorder: a randomized clinical trial. *JAMA Psychiatry* 2022; 79:1153–1161

Sohn MN, Cole J, Bray S, and McGirr A. Intermittent theta-burst stimulation with adjunctive D-Cycloserine rapidly resolves suicidal ideation and decreases implicit association with death/suicide *Psychol. Med.* (2025), Article e13

SYNERGISTIC BIOBEHAVIORAL TREATMENTS TO REDUCE DEPRESSION AND COMPULSIVITY

Shabnam Hossein, University of Pittsburgh

Individual Abstract: Approximately 40-60% of psychiatric patients exhibit treatment resistance to first-line interventions. This is associated with high burden on the health care system and longer suffering for the patients. As such, novel psychiatric interventions that are fast-acting and rooted in disorder pathophysiology are needed. One novel approach is to combine rapid-onset, plasticity enhancing biological interventions with digital behavioral trainings to achieve a synergistic effect. This talk will outline examples of our recent and ongoing work aimed at developing and testing such synergistic treatment combinations in refractory clinical populations. The first example explores adding a brief cognitive training (automated self-association training; ASAT), designed to mechanistically target low self-worth, to enhance the therapeutic effects of ketamine. In a published study, 154 adults with treatment-resistant unipolar depression were randomized in a double-blind, parallel-arm design to receive an active/active treatment combination (ketamine plus active ASAT; N=53) or one of two control arms that lacked either the active drug component (saline plus active ASAT; N=51) or the active behavioral component (ketamine plus sham ASAT; N=50). One day after a single infusion of intravenous ketamine (0.5 mg/kg over 40 minutes) or inert placebo (saline), active ASAT—targeting self-worth through automated “evaluative conditioning” training delivered by computer—or sham ASAT (consisting of identical computer tasks that included no positive or self-referential stimuli) was given, delivered twice daily over 4 consecutive days (eight total sessions, ≤20 minutes per session). Results of this trial showed that depression scores in the ketamine+ASAT group remained significantly and stably low relative to those of the saline+ASAT group for a total of 90 days ($p < 0.05$). By contrast, depression improvements following ketamine+sham treatment were far more transient, remaining significantly improved for < 12 days. These results suggested that after priming the brain with ketamine, training positive self-associations could provide an efficient, low-cost, portable, noninvasive, and highly dissemination-ready strategy for leveraging and extending ketamine’s rapid antidepressant effects. Several ongoing lines of work seek to expand on these promising initial findings, including studies testing the effectiveness of this treatment pairing in real-world populations and settings (e.g., among inpatients hospitalized following a suicide attempt; or when embedding ASAT into real-world specialty ketamine clinics); and a randomized controlled trial pairing ASAT with a novel, investigational NMDA compound in lieu of ketamine. In another line of research focused on compulsive behaviors, we have built directly on optogenetic studies in mice, using non-invasive brain stimulation techniques (Theta Burst Stimulation), paired with computer-based cognitive training, as a novel combination treatment approach. Our first published study showed a beneficial effect of continuous Theta Burst Stimulation (cTBS) followed by a computerized ‘habit override’ task on idiographic compulsive behaviors measured in the lab among 70 patients, with improvements persisting for 1 week following our ultra brief (single session) combination

treatment (p 's < 0.05). This talk will include results of ongoing work in a larger cohort of > 200 patients which leveraged a fully crossed (2x2) factorial design to compare outcomes following a single session of either cTBS or sham TBS paired with either our computer-based 'habit override' task or a sham variant of the training.

Literature References: Price RB, Wallace ML, Mathew SJ, Howland RH. One-year outcomes following intravenous ketamine plus digital training among patients with treatment-resistant depression: a secondary analysis of a randomized clinical trial. *JAMA Netw Open*. 2023;6(5):e2312434.

Price RB, Gillan CM, Hanlon C, et al. Effect of experimental manipulation of the orbitofrontal cortex on short-term markers of compulsive behavior: a theta burst stimulation study. *Am J Psychiatry*. 2021;178(5):459-468.

***NOVEL THERAPEUTICS WITH ENTACTOGENIC EFFECTS - A NEW FRONTIER FOR MOOD AND ANXIETY DISORDERS?**

Hiroe Hu, National Institute of Mental Health

Overall Abstract: This panel will offer an overview of novel entactogenic compounds with potential therapeutic application in mood and anxiety disorders and a platform to discuss assessment of entactogenic outcomes. Entactogens are compounds that enhance prosocial behavior and empathy without necessarily possessing hallucinogenic properties. Empathy in psychiatric illness is a complex and understudied construct, hindered by heterogeneous definitions and limited objective tools. To ground the relevance of entactogenic mechanisms in clinical populations, the panel will begin by describing proposed components of empathy: perception of self and others, emotion regulation, social reward processing, and reinforcement of prosocial behavior through learning. The first presenter will discuss EMP-01, a novel R-MDMA derivative in development to retain the prosocial effects of racemic MDMA—the “prototype” entactogen—while minimizing adverse physiologic effects. The presentation will review mechanistic and clinical data on EMP-01 as a treatment for Social Anxiety Disorder (SAD). This discussion will highlight the rationale for entactogens as candidate treatments targeting heightened social threat sensitivity, reduced social reward, and impaired learning in SAD. The next two presentations will describe the effect of repeated doses of intravenous ketamine on subjective symptoms related to social reward. Though not traditionally considered an entactogen, the entactogenic properties of ketamine were recently demonstrated through a reverse translational study (Hess et al., 2024). The second panelist will summarize ketamine's reported entactogenic effects in the literature, then present new data showing that repeated doses of open-label intravenous ketamine reduce social anhedonia in individuals with treatment-resistant depression (TRD) and suicidal thoughts. The third presenter will report ketamine's effect on subjective loneliness from a randomized midazolam-controlled trial in a cohort of individuals with treatment-resistant bipolar depression (TRBD). Both groups displayed decreases in loneliness over time. The magnitude of change was comparable mid-point, although greater in the ketamine arm only at endpoint, suggesting possible delayed effects. While exploratory, these studies suggest ketamine may influence social reward processing and alleviate subjective social disconnection—core but underappreciated features of mood disorders. The second and third presenters will conclude by discussing potential pharmacological mechanisms underlying ketamine's entactogenic effects and their therapeutic potential in mood disorders. The final presenter will share results from a pilot study in healthy volunteers using a prosocial learning task, which showed that prosocial learning rates to benefit others (but not oneself) correlated with positive mood

during the task, suggesting a link between mood, empathy, and reinforcement. Presenter will outline future directions examining this paradigm in patients with depression and suicidal ideation pre/post-ketamine, and to close, elaborate on the importance of multimodal outcomes (self-report, behavioral, neuroimaging, biomarkers) to assess entactogenic effects. This panel synthesizes emerging work on entactogenic therapeutics and the development of measurable empathy-related constructs as transdiagnostic markers of social impairment. Broader topics—such as how entactogens differ from "empathogens" and psychedelics, designs for future mechanistic trials, and applications to other psychiatric disorders—will also be addressed through discussion.

Learning Objective 1: Describe the neurobiological and clinical rationale for entactogenic compounds—such as EMP-01 and ketamine—as emerging treatments targeting social impairments in mood and anxiety disorders

Learning Objective 2: Evaluate multimodal approaches (e.g., behavioral tasks, neuroimaging, biomarkers) for assessing empathy, social anhedonia, and prosocial learning as transdiagnostic treatment targets in psychiatric populations.

Literary References:

- Hess EM, Greenstein DK, Hutchinson OL, et al. Entactogen Effects of Ketamine: A Reverse-Translational Study. *Am J Psychiatry*. 2024;181(9):815-823.
- Stocker K, Liechti ME. Methylenedioxymethamphetamine is a connectogen with empathogenic, entactogenic, and still further connective properties: It is time to reconcile “the great entactogen-empathogen debate.” *J Psychopharmacol*. 2024;38(8):685-689.

EMP-01 (R-MDMA) AS A NEXT-GENERATION ENTACTOGEN: MECHANISTIC RATIONALE AND THERAPEUTIC POTENTIAL IN SOCIAL ANXIETY DISORDER

Sarah McEwen, Atai Beckley

Individual Abstract: The purpose of this presentation is to review mechanistic and clinical evidence supporting entactogen-mediated modulation of social threat and social reward systems in Social Anxiety Disorder and to outline the clinical development strategy for EMP-01. SAD is a highly prevalent, chronic, fear-based condition involving heightened social threat sensitivity, reduced social reward, impaired social learning and accompanied by persistent avoidance that restricts functioning. Current treatments are only partially effective and often leave these interpersonal fear structures insufficiently addressed. Entactogens—including racemic MDMA and next-generation R-MDMA—derived therapeutics—produce acute prosocial states, including increased emotional openness, self-compassion, and social approach behavior while reducing negative responses to rejection. Rather than producing stimulant-like activation, R-MDMA produces a more introspective experience that may support reprocessing of maladaptive schemas. Preliminary clinical evidence from a pilot RCT of racemic MDMA in patients with SAD supports entactogenic mechanisms (Danforth et al., 2018). It yielded large, durable LSAS reductions and improved interpersonal functioning. Regarding the putative mechanisms underlying the therapeutic efficacy of MDMA, preclinical studies have shown that MDMA can reopen a serotonergic and oxytocin-dependent critical period of social reward learning (Nardou et al., 2019), which may reduce social withdrawal and shame. And studies of racemic and R-MDMA have shown they can facilitate extinction of fear learning. Human neuroimaging studies elucidating the

neurobiological targets of MDMA show that it modulates thalamocortical signaling—enhancing top-down cortical influence and reducing bottom-up threat-related thalamic drive to the insula and ACC—thereby altering sensory, interoceptive, and social evaluative networks implicated in SAD. Theoretical models propose that MDMA modulates affective and cognitive systems underlying social dysfunction by reducing shame and social threat, enhancing affiliative motivation, increasing cognitive flexibility, and supporting corrective social learning. Together these mechanisms align closely with core SAD pathophysiology and provide a strong rationale for entactogenic therapeutics, especially entactogens with an improved safety profile for patients relative to racemic MDMA. EMP-01 is an R-MDMA derivative currently in development to preserve these prosocial and entactogenic properties of racemic MDMA while improving tolerability and reducing physiologic burden. In our Phase 1 first-in-human study, EMP-01 was safe and well tolerated across ascending doses and produced dose-dependent prosocial states - including increased openness, emotional breakthroughs, oceanic boundlessness and interpersonal insight. These results support EMP-01's potential to modulate social threat circuits and enhance adaptive social learning in SAD. Data from the ongoing Phase 2a randomized, placebo-controlled clinical trial of EMP-01 in 60 SAD patients are not yet available; however, late-breaking findings are anticipated for the 2026 ASCP meeting. Together, these mechanistic and clinical findings highlight entactogens as a promising new therapeutic class for conditions characterized by interpersonal fear and maladaptive social learning. EMP-01 represents the first R-MDMA-derived compound to enter Phase 2 testing for SAD, advancing the field by offering a potentially safer, more tolerable entactogenic approach.

Literature References: Nardou R, Lewis EM, Rothhaas R, et al. Oxytocin-dependent reopening of a social reward learning critical period with MDMA. *Nature*. 2019;569(7754):116-120.

Danforth AL, Grob CS, Struble C, et al. MDMA-assisted therapy for social anxiety in autistic adults: A randomized, double-blind, placebo-controlled pilot study. *Psychopharmacology*. 2018;235(11):3137-3148.

INTRAVENOUS KETAMINE IMPROVES SOCIAL ANHEDONIA IN PATIENTS WITH TREATMENT-RESISTANT DEPRESSION AND SUICIDAL IDEATION

Hiroe Hu, National Institute of Mental Health

Individual Abstract: Social anhedonia—reduced pleasure from social interaction—has long been examined in schizophrenia-spectrum disorders but is increasingly recognized as a transdiagnostic phenotype linked to mood disorders and suicide risk. Yet no evidence-based treatments directly target social anhedonia in depression. Emerging work suggests entactogens may enhance social connection, and ketamine has shown putative entactogenic effects, including transient changes in self/other-perception, enhanced social reward sensitivity, and increased prosocial motivation. To test these effects empirically, we examined ketamine-related changes in social anhedonia among patients with mood disorders and suicidal ideation receiving open-label treatment. We hypothesized that 1) ketamine will improve social anhedonia in a dose-dependent manner, 2) that the improvement in social anhedonia would be independent from the general antidepressant effect, and 3) mediated by ketamine's transient dissociative effects altering self- and other-perception. Participants were enrolled in the Neurobiology of Suicide clinical trial (NCT02543983) from 2015–2025 and received up to five intravenous infusions of racemic ketamine (0.5 mg/kg) twice weekly. The

Snaith-Hamilton Pleasure Scale (SHAPS) was administered at –60 and +230 minutes relative to each infusion; four SHAPS items indexing enjoyment of social connection and altruism were used to derive a social anhedonia score. Depressive symptoms were assessed with the Montgomery-Åsberg Depression Rating Scale (MADRS). Dissociation was measured with the Clinician-Administered Dissociative States Scale (CADSS) at +40 minutes; ten items reflecting altered self/other-perception were combined into a “Self-Other” score. Linear mixed models tested changes in social anhedonia across time and infusions, adjusting for age and sex with a random intercept for subjects. Mediation analysis tested whether dissociation explained ketamine’s effects. Alpha was .05. Data from 282 observations across 28 participants (mean age = 40 ± 14 years; 54% female) were included. Social anhedonia significantly decreased after the first ketamine infusion (mean change = –1.0 points, 95% CI: –1.8 to –0.2; $t = -2.5$, $p = .01$). This improvement was maintained but did not significantly increase with repeated infusions. When adjusting for MADRS total score, the effect of ketamine on social anhedonia was no longer statistically significant. CADSS Self-Other scores were significantly associated with lower social anhedonia ($B = -0.1$, 95% CI: –0.2 to –0.02; $p = .02$) but did not mediate ketamine’s effect. Intravenous ketamine improved social anhedonia, though the additional improvements with repeat doses was non-significant. Contrary to our hypotheses, ketamine’s effect on social anhedonia was not independent from its general antidepressant effect, nor was it mediated by ketamine’s dissociative properties pertaining to perception of self and others. This, however, does not rule out that ketamine’s effect on social anhedonia is pharmacologically distinct from the antidepressant mechanisms. Future studies should also replicate analyses using double-blinded studies to overcome the limitation of an open-label study design and incorporate multimodal outcomes. These may include but not limited to neuroimaging correlates; behavioral tasks measuring social anhedonia or prosocial behavior; a more extensive panel of self-report questionnaires measuring social anhedonia, empathy, and self-other relationships; and peripheral markers tied to social affiliative behavior (e.g. oxytocin, vasopressin).

Literature References: Enneking V, Krüssel P, Zaremba D, et al. Social anhedonia in major depressive disorder: a symptom-specific neuroimaging approach. *Neuropsychopharmacology*. 2019;44(5):883-889.

Hu H, Tillman AN, Fujita M, et al. Can ketamine and other glutamate receptor modulators be considered entactogens? *Psychiatry Res*. 2025;349:116513.

KETAMINE’S POTENTIAL FOR TREATING LONELINESS IN TREATMENT RESISTANT BIPOLAR DEPRESSION

Diana Orsini, University of Toronto

Individual Abstract: Introduction: Loneliness is a subjective feeling characterized by decreased social connectedness and dissatisfaction with the quality of relationships. Replicated observational studies have demonstrated a strong association between loneliness with depression, suicidality and numerous other psychiatric and physical disorders making this a potential trans-diagnostic target for treatment. Loneliness has a high prevalence in bipolar disorders and is associated with poorer outcomes to treatments and increased risk of suicidality. Psychedelics, including ketamine, have been shown to potentially enhance one’s connectedness to their surroundings, social engagement and feelings of empathy. In addition to ketamine’s rapid antidepressant properties, replicated clinical trials and real-world effectiveness studies have demonstrated its robust anti-suicidal effects. Taken together,

further research into ketamine's therapeutic potential for reducing loneliness specifically in individuals with treatment resistant bipolar depression (TRBD) is needed.

Methods: We completed the world's first randomized clinical trial (RCT) to evaluate the efficacy, safety and tolerability of an acute course of intravenous (IV) ketamine for TRBD. While the primary outcome was antidepressant efficacy, we also evaluated the effects of ketamine on secondary outcomes of interest for exploratory analysis, including the effects on loneliness. The University of California Los Angeles (UCLA) Loneliness Scale, a self-report assessment evaluating one's subjective feelings of loneliness, was administered at baseline, Day 14 and Day 28. An independent samples t-test was completed comparing the mean change in UCLA score from baseline to Day 14 and baseline to Day 28 in the ketamine arm to the midazolam arm.

Results: This exploratory analysis included 57 participants with a diagnosis of moderate to severe TRBD. We observed significant reductions in the UCLA mean scores in both groups, indicative of clinically significant reductions in symptoms of loneliness. However, no significant difference ($p=0.319$) in mean UCLA Loneliness score from baseline to Day 14 was identified when comparing the ketamine group (mean [SD]= -4.81 [9.39]) to the midazolam group (mean [SD] = -6.00[9.36]). Similarly, when evaluating mean change in UCLA scores from baseline to Day 28, both groups had significant improvements with no significant difference observed between groups ($p=0.077$, mean [SD]: ketamine = -8.23 [8.43], midazolam = -4.84 [9.08]).

Discussion: In this exploratory analysis of individuals with TRBD, ketamine was not statistically superior compared to midazolam in reducing loneliness scores at either Day 14 or Day 28. Although both groups displayed decreases in UCLA Loneliness scores over time, the magnitude of change was comparable at Day 14 with greater reduction in the ketamine arm only at Day 28. The possibility of delayed effects warrants further investigation. This exploratory analysis is limited as it is inadequately powered to detect small differences between groups. As well, reductions in feelings of loneliness observed in both arms may be better explained by nonspecific effects such as therapeutic engagement, consistent study-related support throughout the 19 total study visits in approximately one month, expectancy, or natural fluctuations in social connectedness. Continued research of the relationship of ketamine and loneliness is encouraged in future adequately powered RCTs.

Literature References: Lu A, Chan A, Menon T, et al. Association between loneliness and suicidality among general populations and persons with depressive and bipolar disorders: A systematic review. *J Affect Disord.* 2025;380:777-801. doi:10.1016/j.jad.2025.03.150

Park C, Majeed A, Gill H, et al. The Effect of Loneliness on Distinct Health Outcomes: A Comprehensive Review and Meta-Analysis. *Psychiatry Res.* 2020;294:113514. doi:10.1016/j.psychres.2020.113514

OBJECTIVE MEASURES OF EMPATHY: PROSOCIAL LEARNING AND MOOD STATES

Yoojin Lee, National Institute of Mental Health, National Institutes of Health

Individual Abstract: Empathy, which is crucial for maintaining social functioning in humans, is frequently impaired in people with mental disorders. Given its fundamental role in social functioning, enhancing empathy might offer a promising way to improve treatment outcomes in individuals with mental disorders, such as major depressive disorder or suicide

(Szanto et al., 2012). However, the relationship between empathy and mental disorders is not straightforward, likely due to heterogeneous definitions of empathy and the lack of objective measures. Studying a measurable component of empathy, such as prosocial learning—modifying behaviors by incorporating cues from interpersonal experiences to enhance the quality of social interactions—could help address this challenge. Using objective measures, including a computerized task to quantify degrees of empathy, this pilot study examined whether reported mood states (such as happiness, feeling challenged, and stress) were associated with learning rates for oneself and others. Specifically, the study hypothesized that positive ongoing mood (reported happiness and feeling challenged) would be positively related to learning rates for others, but not for oneself. This pilot study included seven healthy volunteers ($M_{age}=28, SD_{age}=4.69$; 4F/3M). Learning hyperparameters were measured using a prosocial learning task (Lockwood et al., 2016) optimized to quantify degrees of reward-seeking patterns in different social settings involving playing for the self versus others. Empathy was assessed using a Pavlovian reinforcement learning model to evaluate learning parameters, such as learning rates. Participants were instructed to perform their best during the task and report their current mood in every four trials, specifically how much they felt happiness, challenge, and stress. To determine whether learning rates for the self and others differed, we conducted a paired Wilcoxon's test. We then explored fluctuations in mood ratings over time using Levene's Test. To estimate the relationship between the mean and variance of mood ratings and learning rates for the self and others, we conducted a Kendall's tau test. The results indicated that learning rates for the self and others were not significantly different ($V=21, p=.297$), suggesting that participants did not differ in how quickly they adapted their behavior for the task depending on whom they were playing for. Reported challenge ($F(7,159)=6.23, p < .001$) and stress ($F(7,159)=10.63, p < .001$) fluctuated over time, whereas happiness did not ($F(7,159)=1.22, p=.296$). Furthermore, the mean reported happiness was positively correlated with learning rates for others ($r=0.90, p=.005$), but not for oneself ($r=0.05, p=.919$). The increased learning rate for others may indicate that individuals with higher reported happiness are more attentive and motivated when playing for others, potentially serving as a marker for empathy. Contrary to our hypothesis, the mean and variance of other reported mood scores were not significantly related to learning rates for the self or others ($ps > .05$). These findings may indicate that reported happiness during the task is associated with empathy or that empathy may be a prerequisite for empathic behaviors, potentially serving as a cross-diagnostic marker for mental disorders. In the future study, this task will be integrated into future clinical trials to investigate whether changes in learning parameters, as a quasi-index of empathy, in patients with depression and suicide risk are associated with neural markers and ketamine treatment.

Literature References: Lockwood, P. L., Apps, M. A., Roiser, J. P., et al.

Neurocomputational mechanisms of prosocial learning and links to empathy. *Proc Natl Acad Sci U S A*, 2016; 113(35), 9763-9768.

Szanto, K., Dombrovski, A. Y., Sahakian, B. J., et al. Social emotion recognition, social functioning, and attempted suicide in late-life depression. *The American Journal of Geriatric Psychiatry*, 2012; 20(3), 257-265.

***TARGETED INTERVENTIONS FOR SUICIDE PREVENTION**

Jill Harkavy-Friedman, American Foundation for Suicide Prevention

Overall Abstract: There is change happening in clinical trials. In the past, people with current or past suicidal ideation and behavior (SIB) are automatically excluded from clinical

trials. Fortunately, this is changing. With about one third of people with significant mental health disorders, especially affective, psychotic and substance use disorders, having experienced SIB, inclusion becomes critical. We know that certain populations such as older people, and people with substance use disorders have elevated rates of suicide necessitating the inclusion of people with SIB. Youth have higher than expected rates of suicide attempts though, the rate of death by suicide is the lowest when compared to other age groups. The goal of this panel is to highlight research that has been conducted without excluding people with SIB and findings have been informative for more precise treatment decisions. We start with a study examining the trajectory of SIB using digital ecological momentary assessment (EMA) and sleep. Multilevel modeling was used to examine the association between sleep and next-day suicidal ideation among youth, 20% of whom had suicidal thoughts. Data will be presented to demonstrate that worse sleep quality was associated with next-day suicidal ideation among adolescents. This study highlights that suicide risk is not static, it fluctuates in relation to a host of factors including sleep. Monitoring mood, SIB and sleep is feasible and informative and provides important information for understanding and preventing suicide among youth. Next, the first study of a GLP-1 receptor agonist in individuals with moderate-to-severe methamphetamine use disorder. Data will be presented to demonstrate the differential impact of GLP-1 treatment on clinical symptoms and SIB, highlighting the importance of inclusion to identify who may benefit most from GLP-1 receptor agonist in the context of methamphetamine use disorder. Interesting, SIB was unchanged while clinical symptoms were otherwise affected. While those age 65 and up have the highest rates of suicide they are an often neglected population for intervention development, particularly those with mild cognitive impairment. The aims of the study presented are to compare depression, emotion regulation, and suicide-related outcomes between two psychosocial interventions for older adults after a suicide related hospitalization: Problem Adaptation Therapy for Suicide Prevention (PATH-SP) and Supportive Therapy (ST). The forty-six 50 to 90 year-olds who participated were inpatients with depression, mild cognitive impairment and suicidal ideation. The treatments were compared and improvement and subsequent remission rates varied depending on the treatment and variables considered. Most importantly, improvement in depression and suicide was demonstrated. The final study is one of the first to systematically study the use of psilocybin for the treatment of individuals with SIB. To evaluate the efficacy, safety, and durability of a single dose of psilocybin with psychological support employed an open-label, single-arm, naturalistic study with a 12-week follow-up period was conducted. The preliminary data show that SIB severity and depression decreased without any adverse events. The studies presented demonstrate the variability of treatment impact on SIB, highlighting the importance of including people with SIB and using relevant measures to assess impact. Precision medicine includes matching patient with treatment and requires broad based studies that include all potential people who may benefit from treatment. We invite discussion about the methods, considerations and findings of these important, potentially life saving studies.

Learning Objective 1: Attendees will be able to describe at least three methodological considerations that facilitate the study of promising treatments for suicide prevention.

Learning Objective 2: Attendees will be able to list at least two populations with higher rates of suicide.

Literary References: Arslanoglou, E., Banerjee, S., Pantelides, J., Evans, L., and Kiosses, D. N. (2019) Negative Emotions and the Course of Depression During Psychotherapy in Suicidal Older Adults With Depression and Cognitive Impairment. *The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry*, 27(12), 1287-1295. <https://doi.org/10.1016/j.jagp.2019.08.018>

Athey, A., Shaff, J., Kahn, G., Brodie, K., Ryan, T. C., Sawyer, H., DeVinney, A., Nestadt, P. S., and Wilcox, H. C. (2025) Association of substance use with suicide mortality: An updated systematic review and meta-analysis. *Drug and alcohol dependence reports*, 14, 100310. <https://doi.org/10.1016/j.dadr.2024.100310>

Aaronson, S. T., Sackeim, H. A., Jiang, M., Badejo, S., Greco, T., Bunker, M. T., Conway, C. R., Demyttenaere, K., Young, A. H., McAllister-Williams, R. H., and Rush, A. J. (2024) Alternative metrics for characterizing longer-term clinical outcomes in difficult-to-treat depression: II. Sensitivity to treatment effects. *Australian and New Zealand Journal of Psychiatry*, 58(3), 250-259. <https://doi.org/10.1177/00048674231209837>

USING INTENSIVE, REAL-TIME MONITORING DESIGNS TO IDENTIFY PROXIMAL RISK FACTORS FOR SUICIDAL IDEATION AMONG ADOLESCENTS

Jessica Hamilton, Rutgers University

Individual Abstract: Over 1 in 5 U.S. high school students have seriously considered suicide and 1 in 10 have attempted suicide in the past year alone. Yet, suicide risk is not static; suicidal thoughts fluctuate across days and weeks, making it is critical to identify factors that predict when youth are experiencing suicidal ideation. Advancing technology makes it possible to capture suicidal thoughts when they occur in real time, thereby informing suicide prevention and targeted interventions. Intensive monitoring designs and idiographic approaches, such as ecological momentary assessment (EMA), can be used to identify risk factors that proximally predict suicidal ideation among youth. The current study leveraged such a design to examine sleep characteristics (quality, duration, timing, variability) as modifiable risk factors for suicidal ideation among adolescents. The current sample of adolescents were recruited nationwide and were unselected for current or past suicide risk. A total of 131 adolescents (Mean Age =15.9 years; 60% female; 45% White) completed a baseline clinical interview and self-reported surveys, along with two months of ecological momentary assessment (EMA) with 3 prompts per day, including morning sleep diaries and evening reports of suicidal ideation (occurrence and intensity). Adolescents wore actiwatches for two months to capture behavioral sleep metrics and installed an application for smartphone sensing to capture phone use and app patterns. Overall, 45% of adolescents endorsed lifetime active suicidal thoughts and 20% had lifetime suicidal behavior. More than 1 in 5 adolescents also reported active suicidal thoughts during the EMA period, which highlights the importance of including and asking about suicidal thoughts among adolescents in clinical research studies. Multilevel modeling was used to examine the association between sleep and next-day suicidal ideation, finding that worse sleep quality (particularly compared to one's usual experience) was associated with next-day suicidal ideation among adolescents. Actigraphic results capturing behavioral sleep metrics will also be presented related to next-day suicidal ideation. Our study highlights the importance of evaluating suicidal ideation on a daily basis among youth to capture risk as it unfolds. Further, intensive monitoring designs can advance our understanding of modifiable risk factors, such as sleep, to inform interventions and prevent suicide.

Literature References: Hamilton JL, Tsypes A, Zelazny J, et al. Sleep influences daily suicidal ideation through affective reactivity to interpersonal events among high-risk adolescents and young adults. *J Child Psychol Psychiatry*. 2023;64(1):27-38. doi:10.1111/jcpp.13651

Esposito, E. C., Duan, A. M., Kearns, J. C., Kleiman, E. M., Conwell, Y., and Glenn, C. R. (2022). Measuring adolescents' self-injurious thoughts and behaviors: comparing ecological momentary assessment to a traditional interview. *Research on child and adolescent psychopathology*, 50(8), 1095-1105.

CHANGES IN SYMPTOMS OF SUICIDAL IDEATION AND RELATED SYMPTOMS WITH TIRZEPATIDE IN INDIVIDUALS WITH MODERATE-TO-SEVERE METHAMPHETAMINE USE DISORDER

Snoben Kuruwila, UTSW Medical Center Dallas

Individual Abstract Background: Glucagon-like peptide-1 (GLP-1) receptor agonists have gained recent attention for drug repurposing to treat substance use disorder. Yet, tirzepatide, a dual agonist of GLP-1/glucose-dependent insulintropic polypeptide, has not been studied yet, especially for methamphetamine use disorder (MtUD). Furthermore, while these medications are gaining a lot of attention in clinical care, some concerns have been raised about their effect on suicide-related outcomes. Here, we present findings from the first study of a GLP-1 receptor agonist in individuals with MtUD where we systematically studied suicide-related outcomes with weekly self-report and clinician assessments.

Methods: This interim analysis included participants with moderate-to-severe MtUD who received six months of treatment with tirzepatide for a weight-related indication (NCT06745128). Self-reported symptoms of active suicidal ideation (SI), pessimism, helplessness, perceived lack of social support, despair, and impulsivity were assessed with Concise Health Risk Tracking Self-Report (CHRT-SR) measures on a weekly basis. Medical Clinicians also completed assessments of SI, suicidal behavior and non-suicidal self-injurious behavior every week. Repeated measures mixed model analyses were used to measure changes in CHRT-SR domains.

Results: Of the 42 individuals screened, 35 were enrolled [20 females/15 males; mean (standard deviation, SD) age = 46.1 (8.3) years]. Two individuals dropped out after the first dose due to gastrointestinal side effects. After six months of treatment with tirzepatide, there were significant reductions in pessimism [estimate(β) = -2.3, standard error(SE) = 0.25, $p=0.0124$], helplessness (β = -0.81, SE = 0.28, $p=0.0035$), perceived lack of social support (β = -0.70, SE = 0.28, $p=0.0133$), and impulsivity (β = -1.76, SE = 0.31, $p < 0.0001$), but not in despair ($p=0.058$) and active SI ($p=0.56$). No treatment-emergent worsening of SI or occurrence of suicidal behavior or non-suicidal self-injurious behaviors were noted over the six months treatment duration.

Conclusions: This first study of a GLP-1 receptor agonist in individuals with moderate-to-severe methamphetamine use disorder demonstrates significant reduction in symptoms associated with SI, such as impulsivity, pessimism and helplessness. Additionally, there was no signal for worsening of suicidal ideation or occurrence of behaviors with six-month-long treatment with tirzepatide.

Literature References: Wang W, Volkow ND, Berger NA, Davis PB, Kaelber DC, Xu R. Association of semaglutide with risk of suicidal ideation in a real-world cohort. *Nat Med*. 2024 Jan;30(1):168-176.

Chen J, Zhang Q, Wu Q, Zhang X, Xiang Z, Zhu S, Dai T, Si Y. Impact of GLP-1 Receptor Agonists on Suicide Behavior: A Meta-Analysis Based on Randomized Controlled Trials. *J Diabetes*. 2025 Sep;17(9):e70151.

PSYCHOSOCIAL INTERVENTIONS FOR OLDER ADULTS WITH DEPRESSION AND VARYING DEGREES OF COGNITIVE FUNCTIONING AFTER A SUICIDE-RELATED HOSPITALIZATION

Dimitris Kiosses, Weill Cornell Medical College

Individual Abstract: Specific Purpose: Psychosocial interventions for hospitalized older adults with varying degrees of cognitive deficits who have been recently hospitalized for suicidality are understudied. The aims of this presentation are to compare depression, emotion regulation, and suicide-related outcomes between two psychosocial interventions for older adults after a suicide related hospitalization: Problem Adaptation Therapy for Suicide Prevention (PATH-SP) and Supportive Therapy (ST).

Methodology: 46 participants (50-90 years old) were inpatients of Weill Cornell/NY Presbyterian Hospital and were randomized into PATH-SP (N=23) and ST (N=23). PATH-SP utilizes emotion regulation strategies to reduce negative emotions associated with suicidal ideation, employs compensatory strategies to bypass cognitive and functional limitations, and incorporates caregiver participation when necessary. ST focuses on nonspecific therapeutic factors (e.g. conveying empathy, highlighting successful experiences). We assessed depression severity, emotion regulation, suicide outcomes, and treatment satisfaction at discharge, and at 4, 8, and 12 weeks post-discharge.

Results: Participants were severely depressed at admission, actively suicidal, and had on average mild to moderate cognitive deficits and functional impairment. At discharge, participants on average were moderately depressed and had mild suicidal ideation. Participants in both PATH-SP and ST had high treatment satisfaction scores. PATH-SP participants had significantly lower depression scores, high emotion regulation scores, and lower suicide-related re-hospitalization rates than ST participants ($p < 0.05$). Most relapses occurred in the first 5 months post-discharge.

Importance: PATH-SP reduced hospitalization for suicidality rates in older adults with major depression and varying degrees of cognitive functioning, who have been recently discharged after a suicide-related hospitalization. This is clinically significant because psychosocial interventions for this high suicide risk population are underdeveloped.

Literature References:

1. Kiosses DN, Szanto K, Alexopoulos GS. Suicide in older adults: the role of emotions and cognition. *Curr Psychiatry Rep.* 2014 Nov;16(11):495.
2. Bress JN, Arslanoglou E, Banerjee S, Alexopoulos GS, Kiosses DN. Positive valence system function and anhedonia in middle-aged and older adults at high suicide risk. *Biol Psychol.* 2023 Sep;182:108647.

EFFICACY AND SAFETY OF A SINGLE DOSE OF PSILOCYBIN FOR CHRONIC ACTIVE SUICIDAL IDEATION: EXPERIENCES IN AN OPEN LABEL TRIAL

Scott Aaronson, Sheppard Pratt

Individual Abstract Importance: Chronic suicidal ideation is a major public health concern with limited effective and rapidly acting treatments. Historically, clinical trials have excluded this high-risk population, creating a critical gap in knowledge.

Objective: To evaluate the efficacy, safety, and durability of a single dose of psilocybin with psychological support for reducing chronic suicidal ideation.

Design: Open-label, single-arm, naturalistic study with a 12-week follow-up period.

Setting: Conducted at a single academic medical center.

Participants: Twenty adults (12 male; mean age, 36.3 [11.1] years) with chronic suicidal ideation and a history of at least two prior antidepressant treatment failures.

Intervention: A single 25-mg dose of psilocybin (COMP360) administered with a structured protocol for preparatory and integration psychotherapy sessions.

Main Outcomes and Measures: The primary outcome was the change from baseline in the Modified Scale for Suicidal Ideation (MSSI) score at Week 3. Secondary outcomes included changes in MSSI at Weeks 1 and 12, and changes in the Montgomery-Åsberg Depression Rating Scale (MADRS) scores across these timepoints.

Results: The mean (SD) baseline MSSI score was 18.6 (5.1). At the Week 3 primary endpoint, MSSI scores were significantly lower than baseline (mean difference = 13.95 ± 1.81 ; 95% CI [8.63–19.27]; $p < .001$; Cohen's $d = 1.94$). Large reductions were already evident at Week 1 ($d = 2.11$) and remained stable through Week 12 ($d = 1.87$). At Week 12, 14 of 20 participants (70%) had an $MSSI \leq 2$. MADRS scores showed a similarly rapid and durable improvement, with mean reductions of 18.55 points at Week 1 ($d = 1.73$) and 17.55 points at Week 12 (95% CI [11.93–23.17]; $p < .001$; $d = 2.06$). No serious adverse events occurred, although one participant's MSSI increased from 17 to 23 at Week 12.

Conclusions and Relevance: In this open-label naturalistic study in a treatment-resistant population, a single administration of psilocybin with psychological support was associated with rapid, robust, and durable reductions in suicidal ideation. These promising preliminary results warrant further investigation in larger, randomized controlled trials.

Literature References: Aaronson, S. T. et al. Single-Dose Psilocybin for Depression With Severe Treatment Resistance: An Open-Label Trial. *Am J Psychiatry* 182, 104-113 (2025). <https://doi.org/10.1176/appi.ajp.20231063>

Goodwin, G. M. et al. Single-Dose Psilocybin for a Treatment-Resistant Episode of Major Depression. *N Engl J Med* 387, 1637-1648 (2022).

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

Panel Sessions

***IMPROVING METABOLIC HEALTH IN MENTAL ILLNESS: A TRANSDIAGNOSTIC APPROACH**

Mahavir Agarwal, Centre for Addiction and Mental Health, Canada

Overall Abstract: Cardiometabolic comorbidities such as metabolic syndrome, type 2 diabetes, and cardiovascular disease are intrinsically 3-5 times more prevalent among patients with psychiatric illness compared to the general population. 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, co-chaired by Dr. Mahavir Agarwal (University of Toronto, Canada) and Dr. Benjamin Perry (University of Birmingham, United Kingdom), will present recent progress in the understanding, prediction, and management of metabolic dysfunction in various psychiatric disorders. The panel will emphasize the importance of adopting a transdiagnostic perspective for effective prevention and early intervention. Dr. Katharine Liang (University of Washington, USA) will examine risk factors that influence the strength and direction of the relationship between post-traumatic stress disorder and diabetes severity in trauma-exposed Black women with type 2 diabetes. She will focus on potential mediators such as age, smoking, glycemic control, body mass index, and medication use. The findings suggest that PTSD and diabetes may exacerbate each other, creating a cycle of worsening health, and that treating only one condition may be insufficient to reduce long-term risk. Dr. Benjamin Perry will present on the Psychosis Metabolic Risk Calculator (PsyMetRiC), a novel clinic-ready cardiometabolic prediction model for young people with psychosis spectrum disorders. This presentation will outline recent updates to the models, highlight improvements in predictive accuracy, and describe how PsyMetRiC can be used to identify individuals at highest risk for early cardiometabolic disease. Dr. Perry will discuss how integrating these tools into routine care may support individualized monitoring and targeted preventive strategies. Finally, Dr. Nicolette Stogios (Centre for Addiction and Mental Health (CAMH), Canada) will present data from a psychiatrist-led mental health and metabolism clinic aimed at improving the metabolic health of individuals treated with psychotropic medications. This study is the first to evaluate the impact of structured metabolic monitoring and targeted interventions on psychotropic-induced weight gain in individuals with intellectual and developmental disabilities (IDD). This work takes an important step to meet the needs of a vulnerable group often ignored in metabolic dysfunction prevention and management. Dr. Rebecca Hendrickson (University of Washington, USA) will serve as the discussant to review the implications of early identification and treatment of cardiometabolic risk in individuals with mental illness, as well as insights for future directions that can help propel the field forward. Collectively, this symposium will provide attendees with an updated understanding of metabolic risk across psychiatric populations and will identify actionable strategies to improve long-term physical health outcomes for individuals living with mental illness or treated with psychotropic medications. The symposium unites researchers from Canada, the United States, and the United Kingdom, including women scientists (Drs. Liang, Stogios, and Hendrickson), early career investigators (Drs. Liang and Stogios), and clinicians (Drs. Liang, Perry, Agarwal, and Hendrickson).

Learning Objective 1: Identify key factors that contribute to elevated cardiometabolic risk across psychiatric populations and describe how emerging prediction tools, including PsyMetRiC, can support individualized risk stratification and early intervention.

Learning Objective 2: Learn practical strategies to monitor and manage metabolic side effects of psychotropic medications, including in high-risk groups such as people with post-traumatic stress disorder or intellectual and/or developmental disabilities.

Literary References: 1. Stogios N, PrasannaKumar A, Mehra K, Hahn MK, Agarwal SM. Risk Factors and Management Strategies for Antipsychotic-Induced Weight Gain: A Prescriptive Review for Clinicians. *Focus*. 2025;23(4).

2. Perry BI, Osimo EF, Upthegrove R, Mallikarjun PK, et al. Development and external validation of the Psychosis Metabolic Risk Calculator (PsyMetRiC): a cardiometabolic risk

prediction algorithm for young people with psychosis. *Lancet Psychiatry*. 2021 Jul;8(7):589-598.

PSYMETRIC 2.0: DEVELOPMENT, REFINEMENT AND EXTERNAL VALIDATION OF CLINIC-READY CARDIOMETABOLIC PREDICTION MODELS FOR YOUNG PEOPLE WITH PSYCHOSIS SPECTRUM DISORDERS

Benjamin Perry, University of Birmingham

Individual Abstract Background: Young people with psychosis spectrum disorders are at high risk of cardiometabolic morbidity and subsequent premature mortality, but accurate clinic-ready prediction models for this group are lacking.

Methods: We refined the Psychosis Metabolic Risk Calculator (PsyMetRiC) prediction models (comprising age, sex, ethnicity, body mass index, smoking, antipsychotics, high-density lipoprotein, triglycerides), originally developed to predict incident metabolic syndrome within six years of a first recorded psychosis spectrum disorder in people aged 16-35 years. We used primary care (CPRD, n=9,181; QResearch, n=7,457) and secondary care (South London and Maudsley NHS Foundation Trust, n=846) datasets. We revised existing predictors for finer detail (hereafter PsyMetRiC1 models) and added new ones: cardiometabolic disorder family history, antidepressants, systolic blood pressure, glycated haemoglobin (hereafter PsyMetRiC2 models). Different models now predict clinically-significant weight gain within one year (PsyMetRiC2-WG; logistic regression); metabolic syndrome within six years (PsyMetRiC1-MetS; PsyMetRiC2-MetS, logistic regression), and type 2 diabetes within ten years (PsyMetRiC2-T2D; Weibull regression). “Partial” model versions without biochemical results were also developed for weight gain and metabolic syndrome models. We conducted discrimination, calibration, and decision curve analyses (whole sample and by demographic subgroup); involved stakeholders; and implemented the models in a web application compliant with regulatory standards in Great Britain.

Results: Models performed well at internal (PsyMetRiC2-WG full-model: C=0.77, 95% C.I., 0.73-0.82; partial-model: C=0.76, 95% C.I., 0.72-0.80; PsyMetRiC2-T2D full-model: C=0.86, 95% C.I., 0.78-0.94) and external validation (PsyMetRiC2-MetS full-model: C=0.81, 95% C.I., 0.77-0.84; partial-model: C=0.79, 95% C.I., 0.76-0.83; PsyMetRiC2-T2D full-model: C=0.81, 95% C.I., 0.75-0.87). Calibration plots were acceptable. All models displayed evidence of clinical usefulness at all plausible thresholds. Subgroup analysis revealed some accuracy differences that did not impair clinical usefulness. The web application (<https://psymetric.app/>) is available for clinical use in Great Britain.

Importance: We developed prediction models for incident cardiometabolic disorders in young people with psychosis, and a clinically-available web application. PsyMetRiC encourages shared decision-making toward reduction of cardiometabolic morbidity in this high-risk group.

Literature References: Plana-Ripoll O, Pedersen CB, Agerbo E, et al. A comprehensive analysis of mortality-related health metrics associated with mental disorders: a nationwide, register-based cohort study. *Lancet* 2019; 394(10211): 1827-35.

Perry BI, Osimo EF, Upthegrove R, et al. Development and external validation of the Psychosis Metabolic Risk Calculator (PsyMetRiC): a cardiometabolic risk prediction algorithm for young people with psychosis. *Lancet Psychiatry* 2021; 8(7): 589-98.

TREATING PSYCHOTROPIC ASSOCIATED WEIGHT GAIN IN INDIVIDUALS WITH INTELLECTUAL AND DEVELOPMENTAL DISABILITY: A RETROSPECTIVE CHART REVIEW STUDY

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

Individual Abstract: Background: Individuals with intellectual and/or developmental disability (IDD) have higher rates of co-occurring psychiatric disorders and may experience challenges with emotional and behavioural regulation. This often leads to the prescription of antipsychotic medications. These individuals also face an increased risk of metabolic comorbidities, such as type 2 diabetes and cardiovascular disease, which can be further influenced by the metabolic side effects of antipsychotic drugs. Despite the well-established association, there is presently a lack of effective treatment options for antipsychotic-induced metabolic disturbances in people with IDD. 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 treated with psychotropic medications.

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. This study presents a subgroup analysis of individuals with any form of IDD given the specialized risk in this population. The primary outcome measures were change in weight at 3, 6, 9, and 12 months in the clinic.

Results: The sample consisted of 46 patients who were followed in the clinic for at least 6 months (males: 73.9%, age: 27.2 +/- 1.3 years). The mean baseline body weight of the sample was 109.4 +/- 4.4 kg and BMI 37.1 +/- 1.2 kg/m². Approximately 46% of the sample had pre-diabetes, 2% had type 2 diabetes, and 35% had metabolic syndrome. All patients except for two were treated in the clinic with a pharmacological intervention such as metformin (N=35), topiramate (N=1), semaglutide (N=2), or a combination of these medications (N=6). Among the 44 patients receiving pharmacological treatment, a significant effect of the clinic (including all medications) was observed on body weight over time ($F=3.17$, $p=0.015$), while controlling for age, sex, and baseline weight. The mean change in weight was -1.90 +/- 1.66 ($p=0.26$), -1.66 +/- 1.65 ($p=0.32$), -4.06 +/- 1.91 ($p=0.035$), and -6.85 +/- 2.06 ($p=0.001$) at 3, 6, 9 and 12 months, respectively.

Discussion: Individuals with IDD are a vulnerable but currently invisible and largely ignored population when it comes to prevention and treatment of psychotropic-induced weight gain. There is presently a lack of evidence to help guide safe and effective treatment of metabolic comorbidities in this population. Accordingly, we present the first naturalistic cohort study to demonstrate the effectiveness of pharmacological interventions in managing weight gain in individuals with IDD. This provides real world evidence of effective treatment strategies for addressing this persistent health challenge and supports the implementation of psychiatrist-led management of metabolic dysfunction in individuals with IDD.

Literature References:

1. Smith E, Stogios N, Au E, et al. The metabolic adverse effects of antipsychotic use in individuals with intellectual and/or developmental disability: A systematic review and meta-analysis. *Acta Psychiatr Scand*. 2022 Sep;146(3):201-214.
2. Stogios N, Hahn MK, Lunskey Y, Desarkar P, Agarwal SM. Addressing Metabolic Comorbidity in Individuals With Intellectual and Developmental Disability on Antipsychotics: A Clinical Case Series. *J Clin Psychopharmacol*. 2023 Jan-Feb 01;43(1):60-63.

PTSD AND DIABETES: A TWO-WAY STREET IN METABOLIC AND MENTAL HEALTH

Katharine Liang, VA Puget Sound Health Care System

Individual Abstract Background: Posttraumatic stress disorder (PTSD) is linked with metabolic disturbance and increased risk of Type 2 diabetes (DM2). While mounting evidence suggests that trauma is linked to downstream disruption of both brain and metabolic processes, mechanisms explaining the connection between PTSD and DM2 have yet to be defined. Conventional risk factors for worsening DM2 such as obesity, poor diet, and sedentary lifestyle are treatment targets in patients with DM2 but the role that these risks play in the poor glycemic control and associated medical comorbidities seen in the PTSD population remains unclear. Here we examine the commonly hypothesized risk factors influencing the strength and directionality of the relationship between PTSD and DM2 severity in traumatized black women with DM2.

Methods: We examined the relationships among PTSD severity (Clinician-Administered PTSD Scale, CAPS), glycemic control (A1c), age, smoking, body mass index (BMI), depression (Beck Depression Inventory, BDI) and medications in trauma-exposed Black women with DM2 recruited from an urban hospital between 2013-2015 (n=95) as a part of the Grady Trauma Project. Missing data were handled with multiple imputation (mice package, R). The relationship between PTSD severity and glycemic control, along with the influence of common risk factors, was assessed using lasso regression (glmnet package, R) performed on each imputed dataset. Mediation analysis tested whether BMI or depression mediated associations between PTSD severity and glycemic control.

Results: Lasso regression identified BDI, ACE inhibitor/ARB/beta blocker use, and CAPS severity as predictors in the final model predicting A1c. In pooled linear regression analyses across imputed datasets, overall model fit was modest, and none of these predictors were statistically significant. Lasso regression in the reverse direction selecting predictors of PTSD severity yielded BMI, BDI, ACE inhibitor/ARB use, and A1c for the final model predicting CAPS severity. In pooled analyses, model fit was substantially stronger and BDI emerged as the only statistically significant predictor ($p < 0.05$). Mediation analyses indicated that BDI, but not BMI, significantly mediated the effect of A1c on CAPS severity, as well as to a lesser extent the reverse relationship, the causal effect of CAPS severity on A1c.

Conclusion: In this examination of the relationships between PTSD and DM2 severity, CAPS severity and A1c were found to be bidirectionally correlated in lasso regression models, with BDI emerging as a significant predictor and mediator of these relationships. BMI was not found to be a mediator in either direction. These results suggest a possible reciprocal relationship between PTSD and DM2, where worsening of either condition may drive worsening of the other, resulting in a vicious cycle where treating one condition in isolation may not be sufficient to prevent increased overall morbidity and mortality. Further research should include physiological interventions to ascertain directionality in these relationships more definitively.

Literature References: Dixon HD, Michopoulos V, Gluck RL, Mendoza H, Munoz AP, Wilson JG, Powers A, Schwartz AC, Umpierrez GE, Gillespie CF. Trauma exposure and stress-related disorders in African-American women with diabetes mellitus. *Endocrinol Diabetes Metab.* 2020 Jan 14;3(2):e00111. doi: 10.1002/edm2.111. PMID: 32318631; PMCID: PMC7170451.

Powers A, Dixon HD, Conneely K, Gluck R, Munoz A, Rochat C, Mendoza H, Hartzell G, Ressler KJ, Bradley B, Pace TWW, Umpierrez GE, Schwartz AC, Michopoulos V, Gillespie CF. The differential effects of PTSD, MDD, and dissociation on CRP in trauma-exposed women. *Compr Psychiatry*. 2019 Aug;93:33-40. doi: 10.1016/j.comppsy.2019.06.007. Epub 2019 Jul 3. PMID: 31306866; PMCID: PMC6689425.

***STRATEGIES TO IMPROVE TREATMENT EFFECT DETECTION IN MDD TRIALS**

George Papakostas, Massachusetts General Hospital

Overall Abstract: Major depressive disorder (MDD) is a serious and prevalent condition associated with huge patient and family suffering and great socioeconomic loss. Over 50% of patients do not respond to first line antidepressants. Considering the heterogeneity of MDD and the different proposed treatments, response prediction markers may improve treatment effect detection. There is an urgent need to optimize clinical trial methodologies to identify patient characteristics associated with higher probability for response, thereby advancing treatment discovery for MDD. This session will highlight select emerging approaches to enhance treatment-effect detection in MDD trials, including patient subtyping, phenotype enrichment and the use of biomarkers. Optimizing clinical trial methods to detect effective treatments and to understand patient characteristics associated with optimal response is critical to advancing treatment discovery for MDD. This talk will present new data linking brain features to positive outcomes for patients in trials of MDD that utilize novel agents to target the KCNQ channel in the brain. The talk will consider strategies including patient subtyping and phenotype enrichment to move closer to the goal of personalized treatment for depression. The first speaker, Dr. Murrough, will present new data linking specific brain features to positive clinical outcomes in trials evaluating novel KCNQ-channel-targeting agents for MDD. The second speaker, Dr. Guidetti, will provide an overview of evolving definitions and clinical correlates of antidepressant tachyphylaxis, discuss its potential implications for drug development, and present results of a post hoc analysis of Phase 3 trial evaluating an NMDA receptor antagonist as adjunctive treatment in patients with inadequate response to 1-3 first line antidepressants. The final speaker, Dr. Mignot, will discuss the objective assessment of sleep using wearable technology, its value in predicting future disease risk, and its potential applications in the context of depression. Together, these presentations underscore the potential of integrating subgroup analyses, biological and behavioral markers into MDD trials to improve the detection of treatment effects and accelerate progress toward personalized treatment strategies.

Learning Objective 1: By the end of this session, attendees should understand how methodological approaches – such as patient subtyping, phenotype enrichment, and the inclusion of objective biomarkers – can enhance the detection of treatment effects in MDD clinical trials.

Learning Objective 2: By the end of this session, attendees should be able to evaluate the potential of incorporating brain features, subgroups of MDD patients (e.g., patients with antidepressant tachyphylaxis), objective digital measures (e.g., wearable-derived sleep data) to enhance patient characterization and treatment effect detection in MDD clinical trials.

Literary References:

1. Chowdhury A, Boukezzzi S, Costi S, Hameed S, Jacob Y, Salas R, Iosifescu DV, Han MH, Swann A, Mathew SJ, Morris L, Murrough JW. Effects of the KCNQ (Kv7) Channel Opener

Ezogabine on Resting-State Functional Connectivity of Striatal Brain Reward Regions, Depression, and Anhedonia in Major Depressive Disorder: Results From a Randomized Controlled Trial. *Biol Psychiatry*. 2025 Oct 1;98(7):568-577. doi: 10.1016/j.biopsych.2025.02.897. Epub 2025 Mar 4. PMID: 40049579; PMCID: PMC12353514.

2. Guidetti C, Papakostas GI, Pani L, De Martin S, Serra G, Apicella M, Kröger C, Champasa P, Comai S, Mattarei A, Folli F, Pappagallo M, Manfredi PL, Fava M. Esmethadone (REL-1017) in Patients With Major Depressive Disorder and Antidepressant Tachyphylaxis: An Exploratory Post Hoc Analysis From a Phase 3 Randomized Controlled Trial. *J Clin Psychiatry*. 2025 Oct 6;86(4):24m15748. doi: 10.4088/JCP.24m15748. PMID: 41060071.

STRATEGIES TO IMPROVE TREATMENT EFFECT DETECTION IN MDD TRIALS

Clotilde Guidetti, Massachusetts General Hospital, and Harvard Medical School

Individual Abstract: Antidepressant tolerance or tachyphylaxis (AT)—defined as an initial clinically meaningful response ($\geq 50\%$ improvement in depressive symptoms) followed by relapse while continuing the same adequate antidepressant dose—represents a significant yet underrecognized challenge in the treatment of major depressive disorder (MDD). The presence of AT may predict poorer outcomes to subsequent antidepressant therapies, yet most MDD clinical trials fail to systematically assess or report AT, limiting our understanding of its prevalence and impact on treatment response. The development of effective therapeutic strategies for patients with MDD who experience AT therefore remains an important unmet clinical need. The impact of AT as prognostic indicator for response to subsequent antidepressant treatment is unknown.

Objective: This presentation will (1) provide an overview of evolving definitions and clinical correlates of antidepressant tachyphylaxis (2) discuss implications for drug development, and (3) present results of a post hoc analysis from a Phase 3 study of esmethadone (REL-1017) as adjunctive treatment in patients with inadequate response to 1-3 first line antidepressants.

Methodology: Prior to randomization, the presence of AT was independently assessed by clinicians at the Massachusetts General Hospital Clinical Trials Network and Institute (MGH CTNI) using the MGH Antidepressant Treatment Response Questionnaire (ATRQ). Data for the primary efficacy endpoint were analyzed using mean difference (MD) in Montgomery-Åsberg Depression Rating Scale (MADRS) total score from baseline to primary endpoint (Day 28) in the AT subgroup from the intent to treat (ITT) population, the per-protocol (PP) population, and in patients with severe depression (baseline MADRS ≥ 35).

Results and Conclusions: Among 227 ITT patients, 87 experienced AT. For this subgroup, there was a nominally statistically significant mean difference (MD) of 5.4 ($p=0.023$, Cohen's effect size [ES] 0.53) for esmethadone vs placebo in MADRS total score change from baseline to primary endpoint (Day 28). Additionally, there was a nominally statistically significant difference in response rate ($p=0.0004$). Consistent results were seen in the PP population with AT and in the severely depressed subgroup of patients with AT. These preliminary findings suggest that esmethadone may be a safe and effective adjunctive treatment for patients with MDD with antidepressant tolerance or tachyphylaxis. Identifying and targeting AT may meaningfully impact treatment outcomes. Future MDD clinical trials should consider incorporating pre-randomization AT assessment as a prespecified, adequately

powered outcome measure. More studies are needed to better characterize AT and its potential usefulness in developing MDD targeted treatments.

Literature References: Skaff R. Tachyphylaxis and desensitization depression. *CNS Spectrums*. 2021;26(3):191-192. doi:10.1017/S1092852919001445

Guidetti C, Papakostas GI, Pani L, De Martin S, Serra G, Apicella M, Kröger C, Champasa P, Comai S, Mattarei A, Folli F, Pappagallo M, Manfredi PL, Fava M. Esmethadone (REL-1017) in Patients With Major Depressive Disorder and Antidepressant Tachyphylaxis: An Exploratory Post Hoc Analysis From a Phase 3 Randomized Controlled Trial. *J Clin Psychiatry*. 2025 Oct 6;86(4):24m15748. doi: 10.4088/JCP.24m15748. PMID: 41060071.

FUNCTIONAL CONNECTIVITY OF THE STRIATUM AS A BIOMARKER OF TREATMENT RESPONSE TO KCNQ-TARGETED AGENTS IN DEPRESSION

James Murrough, Icahn School of Medicine at Mount Sinai

Individual Abstract: Purpose: MDD is a major driver of suffering and disease-related disability in the world and current treatments fail to lead to remission for many patients. Optimizing clinical trial methods to detect effective treatments and to understand patient characteristics associated with optimal response is critical to advancing treatment discovery for MDD. This talk will present new data linking brain features to positive outcomes for patients in trials of MDD that utilize novel agents to target the KCNQ channel in the brain.

Methods: We examined brain features associated with clinical response to two mechanistically novel agents that target the KCNQ channel – ezogabine (a.k.a., retigabine) and Azetukalner (previously known as XEN1101) – in separate samples of adults with MDD enriched for anhedonia. We used 3T functional MRI to measure resting-state functional connectivity (RSFC) of the ventral striatum, a key reward region, to the whole brain both at baseline and change following treatment.

Results: We report that reduced connectivity at baseline predicted improved outcomes on depression and anhedonia following treatment ($p < 0.05$). In addition, greater change in connectivity between the striatum and posterior cingulate cortex (PCC) was associated with greater improvement in depression and anhedonia during active treatment but not placebo in two independent data sets.

Conclusions: Across two separate, randomized, controlled trials, modulation of striato-cingulate connectivity is a consistent indicator of clinical response to agents targeting the KCNQ channel. The specific correlation between this RSFC change and symptom improvement supports its potential as a pharmacodynamic marker. Future trials should assess comparative efficacy and explore utility in specific depression subtypes.

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.

Chowdhury A, Boukezzzi S, Costi S, Hameed S, Jacob Y, Salas R, Iosifescu DV, Han MH, Swann A, Mathew SJ, Morris L, Murrough JW. Effects of the KCNQ (Kv7) Channel Opener Ezogabine on Resting-State Functional Connectivity of Striatal Brain Reward Regions, Depression, and Anhedonia in Major Depressive Disorder: Results From a Randomized Controlled Trial. *Biol Psychiatry*. 2025 Oct 1;98(7):568-577.

DEPRESSION AND DISTURBANCES IN CIRCADIAN RHYTHMS: PATHWAYS FOR NOVEL TREATMENT DEVELOPMENT

Emmanuel Mignot, Stanford University School of Medicine

Individual Abstract: Major Depressive Disorder (MDD) is a heterogeneous disorder with disturbances in sleep as a prominent symptom. Patients with MDD often experience difficulty falling asleep, staying asleep, waking up too early and/or excessive sleepiness (i.e., sleeping more than 10 hours/day). Furthermore, MDD is often comorbid with other disorders such as obesity and obstructive sleep apnea which further contribute to sleep and circadian rhythm disturbances. Clinical assessments of sleep in patients with MDD is often limited. Recent advances in wearable technologies have now allowed objective characterization of sleep in naturalistic home-based settings without the need for lab-based sleep studies. This presentation will focus on the overlap between depression and circadian disturbances, and the utility of wearable technologies in monitoring these circadian disturbances. Additionally, novel insights will be presented linking these circadian disturbances to dysfunctions in orexin signaling which promises to be a novel treatment approach for improving depression.

Literature References: Thapa R, Kjær MR, He B, Covert I, Moore H, Hanif U, Ganjoo G, Westover MB, Jennum P, Brink-Kjær A, Mignot E, Zou J. A Multimodal Sleep Foundation Model Developed with 500K Hours of Sleep Recordings for Disease Predictions. medRxiv [Preprint]. 2025 Feb 9;2025.02.04.25321675. doi: 10.1101/2025.02.04.25321675.

Hanif U, Gimenez U, Cairns A, Lewin D, Ashraf N, Mignot E. Automatic Detection of Chronic Insomnia from Polysomnographic and Clinical Variables Using Machine Learning. Annu Int Conf IEEE Eng Med Biol Soc. 2023 Jul;2023:1-5. doi: 10.1109/EMBC40787.2023.

^TOWARDS AN INTERNATIONAL, STANDARDIZED MODEL PSYCHOPHARMACOLOGY CURRICULUM FOR PSYCHIATRY RESIDENCY TRAINING: A COMPETENCY-BASED FRAMEWORK FOR IMPLEMENTATION

Matthew Macaluso, The University of Alabama at Birmingham

Overall Abstract: Psychopharmacology remains a crucial element of psychiatric practice. Nonetheless, considerable variation exists in its teaching and supervision across residency programs within the United States and internationally. This inconsistency results in divergent prescribing practices, varying practitioner competency levels, and gaps in evidence-based treatment. Such variability can ultimately affect patient care. This underscores the responsibility of the American Society of Clinical Psychopharmacology (ASCP) to promote and lead standardization of psychopharmacology education worldwide, thereby enhancing clinical education, clinical practice, and patient outcomes. In response to these gaps, we have developed a comprehensive, competency-based psychopharmacology curriculum for implementation in residency programs worldwide. The curriculum encompasses fundamental neurobiology of disease, medication-specific knowledge, including mechanism of action, clinical decision-making, and principles of practice-based learning. It aligns with ACGME milestones, uses contemporary instructional methods such as educational technology, case-based learning, and algorithm-guided prescribing. The product also emphasizes cultural humility, patient safety, rational polypharmacy, and deprescribing strategies. This presentation outlines the curriculum's development process, content domains, assessment strategies, and implementation pathways. Furthermore, we aim to update and engage leaders,

ASCP members, and other essential stakeholders on the ongoing development, adoption, and use of the model psychopharmacology curriculum.

As an update from the previous year, this workshop will:

- a) Briefly review the history of the ASCP model curriculum. Dr. Ira Glick and colleagues developed the American College of Neuropsychopharmacology (ACNP) Model Psychopharmacology Curriculum in the 1980s to enhance national education in psychopharmacology. Over eleven editions, with the latest in 2021, it was transformed for digital learners.
- b) Revisit the needs of modern learners and understand how the curriculum can meet the same. Modern learners differ in that they expect highly interactive, technology-integrated, on-demand educational experiences that are personalized, fast, visually driven, and immediately applicable to real-world clinical decision-making.
- c) Present and discuss the revised curriculum, which now exists as an online, dynamic "living" textbook. The term "living" signifies that the curriculum can be accessed by learners at any time, updated in real time, and integrated with emerging artificial intelligence (AI) technology. The AI component is designed to assist learners in locating literature references and completing board-style review questions. The product is composed of three sections tailored to different training levels: a brief course for PG1 residents and early learners, a fundamental course for PG2 residents and mid-level trainees, and an advanced course for PG3 residents and beyond, including fellows and early-career psychiatrists preparing for board exams.

We expect this workshop to again play a vital role in assessing whether the ongoing development of the curriculum aligns with the needs of key stakeholders including teachers and an end user. Audience engagement, including feedback on attitudes, perceived gaps, and educational needs, will be solicited through focused discussions and responses to product demonstrations. While AI's integration into education remains nascent and not yet standard practice, the next-generation curriculum should incorporate emerging AI technologies to explore how they can support learners of tomorrow.

Learning Objective 1: Understand the evolution of the ASCP model psychopharmacology curriculum.

Learning Objective 2: Review how the updated curriculum can be used by training programs or individual learners.

Literary References: Silberman EK, Pinderhughes CA, Cleveland EC, et al. Training psychiatrists in psychopharmacology: A national survey of psychiatry residencies. *Academic Psychiatry*. 2018;42(6):747-752.

Macaluso M, Espejo E, Shelton R, et al. The ASCP model psychopharmacology curriculum: a standardized framework for residency training worldwide. Panel presented at: 2025 Annual Meeting of the American Society of Clinical Psychopharmacology (ASCP); May 27–30, 2025; Scottsdale, AZ.

THE ASCP MODEL PSYCHOPHARMACOLOGY CURRICULUM UPDATE

Richard Shelton, University of Alabama at Birmingham

Individual Abstract: This presentation will review the entire three-year curriculum, including a first year Crash Course along with Basic and Advanced Courses. The full

curriculum will comprise more than 80 presentations by experts on the full range of psychopharmacology topics.

Literature References: 1. Silberman EK, Pinderhughes CA, Cleveland EC, et al. Training psychiatrists in psychopharmacology: A national survey of psychiatry residencies. *Academic Psychiatry*. 2018;42(6):747-752.

2. Yager J, Greden JF, Riba MB. Educating the psychiatrists of the future: A report from the APA Task Force on Competency-Based Education. *Academic Psychiatry*. 2004;28(2):83-91.

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

TOWARDS AN INTERNATIONAL, STANDARDIZED MODEL PSYCHOPHARMACOLOGY CURRICULUM FOR PSYCHIATRY RESIDENCY TRAINING: A COMPETENCY-BASED FRAMEWORK FOR IMPLEMENTATION

Gemma Espejo, University of California, Irvine School of Medicine

Individual Abstract: Psychopharmacology remains a crucial element of psychiatric practice. Nonetheless, considerable variation exists in its teaching and supervision across residency programs within the United States and internationally. This inconsistency results in divergent prescribing practices, varying practitioner competency levels, and gaps in evidence-based treatment. Such variability can ultimately affect patient care. This underscores the responsibility of the American Society of Clinical Psychopharmacology (ASCP) to promote and lead standardization of psychopharmacology education worldwide, thereby enhancing clinical education, clinical practice, and patient outcomes. In response to these gaps, we have developed a comprehensive, competency-based psychopharmacology curriculum for implementation in residency programs worldwide. The curriculum encompasses fundamental neurobiology of disease, medication-specific knowledge, including mechanism of action, clinical decision-making, and principles of practice-based learning. It aligns with ACGME milestones, uses contemporary instructional methods such as educational technology, case-based learning, and algorithm-guided prescribing. The product also emphasizes cultural humility, patient safety, rational polypharmacy, and deprescribing strategies. This presentation outlines the curriculum's development process, content domains, assessment strategies, and implementation pathways. Furthermore, we aim to update and engage leaders, ASCP members, and other essential stakeholders on the ongoing development, adoption, and use of the model psychopharmacology curriculum.

As an update from the previous year, this workshop will:

a) Briefly review the history of the ASCP model curriculum. Dr. Ira Glick and colleagues developed the American College of Neuropsychopharmacology (ACNP) Model Psychopharmacology Curriculum in the 1980s to enhance national education in psychopharmacology. Over eleven editions, with the latest in 2021, it was transformed for digital learners.

b) Revisit the needs of modern learners and understand how the curriculum can meet the same. Modern learners differ in that they expect highly interactive, technology-integrated, on-demand educational experiences that are personalized, fast, visually driven, and immediately applicable to real-world clinical decision-making.

c) Present and discuss the revised curriculum, which now exists as an online, dynamic "living" textbook. The term "living" signifies that the curriculum can be accessed by learners at any time, updated in real time, and integrated with emerging artificial intelligence (AI) technology. The AI component is designed to assist learners in locating literature references and completing board-style review questions. The product is composed of three sections tailored to different training levels: a brief course for PG1 residents and early learners, a fundamental course for PG2 residents and mid-level trainees, and an advanced course for PG3 residents and beyond, including fellows and early-career psychiatrists preparing for board exams.

We expect this workshop to again play a vital role in assessing whether the ongoing development of the curriculum aligns with the needs of key stakeholders including teachers and an end user. Audience engagement, including feedback on attitudes, perceived gaps, and educational needs, will be solicited through focused discussions and responses to product demonstrations. While AI's integration into education remains nascent and not yet standard practice, the next-generation curriculum should incorporate emerging AI technologies to explore how they can support learners of tomorrow.

Literature References: Silberman EK, Pinderhughes CA, Cleveland EC, et al. Training psychiatrists in psychopharmacology: A national survey of psychiatry residencies. *Academic Psychiatry*. 2018;42(6):747-752.

Yager J, Greden JF, Riba MB. Educating the psychiatrists of the future: A report from the APA Task Force on Competency-Based Education. *Academic Psychiatry*. 2004;28(2):83-91.

TOWARDS AN INTERNATIONAL, STANDARDIZED MODEL PSYCHOPHARMACOLOGY CURRICULUM FOR PSYCHIATRY RESIDENCY TRAINING: A COMPETENCY-BASED FRAMEWORK FOR IMPLEMENTATION

Keanna Lee, edYOU Technologies

Individual Abstract: The purpose of this presentation is to demonstrate the ASCP Interactive AI Curriculum, highlight its role in delivering standardized psychopharmacology education, and gather direct feedback from current and potential users. Variability in psychopharmacology training across institutions continues to create inconsistencies in competency, prescribing practices, and learner preparedness. The ASCP Interactive AI Curriculum was developed to address these gaps by transforming the model curriculum into an adaptive, interactive digital learning environment supported by artificial intelligence. This workshop will provide a focused walkthrough of the platform, including its key features: AI-supported content navigation, adaptive question generation, multimodal instructional components, and its alignment with ACGME milestones and best-practice educational frameworks. There will be a live demonstration, followed by audience engagement. Participants will be invited to respond to targeted questions about usability, curricular value, integration feasibility, and potential barriers to adoption. Data collection will include real-time polling, facilitated discussion prompts, and qualitative feedback based on user impressions during the demonstration. Preliminary findings from early institutional programs indicate strong learner engagement, improved access to evidence-informed decision tools, and increased efficiency in navigating complex psychopharmacology concepts. Users also reported that the AI-assisted question banks enhanced formative assessment and individualized learning. This workshop will expand on these preliminary findings by incorporating insights directly from ASCP members, educators, program leaders, and

trainees. We expect this workshop to play a key role in evaluating how the ongoing development of the ASCP Interactive AI Curriculum aligns with the needs of key stakeholders, including educators, trainees, and program leaders. Through live demonstration of the AI-powered platform, participants will engage directly with the "living" textbook, test-prep features, and adaptive content pathways. Audience input, including perceptions of usability, identified gaps, and emerging educational needs, will be gathered through guided discussion and real-time feedback during the demo.

Literature References: 1. Macaluso M, Espejo E, Shelton R, et al. The ASCP model psychopharmacology curriculum: a standardized framework for residency training worldwide. Panel presented at: 2025 Annual Meeting of the American Society of Clinical Psychopharmacology (ASCP); May 27–30, 2025; Scottsdale, AZ.

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. doi: 10.1176/appi.ap.29.2.134. Erratum in: *Acad Psychiatry*. 2005 Jul-Aug;29(3):324. Erratum in: *Acad Psychiatry*. 2005Jul;29(3):324. PMID: 15937259.

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

Pharmaceutical Pipeline Session

RE104: A NOVEL SEROTONERGIC PSYCHEDELIC 4-OH-DIPT PRODRUG FOR THE TREATMENT OF POSTPARTUM DEPRESSION

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Abstract: We present new results from a Phase 2 trial of RE104, a novel psychedelic 5HT_{2A} agonist prodrug of 4-OH-DIPT, in the first randomized controlled trial of a psychedelic agent for the treatment of postpartum depression (PPD). RE104, a unique, proprietary 4-OH-DIPT prodrug, is a novel psychedelic 5HT_{2A} agonist investigational compound being developed for the treatment of postpartum depression (PPD) and other mental health conditions. Preclinical and clinical characterization confirmed similar pharmacology of RE104 to other well-characterized classical psychedelics such as psilocybin, while demonstrating a significantly shorter and reproducible acute psychedelic experience in the clinic. PPD is a serious disorder occurring in approximately 15% of pregnancies, and is associated with significant distress, dysfunction and disability in affected women as well as adverse effects on infants. Participants (N=84) were randomized to receive a single, subcutaneous dose of 30 mg or 1.5 mg (active control) RE104 for injection at 28 sites across the United States and were subsequently followed for 4 weeks post-treatment. While session monitors were involved in the preparation, dosing session monitoring and

follow-up, the study treatment did not include formal psychotherapy. Eligible participants were women aged 18-45, ≤ 15 months post-partum, not breastfeeding, with moderate to severe depression based on an entry HAM-D-17 score of ≥ 24 at screening and baseline. In addition, if applicable, eligible participants could remain on a pre-existing stable regimen of SSRIs or therapy during the study. The primary endpoint was change from baseline at Day 7 in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score. Additional endpoints included changes in the MADRS over the course of the study, rates of response and remission, and changes in maternal function including care and relationship with the infant as assessed by the Barkin Index of Maternal Function (BIMF). Analysis of the primary outcome was via MMRM including treatment, visit and visit-by treatment interaction, and baseline MADRS; an unstructured covariance structure. Analysis of secondary endpoints was performed using descriptive statistics. A single 30 mg dose of RE104 resulted in a statistically and clinically significant reduction from baseline of 23.0 points in the MADRS total score on Day 7, as compared to a reduction of 17.2 points in the active control arm (difference of 5.80; one-sided $p=0.0094$). Clinically meaningful reductions in the MADRS were also observed for RE104 30 mg on the first day following administration and maintained through the Day 28 follow-up. 77.1% of participants treated with RE104 30 mg were responders (with at least 50% improvement from baseline MADRS) to therapy at Day 7 compared to 61.6% of participants on active control. 71.4% of participants on RE104 30 mg achieved remission (with a MADRS score of ≤ 10) at Day 7 compared to 41.0% on active control. Both response and remission improvements were maintained through the Day 28 follow-up period. Maternal well-being and function, including care of the infant as assessed by the BIMF, also demonstrated substantial improvement. RE104 was observed to be well-tolerated, during the trial with the majority of adverse events being mild to moderate in intensity, resolving spontaneously and consistent with the pharmacology observed with other agents in the class. Consistent with its pharmacokinetics, over 90% of participants on RE104 30mg showed no signs or symptoms posing a risk for discharge at the first measure of discharge readiness, taken 4 hours following treatment. Preliminary results from a contemporaneous lactation study suggest that the total amount of metabolites observed in the breastmilk represents less than 0.1% of the 30 mg RE104 administered to the mother representing a safety margin that is an order of magnitude below levels that might be considered of potential concern relative to the infant. These results suggest that breastfeeding following RE104 treatment may be able to resume with limited interruption. In this first sizable randomized controlled trial of a psychedelic agent for the treatment of Postpartum Depression, administration of 30 mg of RE104, was safe and well-tolerated and resulted in rapid, significant and durable improvement.

A NEW DAWN FOR SOCIAL ANXIETY TREATMENT: CLINICAL ADVANCEMENT OF THE NOVEL V1aR ANTAGONIST, NTX-1472

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Abstract: Background: NTX-1472 is a potent and selective vasopressin 1a receptor (V1aR) antagonist that has been studied in two completed Phase 1 clinical trials. Currently, NTX-

1472 is in clinical development by Newleos Therapeutics, Inc. for the treatment of Social Anxiety Disorder. The disease includes 2 subtypes, generalized (SAD-g) and performance-only (SAD-p). SAD-g is characterized by marked fear or anxiety about various social situations. These situations are avoided or endured with intense discomfort, leading to significant impairment and decreased quality of life (Kessler et al., 2005; Stein and Stein, 2008). The SOcial Anxiety Reduction (SOAR) study (NTX-1472-201) is an ongoing, Phase 2, proof-of-concept study that aims to assess the safety, tolerability, and efficacy of NTX-1472 compared to placebo (PLC) in adults with SAD-g.

Methods: The first clinical trial of NTX-1472 (Study BP41695) was a 3-part study that assessed the safety, tolerability and pharmacokinetics (PK) of single- and multiple-ascending doses of NTX-1472 (Part 1: single-ascending dose and food effect [n=48], Part 2: multiple-ascending dose [n=24]; Part 3: midazolam drug-drug-interaction [n=16]). The second clinical trial (Study BP43293) was an open-label, 2-period study to investigate the effect of repeat doses of itraconazole on the PK of a single dose of NTX-1472 (n=16). The SOAR study has a double-blind, placebo (PLC)-controlled, parallel-arm study design. Participants must be between 18 and 65 years of age (inclusive) and have a diagnosis of SAD-g as defined by the Diagnostic and Statistical Manual of Mental Disorders 5th Edition and confirmed by the Structured Clinical Interview for DSM-5 Disorders. Participants are randomized, stratified by sex, to receive either NTX-1472 (single dose level, n=50) or PLC (n=50) daily for 8 weeks. The study duration is 99 days for each participant, including a Screening Period of up to 30 days, a Treatment Period of up to 59 days, and a Follow-up Period of up to 10 days.

Results: NTX-1472 has been administered to a total of 86 healthy participants in 2 completed Phase I studies. NTX-1472 was rapidly absorbed with Tmax achieved at 1-3 hours (h) post-dose. Food increased the Cmax of NTX-1472 but had no effect on the AUC, and the half-life was about 5-7 h. NTX-1472 given daily had no effect on the PK of midazolam, a CYP3A4 substrate. Multiple doses of the strong CYP3A4 inhibitor itraconazole increased the AUCinf of NTX-1472 by 2.5-fold. Across both studies, NTX-1472 was well tolerated, as all treatment-emergent adverse events (TEAEs) were non-serious and not dose-limiting. Building on the Phase 1 program, the SOAR study is currently enrolling in 11 sites across the United States, with planned completion in early 2027. The primary endpoint is incidence and severity of TEAEs. Key secondary endpoints include change in the clinician-administered Liebowitz Social Anxiety Scale (LSAS) and the Clinical Global Impression – Severity (CGI-S) scale.

Conclusion: In humans, V1aR antagonists have been shown to decrease amygdala activation to threatening social cues (Lee et al., 2013) and to reduce anxiety-potentiated startle, a biomarker associated with treatment response in SAD (Hoge et al., 2024; Lago et al., 2021). These, as well as other, findings support the development of NTX-1472, a novel V1aR antagonist, for the treatment of anxiety disorders. The ongoing Phase 2 study will help determine the therapeutic potential of NTX-1472 in SAD-g.

DT-101 – A NOVEL ALPHA-AMINO-3-HYDROXY-5-METHYL-4-ISOXAZOLE RECEPTOR (AMPA) POSITIVE ALLOSTERIC MODULATOR DEMONSTRATES FAVORABLE TOLERABILITY AND FUNCTIONAL BIOMARKERS IN PHASE 1 HEALTHY VOLUNTEER TRIAL

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Simon Ward, Draig Therapeutics

Abstract: Positive allosteric modulators (PAMs) of the α -amino-3-hydroxy-5-methyl-4-isoxazole subtype of ionotropic glutamate receptor (AMPA) enhance glutamatergic signaling and synaptic plasticity, but the clinical development of earlier compounds have been constrained by suboptimal pharmacokinetics and limited therapeutic index (TI). DT-101 is a next-generation, structurally novel, orally bioavailable AMPAR PAM designed to achieve much broader TI through optimized receptor modulation. Importantly, DT-101 has a differentiated pharmacokinetic profile enabling once-a-day pulsatile dosing that is optimal for engaging synaptic plasticity mechanisms. A Phase 1 randomized, double-blind, placebo-controlled trial was conducted with single-ascending dose (SAD) and multiple-ascending dose (MAD) in healthy adult volunteers. The primary objectives were safety and tolerability of DT-101. Secondary and exploratory objectives included the plasma pharmacokinetics (PK) of DT-101 as well as measurements of cerebrospinal fluid (CSF) drug concentration. A separate cohort of healthy volunteers was used to assess the pharmacodynamic responses to single doses of DT-101 using magnetoencephalography (MEG), a method previously shown to be sensitive to modulators of excitatory/inhibitory tone in the brain. DT-101 was considered safe and well tolerated, with no dose-limiting toxicities or clinically meaningful safety findings. DT-101 achieved its predefined target PK profile, demonstrating dose-proportional exposure and favorable half-life supportive of once-daily dosing. DT-101 concentration in CSF was equivalent to unbound plasma concentration, consistent with good exposure into the CNS. MEG analyses demonstrated a clear DT-101-mediated modulation of cortical oscillatory activity and network dynamics consistent with AMPA receptor potentiation, providing direct evidence of functional DT-101 effects in the brain. MEG effects correlated with plasma exposure, enabling data-driven refinement of Phase 2 dose selection. In summary, DT-101 exhibits a favorable safety profile with target-aligned PK, confirmed CSF exposure, and sensitive MEG-based demonstration of functional glutamatergic modulation. These Phase 1 findings supported advancement of DT-101 into a large, global Phase 2 trial in major depressive disorder (MDD).

SELTOREXANT, ADJUNCTIVE TO ANTIDEPRESSANTS, IN ADULTS WITH MAJOR DEPRESSIVE DISORDER WITH INSOMNIA SYMPTOMS: PHASE 3 STUDIES

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Gahan Pandina, Johnson and Johnson

Abstract Background: Seltorexant is a first-in-class, selective, orexin-2 receptor antagonist being investigated as adjunctive treatment to standard antidepressant therapy for major

depressive disorder (MDD) with insomnia symptoms (IS) in randomized, international, phase 3 studies. We report results from the placebo (PBO)-controlled, double-blind (DB) phase of NCT04533529, (Study 1) with open-label extension (OLE), and from NCT04513912 (Study 2), a DB study with quetiapine extended release (XR) as an active comparator.

Methods: Participants (pts) aged 18-74 years with DSM-5 diagnosis of MDD without psychotic features who had an inadequate response to 1-2 SSRI/SNRI (while continuing their current regimen) were included in both studies. In the DB phase of Study 1, pts (with and without moderate-to-severe IS) were randomized 1:1 to adjunctive seltorexant 20 mg or PBO for 6 weeks. The primary endpoint was change from baseline to Day 43 in Montgomery-Åsberg Depression Rating Scale (MADRS) total score; key secondary endpoints were changes from baseline to Day 43 in MADRS without sleep item (WOSI) and in Patient Reported Outcome Measurement Information System-Sleep Disturbance (PROMIS-SD) 8a T-score. In the OLE, eligible DB phase pts received adjunctive seltorexant 20 mg for an additional 52 weeks; long-term MADRS total score change was assessed. In Study 2 pts with moderate-to-severe IS were randomized 1:1 to adjunctive seltorexant 20 mg or quetiapine XR (labeled dosage) for 26 weeks. The primary endpoint was Week 26 MADRS total score response rate ($\geq 50\%$ improvement from baseline); key secondary endpoint was change from baseline to Week 26 in body weight. Treatment-emergent adverse events (TEAEs) were assessed in both studies.

Results: In Study 1, 586 (283 seltorexant, 303 PBO) pts with MDD received ≥ 1 dose of study drug in the DB phase. Primary and key secondary endpoints significantly improved with seltorexant (n=196) vs PBO (n=195) at Day 43 in pts with IS; least squares mean difference (95% CI; 2-sided p) of change in MADRS: -2.6 (-4.53, -0.74; p=0.007), in MADRS-WOSI: -2.0 (-3.75, -0.28; p=0.023), and in PROMIS-SD 8a T-score: -3.7 (-5.48, -2.00; p < 0.001). TEAEs occurred in 104/283 (36.7%) seltorexant and 124/303 (40.9%) PBO pts. 522 (96.7%) DB phase completers received ≥ 1 dose of study drug in the OLE; 360 (69.0%) completed the OLE. Mean (SD) change in MADRS from OLE baseline to OLE Week 52 was -11.0 (10.55; n=359). No new safety concerns were identified. In Study 2, 756 (366 seltorexant, 390 quetiapine XR) pts with MDD with IS received ≥ 1 dose of study drug. Week 26 MADRS response rate was 57.4% (201/350) for seltorexant and 53.4% (194/363) for quetiapine XR. Mean (SD) change from baseline to Week 26 in body weight (kg) was 0.5 (2.89; n=268) for seltorexant and 2.1 (3.93; n=263) for quetiapine XR. TEAEs occurred in 198/366 (54.1%) seltorexant and 264/390 (67.7%) quetiapine XR pts. Lower incidences of somnolence and fewer TEAEs leading to study drug discontinuation occurred with seltorexant vs quetiapine XR.

Conclusion: In Study 1, adjunctive seltorexant showed significant and clinically meaningful antidepressant effects in the DB phase, beyond improvement of IS. Depressive symptoms continued to improve up to 1 year. In Study 2, both treatments demonstrated comparable robust antidepressant response rates, with no statistical difference between groups. Safety findings suggest seltorexant is well tolerated and a potentially good alternative to long-term antipsychotics for MDD with IS.

KETAMINE TREATMENT FOR NON-MOTOR SYMPTOMS OF PARKINSON'S DISEASE

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Gerard Sanacora, Yale University

Abstract Background: Parkinson's disease (PD) is a neurodegenerative disorder characterized not only by motor impairment but also significant reductions in overall quality of life secondary to the presence of non-motor symptoms such as apathy, anhedonia, anxiety, and pain. Advances in our understanding of PD pathophysiology have increased, revealing promising new targets for interventions aimed at alleviating non-motor symptoms. Emerging evidence suggests that impaired regulation of synaptic plasticity in brain networks outside of primary motor circuits could contribute to these burdensome features of the disease. Ketamine has been shown to enhance synaptic plasticity in brain regions related to motivated behavior and reward sensitivity, as well as well-established antidepressant effects in major depressive disorder. Together, there is strong rationale for investigating ketamine as a treatment for non-motor symptoms in PD.

Methods: In this single-site phase II clinical trial funded by the Michael J Fox Foundation, 51 participants with confirmed PD and depressive symptoms meeting criteria for a current major depressive episode [Montgomery Asberg Depression Rating scale (MADRS) ≥ 15] were randomized to treatment with either IV ketamine 0.5mg/kg/40mins or IV saline placebo delivered over 40mins at an interval of 2 times per week for 3 weeks. The primary outcome measure was change in MADRS score from baseline to end-of-treatment (EOT) [24-72hrs after last dose of study drug]. Other key measures included, MADRS determined response [$\geq 50\%$ reduction in score] and remission [score ≤ 10] at EOT and 1-month after last study drug administration. Additional measures assessing non-motor symptoms, including apathy (Starkstein Apathy Scale, SAS), Anhedonia (Snaith-Hamilton Pleasure Scale, SHAPS), anxiety (State-Trait Anxiety Inventory, STAI), and pain (King's Parkinson's Disease Pain Scale, KPPS) were also collected and analyzed. To evaluate the adequacy of masking, patients and research staff were asked at EOT to guess treatment allocation.

Results: There were no meaningful baseline differences in age, sex distribution, Parkinson's motor symptom severity, depressive symptom severity, or cognitive impairment at baseline. Fifty of the 51 participants randomized (25 placebo, 26 ketamine) received at least one treatment and completed the study. Ketamine was associated with transient increases in systolic and diastolic blood pressure. However, no patients were discontinued from treatment due to cardiovascular events. No evidence of decreased oxygen saturation was observed in the ketamine group compared to the placebo group. One Serious Adverse Event was reported in a participant receiving placebo, consisting of new onset atrial fibrillation and metabolic abnormalities. Most common treatment emergent adverse events in the study were headache (22% ketamine, 31% placebo), nausea (12% ketamine, 12% placebo), dizziness/faintness (8% ketamine, 10% placebo), and early morning awakenings (10% ketamine, 2% placebo). No Treatment emergent adverse events led to withdrawal. Ketamine was associated with a significantly greater reduction in MADRS score from baseline to the EOT compared to placebo, with a significant group $\times$ time interaction on MADRS ($F=5.26$, $p=0.001$). From baseline to post-treatment, MADRS scores decreased by an average 16-points in the ketamine group, compared with 10-points in the placebo group ($p=0.006$). Additional outcome measures showed the effect was sustained at 1-month follow-up ($p=0.002$) and that response rates were significantly higher with ketamine (73%) compared with in the placebo group (38%) at EOT (Chi =0.01); this difference also persisted at the 1-month follow-up (69% vs 29%; Chi =0.005). Significant differences were also observed for remission rates at EOT (54% vs 25%; Chi =0.04) and at 1-month follow-up (50% vs 17%; Chi =0.01). Measures of

other associated non-motor symptoms also showed significant and clinically meaningful improvements in apathy (SAS) ($p=0.015$) and anxiety (STAI) ($p=0.005$) at EOT. Both measures showed trends towards sustained benefit at 1-month follow-up (SAS, $p=0.07$; STAI, $p=0.06$). Improvement in anhedonia approached significance at post-treatment ($p=0.055$). Pain, assessed using the KPPS improved over the treatment period in both groups, but appeared to rebound at the 1-month follow-up for participants in the placebo group but not the ketamine treated group, resulting in a 6.3-point difference between groups at that timepoint. 78% of the patients correctly guessed treatment assignment. Of the patients receiving placebo 62% correctly guessed assignment while 92% of those allocated to ketamine correctly guessed treatment assignment. Clinicians correctly guessed assignment for 90% of participants.

Discussion: Overall, this phase II study provides strong preliminary evidence that IV ketamine delivered at 0.5mg/kg/40mins twice a week for three weeks is generally safe and can provide significant and clinically meaningful benefits to patients suffering with a range of non-motor symptoms commonly associated with PD. These treatment effects were evident despite a relatively high level of placebo response. Measures of depression severity, apathy, and anxiety all showed improvement following treatment and the benefits were largely sustained at the 1-month follow up time point. There was additional evidence of beneficial effects on anhedonia and pain at the end of treatment and the one-month follow up respectively. Imperfect treatment allocation masking was suggested by both patient and study team guesses. However, allocation guesses were collected at the end of treatment, and may therefore have been influenced not only by the transient effects of ketamine but also by the longer-term response experienced or observed during the study. Interestingly, despite the likely effect of unblinding, a relatively large placebo response was still observed and adverse events were relatively similar between groups. In sum, the data provide strong preliminary evidence of ketamine's ability to provide benefits to patients suffering from a range of non-motor symptoms associated with PD. Considering the growing prevalence and burden of PD, and the large unmet need for effective treatments of the non-motor symptoms associated with PD, it appears future studies examining Ketamine's potential role in the overall management of PD for some individuals are warranted.

FORVISIRVAT (SP-624), A FIRST-IN-HUMAN SIRT6 ACTIVATOR WITH AN EPIGENETIC MECHANISM OF ACTION, CURRENTLY IN A PHASE 2B-3 STUDY FOR THE TREATMENT OF MAJOR DEPRESSIVE DISORDER

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Abstract: Sirtsei Pharmaceuticals is developing forvisirvat, a first-in-human SIRT6 activator with an epigenetic mechanism of action (MoA), for the treatment of MDD. SIRT6 is a NAD⁺ dependent enzyme. SIRT6-deficient mice have a shortened lifespan and phenotypes associated with age-related impairments, cancer, and metabolic disorders. SIRT6 over-expression in mice protects against metabolic pathologies and increases lifespan. SIRT6 has an epigenetic MoA that includes reduced inflammation, enhanced mitochondrial health, metabolic homeostasis and DNA repair. Each of these may play a role in neurodegeneration, metabolic disorders, and psychiatric disorders such as MDD. Both in vitro and animal studies

support forvisirvat's role in MDD. It activates SIRT6 deacetylation of histones preventing transcription of DNA. Forvisirvat reduces lipopolysaccharide (LPS)-induced inflammatory cytokines, silences gene pathways responsible for neuroinflammation including the NFκB pathway. It enhances neuroplasticity as evidenced by long-term potentiation assay in vitro and in vivo and prevents cognitive deficits induced by scopolamine (anticholinergic) or phencyclidine (NMDA antagonist) in the novel object recognition test. Forvisirvat works in multiple depression models including LPS- and ACTH-treated mice, olfactory bulbectomized rats and in a model of treatment-resistant depression (forced swim test in Wistar-Kyoto rats). Four phase 1 trials of single oral doses up to 80mg, and 20 and 40mg for 10 days demonstrated forvisirvat was well tolerated and reached target plasma concentrations in healthy adults, supporting progression of 20 mg daily into a Phase 2 study. A Phase 2 study evaluated the safety and efficacy of forvisirvat 20 mg daily vs placebo for 4 weeks in participants with MDD. No significant difference in the primary endpoint was observed between treatment groups. However, post-hoc analyses found that women treated with forvisirvat experienced consistent significant overall improvement on the primary and secondary efficacy measures whereas men showed no effect on any scale. Safety was comparable to placebo. A Phase 1 quantitative EEG study using brain network analytics (BNA) is ongoing. The first cohort in healthy adults is complete and showed that 20 mg once daily was centrally active and changed BNA profiles relative to placebo after 1 day and 2 weeks of daily treatment. Observed post-dose increases across high-frequency bands support improved cognition, while reduction in delta power support potential antidepressant effects. Evoked response potentials showed improved decision-making speed and context updating and reversing functions, often impaired in MDD. Enrollment of a second cohort of adults with MDD is underway. A phase 2b-3 study is nearing completion. This study is nearly identical in design to the previous Phase 2 study but with a larger n and includes a cognitive test. It seeks to confirm the results from the prior study, with the primary efficacy endpoint in agreement with the FDA pre-specified in females only. Efficacy and tolerability remain challenges to successful MDD treatment. Forvisirvat, a novel SIRT6 activator with effects in preclinical models of depression and cognition, is associated with several mechanisms implicated in MDD. A Phase 2 study suggested efficacy in females, a Phase 2b-3 study is ongoing in an attempt to confirm these findings.

UNLOCKING MEDICINES FOR NEUROPSYCHIATRY BY ENHANCING ORAL ABSORPTION USING A LYMPHATIC-TARGETING PRODRUG TECHNOLOGY

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¹Seaport Therapeutics

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Abstract: Introduction: Depression and anxiety are disabling mental health conditions with a significant need for new treatment options. The Glyph™ platform, a lymphatic-targeting prodrug technology, can be applied to overcome limitations such as high first-pass metabolism, low oral bioavailability, and/or side effects, which may otherwise present barriers to patient use. The platform reversibly conjugates a drug of interest to a dietary fat molecule using proprietary chemistry, shifting absorption toward intestinal lymphatics to avoid first-pass hepatic metabolism and enhance oral bioavailability while reducing dose. GlyphAllo™ (SPT-300 or Glyph Allopregnanolone), an oral prodrug of allopregnanolone, is designed to overcome allopregnanolone's poor oral bioavailability from substantial first-pass

hepatic metabolism. Allopregnanolone is an endogenous neurosteroid that has been clinically validated as a rapidly acting antidepressant with anxiolytic and sleep-promoting effects through its pharmacology as a GABAA receptor positive allosteric modulator. Here, we discuss how GlyphAllo was developed using the Glyph platform and present initial proof-of-concept and safety results from phase 1 and phase 2a clinical trials in healthy volunteers.

Methods: A series of lymphatic-targeting allopregnanolone prodrugs was evaluated by screening for in vitro plasma release and assessing plasma levels after oral administration across species. GlyphAllo was evaluated in a multipart phase 1 clinical trial (NCT05129865) of healthy volunteers including single and multiple ascending dose components. Safety, pharmacokinetic data, and pharmacodynamic assessments, including the Stanford Sleepiness Scale (SSS), quantitative EEG (qEEG), and video-oculography for saccadic eye velocity (SEV), were collected. GlyphAllo's potential to reduce physiological stress in healthy volunteers was evaluated in an initial proof-of-concept phase 2a (NCT05129865) pharmacodynamic trial using the Trier Social Stress Test (TSST), a clinical validated model of anxiety.

Results: Based on the discovery and preclinical screening methods, GlyphAllo (SPT-300) was selected as the lead development candidate. In a phase 1 clinical trial in healthy volunteers, oral dosing of GlyphAllo was generally well-tolerated and resulted in a greater than nine-fold increase in allopregnanolone plasma levels compared to previously reported bioavailability of oral allopregnanolone. Peak allopregnanolone plasma levels and pharmacodynamic markers, including increased beta EEG power and reduced SEV, were observed 3-5 hours post-dose. GlyphAllo demonstrated initial proof-of-concept in a phase 2a TSST clinical trial, significantly blunting the salivary cortisol stress response compared to placebo in healthy volunteers ($p=0.0001$). No treatment-related severe or serious adverse events were reported. The most common adverse event was somnolence, which was mild or moderate and transient in all cases. SSS scores returned to baseline by six hours post dose.

Conclusion: These data validate the Glyph platform's ability to enhance oral bioavailability and confirm that the pharmacodynamic activity of GlyphAllo is consistent with the pharmacology of allopregnanolone. A phase 2b, placebo-controlled trial (BUOY-1) is currently underway to evaluate the efficacy and safety of GlyphAllo in patients with major depressive disorder, with or without anxious distress (NCT07065240). GlyphAllo's development and demonstration of enhanced oral bioavailability provides an initial proof-of-concept supporting the wider applicability of the lymphatic-targeting prodrug approach to therapeutic molecules with previous limitations.

BH-200 (NELIVAPTAN), A VASOPRESSIN V1B RECEPTOR ANTAGONIST, IN GENETICALLY DEFINED SUBGROUPS OF MDD: PRECISION TARGETING OF HPA-AXIS DYSREGULATION IN THE OLIVE PHASE 2 PROGRAM

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Abstract: Disturbances of hypothalamic–pituitary–adrenal (HPA) axis function are implicated in a biologically defined subset of patients with major depressive disorder (MDD). Pharmacologic modulation of the stress hormone system, including CRHR1 and vasopressin V1b receptor (V1bR) antagonism, has been explored for decades; however, trials conducted in unselected MDD populations have not led to regulatory approval. We hypothesized that biological heterogeneity dilutes treatment effects and that stress-axis–driven subgroups can be prospectively identified. In a prior positive Phase 2 trial with the selective V1bR antagonist BH-200 (nelivaptan), a bimodal distribution of response suggested distinct responder populations. Because the dexamethasone–CRH (Dex-CRH) test is not practical for routine use, a genetic classifier (V1b polygenic score; V1bPGS) was developed based on vasopressin signaling biology and Dex-CRH–characterized cohorts. The 14-SNP tool assigns patients to three subgroups (A, B, C), reflecting differential ACTH suppression profiles and putative vasopressin pathway activity. The OLIVE trial was a randomized, double-blind, placebo-controlled Phase 2 trial conducted in eight European countries. A total of 338 patients with MDD were randomized 2:1 to BH-200 250 mg BID or placebo for eight weeks. The prespecified primary endpoint was change from baseline to Week 8 on the 17-item Hamilton Depression Rating Scale (HAM-D-17) in patients classified as Subgroup C. In the modified intention-to-treat population (N=331), BH-200 demonstrated clinically meaningful improvement versus placebo ($\Delta = -2.98$, $p = 0.0003$). Treatment separation emerged early and was sustained through a 4-week follow-up. Response rates ($\geq 50\%$ reduction in HAM-D-17) were 50.0% with BH-200 versus 25.7% with placebo, odds ratio (OR), 2.98 (95% CI, 1.74, 5.10), and remission rates (HAM-D-17 ≤ 7) were 25.8% versus 16.8%, OR 1.62 (95% CI, 0.86, 3.08) respectively. In the prespecified primary analysis population (Subgroup C; $n=123$), the treatment difference was $\Delta = -1.94$ ($p = 0.153$; Cohen's d 0.28). However, genetic stratification revealed marked heterogeneity of effect. The largest benefit was observed in Subgroup A ($n=89$), with $\Delta = -4.47$ ($p = 0.005$; Cohen's d 0.55), response rate 58.9% versus 25.9%, OR 4.22 (95% CI, 1.51, 11.83), and remission rate 33.9% versus 11.1%, OR 3.82 (95% CI, 0.98, 14.98), with separation evident from Week 1 onward. Subgroup B ($n=119$) showed intermediate benefit with $\Delta = -2.85$ ($p = 0.037$, Cohen's d 0.49). These findings suggest biologically informative refinement of the classifier, and support optimization of patient enrichment strategies for subsequent development. BH-200 was generally well tolerated. The most frequent adverse event was headache (8.9%). Elevations of ALT or AST $> 3 \times$ ULN occurred in 5.8% of treated patients. These changes were asymptomatic and reversible during treatment or after discontinuation. No serious adverse events occurred in the active arm, and the hepatic signal appears monitorable within standard safety frameworks. The OLIVE program demonstrates that vasopressin V1b receptor antagonism is a viable antidepressant mechanism, and that integration of a biologically grounded genetic companion diagnostic can enhance signal detection and enrich for larger clinical benefit. This precision psychiatry strategy informs the next phase of clinical development for BH-200.

NOVEL ORAL RAPID-ACTING NEUROACTIVE STEROID FOR TREATMENT OF POSTPARTUM DEPRESSION: A PLACEBO-CONTROLLED PHASE 3 CLINICAL TRIAL OF LPCN 1154A

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Anthony DelConte, Lipocine

Abstract Background: Postpartum depression (PPD), a potentially life-threatening condition, affects 10-20% of new mothers, negatively impacts maternal-infant bonding, maternal mental health, and child development. Treatment options for PPD remain limited, underscoring a clear unmet need for a rapid-acting antidepressant with superior tolerability. LPCN 1154A is an investigational oral neuroactive steroid and positive allosteric modulator of the GABAA receptor being developed as a short-duration (48-hour), at-home treatment designed to provide rapid and sustained antidepressant effects in women with PPD. This Phase 3 trial aimed to evaluate the efficacy, safety, and tolerability of LPCN 1154A in women with PPD.

Methods: This randomized, double-blind, placebo-controlled Phase 3 study (NCT06979544) enrolled women aged 15–45 years with DSM-5–defined major depressive disorder with a peripartum onset and 17-item Hamilton Depression Rating Scale (HAM-D) ≥ 26 . Participants were randomized 1:1 to receive LPCN 1154A or matching placebo for a 48hr at-home treatment period. Antidepressant effects were evaluated with respect to both rapid onset (at 12, 36, and 60 hours) and durability of response (on Days 7 and 30).” The primary endpoint was change from baseline in total HAM-D scores at hour 60, with secondary assessments including Montgomery-Åsberg Depression Rating Scale (MADRS) and Patient Global Index of Change to capture broader symptom domains and patient-reported improvement.

Results: At the time of this submission, all participants have completed study procedure, with 90 individuals randomized (mean $\pm$ SD age: 31 ± 6 yrs; BMI 30 ± 6 kg/m²) and the dataset remains blinded. The randomized cohort was predominately White (64%), followed by Black/African American (32%), and other racial groups (3%), with 62% identifying as Hispanic or Latino. The mean interval between delivery and Day 1 of treatment was 26 ± 15 weeks.

Baseline HAM-D total score was 28 ± 3 and was not significantly different by race, ethnicity, parity, delivery method of current pregnancy, nor concomitant antidepressant use. These same participants were classified by MADRS as moderate (20–34; n=32, 36%) or severe (> 34 ; n=58, 64%), with the severe group showing significantly higher scores on most items (9/10). There have been no reports of drug discontinuations, excessive sedation, loss of consciousness, or serious adverse events (SAEs) related to the study drug.

Conclusions: This presentation will report primary and secondary efficacy outcomes, onset of antidepressant response, durability through Day 30, and detailed safety findings. As a novel, rapid-acting, short-course oral therapy for at-home administration, LPCN 1154A has the potential to address critical unmet needs in PPD and broaden the clinical application of neuroactive steroid modulation in mood disorders. Furthermore, the favorable safety profile of LPCN 1154A supports its potential to deliver a well-tolerated oral treatment option that could meaningfully expand the safety and accessibility of care in women’s mental health and related therapeutic areas. This study was supported by Lipocine Inc.

A RANDOMIZED, PLACEBO-CONTROLLED TRIAL OF THE FATTY ACID AMIDE HYDROLASE INHIBITOR PALMITOYLETHANOLAMIDE IN BIPOLAR DEPRESSION

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

Abstract: There is growing interest in the endocannabinoid system (ECS) as an alternative signaling pathway involved in mood disorders. In response to stressors such as mood episodes, the breakdown of endocannabinoids by the Fatty Acid Amide Hydrolase (FAAH), a degrading enzyme located in the somatodendritic compartments of neurons, reduces endocannabinoid levels and increases HPA stress and inflammation. Higher FAAH breakdown has been described in subjects with depression, PTSD, and suicide ideation. Thus, FAAH inhibition may also represent a unique, valuable target in the therapeutics of Bipolar Depression. Palmitoylethanolamide (PEA) is an FAAH inhibitor, a member of the extended endocannabinoid family. PEA significantly increases the levels of key endocannabinoids (ECs), such as anandamide (AEA), and, through the so-called entourage effect, indirectly activates CB1 receptors. PEA also has shown potent anti-inflammatory and antioxidant effects in humans. Lower PEA levels were observed in depression, inversely associated with depressed mood, diminished interest/pleasure, and psychomotor retardation. In Depression, the first clinical trial examining the antidepressant effects of PEA (600 mg twice daily for six weeks, double-blind, placebo-controlled design) showed a significant improvement in depression scores compared to placebo. The PEA group showed a rapid onset and significantly greater improvements in depressive symptoms score from week 2 compared to the placebo group. The objective of this 6-week, double-blind, placebo-controlled study is to evaluate the antidepressant efficacy of the PEA in Bipolar Depression and the association between antidepressant response with endogenous cannabinoids and cytokines (PEA, AEA, 2-AG, OEA; TNF, IL2, 4, 6, 10, 12). Outpatients with BD in a depressive episode will be followed up for six weeks, with baseline, week 2, 4, and endpoint (post-treatment) assessments. Two groups will be randomized: treatment as usual (TAU, mood stabilizer) plus placebo (n=25) versus TAU plus PEA (600mg/day bid) (n=25). Overall, PEA showed a significant improvement of depressive symptoms in 6 weeks, but not statistically different from placebo. Further studies are warranted.

PROSPECTIVE REPLICATION OF AN EEG BIOMARKER FOR PREDICTING CHANGES IN ATTENTION IN ALTO-203, AN H3 INVERSE AGONIST

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¹Alto Neuroscience

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Abstract Background: Psychiatric disorders are heterogeneous, leading to drugs developed in broad populations showing no or minimal benefit over placebo. Predictive biomarkers may enhance treatment effects by targeting subpopulations for a given drug and reducing trial and

error prescribing. ALTO-203 is an H3 inverse agonist that releases dopamine, norepinephrine, acetylcholine, and histamine, suggesting a pro-wakeful, pro-cognitive profile that may be beneficial for Major Depressive Disorder (MDD) and other disorders. A prior Phase 1 trial in healthy volunteers showed acute benefits on subjective positive emotion and alertness, along with improved attention and reduced theta/beta ratio (TBR), a neurophysiological index of cortical arousal and attentional control. Moreover, subjects with higher TBRs at baseline showed greater changes in attention with ALTO-203 than subjects with lower TBRs, suggesting that ALTO-203 may be better at improving attention in those with higher TBRs ratios. A subsequent study was conducted with a goal of replicating the Phase 1 findings in MDD participants.

Methods: 69 participants with MDD and anhedonia (defined as a Snaith Hamilton Pleasure Scale [SHAPS] > 28) were enrolled in a Phase 2 proof-of-concept (POC) trial of ALTO-203 (NCT06391593). Participants underwent a single-dose period, in which they received two single-doses of ALTO-203 (25µg and 75µg) and placebo in a three-way crossover design with an at least 10-day washout period. The primary outcome was an acute change in positive emotion assessed by the Bond-Lader Visual Analog Scale (BL-VAS). Participants underwent cognitive assessments, electroencephalography (EEG), and sleep and activity monitoring using a wearable device. Following the single-dose period, participants received daily administration of ALTO-203 (25µg or 75µg QD) or placebo over 28 days to evaluate extended safety, tolerability and pharmacokinetics. Our analysis set includes 52 participants that passed blinded prospective central review and completed the single-dose period. Mixed-effects models evaluated the efficacy of ALTO-203 versus placebo; subgroup analyses of subjects with higher TBRs were also tested. Statistical significance was evaluated with two-sided p-values with no correction for multiple comparisons.

Results: There was no significant difference between ALTO-203 and placebo on the BL-VAS as there was a higher than expected placebo response ($p > 0.407$). Compared to placebo, ALTO-203 improved attention (25µg $p < 0.05$; 75µg $p = 0.06$) and decreased TBRs (25µg $p < 0.05$). Improvement in attention with ALTO-203 was greatest among participants with high baseline TBRs (25µg: $p < 0.01$; 75µg: $p < 0.05$ vs. placebo). Increased wakefulness (reduced minutes asleep) supported the wake-promoting effects of ALTO-203 (25µg: $p < 0.05$; 75µg: $p < 0.001$ vs. placebo). ALTO-203 displayed predictable accumulation over multiple doses and was well tolerated, with insomnia as the most frequent adverse event.

Conclusions: These data replicate prior findings that ALTO-203, a novel H3 inverse agonist, improves sustained attention and cortical arousal, and that individuals with higher TBRs are more likely to realize the greatest benefit in sustained attention. These data suggest that ALTO-203 may be best suited for disorders with hypersomnolence or excessive daytime sleepiness, along with deficits in attention. The cross-over design of the study allowed an efficient assessment of ALTO-203 in patients.

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

Workshops

***FINDINGS FROM THE ASCP PRESIDENTIAL TASK FORCE ON PSYCHOTROPIC DRUG POLYPHARMACOTHERAPY**

Joseph Goldberg, Icahn School of Medicine at Mount Sinai

Overall Abstract: Prescribers often undertake combination polypharmacy regimens for serious mental illnesses (SMIs) when monotherapies or simpler drug pairings are not efficacious. However, there has been little systematic research to inform best practices for devising combinations of 3 or more psychotropic medications. Numerous factors bear on the crafting of polypharmacy regimens, including the recognition of pharmacodynamic synergies versus mechanistic redundancies, avoiding contradictory drug mechanisms of actions and potential toxicity states, pharmacokinetic drug-drug interactions and drug dosing implications, cumulative burden of adverse effects and impact on adherence and cost, patient preference, differential intended symptom targets when treating complex or comorbid conditions, augmentations before dose optimization of single agents, and milestone decision points when opting to switch versus augment an existing treatment. To shed greater light on these issues, the ASCP undertook a presidentially-appointed task force comprised of 60 international psychopharmacology experts, including clinical trialists, psychopharmacology educators and investigators, academic pharmacists, psychiatrists, and authors of previous practice guidelines. A Delphi survey queried panelists' attitudes and beliefs about decisions to initiate combination pharmacologies, focusing on identifying patient candidacy and criteria for polypharmacy treatments, recognizing drug mechanisms and drug-drug interactions, timing sequential versus simultaneous augmentation strategies, controversies involving the combining of atypical antipsychotics, and issues of safety and tolerability. This workshop will provide a brief historical perspective on the evolution of polypharmacy within psychiatry, and then present key findings from the Delphi survey responses and task force members' consensus recommendations, as an impetus to generate group discussion through interactive audience participation that will provide both knowledge about polypharmacy decision-making to participants as well as feedback to the task force as it finalizes its ultimate recommendations on behalf of the ASCP to the broader scientific community as well as the general public.

Learning Objective 1: Differentiate polypharmacy combinations that are rational from irrational, evidence-based from non-evidence-based, and safe or unsafe, across major psychiatric disorders

Learning Objective 2: Recognize when, how, and why specific combination pharmacotherapy approaches are or are not likely to produce better clinical outcomes for patients with serious mental illnesses.

Literary References: Zigman D, Blier P. A framework to avoid irrational polypharmacy in psychiatry. *J Psychopharmacol* 2012 Dec;26(12):1507-11.

UNDERUTILIZED AUGMENTERS IN POLYPHARMACY REGIMENS: THE CASE FOR LITHIUM

Nassir Ghaemi, Tufts University/Harvard Medical School

Individual Abstract: Lithium is an underutilized medication in general, especially in monotherapy. When used, it is more commonly added to other agents in polypharmacy, as in augmentation of antidepressants in unipolar depression, or when added to antipsychotics or anticonvulsants in bipolar illness. One of the advantages of lithium in polypharmacy is pharmacokinetic; since it is not metabolized by the liver, but is excreted unchanged in the kidney, it does not have liver-based drug interactions with antipsychotics, anticonvulsants,

and antidepressants. It is thus safer in polypharmacy rather than combining two anticonvulsants or two antipsychotics. Further, because of its second messenger mechanisms, it has different pharmacodynamic effects than most standard psychiatric drugs, which tend to have synapse-based mechanisms. These different mechanisms likely allow for more synergy for efficacy. Clinical trial data in bipolar illness support the idea that the most effective polypharmacy regimens involve lithium as a core agent, while polypharmacy regimens without lithium are less effective. Similar data, though less replicated, exist in unipolar depression. In this lecture I will examine these pharmacological and clinical lines of evidence supporting the unique utility of lithium in polypharmacy treatment of mood illnesses. One added line of clinical practice is the use of lithium specifically for prevention of suicide and dementia, in very low doses. This additional utility of lithium, added to other standard treatments, also will be reviewed.

Literature References: 1. Amerio, A., Russo, D., Miletto, N., Aguglia, A., Costanza, A., Benatti, B., Odone A, Barroilhet SA, Brakoulis V, Dell-Osso B, Serafini G, Amore M, Ghaemi, SN. Polypharmacy as maintenance treatment in bipolar illness: A systematic review. *Acta Psychiatrica Scandinavica*. 2021; 144(3), 259-276.

2. Kim AM, Salstein L, Goldberg JF. A systematic review of complex polypharmacy in bipolar disorder: prevalence, clinical features, adherence, and preliminary recommendations for practitioners. *The Journal of Clinical Psychiatry*. 2021 Jun 1;82(3):34070.

RATIONAL AND IRRATIONAL PSYCHOPHARMACOLOGY COMBINATIONS

Joseph Goldberg, Icahn School of Medicine at Mount Sinai

Individual Abstract: Combination drug therapy regimens in psychiatry ideally reflect well-crafted thoughtful, complementary, synergistic mechanisms or purposefully targeted interventions designed to address complex psychopathology or comorbid conditions. At other times, combinations may arise more haphazardly, resulting from inaccurate diagnoses, suboptimal dosing of primary agents, and iterative prescribing habits that retain previously-prescribed medications that could be ineffective, obsolete or otherwise inappropriate and therefore warrant deprescribing. Irrational polypharmacy regimens may fail to account for redundant or contradictory drug mechanisms of action, can exacerbate rather than ameliorate key target symptoms (e.g., antidepressants during mania), may ignore the relative merits of monotherapy dosing optimization strategies, impose complexities that foster nonadherence, fail to recognize or minimize additive adverse drug effects, or pose hazards that outweigh benefits. Because many forms of serious mental illness may not respond adequately to monotherapies, even when dosing and duration are deemed adequate or optimized, properly devised combination pharmacotherapy regimens can offer more effective strategies for difficult-to-treat psychiatric conditions. This interactive audience presentation will review new findings from the ASCP presidential task force on polypharmacy Delphi survey items related to desirable versus undesirable pharmacokinetic effects (e.g., drug-drug interactions), pharmacodynamic redundancies versus complementary or synergistic effects, and other mechanistic considerations that avoid irrational combinations and reflect logical strategies to maximize favorable clinical outcomes.

Literature References: Goldberg JF. Complex combination pharmacotherapy for bipolar disorder: knowing when less is more or more is better. *Focus (Am Psychiatr Publ)* 2019 Jul;17(3):218-231

Shekho D, Mishra R, Kamal R, et al. Polypharmacy in psychiatry: an in-depth examination of drug-drug interactions and treatment challenges. *Curr Pharm Des* 2024; 30: 1641-1649

WHEN TO SWITCH VERSUS AUGMENT PHARMACOTHERAPIES

Snoben Kuruvila, UTSW Medical Center Dallas

Individual Abstract: Determining when to switch versus augment pharmacotherapy is a central challenge in the treatment of psychiatric disorders, including major depressive disorder. Clinicians must balance symptom severity, treatment history, side-effect burden, and functional impairment while navigating an expanding evidence base and evolving clinical guidelines. Switching may be preferred when patients experience intolerable adverse effects, lack of response or only partial response, and clear mechanistic mismatch with the underlying disorder. Augmentation strategies can be highly effective when partial but inadequate improvement is observed, or continuation of background treatment is clinically indicated. The decision is further influenced by comorbidities, patient preferences, pharmacokinetic considerations, and the risk-benefit profile of potential adjunctive agents. Understanding the nuances that guide switching versus augmentation is therefore essential for optimizing outcomes across major psychiatric disorders and their complex presentations. This presentation will also focus on shared decision-making approaches that can be utilized to make the decision of switch versus augment.

Literature References: Papakostas GI, Trivedi MH, Shelton RC, Iosifescu DV, Thase ME, Jha MK, Mathew SJ, DeBattista C, Dokucu ME, Brawman-Mintzer O, Currier GW, McCall WV, Modirrousta M, Macaluso M, Bystritsky A, Rodriguez FV, Nelson EB, Yeung AS, Feeney A, MacGregor LC, Carmody T, Fava M. Comparative effectiveness research trial for antidepressant incomplete and non-responders with treatment resistant depression (ASCERTAIN-TRD) a randomized clinical trial. *Mol Psychiatry*. 2024 Aug;29(8):2287-2295.

Lenze EJ, Mulsant BH, Roose SP, Lavretsky H, Reynolds CF 3rd, Blumberger DM, Brown PJ, Cristancho P, Flint AJ, Gebara MA, Gettinger TR, Lenard E, Miller JP, Nicol GE, Oughli HA, Pham VT, Rollman BL, Yang L, Karp JF. Antidepressant Augmentation versus Switch in Treatment-Resistant Geriatric Depression. *N Engl J Med*. 2023 Mar 23;388(12):1067-1079.

MONDO COMBO: DO COMBINATIONS OF ANTIPSYCHOTICS EVER MAKE ANY SENSE?

Leslie Citrome, New York Medical College

Individual Abstract: Treating people with schizophrenia with a combination of antipsychotic medications is common, with estimates of prevalence ranging from about 10% to 30%, with higher rates in forensic populations. Several explanations have been proffered: augmentation of clinical efficacy for treatment resistant schizophrenia (TRS), augmentation of clinical efficacy for non-TRS, addressing metabolic concerns with the antipsychotic currently being prescribed, a hoped-for fail-safe strategy when the added antipsychotic is a long-acting injectable, or, in some cases, poly-antipsychotic treatment is the result of a cross-titration that was never completed. The evidence supporting combining antipsychotics for the treatment of schizophrenia is generally weak, with the possible exception of the combination of clozapine with aripiprazole. This presentation will summarize the extant short-term and long-term literature that has examined this approach to treatment.

Literature References:

1. Højlund M, Köhler-Forsberg O, Gregersen AT, et al. Prevalence, correlates, tolerability-related outcomes, and efficacy-related outcomes of antipsychotic polypharmacy: a systematic review and meta-analysis. *Lancet Psychiatry*. 2024;11(12):975-989.
2. Horvitz-Lennon M, Volya R, Zelevinsky K, et al. Significance and Factors Associated with Antipsychotic Polypharmacy Utilization Among Publicly Insured US Adults. *Adm Policy Ment Health*. 2022;49(1):59-70.

COMORBIDITY POLYPHARMACY: SIMULTANEOUS VS. SUCCESSIVE INTRODUCTION OF CO-PHARMACOTHERAPIES

Anita Clayton, University of Virginia SOM

Individual Abstract: Among the considerations in diagnoses are co-morbidities vs. symptoms consistent with single disorder (e.g., Attention Deficit Hyperactivity Disorder [ADHD] +/- bipolar disorder +/- substance use disorder when impulsivity, restlessness and emotional dysregulation are present); risk of initial medication triggering onset of another condition (e.g., stimulants or antidepressants inducing mania); severity of symptoms/functional impairment; past treatments and responses; and family history of psychiatric disorders. Common comorbidities include ADHD and substance use disorder (SUD), bipolar disorder (BPAD), antisocial personality disorder (ASPD), anxiety disorder, eating disorder; and major depressive disorder (MDD) +/- BPAD, SUD, anxiety disorder, personality disorders. Individuals with > 2 comorbid conditions may experience significant disease burden, prolonged illness duration and reduced therapeutic response to treatments, increasing the need for rapid definitive intervention(s). Bidirectional symptom overlap may be related to shared neurobiological mechanisms, common/overlapping traits/symptoms (MDD, anxiety disorders, SUD, ADHD all impact concentration/cognition), impact of SUD on presenting symptoms (e.g., effect of chronic daily cannabis use may mimic symptoms of ADHD), and/or 1 disorder is a risk factor a second disorder. An initial treatment plan must include patient education about diagnosis(es), obtain a detailed family history of psychiatric illness and treatment, agreement on a blueprint for monitoring over the course of treatment, consideration of the severity and trajectory of each disorder, discussion of risks/benefits with each treatment choice, and stabilizing the most severe and/or potentially harmful condition initially (e.g., bipolar disorder before ADHD, SUD before anxiety disorder). However, if comorbidities are present, but neither are severe or endangering, initiation of 2 simultaneous treatments may improve both. Consideration of medication + psychotherapy is the safest prescription but usually not the fastest.

Literature References:

1. Won-Seok Choi, Young Sup Woo, Sheng-Min Wang, Hyun Kook Lim, Won-Myong Bahk. The prevalence of psychiatric comorbidities in adult ADHD compared with non-ADHD populations: A systematic literature review. *Plos One*. Published: November 4, 2022 <https://doi.org/10.1371/journal.pone.0277175>
2. Xinyu Fu, Wiege Wu, Yuru Wu, Xiaofu Liu, Wanting Liang, Rongchuan Wu, Yun Li. Adult ADHD and Comorbid Anxiety and Depressive Disorders: A Review of Etiology and Treatment. *Frontiers in Psychiatry*. Published 06 June 2025. DOI: 10.3389/fpsyt.2025.1597559

SAFETY, TOLERABILITY, AND DRUG-DRUG INTERACTION CONCERNS IN POLYPHARMACOLOGY REGIMENS

Rajnish Mago, Simple and Practical Medical Education, LLC

Individual Abstract: Polypharmacy involving psychiatric medications continues to be common despite awareness that it may lead to increased incidence and/or severity of side effects or to potentially significant drug-drug interactions. This talk will draw attention to less obvious negative consequences of polypharmacy involving psychiatric medications. One scenario is where the effects of multiple medications add up, with potentially serious consequences. For example, clinically-significant anticholinergic side effects frequently occur due to a lack of recognition of the anticholinergic activity of psychiatric and non-psychiatric medications that are not classified as anticholinergics (Al Rihani et al., 2021). Especially in older adults, this additive “anticholinergic burden” not infrequently leads to cognitive and functional impairment. Other examples of additive effects are falls and other accidents due to the additive effects of multiple medications on blood pressure and/or sedation. It is important to realize that the additive anticholinergic burden and sedative load are unintentional in most cases (Al Rihani et al., 2021). Therefore, it is essential that structured tools be used routinely to evaluate the risk of anticholinergic side effects, oversedation, and falls (Seppala et al., 2021; Al Rihani et al., 2021). Another scenario is where two or more medications are used together, and a side effect occurs if one of them is stopped abruptly. For example, stimulant and antipsychotic medications are often prescribed together for the management of ADHD with agitation or aggressive behavior (Scholle et al., 2018). If the stimulant is then stopped abruptly or is missed, acute dystonia has been reported to occur (Guler et al., 2015). Polypharmacy leading to an increased incidence of a side effect must also take into account the concomitant use of psychiatric and non-psychiatric medications. The example of additive effects of psychiatric medications that are antagonists at post-synaptic alpha-1 receptors (for example, clozapine, risperidone, trazodone) and antihypertensive medications is, or should be, well-known. However, an important but lesser-known example is the fairly common case of a serotonergic antidepressant and a thiazide diuretic being used together (Burroughs-Ray et al., 2025; Mago et al., 2008). On the other hand, using multiple medications together can sometimes reduce rather than increase the incidence and/or severity of certain side effects.

For example:

1. The addition of aripiprazole to another antipsychotic like risperidone has been shown in multiple randomized controlled trials to reduce antipsychotic-induced hyperprolactinemia (Zheng et al., 2019).
2. In a randomized, placebo-controlled clinical trial, the addition of aripiprazole to a stable dose of clozapine was found to reduce body weight and dyslipidemia (Fleischhacker et al., 2010).
3. The combination of a stimulant and guanfacine may attenuate effects on heart rate, systolic BP, and the QTc interval (Sayer et al., 2016).

Throughout the workshop, active engagement and interaction with the audience will be facilitated in several ways, including the following:

1. Before discussing each instance of additive effects, examples of medication lists will be shown, and the audience will be polled about what concerns they would have with that medication list.

2. The audience will be encouraged to share their experiences with each of the medication combinations discussed.
3. Findings regarding safety and tolerability concerns from the ASCP task force on polypharmacy will be shared with the audience to prompt interactive discussion and dialogue about optimal risk-benefit management strategies.

Literature References: 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.

Zheng W, Cai DB, Yang XH, et al. Adjunctive aripiprazole for antipsychotic-related hyperprolactinaemia in patients with first-episode schizophrenia: a meta-analysis. *Gen Psychiatr*. 2019;32(5):e100091.

***^WAKING UP TO EXCESSIVE DAYTIME SLEEPINESS IN PSYCHIATRY AND HOW TO MAKE WEARABLES WORK FOR MEASURING SLEEP AND ACTIVITY**

Manish Jha, University of Texas Southwestern Medical Center

Overall Abstract: Excessive daytime sleepiness (EDS) is pervasive across psychiatric disorders but remains under-measured, under-treated, and mechanistically opaque. Current practice relies on coarse self-report instruments and clinic-based snapshots that miss day-to-day variability, medication effects, circadian misalignment, and the bidirectional links among sleep, activity, mood, and cognition. Wearable sensors offer continuous, low-burden assessment of sleep and activity in naturalistic settings, but their clinical utility in psychiatry is limited by heterogeneous algorithms, sparse validation against gold standards, and insufficient attention to disorder-specific confounds (e.g., psychomotor retardation/activation, antipsychotic sedation, stimulant rebound, irregular schedules). This proposed workshop brings two world experts with the common theme of making wearables work for psychiatry. Dr. Mignot will take a deeper dive in the phenomenology, neurobiology, clinical characterization, and health-related burdens associated with excessive daytime sleepiness. Dr. Athreya will present in detail about his longitudinal study that monitored sleep and activity related biomarkers with commercially available wearable devices. Dr. Bill Bobo, a leading psychiatric researcher, will then lead the audience in an engaged conversation to provide practical hands-on experience in working with these devices to monitor health related outcomes in individuals with psychiatric disorders.

Learning Objective 1: Describe the burden associated with excessive daytime sleepiness in psychiatric disorders

Learning Objective 2: Discuss the utility of commercially available wearable devices in monitoring sleep and activity for patients with psychiatric disorders

Literary References: Pérez-Carbonell, L., Mignot, E., Leschziner, G., and Dauvilliers, Y. (2022). Understanding and approaching excessive daytime sleepiness. *The Lancet*, 400(10357), 1033-1046.

Dyrbye LN, West CP, Wilton AR, Satele DV, Athreya AP. Smartwatch Use and Physician Well-Being: A Randomized Clinical Trial. *JAMA Netw Open*. 2025 Aug 1;8(8):e2527275.

SLEEP ASSESSMENTS AS PREDICTORS OF HEALTH RISK AND DEPRESSION

Emmanuel Mignot, Stanford University School of Medicine

Individual Abstract: Sleep symptoms and comorbidities, including insomnia, hypersomnia and parasomnias are strongly correlated with depression and anxiety. Genetic studies support bilateral causality. Managing sleep symptoms using pharmacology or behavioral therapy improves therapeutic response for depression. Objective sleep assessment through sleep studies or wearables, with the assistance of deep learning, has been shown to predict various health outcomes, medical and psychiatric. Some studies even suggest these could have a role as biomarkers of treatment response. Yet studies done to date have not used large sample sizes or taken advantage of the most recent deep learning algorithms or nascent wearable EEG technology. We will review the area and propose a road map for this rapidly evolving area.

Literature References: Pérez-Carbonell, L., Mignot, E., Leschziner, G., and Dauvilliers, Y. (2022). Understanding and approaching excessive daytime sleepiness. *The Lancet*, 400(10357), 1033-1046.

Nishino S, Ripley B, Overeem S, Lammers GJ, Mignot E. Hypocretin (orexin) deficiency in human narcolepsy. *Lancet*. 2000 Jan 1;355(9197):39-40.

SMARTWATCH MEASUREMENTS AND CONTROLLED DEPRESSION: COMPARATIVE ANALYSES ON PHYSICAL ACTIVITY AND SLEEP

Arjun Athreya, Mayo Clinic

Individual Abstract: Background: Digital technology engagement has the potential as an adjunct to supporting depression management by improving physical wellbeing. However, there is a need for long-term (e.g., 12-month) longitudinal studies that characterize the digital phenotype of those who managing their depressive symptoms compared to non-depressed controls.

Methods: Participants in a 12-month decentralized wellbeing study at the Mayo Clinic wore a commodity smartwatch as a digital health technology (DHT) and completed electronic surveys on mental and overall functioning at baseline and on a quarterly basis. Participants included in this study wore the smartwatch for $\geq 50\%$ daily for $\geq 70\%$ of days in the year. The Center for Epidemiological Studies – Depression (CES-D) scale was used to measure depression symptom severity. Individuals with stable, controlled depression were those with baseline CES-D total score < 16 and reported current antidepressant use. Non-depressed controls had a CES-D total score < 16 and no reported antidepressant use. A 4 point or greater decrease in the CES-D total score from baseline to 12-months was considered a clinically meaningful improvement in depressive symptoms. To better understand the associations between perceived smartwatch helpfulness and recorded metrics in controlled depression, an inductive thematic analysis (ITA)-derived perceived helpfulness score was utilized, with higher scores indicating more behavioral change and improved wellbeing themes and lower scores indicating more discomfort and stress themes. Linear mixed-effects models were used to examine differences in daily functioning between those with controlled depression and non-depressed controls, with participants included as random effects and sex, age, marital status, and enrollment duration as covariates. Additional analyses were done to also examine differences in CESD improvement groups and perceived helpfulness groups.

Results: Of 531 participants, 244 (46%) reported either taking antidepressants or no other medication and completed the study survey. Of these, 220 of 244 (90%) met the smartwatch adherence criteria and 110 (45%) were non-depressed at baseline. Among these 110 participants, 55 had controlled depression and 55 were non-depressed controls. Of the controlled depression group, 8 (15%) improved their depressive symptoms at endpoint, compared to 16 (30%) in non-depressed controls. Compared to non-depressed controls, controlled depression had these daily associations: 0.90 less miles walked ($p < 0.001$), 16 mins less exercise ($p < 0.017$), 25.6 mins more sleep ($p < 0.042$), 25 mins more light sleep ($p < 0.001$), and 6.2 mins more times of sleep interruption ($p < 0.038$). When both groups improved in their CESD, non-depressed controls walked significantly more miles per day (2.17, $p < 0.002$) and vigorously exercised 7.3 mins more per day compared to participants with controlled depression. Finally, for every increase in perceived smartwatch helpfulness, participants with controlled depression vigorously exercised 3 mins more per day.

Conclusions: The digital phenotype of controlled depression is distinct from those who are non-depressed controls, even when both have comparative lower depressive symptoms and both improve over time. Individualized digital data engagement may promote behavior activation in both groups and future studies should test whether these associations can serve as a scalable guide for improving the physical wellbeing of individuals with controlled depression.

Literature References: Dunn AL, Trivedi MH, Kampert JB, Clark CG, Chambliss HO. Exercise treatment for depression: efficacy and dose response. *Am J Prev Med.* 2005 Jan;28(1):1-8. doi: 10.1016/j.amepre.2004.09.003. PMID: 15626549.

Pearce M, Garcia L, Abbas A, Strain T, Schuch FB, Golubic R, Kelly P, Khan S, Utukuri M, Laird Y, Mok A, Smith A, Tainio M, Brage S, Woodcock J. Association Between Physical Activity and Risk of Depression: A Systematic Review and Meta-analysis. *JAMA Psychiatry.* 2022 Jun 1;79(6):550-559. doi: 10.1001/jamapsychiatry.2022.0609. PMID: 35416941; PMCID: PMC9008579.

SLEEP AND ITS UTILITY FOR MENTAL HEALTH AND WELL-BEING RESEARCH: THE CASE FOR LONGITUDINAL MEASUREMENTS

Milica Barac, Mayo Clinic

Individual Abstract: While extensive literature supports a bidirectional relationship between sleep and mental health, the temporal nature of this relationship remains unclear. Understanding this relationship is essential for characterizing sleep's role in psychiatric disease risk, symptom severity, and potential use as a biomarker and mediator of pharmacologic treatment response. With the increasing popularity and accessibility of wearable technologies, specifically smartwatches, the collection of long-term sleep data has become possible across a variety of psychiatric and wellness conditions, including major depressive disorder, bipolar disorder, and occupational burnout. Despite a broad consensus regarding the relationship between sleep health and psychiatric outcomes, findings across wearable studies have varied. Differences in measurement approaches, study design, and feature engineering of sleep metrics have contributed to this inconsistency. In this presentation, the range of metrics and engineered sleep features that can be derived from smartwatches will be examined with an emphasis on metrics collected from longitudinal studies. Relevant literature and new findings on smartwatch-collected sleep metrics correlated with major depressive disorder and occupational burnout will be discussed.

Examining wearable-derived sleep features and how these features relate to psychiatric outcomes is crucial for advancing the utility of longitudinal sleep monitoring for psychiatric research.

Literature References: Li DR, Li ZX, Li MH, et al. Regular sleep patterns, not just duration, critical for mental health: association of accelerometer-derived sleep regularity with incident depression and anxiety. *Psychol Med.* 2025;55:e239.

Bowman MA, Kline CE, Buysse DJ, et al. Longitudinal Association Between Depressive Symptoms and Multidimensional Sleep Health: The SWAN Sleep Study. *Ann Behav Med.* 2021;55(7):641-652.

***DEPLOYING ARTIFICIAL INTELLIGENCE (AI) AND LARGE LANGUAGE MODELS (LLMS) IN PSYCHIATRY DRUG DEVELOPMENT**

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

Todd Solomon, Mind Medicine Inc.

Anzar Abbas, Brooklyn Health

Michelle Worthington, Brooklyn Health

Isaac Galatzer-Levy, Google

Overall Abstract: Artificial Intelligence (AI) and Large Language Models (LLMs) are driving transformative change across healthcare and drug development. While these technologies have begun to address challenges in psychiatric clinical practice, their application in psychiatry drug development remains in its early stages. Nevertheless, they hold tremendous promise for mitigating many of the methodological challenges that have historically hindered progress in this field. Psychiatry clinical trials continue to have among the lowest success rates across all therapeutic areas of drug development, contributing to the limited availability of new and effective treatments for brain health disorders. This low success rate stems from several factors, including uncertainty around the biological mechanisms of psychiatric illnesses, high placebo response rates, reliance on subjective efficacy endpoints, and variability in rater training, assessment and performance. These issues increase data variability and reduce the ability to detect true drug effects amid study noise. Large Language Models such as GPT4, Claude and Llama are advanced AI systems trained on vast text corpora—such as books, scientific literature, and online content—to learn the structure, meaning, and context of human language. By recognizing linguistic patterns, LLMs can perform diverse tasks such as answering questions, translating text, and summarizing information, demonstrating powerful language understanding and generation capabilities. Psychiatric drug development heavily relies on clinician-reported rating scales (ClinROs) as primary endpoints in pivotal trials. Instruments such as the Montgomery–Åsberg Depression Rating Scale (MADRS), Hamilton Anxiety Rating Scale (HAM-A), and Positive and Negative Syndrome Scale (PANSS) are all semi-structured clinical interviews that quantify symptom severity through standardized questions and scoring rubrics. Despite their widespread use, these tools are limited by clinician bias, inter- and intra-rater variability, and the inherent subjectivity of psychological evaluation. As such, drug developers have implemented measures such as rater training, centralized assessments, blinded data analytics, and third-party endpoint reviews to improve data quality, but these approaches add operational complexity and cost without fully resolving reliability concerns. The structured and language-based nature of ClinROs makes them particularly well suited for application of

LLMs through prompt engineering and model fine-tuning. LLMs have the potential to transform psychiatric clinical trials by serving both as training tools to improve rater consistency and as oversight systems capable of independently scoring rating scales to provide objective comparators to human assessments leading to significantly increased reliability and validity of study endpoints. This panel brings together psychometricians, drug developers, and AI experts who are actively integrating LLMs into late-stage psychiatry clinical trials.

Learning Objective 1: Explore how Large Language Models (LLMs) such as GPT-4 can be applied to enhance the reliability, objectivity, and efficiency of clinician-reported outcomes in psychiatry clinical trials.

Learning Objective 2: Discuss the practical, operational, and regulatory considerations for integrating LLMs into late-stage psychiatry clinical development based on emerging real-world implementations

Literary References: Volkmer, Sebastian, Andreas Meyer-Lindenberg, and Emanuel Schwarz. "Large language models in psychiatry: Opportunities and challenges." *Psychiatry research* 339 (2024): 116026.

Kolar, A., et al. Using Large Language Models for Endpoint Oversight. (October, 2025). Poster presented at the International Society for CNS Clinical Trials Methodology (ISCTM), Amsterdam, Netherlands.

***DESIGNING THE NEXT GENERATION OF STUDIES OF PSYCHEDELICS FOR DIFFICULT TO TREAT DEPRESSION**

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

Overall Abstract: The past decade has witnessed an veritable explosion of interest in psychedelics for treatment of depressive episodes that do not respond to standard antidepressant medications. This workshop will provide an overview of the current state of the clinical science and highlight important differences among the various psychedelics currently being investigated. This workshop will highlight issues pertaining to functional unblinding and measurement of duration of benefit (Dr. Fava), the neuroimaging correlates of psychedelic exposure (Dr. Shelton), the importance of psychotherapeutic support and acute and sustained outcomes (Dr. Suppes) and meaningful differences across psychedelic drugs in terms of the initial experience, the intensity of psychoactive experience and research designs to study between-drug differences (Dr. Thase).

Learning Objective 1: The participant will be able to discuss the current state of the art of studies of psychedelics for difficult to treat depression AND the important individual differences among the various drugs being studied

Learning Objective 2: The participant will learn about the recommended **Methods** to minimize functional unblinding and to evaluate the persistence of therapeutic effects

Literary References: Fava M. How should we design future mechanistic and/or efficacy clinical trials? *Neuropsychopharmacology*. 2024 Jan;49(1):197-204. doi: 10.1038/s41386-023-01600-9. Epub 2023 May 26. PMID: 37237086; PMCID: PMC10700333

McIntyre RS, Kwan ATH, Mansur RB, Oliveira-Maia AJ, Teopiz KM, Maletic V, Suppes T, Stahl SM, Rosenblatt JD. Psychedelics for the Treatment of Psychiatric Disorders:

Interpreting and Translating Available Evidence and Guidance for Future Research. Am J Psychiatry. 2025 Jan 1;182(1):21-32. doi: 10.1176/appi.ajp.20230902. PMID: 39741444.

USING NEUROIMAGING TO ELUCIDATE PSYCHEDELIC MECHANISMS OF ACTION ON BRAIN CIRCUITS

Yvette Sheline, University of Pennsylvania

Individual Abstract: This talk will review the relatively sparse literature on imaging results in psychedelics. In addition, it will describe results from imaging psychedelics in mood disorders. It is well known that psychedelics can induce powerful acute changes in perception of self, the environment and time. Further, in clinical trials, a single dose of psilocybin can produce rapid symptom relief in depression, addiction and anxiety. These acute effects last for approximately 6 hours and persist for 24 hours-21 days and are related to agonism of the 5-HT_{2A} receptor. Newer shorter duration of action psychedelics, while sharing similar pharmacology to other classical psychedelics also have distinct actions. Among these are greater selectivity of the 5-HT_{1A} receptor than the 2A receptor. Given the preponderance of 1A receptors in the limbic system this offers an opportunity to examine differential effects on limbic networks. Understanding the effects of psychedelics on human brain networks is critical to insights about their therapeutic mechanisms. This talk will describe studies using functional connectivity (FC) to delineate whole brain and regional changes in connectivity. In broad strokes, for psilocybin these changes involve profound and pervasive changes in FC across large swaths of the cerebral cortex, most prominently in association networks. The result is network desynchronization which reduces correlations within networks and decreases anticorrelations between networks, producing networks that are less segregated. In addition we will examine the relationship between the subjective psychedelic experience (30 item Mystical Experience Questionnaire, MEQ30) and brain changes. Newer short acting psychedelics 5-MeO-DMT and DMT have not as yet been used in imaging experiments however the potential for these ultra-fast and ultra-short acting psychedelics to shed light on brain mechanisms will be discussed. The potential for new insights is especially promising given their 300 fold selectivity for 5-HT_{1A} over 5-HT_{2A} receptors. Potential limbic mechanisms in neuroplasticity and symptom resolution will be discussed.

Literature References: 1. Siegel J, Subramanian S, Perry D, et al. Psilocybin desynchronizes the human brain. Nature. 2024; 632: 131.

2. Ramaekers J, Reckweg, J., Jason N. Benefits and challenges of ultra-fast, short-acting psychedelics in the treatment of depression. Am J Psychiatry. 2025; 182: 33.

LONG TERM OUTCOMES FROM PSILOCYBIN AND RESPONSE TO RE-DOSING FOR DIFFICULT TO TREAT DEPRESSION

Trisha Suppes, Stanford University

Individual Abstract: The questions of how durable are responses to psilocybin, a classic psychedelic, and are there ways to optimize responses in difficult to treat depression (TRD). While the relative percent of patients treated for depression that will have limited response is known and substantial (up to 30%), it is also known when patients experience TRD the likelihood of relapse is greater even after a response to treatment. While early acute results in

Phase 2 and both open and controlled pilot studies is promising, there have been few observations beyond acute effects for the impact longer term of psilocybin treatment for TRD. Clinical trials of psilocybin for acute depression in smaller trials both controlled and open report striking acute response rates of 50% or greater at primary outcome. The larger Phase 2 studies are less optimistic but still reporting significant positive impact for acute effects. Phase 3 studies are currently ongoing for TRD. By contrast few studies to date have followed up patients longer term with only two reporting six-month outcomes (Carhart-Harris et al., 2018; Erritzoe et al., 2024) and two reporting 12-month outcomes (Ellis et al., 2025; Goodwin et al., 2025). Results from longer term follow up studies will be presented and discussed. Of particular interest there have been almost no reports of redosing following a period after the first doses. We will focus on a recent case series completed more than one year after acute dosing. Of note, this case series demonstrated greater variability of response compared to the first dosing with some participants making greater improvements, some recapturing a previous response but lacking durability, and some with limited response.

During the workshop we will review studies on the long-term durability of depression response to psilocybin, and the results from a recent case series examining redosing after more than a year from first dosing.

Literature References: Ellis S, Bostian C, Donnelly A, Feng W, Eisen K, Lean M, Conlan E, Ostacher M, Aaronson S, Suppes T. Long-term outcomes of single-dose psilocybin for U.S. military Veterans with severe treatment-resistant depression - 12-month data from an open-label pilot study. *J Affect Disord.* 2025 Nov 15;389:119655. doi: 10.1016/j.jad.2025.119655. Epub 2025 Jun 9. PMID: 40499827

Goodwin, G.M., Aaronson, S.T., Alvarez, O., Carhart-Harris, R., Chai-Rees, J., Croal, M., DeBattista, C., Dunlop, B.W., Feifel, D., Hellerstein, D.J., Husain, M.I., Kelly, J.R., Kirlic, N., Licht, R.W., Marwood, L., Meyer, T.D., Mistry, S., Nowakowska, A., P'aleníček, T., Repantis, D., Schoevers, R.A., Simmons, H., Somers, M., Teoh, E., Tsai, J., Wahba, M., Williams, S., Young, A.H., Young, M.B., Zisook, S., Malievskaia, E., 2025. The role of the psychedelic experience in psilocybin treatment for treatment-resistant depression. *J. Affect. Disord.* 372, 523–532. <https://doi.org/10.1016/j.jad.2024.12.061>.

CRITICAL METHODOLOGICAL DECISIONS IN PSYCHEDELIC DRUG TRIALS

Maurizio Fava, Massachusetts General Hospital

Individual Abstract: Over the past decade there has been a surge in interest in placebo-controlled trials using non-classical 3,4-methylenedioxymethamphetamine (MDMA) and classical psychedelics such as psilocybin, lysergic acid diethylamide (LSD) and N,N-dimethyltryptamine (DMT) to treat neuropsychiatric disorders. However, the success and reliability of these trials depend on the design of the trials, the choice of control conditions, and the ability to blind both participants and researchers. When appropriate control conditions are lacking, it becomes difficult to disentangle placebo and expectation effects from medication effects. Principal Investigators need to make critical methodological decisions as they trials of psychedelic drugs. The first decision concerns the selection of the control, for example whether to use an active control or a placebo. The second decision concerns the adoption of methodologies aimed at reducing the effects of placebo or of the active control. Approaches range from independent verification of the appropriateness of subjects selection to the use of study designs aimed at manipulating expectations and reducing placebo response. The third decision concerns ensuring the blinding of the ratings to

minimize the risk of biased assessments. The fourth decision concerns the selection of the appropriate measures to evaluate outcome. The fifth and final decision involves the selection of the appropriate statistical analysis plan. These methodological considerations require examining the advantages and disadvantages of these approaches with the goal of enhancing the validity of these trials and their regulatory science. By doing so, we aim to improve the reliability of psychedelic research in uncovering the therapeutic benefits of psychedelics beyond placebo and expectation effects.

Literature References: Colloca L, Fava M: What should constitute a control condition in psychedelic drug trials? *Nat Ment Health*. 2024 Oct;2(10):1152-1160. doi: 10.1038/s44220-024-00321-2. Epub 2024 Sep 30.

Fava M: How should we design future mechanistic and/or efficacy clinical trials? *Neuropsychopharmacology*. 2024 Jan;49(1):197-204. doi: 10.1038/s41386-023-01600-9. Epub 2023 May 26.

Wednesday, May 27, 2026

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

Regulatory Plenary: AI-Based Tools in CNS Drug Development: A Regulatory Framework for Clinical Trial Applications

REGULATORY PLENARY: AI-BASED TOOLS IN CNS DRUG DEVELOPMENT: A REGULATORY FRAMEWORK FOR CLINICAL TRIAL APPLICATIONS

Tiffany Farchione, US Food and Drug Administration

Valentina Mantua, Center for Drug Evaluation and Research, Food and Drug Administration

Bernard Fischer, U.S. Food and Drug Administration

Qi Liu, Center for Drug Evaluation and Research, Food and Drug Administration

Roberta Rasetti, FDA/CDER/DP

Overall Abstract: This session examines the evolving role of artificial intelligence (AI) and machine learning (ML) in FDA drug review processes, with particular focus on central nervous system (CNS) therapeutics. The session will explore how AI tools are currently integrated within FDA operations, their impact on clinical review practices, and emerging applications in psychiatric and neurological drug development. The first presentation will provide an overview of AI implementation across FDA's Center for Drug Evaluation and Research (CDER) and Center for Devices and Radiological Health (CDRH), highlighting internal tools that enhance regulatory efficiency while maintaining scientific rigor. The second presentation will focus on AI applications in CNS drug development, reviewing FDA's Risk-Based Evaluation Framework for AI/ML tools and examining real-world examples of how these technologies address traditional challenges in psychiatric research, including patient stratification, digital endpoints, and placebo response variability. Following the two presentations, we will have a panel discussion focused on how clinical reviewers integrate AI resources into their workflow, addressing concerns about maintaining independent clinical judgment and ensuring that AI augments rather than replaces critical thinking in regulatory decision-making. This session will provide attendees with practical insights into current FDA AI capabilities, regulatory expectations for AI-enabled

submissions, and emerging opportunities for leveraging these technologies in CNS therapeutic development.

Learning Objective 1: Evaluate opportunities to incorporate AI/ML technologies into CNS trial design

Learning Objective 2: Understand FDA's Risk-Based Evaluation Framework for AI/ML tools in CNS drug development and recognize key regulatory considerations when planning to incorporate these technologies into clinical trial design.

Literature References: Liu, Q., Huang, R., Hsieh, J., Zhu, H., Tiwari, M., Liu, G., Jean, D., ElZarrad, M.K., Fakhouri, T., Berman, S., Dunn, B., Diamond, M.C. and Huang, S.-M. (2023), Landscape Analysis of the Application of Artificial Intelligence and Machine Learning in Regulatory Submissions for Drug Development From 2016 to 2021. *Clin Pharmacol Ther*, 113: 771-774.

Podichetty JT, Bauer AM, Xu R, Henscheid N, Anderson W, Khan A, Ma SC, Huynh H, Romero K. How AI Transforms Regulatory Submission: Current Clinical Implementation and Future Prospects. *Clin Transl Sci*. 2025 Dec;18(12)

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

ASCP Awards Ceremony: ASCP Lifetime Awardee Talk and Nasrallah Award Winner

ASCP LIFETIME AWARDEE TALK AND NASRALLAH AWARDEE

Joseph Goldberg, Icahn School of Medicine at Mount Sinai

Anita Clayton, University of Virginia

THE TYRANNY OF THE P-VALUE: EFFECT SIZE MATTERS

Leslie Citrome, New York Medical College

Abstract: The “tyranny of the P” can lead researchers astray, allow irrelevant findings to be published, and confuse clinicians eager for guidance as to the usefulness of potential interventions. In order to quantify the clinical importance of a statistically significant result, we need to calculate the effect size. Although there are several absolute and relative effect size measures available, Number Needed to Treat (NNT) is arguably the most intuitive, and is simple to calculate. Advantages and disadvantages of the NNT metric are discussed.

Learning Objective 1: Understand how the P-value can be misused.

Learning Objective 2: Be able to calculate Number Needed to Treat.

Literature References:

1. Citrome L. Compelling or irrelevant? Using number needed to treat can help decide. *Acta Psychiatr Scand*. 2008 Jun;117(6):412-9. doi: 10.1111/j.1600-0447.2008.01194.x. PMID: 18479317.

2. Citrome L. Relative vs. absolute measures of benefit and risk: what's the difference? *Acta Psychiatr Scand*. 2010 Feb;121(2):94-102. doi: 10.1111/j.1600-0447.2009.01449.x. Epub 2009 Aug 19. PMID: 19694632.

A SHORT JOURNEY THROUGH A 50 YEARS OF PROGRESS IN THE TREATMENT OF DEPRESSION

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

Abstract: This plenary talk will highlight the progress in treatment of people suffering from depression that has occurred since 1976, when I began medical school, and 2026. I will describe some of the early research that I participated in as a young investigator, working with mentors such as Drs. David Kupfer and Jonathan Himmelhoch. I next will highlight broadening research collaborations with more senior colleagues such as Drs. Ellen Frank, Charles F. Reynolds III and A. John Rush, which coincided with the transition into a second generation of psychopharmacology. I will next provide a far too brief overview of mid- to later-career collaborations with literally 100s of colleagues in multicenter studies variously funded by the National Institutes of Health, the pharmaceutical industry, the Patient Centered Research Outcome Institute and the Veterans Health Administration. I will close with what may well be the last act of my career in clinical psychopharmacology, briefly illustrating how the discovery of remarkable therapeutic effect of ketamine has opened the door to a new generation of discovery pertaining to the antidepressant effects of various drugs that were formerly stigmatized and criminalized as hallucinogens or psychedelics.

Learning Objective 1: The participant will learn about the progress in the psychopharmacology of treatment of depression.

Learning Objective 2: The participant will be able to discuss how unmet needs in the treatment of depression in 2000 coincided with the discovery of ketamine's antidepressant effects and set the stage for a new generation of research on drugs with psychedelic properties.

Literature References: Thase, M.E. (2023), Recent developments pertaining to treatment-resistant depression: a 40-year perspective. *World Psychiatry*, 22: 413-414. <https://doi.org/10.1002/wps.21134>

Cubała WJ, Bajbouj M, Bauer M.....Thase, M.E. (2026) GH001 vs Placebo in Patients With Treatment-Resistant Depression: A Randomized Clinical Trial. *JAMA Psychiatry*. Published online March 25, 2026. doi:10.1001/jamapsychiatry.2026.0096

1:30 p.m. - 3:00 p.m.

Clinical Updates on Neurotherapeutics: Disease State

CLINICAL UPDATES ON NEUROTHERAPEUTICS: DISEASE STATE

Joseph Goldberg, Icahn School of Medicine at Mount Sinai

Overall Abstract: This plenary session will provide clinicians and clinical investigators with an up-to-date overview of state of the art treatment in three key disease states: bipolar disorder, posttraumatic stress disorder, and schizophrenia. An expert panel will discuss current literature and findings from clinical trials as translating to everyday real-world clinical practice. Presentations will include an in-depth focus on the merits and shortcomings of guideline-based treatment for bipolar disorder and devising optimal treatment protocols and paradigms; the emerging role of second generation antipsychotics (SGAs) as foundational treatments for bipolar disorder and short- and long-term breadth of spectrum

relative to that of mood stabilizers such as lithium, valproate or lamotrigine; new findings in the pharmacotherapy of posttraumatic stress disorder; and contemporary approaches (and newly emerging treatment options) for the management of schizophrenia.

SGAS VS MOOD STABILIZERS: THE PARADIGM SHIFT IN CORE TREATMENT FOR BIPOLAR DISORDER

Joseph Goldberg, Icahn School of Medicine at Mount Sinai

Abstract: Mood stabilizers have traditionally been regarded as the foundational treatment for bipolar disorder, but recent years have witnessed a growing array of clinical trials revealing their limited breadth of spectrum. Lithium shows greater efficacy for mania than depression and produces robust effects in only a relatively small patient subgroup definable by mania polarity-proneness, positive family history of lithium-responsive bipolar disorder, and the absence of mixed features, rapid cycling, psychosis, or substance use and/or psychiatric comorbidities. Valproate similarly exerts greater antimanic than antidepressant value and has not been shown to prevent recurrences better than placebo. Lamotrigine lacks discernible antimanic acute or prophylactic efficacy and data are inconsistent for its use in acute depressive episodes. Carbamazepine is limited by its hepatic, hematologic and pharmacokinetic adverse effects and lacks data in bipolar depression or maintenance prophylaxis. No other anticonvulsants have demonstrated superiority to placebo as thymoleptics. By contrast, a number of second generation antipsychotics (SGAs) have demonstrated breadth of spectrum across all phases of illness with outcomes that are least noninferior (if not in some cases superior) to mood stabilizers, particularly for depressive episodes and those with mixed features. The availability of long-acting injectable SGA formulations also substantially helps to mitigate the risk for relapse due to treatment nonadherence. As a class, the limitations of SGAs coalesce mainly around 2 areas: long-term cardiometabolic and neurological tolerability, and within-class differences in the treatment or prevention of depressive episodes. This presentation will examine both the relative merits and shortcomings of SGAs as the emerging foundational treatment class for bipolar disorder, with the concept that medications identified as "mood stabilizers" may in fact play a more limited, supplemental, or adjunctive role in both short- and long-term treatment. Examples of within-class agents among both SGAs and mood stabilizers will be reviewed with respect to breadth of spectrum across clinical presentations and choosing patient clinical profiles that correspond to a best fit for a given core treatment approach.

Learning Objective 1: Understand the pharmacodynamic treatment limitations of lithium and anticonvulsant mood stabilizers across phases of bipolar disorder

Learning Objective 2: Recognize the breadth of spectrum, and within-class differences, among second generation antipsychotics as mono- or adjunctive therapies in the treatment of bipolar mania, mixed episodes, depressive episodes, and relapse prevention of both manias and depressions.

Literature References: Rhee TG, Olfson M, Nierenberg AA, et al. 20-Year Trends in the Pharmacologic Treatment of Bipolar Disorder by Psychiatrists in Outpatient Care Settings. *Am J Psychiatry* 2020; 177: 706-715

Lindström L, Lindström E, Nilsson M, et al. Maintenance therapy with second generation antipsychotics for bipolar disorder - A systematic review and meta-analysis. *J Affect Disord* 2017; 213: 138-150

AN UPDATE ON BIPOLAR DISORDER: EVIDENCE, CHALLENGES, AND SOLUTIONS

Andrew Nierenberg, Massachusetts General Hospital

Abstract: Despite best practices, bipolar disorder continues to be a challenge to get our patients to recover from an acute mood episode and then keep them well. Guideline-informed treatment, while reasonable, may be difficult for clinicians to implement. Furthermore, there is a notable lack of data demonstrating that guideline-informed treatment yields better outcomes. Part of the challenge of guideline-informed care is that it is derived from narrow RCTs and usually does not apply to people with complex patterns of multiple comorbid conditions. Additionally, while evidence-based psychotherapy for bipolar disorder improves outcomes, it can be difficult for patients to access. This presentation will review the current state of evidence for treating people with bipolar disorder (with the caveats above) and discuss progress in developing the Bipolar Action Network. The network aims to utilize data from clinical encounters and the collective wisdom of clinicians to continually learn and improve outcomes.

Learning Objective 1: Analyze the limitations of current guideline-informed treatments for bipolar disorder—including challenges in implementation, restricted generalizability of RCT-derived recommendations, and barriers to accessing evidence-based psychotherapy—and evaluate how these limitations contribute to persistent difficulties in achieving and sustaining recovery.

Learning Objective 2: Describe the goals and emerging structure of the Bipolar Action Network and explain how leveraging real-world clinical data and clinician expertise within a learning health system can promote continuous improvement and better outcomes for individuals across the spectrum of bipolar disorder.

Literature References:

1. Nierenberg AA, Margolis P, Strakowski S, Trivedi M, Yatham LN. A Bipolar Learning Health Network: An innovation whose time has come. *Bipolar Disord*. May 2023;25(3):177-180.
2. Nierenberg AA, Agustini B, Kohler-Forsberg O, et al. Diagnosis and Treatment of Bipolar Disorder: A Review. *JAMA*. Oct 10 2023;330(14):1370-1380. doi:10.1001/jama.2023.18588

THE PHARMACOLOGIC TREATMENT OF SCHIZOPHRENIA: STATUS REPORT

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

Abstract: Despite the availability of numerous medications to treat schizophrenia the proportion of patients who either experience residual psychotic symptoms, are considered treatment resistant, relapse despite medication, or have meaningful challenges with treatment acceptance or adherence remains very high. At the same time there is renewed debate about medication dose reduction and discontinuation. As the field has tried to promulgate the implementation of evidenced based medicine and measurement-based care, we continue to witness limited and inconsistent utilization of evidenced based treatments such as long-acting formulations of antipsychotic medications or clozapine. The introduction of muscarinic agonists represents an important advance in providing alternatives to the direct dopamine receptor antagonism which has been the long-standing basis for antipsychotic drug development. We now must understand the full

implications of such alternatives and the degree to which they are associated with different or better outcomes.

Learning Objective 1: To bring the audience up to date on the data regarding a new class of medicines-the muscarinic agonists.

Learning Objective 2: To review data on the underutilization of evidenced based treatments and discuss potential reasons for this problem.

Literature References: McCutcheon RA, Taylor D, Rubio J, et al. Does Slow and Steady Win the Race? Rates of Antipsychotic Discontinuation, Antipsychotic Dose, and Risk of Psychotic Relapse. *Schizophr Bull.* 2024 Apr 30;50(3):513-520.

Takeuchi H, Siu C, Remington G, et al. Does relapse contribute to treatment resistance? Antipsychotic response in first- vs. second-episode schizophrenia. *Neuropsychopharmacology.* 2019 May;44(6):1036-1042.

EXCITING NEW FINDINGS FROM CLINICAL TRIALS IN THE TREATMENT OF POST-TRAUMATIC STRESS DISORDER

Lori Davis, Veterans Affairs Medical Center

Abstract: Post-traumatic stress disorder (PTSD) is a prevalent and often difficult to treat psychiatric disorder. Over the last several years, the field has seen a modest uptick in the number of novel treatment interventions showing some promise in the treatment of PTSD. These include novel medication combinations, medication-assisted psychotherapy, neuromodulation as stand-alone or adjunct to psychotherapy and other novel devices, such as electroencephalogram-driven neurofeedback. Despite consumer excitement for stellate ganglion block and hyperbaric oxygen therapy, results from studies are mixed. This update provides a comprehensive review of recent findings from clinical trials and highlight ongoing studies in the treatment of PTSD.

Learning Objective 1: The attendee will be able to discuss a range of novel treatments for PTSD that are currently being tested in clinical trials.

Learning Objective 2: The attendee will be able to identify emerging treatments for PTSD that warrant and/or need additional research.

Literature References: 1. Sippel LM, Hamblen JL, Kelmendi B, et al; APA Council of Research Task Force on Novel Biomarkers and Treatments. Novel Pharmacologic and Other Somatic Treatment Approaches for Posttraumatic Stress Disorder in Adults: State of the Evidence. *Am J Psychiatry.* 2024;181(12):1045-1058. doi: 10.1176/appi.ajp.20230950. PMID: 39616450.

2. Davis LL, Behl S, Lee D, et al. Brexpiprazole and Sertraline Combination Treatment in Posttraumatic Stress Disorder: A Phase 3 Randomized Clinical Trial. *JAMA Psychiatry.* 2025;82(3):218-227. doi: 10.1001/jamapsychiatry.2024.3996. PMID: 39693081; PMCID: PMC11883513.

3:15 p.m. - 4:45 p.m.

Individual Research Reports (IRRs) 1: Psychosis, Sleep, and Learning

SCHIZOPHRENIA POLYGENIC RISK IS NEGATIVELY ASSOCIATED WITH BODY MASS INDEX IN TWO POPULATION COHORTS

Olaoluwa Okusaga^{*1}, Chris Chatzinakos², Gleda Kutrolli², Rachel L. Kember³, Tim Bigdeli², Roseann E. Peterson²

¹Michael E DeBakey VA Medical Center/Baylor College of Medicine, ²SUNY Downstate Medical Center, ³University of Pennsylvania

Olaoluwa Okusaga, Michael E DeBakey VA Medical Center/Baylor College of Medicine

Abstract Background: Obesity is highly prevalent among individuals with schizophrenia and contributes to cardiovascular mortality and reduced life expectancy. Despite this, a few studies have reported a negative association between schizophrenia polygenic risk scores (PRS) and body mass index (BMI). However, the nature of the relationship between schizophrenia genetic liability and BMI remains unclear. To further clarify this association, we evaluated the relationship between schizophrenia PRS and BMI across two independent biobanks.

Methods: Data were derived from two sources: 1) The Health and Retirement Study (HRS); and 2) UK biobank (UKB, conducted using the UK Biobank Resource application number 30782). Data on age, sex, and BMI for each participant were extracted from both biobanks. In UKB, we calculated schizophrenia PRS based on the most recent PGC GWAS, but for HRS, we employed the precalculated schizophrenia PRS (based on PGC 2) on the HRS website. In separate analyses in HRS and UKB, we evaluated the association between schizophrenia PRS and BMI using linear regression, with BMI as the dependent variable and schizophrenia PRS as the primary independent variable. Covariates included age, sex, and the first ten genetic principal components in both datasets, with years of education additionally included in the HRS analyses.

Results: 7,984 middle-aged and older adults (3612 male, 4372 female, mean age 65.4 years) were included in the HRS analyses and 458,547 participants in UKB (209792 male, 248755 female, mean age 57.3 years). All the participants were of European ancestry. Schizophrenia PRS were negatively associated with BMI in HRS ($\beta = -0.04$; 95% CI -0.004 to -0.08, $p < 0.05$, $R^2 = 0.05$) and UKB (-0.140 ; 95% CI -0.154 to -0.126 , $p < 1 \times 10^{-5}$, $\Delta R^2 = 0.0008$).

Discussion: We replicated the negative association between Schizophrenia PGS and BMI in two different cohorts and life stages. Specifically in UKB, a one-unit increase in SCZ-PRS was associated with an approximately 0.14 unit decrease in BMI. Our findings contribute to the accumulating evidence suggesting that the high rates of obesity observed among persons with schizophrenia is not explained by genetic liability to high BMI but is likely related to several extrinsic factors including antipsychotic medications, sedentary lifestyle, and diet. Additional research is warranted to examine how schizophrenia genetic liability impacts BMI and metabolic traits across the life course.

Learning Objective 1: Show that obesity is highly prevalent among individuals with schizophrenia

Learning Objective 2: Demonstrate that genetic liability for schizophrenia is inversely related to BMI

Literature References:

1. Zheutlin, A. B., Dennis, J., Karlsson Linnér, R., et al. Penetrance and Pleiotropy of Polygenic Risk Scores for Schizophrenia in 106,160 Patients Across Four Health Care Systems. *The American journal of psychiatry*. 2019;176(10) 846–855.
2. Solmi, F., Mascarell, M. C., Zammit, S., et al. Polygenic risk for schizophrenia, disordered eating behaviors and body mass index in adolescents. *The British journal of psychiatry*. 2019;215(1), 428–433.

RETROSPECTIVE ANALYSIS OF REAL-WORLD TRANSITION STRATEGIES FOR XANOMELINE AND TROSPIUM CHLORIDE IN ADULT PATIENTS WITH SCHIZOPHRENIA

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¹Colorado Neurological Clinic Research of the Rockies, LLC, ²Bristol Myers Squibb,

⁴Mentally Strong

Jenna Hoogerheyde, Bristol Myers Squibb

Abstract: Approximately 30%-50% of adults with schizophrenia switch antipsychotic medication within 6-24 months of treatment initiation. This study aims to analyze retrospective real-world data from psychiatry healthcare providers (HCPs) to describe the methodology utilized in successfully transitioning adults with schizophrenia from other antipsychotic medications to xanomeline and trospium chloride (KarXT).

Methods: This retrospective study of adults with schizophrenia who have transitioned to KarXT after previous treatment with a typical or atypical antipsychotic was conducted using an electronic survey sent to psychiatry HCPs. Successful transition was defined as maintained treatment with KarXT for ≥ 1 month with no discontinuation. Data were de-identified at the time of collection.

Results: Data collection is ongoing. During an interim evaluation as of August 29, 2025, 90 patients were 59% male, 69% White, 13% Hispanic/Latino, and 12% African American. Top reasons for previous antipsychotic medication discontinuation were lack of adequate control of positive symptoms and worsened or lack of improvement of negative symptoms. The majority transitioned using a cross-titration approach over 2-4 weeks. Previous antipsychotics were most often tapered by 25% (36%) or 50% (33%) per step, and KarXT was up-titrated from 50 mg/20 mg to 100 mg/20 mg or 125 mg/30 mg over the titration period. Most HCPs provided their patients with an antiemetic either as a prophylactic treatment (21%) or as needed (44%) if nausea/vomiting occurred.

Conclusions: A variety of real-world strategies have been implemented by HCPs to transition adults with schizophrenia to the novel KarXT treatment. Most common strategies utilized in successful switches include cross-titration and consideration of an antiemetic medication for the transient nausea and vomiting that may occur during titration.

Learning Objective 1: To gain an understanding of how psychiatric healthcare providers are transitioning adults with schizophrenia from their current antipsychotic to a novel agent,

xanomeline and trospium chloride (KarXT), and identifying strategies used to mitigate potential side effects.

Learning Objective 2: To ascertain the demographics of real-world patients with schizophrenia in the United States treated with KarXT and the reasons for switching from a previous antipsychotic.

Literature References::

1. Khandker R, Mohit B, Fonseca E, et al: Treatment discontinuation and switching of antipsychotics among adult patients with schizophrenia in the United States. *Schizophrenia Res* 2025; 283:152-162

2. Ramey OL, Silva Almodovar A: Xanomeline-trospium: a novel therapeutic for the treatment of schizophrenia. *Ann Pharmacother* 2025; 59:937-950

SLEEP ESTIMATION FROM LOW-FREQUENCY SMARTPHONE SENSORS VIA BAYESIAN HIDDEN MARKOV MODEL

*Jin Soo Byun*¹, John Torous¹*

¹Beth Israel Deaconess Medical Center and Harvard Medical School

Jin Soo Byun, Beth Israel Deaconess Medical Center and Harvard Medical School

Abstract: Objective: Sleep disturbances are recognized as transdiagnostic markers of psychiatric illness, yet objective monitoring is rare in large-scale research due to the infrastructure burdens of PSG and the cost of dedicated wearables. While smartphones offer a scalable solution for passive sensing, current approaches often lack validation in diverse psychiatric populations. This study introduces and validates a probabilistic Bayesian Hidden Markov Model (HMM) that integrates low-frequency accelerometer, GPS, and screen data to infer nightly sleep states and extract behavioral metrics without requiring additional hardware.

Methods: We designed a modular pipeline that processes passive smartphone data (accelerometer, GPS context, screen state) through a Bayesian HMM. The model utilizes a 'sticky' transition prior to enforce state persistence and a participant-specific Empirical Bayes initialization to adapt to individual chronotypes without imposing arbitrary timing constraints. We evaluated performance through a multi-tiered validation strategy: 1) We generated synthetic datasets based on empirical parameters to stress-test the model against varying signal-to-noise ratios and fragmentation. 2) We benchmarked estimates against concurrent research-grade wrist actigraphy (processed via the GGIR algorithm) in the AMPSCZ dataset (N = 169). 3) We compared model outputs with daily Ecological Momentary Assessment (EMA) self-reports across a diverse sample (N = 516) including individuals at Clinical High Risk for psychosis, depression, and healthy controls. Finally, we applied unsupervised clustering to 15,530 nights from 868 participants to identify latent behavioral phenotypes.

Results: Simulation analysis demonstrated high robustness, with mean accuracy reaching 0.98 in linear drift scenarios. In real-world validation, the smartphone model showed strong agreement with wrist actigraphy, with Bland-Altman analysis indicating minimal systematic bias. Comparison with EMA self-reports revealed significant population-level alignment for bedtime ($r = 0.68$), waketime ($r = 0.65$), and sleep duration ($r = 0.48$). Importantly, filtering

out a small subset of high-noise participants (RMSE over 1.2 hours) improved correlations to $r = 0.89$ for bedtime and $r = 0.90$ for waketime, demonstrating high precision for the majority of users. Discrepancies between model and EMA estimates were not systematically related to psychiatric symptom severity, supporting validity across clinical states. Unsupervised clustering revealed five distinct phenotypes, such as 'High symptom burden with short sleep' and 'Moderate symptoms with fragmented sleep,' highlighting that similar clinical profiles map to vastly different underlying sleep behaviors.

Conclusions: This study presents a robust, validated framework for large-scale, non-invasive sleep monitoring using standard smartphones. By effectively capturing sleep-wake dynamics and revealing heterogeneity in sleep-symptom coupling, this approach offers a scalable tool for digital phenotyping and anomaly detection. This presentation is critical for researchers seeking to overcome the scalability limits of actigraphy; attendees will gain a validated methodology for implementing zero-cost, objective sleep monitoring in large cohorts, alongside new insights into how passive behavioral phenotypes can map distinct clinical trajectories.

Learning Objective 1: Demonstrate how low-frequency passive smartphone data (accelerometer, GPS, screen state) can be utilized via a Bayesian Hidden Markov Model to accurately estimate sleep metrics without the need for dedicated wearable devices.

Learning Objective 2: Evaluate the heterogeneity of sleep-symptom coupling in psychiatric populations and identify how distinct behavioral phenotypes can be derived from unsupervised clustering of objective sleep and symptom data.

Literature References:

1. Byun AJS, Li Y, Cong S, et al. Sleep Estimation from Low Frequency Smartphone Sensors via Bayesian Hidden Markov Model. Research Square. 2025;rs.3.rs-7217304.
2. Langholm C, Byun AJS, Mullington J, Torous J. Monitoring sleep using smartphone data in a population of college students. Npj Ment Health Res. 2023;2:3.

NEURAL AND BEHAVIORAL EVIDENCE FROM REINFORCEMENT LEARNING CONVERGE IN SUPPORT OF RELAXED BELIEFS UNDER LSD

*Jonathan Kanen*¹, Andrea Luppi², Qiang Luo³, Leor Roseman⁴, Rudolf Cardinal², Trevor Robbins², David Nutt⁵, Hanneke den Ouden⁶, Robin Carhart-Harris⁷*

¹Icahn School of Medicine at Mount Sinai, ²University of Cambridge, ³Fudan University, ⁴University of Exeter, ⁵Imperial College London, ⁶Donders Institute for Brain Cognition and Behaviour, ⁷University of California at San Francisco

Jonathan Kanen, Icahn School of Medicine at Mount Sinai

Abstract: The REBUS (RElaxed Beliefs Under pSychedelics) and the anarchic brain model of psychedelic drug action proposes that confidence in beliefs – and thus expectations (priors) – are relaxed under these drugs. The brain makes inferences to minimize surprise, or discrepant expectations and outcomes (prediction error [PE]), and better model the world. We recently showed that the non-specific 5-HT_{2A} receptor agonist LSD heightened sensitivity to PEs, reflected by speeded updating of value representations following better and worse than expected outcomes. Indeed, events that are surprising are inherently less expected. There is evidence that LSD produces ego dissolution that is positively correlated with disintegration of

the default mode network (DMN), assessed using resting state functional connectivity (RSFC), and is correlated inversely with alpha oscillatory power. The DMN has been proposed to be a seat at the ego's table and decreased alpha power has been posited to reflect relaxation of the cognitive hierarchy, mediated by 5-HT_{2A} receptors on deep layer V pyramidal neurons in cortex. Here we aim to demonstrate neural correlates of an objective, behaviorally derived marker of REBUS. Greater speed at which choice value increased following a reward PE – higher reward learning rates (RLRs) – was operationalized as enhanced sensitivity to surprise. We tested whether medial prefrontal cortex (mPFC) RSFC within the DMN – a region often associated with value – and diminished alpha power correlated significantly with the RLR. Alpha power was derived from magnetoencephalography (MEG). The functional magnetic resonance imaging (fMRI) resting state functional connectivity (RSFC) data of interest were extracted from mPFC regions of the DMN. To assess anatomical specificity, we also predicted that static RSFC of primary visual cortex (V1) would not be correlated with the RLR. We additionally extended our analysis to the brain's temporal organization, parsing the data into dynamic states where network integration or segregation predominate, again focusing on mPFC regions of the DMN. The RLR was inversely correlated with MEG alpha power ($r(13) = -.618, p = .024$), and positively correlated with the extent of disintegration of the DMN as assessed using static RSFC ($r(15) = .641, p = .010$). V1 static RSFC did not correlate with the RLR, as hypothesized ($r(15) = .204, p = .465$). The RLR was positively correlated with dynamic RSFC in a mPFC a priori region of interest during a predominantly integrated sub-state of brain dynamics ($r(15) = .624, p = .013$). A behaviorally derived computational marker of surprise was correlated with neural signatures of relaxed beliefs under psychedelics (REBUS).

Learning Objective 1: A behaviorally derived computational marker of surprise was correlated with neural signatures of relaxed beliefs under LSD

Learning Objective 2: This study provided converging neural and behavioral evidence that LSD enhanced a fundamental belief updating mechanism

Literature References:: Carhart-Harris RL, Muthukumaraswamy S, Roseman L, Kaelen M, Droog W, Murphy K, Tagliazucchi E, Schenberg EE, Nest T, Orban C, Leech R, Williams LT, Williams TM, Bolstridge M, Sessa B, McGonigle J, Sereno MI, Nichols D, Hellyer PJ, [...] and Nutt DJ, Neural correlates of the LSD experience revealed by multimodal neuroimaging, *Proc. Natl. Acad. Sci. U.S.A.* 2016;113 (17) 4853-4858.

Carhart-Harris RL, Friston KJ. REBUS and the Anarchic Brain: Toward a Unified Model of the Brain Action of Psychedelics, *Pharmacological Reviews*. 2019; 71, (3) 316-344

3:15 p.m. - 4:45 p.m.

Individual Research Reports (IRRs) 2: Stimulant Medications and Drugs

AUGMENTING DORSOLATERAL PREFRONTAL CORTEX-TARGETED TDCS WITH COGNITIVE REAPPRAISAL IN COCAINE USE DISORDER

Yuefeng Huang¹, Pierre-Olivier Gaudreault¹, Maggie Boros¹, Rachel Drury¹, Yui Ying Wong¹, Abhishek Datta², Muhammad Parvaz¹, Nelly Alia-Klein¹, Rita Goldstein¹

¹Icahn School of Medicine at Mount Sinai, ²Soterix Medical Inc.

Abstract Background: Cocaine use disorder (CUD) remains a major public health challenge in the United States. In 2022, approximately 5.3 million individuals reported past-year crack or cocaine use, 1.4 million met criteria for CUD, and cocaine-related overdose deaths continued to rise, highlighting the absence of FDA-approved pharmacological treatments and the urgent need for additional evidence-based treatment options. Transcranial direct current stimulation (tDCS) targeting the dorsolateral prefrontal cortex (dlPFC), a key node in inhibitory control and salience regulation, has demonstrated efficacy in reducing craving in CUD. Cognitive reappraisal (CR) is a dlPFC-dependent learning strategy that we have shown to reduce drug cue-reactivity in CUD. Whether combining dlPFC-targeted tDCS with CR produces superior regulatory effects remains unknown.

Methods: Thirty-six individuals with CUD were randomized to sham (n=13), real (n=13), or real+CR (n=13) conditions to receive 15 sessions of dlPFC-targeted tDCS over 5 weeks. Following Phase 1 procedures, in this Phase 2 study, cocaine craving was measured using the Obsessive-Compulsive Cocaine Scale subscale and item 5 of the five-item Cocaine Craving Questionnaire before and after treatment; at the same times, drug cue-reactivity was measured using late positive potentials (LPP) during an EEG cue-reactivity task. Rest-activity rhythms were continuously monitored over the 5 weeks using 24/7 ActiGraph and processed with GGIR package to derive daily activity and circadian rhythm metrics. Hidden Markov models will be applied to characterize latent rest-activity states and circadian transitions, and multivariate models will be used to integrate craving, LPP, and rest-activity rhythm features to identify markers of treatment response.

Results: There was a significant group by time interaction on combined cravings, $F(2,18)=3.77$, $p=.043$, partial eta squared (η^2)=.295, driven by greater craving reductions in the real+CR group, $t(8.98)=2.79$, $p=.021$, $d=1.49$, and the real group, $t(9.55)=2.13$, $p=.059$, $d=1.14$, relative to sham. We hypothesize that craving reductions will be accompanied by decreased drug-biased LPPs and by normalization of rest-activity rhythms, with the strongest effects in the real+CR group.

Conclusions: These findings suggest that dlPFC-targeted tDCS, particularly when combined with CR, significantly reduces cocaine craving. Ongoing analyses of LPP and rest-activity rhythms will clarify whether treatment-related changes in brain reactivity and circadian organization track craving reduction. Together, this work supports cognitively enhanced neuromodulation approaches that combine cognitive strategies with brain stimulation to improve therapeutic outcomes in cocaine use disorder. Supported By NIDA 5N95020C00024

Learning Objective 1: Describe how dlPFC-targeted tDCS, alone and combined with cognitive reappraisal, modulates craving, rest-activity rhythms, and drug cue-reactivity in cocaine use disorder.

Learning Objective 2: Explain how multimodal measures, including EEG-derived LPP and rest-activity rhythm modeling, can be used to identify neural and behavioral markers of treatment response in interventional psychiatry.

Literature References:: Gaudreault P-O, Sharma A, Datta A, et al. A double-blind sham-controlled phase 1 clinical trial of tDCS of the dorsolateral prefrontal cortex in cocaine inpatients: Craving, sleepiness, and contemplation to change. *Eur J Neurosci.* 2021; 53: 3212–3230.

M.A. Parvaz, P. Malaker, A. Zilverstand, S.J. Moeller, N. Alia-Klein, and R.Z. Goldstein, Attention bias modification in drug addiction: Enhancing control of subsequent habits, Proc. Natl. Acad. Sci. U.S.A. 118 (23) e2012941118

MIXED AMPHETAMINE SALTS AND LISDEXAMFETAMINE AS ADJUNCTIVE TREATMENT FOR BIPOLAR DEPRESSION: POOLED ANALYSIS OF TWO RANDOMIZED CONTROLLED TRIALS

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¹Mayo Clinic, ²Lindner Center of HOPE, University of Cincinnati College of Medicine

Mark Frye, Mayo Clinic

Abstract: Objective: Depression is the predominant mood state in bipolar disorder (BD) and is often accompanied by significant attentional deficits. Adjunctive amphetamine derivatives may effectively target both mood and cognitive symptoms in this patient population. In this analysis, we aim to evaluate the efficacy and safety of adjunctive mixed amphetamine salts (MAS) Mydayis® and lisdexamfetamine (LDX) Vyvanse® in bipolar depression.

Methods: This pooled analysis combined two 8-week, randomized, placebo-controlled clinical trials of adjunctive amphetamine treatment (MAS and LDX) in bipolar depression. The primary outcome was baseline-to-endpoint change in Montgomery-Asberg Depression Rating Scale (MADRS) score. Secondary outcomes included response ($\geq 50\%$ MADRS reduction), remission (MADRS < 10), and baseline-to-endpoint change in the Digit Symbol Substitution Test (DSST). The primary safety measure was the change in Young Mania Rating Scale (YMRS) score.

Results: In this pooled sample of 57 participants (amphetamine $n=26$; placebo $n=31$), adjunctive amphetamine treatment demonstrated superior antidepressant efficacy versus placebo, with greater MADRS reduction (52.8% vs 27.1%), higher response rates (61.5% vs 19.4%), and higher remission rates (46.2% vs 16.1%) (all $p \leq 0.02$). Effect sizes were medium-to-large for depression outcomes (MADRS: $d = 0.69$; response: $\phi = 0.43$; remission: $\phi = 0.33$), with no evidence of increased manic symptoms (YMRS: $d = -0.16$). Treatment effects were consistent regardless of concomitant antidepressant or antipsychotic use (all interaction $p \geq 0.18$). There was no statistically significant between-group difference in DSST percent change (amphetamine 22.7% vs placebo 11.5%; $p=0.11$).

Conclusions: Adjunctive amphetamine treatment demonstrates robust antidepressant efficacy in bipolar depression with medium-to-large effect sizes and minimal manic switch risk. These findings challenge traditional concerns about stimulant use in BD and suggest amphetamine derivatives represent a valuable therapeutic option for patients with inadequate response to standard treatments, warranting further investigation in larger trials.

Learning Objective 1: Assess the efficacy of adjunctive amphetamine derivatives for bipolar depression by interpreting MADRS change, response, and remission outcomes from pooled randomized clinical trial data.

Learning Objective 2: Evaluate clinical safety of stimulant augmentation in BD—particularly manic switch risk (YMRS) and cognitive effects (DSST), to inform treatment decisions in patients with inadequate response to standard therapies.

Literature References:

1. McElroy, S.L., et al., Adjunctive lisdexamfetamine in bipolar depression: a preliminary randomized, placebo-controlled trial. *International Clinical Psychopharmacology*, 2015. 30(1): p. 6-13.
2. Miskowiak, K.W., et al., Efficacy and safety of established and off-label ADHD drug therapies for cognitive impairment or attention-deficit hyperactivity disorder symptoms in bipolar disorder: A systematic review by the ISBD Targeting Cognition Task Force. *Bipolar Disord*, 2024. 26(3): p. 216-239.

BRAIN-TO-BRAIN MOVIE NEUROFEEDBACK REDUCES CRAVING IN OPIOID USE DISORDER

Natalie McClain^{*1}, Greg Kronberg¹, Nelly Alia-Klein¹, Rita Z. Goldstein¹

¹Icahn School of Medicine at Mount Sinai

Natalie McClain, Icahn School of Medicine at Mount Sinai

Abstract Background: Despite the escalating overdose crisis, effective brain-based treatments for opioid use disorder (OUD) remain scarce. In a recent fMRI study in inpatients with OUD, we reported malleability with treatment in shared brain dynamics across a network of brain regions during a drug-themed movie, suggesting that helping individuals learn these patterns could facilitate recovery. Real-time fMRI neurofeedback (NF) offers a promising method to directly modulate brain dynamics. However, traditional NF paradigms typically target single brain regions and rely exclusively on an individual's own neural signals, limiting impact on complex recovery behavior in addiction. Here, for the first time, we develop brain-to-brain NF using a multivariate target signal derived from patients with OUD further along in recovery to facilitate recovery in individuals earlier in treatment. To increase ecological validity and better approximate real-world experiences in OUD, the stimulus was a dynamic, narrative-based, and context-rich movie.

Methods: The NF target signal was derived from an existing dataset of individuals with OUD [(iOUD), n=37] who underwent fMRI while viewing the first 17 minutes of *Trainspotting* twice, earlier in inpatient treatment and again three months later. We identified a linear transform of ROI-level BOLD signals, such that the resulting 1-dimensional time series reliably classified early vs. late treatment movie viewings (mean accuracy: 77.5%, $p < 0.001$). The average late treatment signal in this transformed space was then used as the NF target signal. We then implemented a novel real-time movie NF task in a new cohort of early-abstinent iOUD (n=10; 44 ± 11 years old), where the movie was paused after select scenes to display NF scores that reflected the alignment of these participants' own brain activity with the target signal. A yoked control group of iOUD (n=10; 41 ± 7 years old) received sham feedback that was identical to their matched counterpart in the active NF group. NF training involved 8 runs of the task across 4 consecutive days. We evaluated its efficacy by comparing changes in NF performance, self-reported cue-induced craving, and standard affective ratings between groups over the course of NF training.

Results: NF performance increased in the active NF group (one-sample $t=2.6$, $p=0.015$) but not the sham (one-sample $t=0.5$, $p=0.30$; two-sample $t=1.4$, $p=.093$) during the first four runs. The active group also showed a significantly greater reduction in cue-induced craving after four runs ($t=2.77$, $p=0.01$). Linear mixed-effects models controlling for baseline pre-NF craving revealed that, across the first four runs, the active NF group demonstrated a significantly more negative relationship between NF performance and craving compared to sham (interaction $\beta=0.2$, $p=0.019$). Finally, the active NF group exhibited a greater increase in positive affect compared to the sham group ($t=2.2$, $p=0.043$).

Conclusion: This study provides the first evidence that a novel brain-to-brain NF paradigm during the processing of a naturalistic context can effectively reduce cue-induced craving in OUD. Unlike sham, active NF enabled participants to increasingly align their neural activity with the recovery-related target signal. Crucially, improvement in NF performance (observed after only 4 runs) was clinically meaningful, tracking with reductions in cue-induced craving and improved positive affect. These results suggest that guiding early-abstinent iOUD towards the neural signatures of those later in recovery may offer scaffolding for the nascent recovery process early in treatment, on route to developing a potent, ecologically valid treatment intervention for opioid addiction.

Learning Objective 1: Be able to describe how multivariate neural signals from patients further along in recovery can be leveraged as neurofeedback targets to reduce craving in early-abstinent individuals with opioid use disorder.

Learning Objective 2: Be able to assess the clinical potential of brain-to-brain neurofeedback for improving craving and positive affect in opioid use disorder treatment.

Literature References: Kronberg G, Ceceli AO, Huang Y, et al. Shared orbitofrontal dynamics to a drug-themed movie track craving and recovery in heroin addiction. *Brain*. 2025;148(5):1778-1788. doi:10.1093/brain/awae369

Mennen AC, Nastase SA, Yeshurun Y, et al. Real-time neurofeedback to alter interpretations of a naturalistic narrative. *Neuroimage Rep*. 2022;2(3):100111. doi:10.1016/j.ynirp.2022.100111

ASCP TASK FORCE ON DEPRESCRIBING STIMULANTS FOR ADHD IN ADULTS

David Goodman^{*1}

¹Johns Hopkins School of Medicine

David Goodman, Johns Hopkins School of Medicine

Abstract: The American Society of Clinical Pharmacology (ASCP) convened a task force on the deprescribing of psychotropic medications, including stimulant medications for adult ADHD, which entailed a focused literature review and 2-round Delphi survey querying 47 international psychopharmacology experts on factors related to deprescribing. The publication of these findings will represent the first worldwide published expert consensus recommendations for deprescribing stimulant medications in treated ADHD adults. With the survey as a basis, the panel generated expert consensus recommendations for the deprescription of stimulant medications for adults treated for ADHD for specific clinical presentations. This workshop will review the specific 11 Delphi statements and the voting outcomes. Eighty-two percent (9 of 11) reached consensus as defined by > 75% agreement

(defined by “strong” or “moderately strong” endorsements). Consensus was not reached on (1) eliminating one of two co-administered stimulant medications from different classes (i.e., methylphenidate versus amphetamine-type), and (2) whether regular use of cannabis is sufficient reason to deprescribe stimulant medications in adult ADHD patients. We'll review the clinical implication for the care of adults with ADHD.

Learning Objective 1: Understand the ASCP Task Force recommendations for deprescribing stimulant medication for adults with ADHD.

Learning Objective 2: Understand the clinical considerations and implications of deprescribing stimulants for adults with ADHD.

Literature References: Faraone SV., Banaschewski T, Coghill D, et al. “The World Federation of ADHD International Consensus Statement: 208 Evidence-based conclusions about the disorder,” *Neurosci. Biobehav. Rev.*, vol. 128, pp. 789–818, Sep. 2021, doi: 10.1016/j.neubiorev.2021.01.022.

Lohr WD, Wanta JW, Baker M, Grudnikoff E, Morgan W, Chhabra D, Lee T. Intentional Discontinuation of Psychostimulants Used to Treat ADHD in Youth: A Review and Analysis. *Front Psychiatry*. 2021 Apr 20;12:642798. doi: 10.3389/fpsy.2021.642798. PMID: 33959050; PMCID: PMC8093505.

Goodman DW, Mago R, Aaronson S, Citrome L, Clayton A, Cohen JC, Correll C, Frye MA, Gitlin M, Gorwood P, Friedman M, Iosifescu D, Jha M, Kasper S, Kupka R, Macaluso M, Malhi GS, McIntyre R, Mitchell P, Sajatovic M, Steingard S, Swartz H, Tohen M, Vieta E, Young J, Zohar J, Goldberg JF. ASCP Expert Consensus Task Force Guidelines on the Deprescribing of Stimulant Medications in Adults with ADHD. *J Clin Psych* 2025, in press.

3:15 p.m. - 4:45 p.m.

Individual Research Reports (IRRs) 3: Glutamate Modulators

EVALUATING HEPATIC EFFECTS OF SERIAL KETAMINE INFUSIONS FOR TREATMENT-RESISTANT BIPOLAR DEPRESSION

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Gabrielle Lovell, University of Toronto

Abstract Background: Ketamine has been identified as a promising treatment for treatment resistant depression (TRD) demonstrating rapid and robust antidepressant effects. Concerns from regulatory agencies have emerged regarding the risk of hepatotoxicity of prolonged ketamine use after identifying cases of liver impairment, typically following ketamine for chronic pain treatment or misuse. Bipolar disorder (BD) is associated with higher rates of hepatic impairment, however, the risk of hepatic dysfunction following serial ketamine infusions in BD remains unknown.

Methods: In a double-blinded, randomized controlled trial (RCT) (KET-BD, NCT05004896), participants with a diagnosis of treatment-resistant bipolar depression (TRBD) received four infusions over two weeks of either intravenous ketamine (0.5 -

0.75mg/kg) or an active placebo (midazolam; 0.02-0.03 mg/kg). Liver function tests (i.e., aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), C-reactive protein (CRP), albumin, total protein, bilirubin) were conducted at baseline and following an acute course of treatment (primary endpoint; Day 14). The results of 62 participants were analyzed.

Results: In the ketamine group, 9.7% (n = 6) of participants demonstrating normal liver function ranges at baseline developed transaminitis by Day 14 (elevation of AST/ALT), with no participants exceeding 2x the upper limit of normal (ULN). In the midazolam group, 1.6% (n = 1) of participants demonstrating normal liver function at baseline developed transaminitis. One participant had > 2x ULN ALT at primary endpoint and another participant had > 2x ULN CRP at primary endpoint, however both participants had elevated ALT or CRP respectively at baseline, and were in the midazolam group. For both albumin and total protein, 6.5% (n=2) from the ketamine group and 3.2% (n=1) from the midazolam group were within the normal range at baseline but elevated at primary endpoint, however no participants exceeded 2x ULN. No patients demonstrated elevated bilirubin levels at any point in the trial.

Conclusion: To our knowledge, this is the largest analysis of hepatotoxicity of ketamine in the context of BD treatment. Based on these findings, four repeated doses of intravenous ketamine may result in transaminitis, however impaired liver function was not demonstrated, as suggested by bilirubin levels remaining in normal range. With the rise of repeated and prolonged dosing methodologies in clinical trials and clinical practice, these results contribute to a greater understanding of the risk profile associated with ketamine treatment. Given how commonly transaminitis was observed, routine liver monitoring is merited with serial ketamine infusions.

Learning Objective 1: Evaluate evidence of hepatic injury and/or impaired hepatic function from the largest RCT investigating serial intravenous ketamine infusions in a treatment-resistant bipolar depression

Learning Objective 2: Describe the need for evidence quantifying the risk for hepatotoxicity related to ketamine treatment for patients with treatment resistant bipolar depression

Literature References:: Hsu JH, Chien IC, Lin CH. Increased risk of chronic liver disease in patients with bipolar disorder: A population-based study. *General Hospital Psychiatry*. 2016;42:54-59.

Thakkar, B.; Wu, G.Y. Ketamine Hepatotoxicity: An Underappreciated Cause of Liver Damage - Analysis by RUCAM. *Journal of Clinical and Translational Hepatology* 2025, 13, 524–531,

DRUG LIKING AND CRAVING OF INTRAVENOUS KETAMINE WHEN PRESCRIBED FOR THE TREATMENT OF MOOD DISORDERS IN A MONITORED SETTING: A DESCRIPTIVE ANALYSIS

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Shreya Vasudeva, University of Toronto

Abstract Background: Ketamine has emerged as a promising treatment for mood disorders, particularly major depressive disorder (MDD) and bipolar depression (BD). However, its dissociative and psychoactive properties, along with weak mu opioid agonist activity, raise concerns regarding abuse liability, especially as ketamine use expands into routine clinical practice. While its antidepressant effects are well established, characterization of acute subjective effects such as drug liking and craving, is essential for understanding abuse liability and informing evidence-based dosing, monitoring, and risk mitigation strategies.

Methods: 254 patients with a treatment-resistant mood disorder, including MDD or BD, received an acute course of intravenous ketamine (four infusions over two weeks) at an outpatient community clinic in Ontario, Canada (ClinicalTrials.gov: NCT04209296). Patients were grouped by dose received at infusion four (0.45–1.2 mg/kg): ≤ 0.50 mg/kg (n=51), 0.55–0.70 mg/kg (n=24), 0.75–0.90 mg/kg (n=175), and ≥ 0.91 mg/kg (n=4). Drug liking and craving were assessed immediately after infusion four using the Drug Liking and Craving Questionnaire (DLCQ). Craving for non-therapeutic and higher/unprescribed use was assessed using Craving A and Craving B subscales respectively. All items were scored on a 0–100 scale. Descriptive statistics included median and interquartile range (IQR). All patients were assessed by a mental health care provider after the fourth infusion to proactively assess for signs of substance use disorders or use of ketamine outside of clinical care.

Results: In patients receiving ≤ 0.5 mg/kg, median drug liking was 55 (IQR 20.5), with median Craving A and Craving B scores of 0 (IQR 10.5) and 0 (IQR 11.0), respectively. Among those receiving 0.55–0.70 mg/kg, median drug liking was 50 (IQR 2.3), while median Craving A was 5 (IQR 15.8) and Craving B was 11.5 (IQR 42.5). For patients receiving 0.75–0.90 mg/kg, median drug liking was 60 (IQR 24.5), with median Craving A of 4 (IQR 28.0) and Craving B of 3 (IQR 44.5). In the ≥ 0.91 mg/kg group (n = 4), median drug liking was 50.5 (IQR 18.8), while both craving medians were 0 (IQR 5). On clinical assessment, no cases of treatment-emergent substance use disorders were identified in this sample. There were no known instances of patients using ketamine illicitly or other signs or symptoms of potential misuse or development of a treatment-emergent substance use disorder.

Conclusion: To our knowledge, this study represents the largest real-world clinical sample assessing drug liking and craving of an acute course of ketamine with a standardized scale. Ketamine generally produced moderate drug liking and low craving at the fourth infusion across clinically administered doses. On clinical assessment, no patients were found to develop a treatment-emergent substance use disorder and there were no known cases of illicit ketamine use in this sample. These findings provide valuable insight into patients' acute subjective experiences and may inform future evaluations of ketamine's abuse liability.

Learning Objective 1: Characterize acute drug liking and craving following an acute course of treatment of intravenous ketamine for treatment-resistant mood disorders using a standardized assessment tool.

Learning Objective 2: Evaluate indicators of ketamine abuse liability across clinically administered doses, including subjective craving and the presence of treatment-emergent misuse or substance use disorders.

Literature References: Le TT, Cordero IP, Jawad MY, et al. The abuse liability of ketamine: a scoping review of preclinical and clinical studies. *J Psychiatr Res.* 2022;151:476–496.

Juneja K, Afroze S, Goti Z, et al. Beyond therapeutic potential: a systematic investigation of ketamine misuse in patients with depressive disorders. *Discov Ment Health.* 2024;4(1):23.

COMBINED KETAMINE AND COGNITIVE BEHAVIORAL THERAPY: LEVERAGING METAPLASTICITY TO ENHANCE OUTCOMES

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¹*Yale, Yale University School of Medicine*

Songjun Li, Yale

Abstract Background and Purpose: Ketamine and intranasal esketamine have transformed the landscape of Treatment-Resistant Depression (TRD) by offering rapid and robust symptom relief. However, a critical limitation remains: durability. The antidepressant effects of NMDA receptor antagonists are often transient, leading to high relapse rates upon discontinuation and necessitating indefinite, resource-intensive maintenance schedules, which miss a fundamental biological opportunity. Ketamine induces not only immediate synaptic plasticity (synaptogenesis) but also metaplasticity, a transient increase in the brain's capacity for future rewiring. This creates a critical post-treatment window (approximately 12–72 hours post-dosing) during which neural circuits are hypersensitive to reshaping.

Methodology: We conducted a systematic review of the literature through December 2025 to evaluate the theoretical rationale and empirical efficacy of pairing ketamine with cognitive-behavioral interventions. We specifically distinguished this mechanistically grounded approach from Ketamine-Assisted Psychotherapy, focusing instead on structured cognitive retraining delivered during the post-acute consolidation window rather than during the acute dissociative state.

Results: Our review identified a consistent signal across multiple trials, suggesting synergistic effects between ketamine and cognitive interventions. Early open-label data and subsequent randomized controlled trials (e.g., Wilkinson et al., 2021) demonstrate that initiating CBT during the ketamine course significantly extends time-to-relapse compared to standard care. Furthermore, large-scale studies utilizing automated digital cognitive training (e.g., Price et al., 2022) delivered post-infusion have shown statistical superiority in sustaining antidepressant effects, validating the concept of leveraging the "plasticity window". Based on these findings, we propose a novel model for clinical workflow: an Induction phase focused on rapid symptom reduction, followed by a Consolidation phase where high-intensity CBT is introduced to reshape adaptive circuits during peak metaplasticity, transitioning to a Maintenance phase focused on skill reinforcement.

Conclusion and Importance: This review highlights a critical opportunity to shift the ketamine/esketamine paradigm from symptom reduction to durable circuit rewiring. We also propose that prescription digital therapeutics (PDTs) offer a pragmatic solution, enabling the precise delivery of behavioral therapies during the optimal post-treatment "plasticity window" without overburdening clinical workforce capacity. Future studies should evaluate this model to determine if combinatorial, digital-and-pharmacotherapeutic neuroplasticity can successfully reduce pharmacologic maintenance, ultimately establishing a new standard of multimodal care for treatment-resistant depression.

Learning Objective 1: Describe the theoretical framework of metaplasticity induced by NMDA receptor antagonists and how it creates a time-sensitive window for cognitive retraining.

Learning Objective 2: Identify a novel, three-phase clinical workflow that integrates scalable digital therapeutics to extend the durability of interventional depression treatments.

Literature References: - Wilkinson ST, Rhee TG, Joormann J, et al. Cognitive Behavioral Therapy to Sustain the Antidepressant Effects of Ketamine in Treatment-Resistant Depression: A Randomized Clinical Trial. *Psychother Psychosom.* 2021;90(5):318–327.

- Price RB, Spotts C, Panny 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(12):959–968.

REPEATED KETAMINE INFUSIONS FOR TREATMENT-RESISTANT BIPOLAR DEPRESSION: A RANDOMIZED, MIDAZOLAM-CONTROLLED CLINICAL TRIAL

*Diana Orsini*¹, Sara Di Luch¹, George Tomlinson¹, Gabrielle Lovell¹, Shreya Vasudeva¹, Nelson Rodrigues¹, Danica Johnson¹, Alastair Flint¹, Roger McIntyre¹, Rodrigo Mansur¹, Keyvan Karkouti¹, Amer Burhan², Erica Kaczmarek¹, Noah Chisamore¹, Joshua Rosenblat¹*

¹University of Toronto, ²Ontario Shores Centre for Mental Health Sciences

Diana Orsini, University of Toronto

Abstract Background: Antidepressant efficacy of intravenous (IV) ketamine has been demonstrated in major depressive disorder (MDD); however, it is not known whether an acute course of IV ketamine is also effective for bipolar depression.

Methods: We conducted a multi-site, randomized, midazolam-controlled clinical trial to assess the antidepressant efficacy, safety and tolerability of adjunctive IV ketamine compared with midazolam for treatment resistant bipolar I/II depression (TRBD). Participants were randomized to receive four flexibly dosed 40-minute infusions over two weeks of either ketamine (0.5-0.75 mg/kg) or midazolam (0.02-0.03 mg/kg). The primary outcome was change in depression symptom severity measured by the Montgomery–Åsberg Depression Rating Scale (MADRS) score from baseline to end of treatment (day 14).

Results: A total of 68 participants were randomized with 5 withdrawn (1 ketamine, 4 midazolam) before day 14. Based on the primary efficacy analysis, controlling for sex, bipolar type and baseline MADRS, the mean MADRS score at day 14 was significantly lower in the ketamine group compared to the midazolam group (between group difference = -7.3 points; 95% CI: -12.0 to -2.5; $p = 0.003$). No cases of mania, hypomania, psychosis or suicide attempts were observed in either group. One case of mixed features (subthreshold hypomanic symptoms) was observed in each group. After the first infusion, 47% of participants correctly guessed treatment allocation.

Conclusions: An acute course of IV ketamine was well tolerated and associated with significant antidepressant effects for TRBD. (Funded by Canadian Institute of Health Research; Registered: NCT05004896, clinicaltrials.gov)

Learning Objective 1: Describe the need for clinical trials investigating novel interventions for treatment resistant bipolar depression

Learning Objective 2: Evaluate the antidepressant efficacy, safety and tolerability of an acute course of intravenous ketamine compared with midazolam in individuals with treatment resistant bipolar depression

Literature References: Fancy F, Haikazian S, Johnson DE, Chen-Li DCJ, Levinta A, Husain MI, Mansur RB, Rosenblat JD. Ketamine for bipolar depression: an updated systematic review. *Ther Adv Psychopharmacol*. 2023 Sep 26;13:20451253231202723. doi: 10.1177/20451253231202723. PMID: 37771417; PMCID: PMC10524067.

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>

3:15 p.m. - 4:45 p.m.

Individual Research Reports (IRRs) 4: Depression and PTSD

AMPA RECEPTOR BINDING POTENTIAL IS REDUCED IN THE ANTERIOR CINGULATE CORTEX OF FEMALE PATIENTS WITH PTSD

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Nicholas Murphy, Texas A and M University, Naresh K. Vashisht College of Medicine

Abstract: Post-traumatic stress disorder (PTSD) is a common, serious, and disabling condition with few effective treatments. Improved understanding of PTSD brain mechanisms is critical to the development of novel therapeutics. Glutamatergic modulation in PTSD is associated with the relief of behavioral symptoms. However, current approaches that focus on the NMDA receptor may not be sufficient targets for long term maintenance of improvements. Targeting AMPA receptors may provide the dynamic modulation of long-term potential necessary to sustain clinical benefits. Pre-clinical work presents strong support for the role of AMPA receptor (AMPA) mediated impairments to synaptic plasticity in the pathophysiology of PTSD. Accordingly, the recent discovery of a selective positron emission tomography (PET) radiotracer ([¹¹C]K-2) for AMPA glutamate receptors has broad potential applications for PTSD and CNS disorders marked by imbalances in excitatory/inhibitory synapses. [C11]K2 is a novel PET radioligand which targets an AMPA glutamate receptor allosteric modulatory site, a target of critical importance in PTSD due to their role in E/I synaptic transmission. We present findings from a cross-sectional study of [C11]K2 AMPA receptor binding potential (AMPABPND) in PTSD. Participants were N=10 PTSD (31.6 years $\pm$ 8.19) and N=10 trauma-naïve controls (25.6 years $\pm$ 3.78). We restricted recruitment to female patients to limit biological heterogeneity and the influence of menstrual hormones. Patients met DSM-5 criteria for chronic PTSD and had a CAPS-5 score (past month) $\geq$ 35. PET imaging of the brain used a Siemens Biograph Vision PET/CT Scanner. White matter served as the reference region. Statistical modeling used one-way ANCOVA with one factor (Diagnosis) and one behavioral covariate (CAPS-5). Voxel-wise, whole-brain statistical analyses were completed within Statistical Parametric Mapping software. Significance was set to $p_{\text{uncorr}} < 0.01$ for a-priori hypothesized brain regions (PFC, OFC, amygdala,

hippocampus) and $p_{\text{uncorr}} < 0.005$ for other regions. Wholebrain voxelwise analyses revealed significantly lower AMPAR binding potential in PTSD relative to controls within the bilateral middle cingulate cortex. Left MCC: $T_{17} = 2.93$, $p < 0.005$; Right MCC: $T_{17} = 2.95$, $p < 0.004$. Within the PTSD group, ACC AMPAR BPND was strongly negatively correlated with symptom severity, such that lower receptor availability predicted higher CAPS-5 scores: $T_8 = 5.02$, $r = -0.87$, $p < 0.0005$. No significant group differences or correlations emerged in other a priori ROIs. This pilot study provides the first PET-based evidence that cingulate AMPA receptor availability is reduced in women with chronic PTSD, aligning with preclinical models implicating disrupted excitatory synaptic plasticity in fear-learning circuits. The robust association between ACC AMPAR BPND and symptom severity suggests that AMPAR-mediated signaling may be a mechanistic contributor to core PTSD pathology and a potential biomarker for treatment response. Preliminary evidence of reduced ACC AMPAR BPND in PTSD helps to advance translation of animal models of fear response learning. Larger, mixed-sex, and longitudinal studies are needed to establish causal relationships, evaluate treatment sensitivity (e.g., ketamine, AMPAR PAMs), and determine whether AMPAR PET imaging can guide patient-specific therapeutic strategies.

Learning Objective 1: Understand the need for glutamate based clinical targets related to PTSD pathophysiology

Learning Objective 2: Understand how PET imaging can be used to study the molecular mechanisms of clinical symptoms

Literature References:: Miyazaki T, Nakajima W, Hatano M, Shibata Y, Kuroki Y, Arisawa T, Serizawa A, Sano A, Kogami S, Yamanoue T, Kimura K, Hirata Y, Takada Y, Ishiwata Y, Sonoda M, Tokunaga M, Seki C, Nagai Y, Minamimoto T, Kawamura K, Zhang MR, Ikegaya N, Iwasaki M, Kunii N, Kimura Y, Yamashita F, Taguri M, Tani H, Nagai N, Koizumi T, Nakajima S, Mimura M, Yuzaki M, Kato H, Higuchi M, Uchida H, Takahashi T. Visualization of AMPA receptors in living human brain with positron emission tomography. *Nat Med.* 2020 Feb;26(2):281-288. doi: 10.1038/s41591-019-0723-9. Epub 2020 Jan 20. PMID: 31959988.

Nair J, Singh Ajit S. The role of the glutamatergic system in posttraumatic stress disorder. *CNS Spectr.* 2008 Jul;13(7):585-91. doi: 10.1017/s1092852900016862. PMID: 18622363.

DURABILITY OF TMS TREATMENT FOR VETERANS WITH MDD EXAMINED VIA SIGNIFICANT PSYCHIATRIC EVENTS ASSOCIATED WITH RELAPSE (SPEAR): A PROPOSED NEW COMPOSITE OUTCOME MEASURE FOR HIGH SEVERITY/LOW FREQUENCY MENTAL HEALTH EVENTS

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Zachary Zuschlag, James A. Haley Veterans Hospital

Abstract Background: Transcranial Magnetic Stimulation (TMS) has established efficacy for treatment resistant major depressive disorder (MDD-TR), however, the durability of response to this treatment intervention is an area in need of further investigation particularly in the Veteran population. Historically, TMS durability has been examined utilizing

measurement based care (MBC) mental health assessment scale scores given at pre-determined time points which allows calculations of durability based on relapse utilizing numerical threshold scores. Although this approach has been the standard for research purposes and allows systematic monitoring with high reproducibility, MBC scales often have poor or limited known correlations to clinically relevant relapse events such as hospitalizations and suicide. Subsequently, the authors developed a new composite marker termed Significant Psychiatric Events Associated with Relapse (SPEAR) consisting of mental health hospitalization, suicide attempt, death by suicide, or requirement for additional neuromodulation interventions; a clinically relevant aggregate marker that represents events that are highly impactful to patients and to health care systems, and may be a more important and accurate marker of true psychiatric relapse. This research report will review data from the national VA Clinical TMS Program looking at TMS durability for MDD utilizing traditional MBC methodology, then will present results from a study analyzing TMS durability utilizing SPEAR criteria.

Methods: A longitudinal retrospective cohort analysis was conducted on all Veterans receiving TMS treatment for MDD at a large academic VA medical center from November 1, 2013, through December 31, 2021. For the primary endpoint, the composite measure SPEAR was utilized to assess relapse. Secondary endpoints included examining post-TMS changes in psychopharmacological regimens as a marker for relapse. Data collected included demographic information, psychiatric history, and psychiatric treatment. Medication data was captured and reported by class. MADRS was used to determine response to treatment. Durability was examined at the 3-month, 6-month, one year and two years post TMS treatment timepoints for primary and secondary outcomes. Associations between covariates of interest and durability of response were analyzed.

Results: Study cohort consisted of 217 Veterans, of whom 159 had the required assessments and were included in analyses. TMS was shown to be a durable treatment for MDD with durability rates of 96.18% at 90 days post treatment, 92.37% at 180 days, 87.79% at one year, and 84.73% at two years when utilizing SPEAR criteria. Durability rates based on pharmacological medication changes were 72.52% at 90 days, 59.54% at 180 days, 44.25% at 1 year, and 35.38% at 2 years. Associations between covariates of interest and durability rates as per SPEAR criteria were analyzed utilizing univariate survival analyses. On initial analysis, prior course of TMS, prior course of ECT, and SSRI at the time of treatment were all associated with differences in durability rates. However, these were no longer significant after adjusting for multiple comparisons.

Conclusions: TMS is a durable treatment for Veterans with MDD with 84.73% of Veterans having at least a 2-year period without significant relapse as defined by SPEAR. No covariates analyzed were associated with differences in TMS durability. Prospective studies analyzing different markers of relapse and larger sample sizes are needed. Further studies are also warranted to assess the utility of SPEAR as a composite measure to capture high severity/low frequency mental health events associated with relapse.

Learning Objective 1: Understand SPEAR (Significant Psychiatry Events Associated with Relapse), a proposed new composite end point to capture high severity/low frequency mental health events

Learning Objective 2: Describe differences between SPEAR and traditional measures of relapse and compare durability rates between approaches

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) Lisha I, Godbole Kroger NB, Tsalatsanis A, Norred MA, Daneman LEW, Tindall B, Grewal EP, Araque SM, Zuschlag ZD. The durability of response to transcranial magnetic stimulation in veterans with major depressive disorder. *J Affect Disord.* 2025 Dec 27;399:121032. doi: 10.1016/j.jad.2025.121032. Epub ahead of print. PMID: 41461238.

IS BRAIN INSULIN ACTION IMPLICATED IN THE BIOLOGY OF DEPRESSION? A PILOT NEUROIMAGING STUDY IN ADOLESCENTS

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Abstract: Depression is associated with metabolic dysfunction including insulin resistance, while insulin resistance is associated with greater depression severity and worse cognition. This bidirectional relationship has encouraged a reconceptualization of depression as a metabolic disorder, with brain insulin action implicated as a unifying mechanism. This has not been studied directly in humans. The aim of this study was to examine if brain insulin action is implicated in the biology of depression in adolescents.

Methods: Twelve patients with depression, 14-18 years of age, and twelve age-, sex-, and BMI-matched healthy controls were recruited for this single-blinded crossover pilot study. To quantify insulin action in the brain, resting state function MRI (rs-fMRI) scans were performed twice: the first following intranasal placebo (INP) and the second following intranasal insulin (INI) challenge (80 IU). This protocol leverages the property of INI to induce changes in resting-state functional connectivity (rsFC) in the brain. The difference in changes induced by INI compared to that with INP were used as an index of insulin action, since any difference observed between treatments during this controlled manipulation is likely to be due to INI. Absence or reduction in the magnitude of change was interpreted as impaired brain insulin action. Cognitive function and depression severity were also assessed. For cases, clinical assessments were repeated after six months to study the short-term effects of brain insulin action. Two-way repeated measures ANOVA was conducted to assess the main effect of treatment (INI vs. INP) as within-subject factor, the participant group (Cases vs. Controls) as between-subject factor, and their interaction on whole-brain ROI-to-ROI connectivity. Statistically significant connections were identified using a whole-brain false discovery rate (FDR) corrected p-value < 0.05, controlling for multiple comparisons. Post hoc pairwise comparisons were performed. Correlations between insulin-induced changes in rsFC with depression severity and cognition were assessed using multiple regressions. Age, sex, and BMI were controlled for in analyses.

Results: A significant Group × Condition interaction effect was identified for INI > INP, Controls > Cases contrast. Only controls, and not cases, exhibited a significant increase in rsFC in response to INI vs. INP between the following brain regions: 1) the left Hippocampus left and Occipital Fusiform Gyrus (OFusG-l); 2) right Parahippocampal Gyrus, anterior

division (aPaHc-r) and left Temporal Pole ($F = 19.3$, $p < 0.001$); and 3) aPaHC-r and right Temporal Fusiform Cortex, anterior division (aTFusCr) ($F = 17.5$, $p < 0.001$). At baseline, subjective cognitive performance was positively associated with changes in connectivity between the aPaHC-r and TP-l ($\beta = 0.571$, $p = 0.004$); and aPaHC-r and aTFusC-r ($\beta = 0.453$, $p = 0.026$). In longitudinal analyses, cases with less increase in rsFC between the TP-l and aPaHc-r in response to INI vs. INP at baseline exhibited greater depression severity after 6 months ($\beta = -0.62$, $p = 0.031$).

Conclusions: Demonstrating disrupted brain insulin action can provide novel insights into poorly understood mechanisms underlying the relationship between depression and metabolic dysfunction. Evidence of impaired brain insulin action early in the course of illness may provide us with a modifiable risk factor that can be targeted using insulin sensitizers as an early intervention.

Learning Objective 1: Insulin action in the brain may be disrupted in individuals with depressive disorders.

Learning Objective 2: Insulin action in the brain may predict long-term clinical outcomes, such as depression severity.

Literature References:

1) Kullmann S, Heni M, Hallschmid M, Fritsche A, Preissl H, Häring HU. Brain Insulin Resistance at the Crossroads of Metabolic and Cognitive Disorders in Humans. *Physiol Rev.* 2016 Oct;96(4):1169-209.

2) Kullmann S, Heni M, Veit R, Scheffler K, Machann J, Häring HU, Fritsche A, Preissl H. Intranasal insulin enhances brain functional connectivity mediating the relationship between adiposity and subjective feeling of hunger. *Sci Rep.* 2017 May 9;7(1):1627.

SEMAGLUTIDE IMPROVES HEALTH-RELATED QUALITY OF LIFE IN MAJOR DEPRESSIVE DISORDER INDEPENDENT OF MOOD CHANGE: EVIDENCE FOR METABOLIC AND MOTIVATIONAL PATHWAYS

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Cristian-Daniel Llach Lopez, University of Toronto

Abstract Background: Health-related quality of life (HRQoL) and motivation are core determinants of functional recovery in major depressive disorder (MDD), yet they remain insufficiently addressed by existing antidepressant treatments. Patients frequently report persistent impairments in motivation, vitality, and day-to-day functioning even when mood symptoms improve, underscoring the need for interventions that target broader dimensions of well-being. Glucagon-like peptide-1 receptor agonists (GLP-1RAs) improve metabolic health, reward behavior, and HRQoL in obesity and diabetes, raising the possibility that they may influence motivational and functional outcomes in MDD. However, no randomized controlled trial has evaluated the effects of a GLP-1RA on HRQoL, effort-based motivation, or reward behavior in MDD.

Purpose: The objective of this analysis was to determine whether adjunctive semaglutide improves HRQoL in adults with MDD, and to test whether motivational and/or metabolic pathways help explain these effects. This trial therefore aimed to evaluate semaglutide's potential as a mechanistically novel, patient-centered intervention targeting domains of functioning not captured by conventional antidepressant endpoints.

Methods: This secondary analysis evaluated data from a 16-week, double-blind, placebo-controlled trial of adjunctive oral semaglutide in adults with MDD, cognitive dysfunction, and overweight/obesity. Participants continued stable antidepressant therapy. HRQoL (SF-36), depressive symptoms (HAMD-17), cognition, metabolic markers (HbA1c, fasting glucose, HOMA2-IR), and reward-related motivation (Effort Expenditure for Rewards Task; EEfRT) were assessed from baseline to week 20. Generalized estimating equations tested longitudinal effects, and moderation/mediation analyses evaluated motivational and metabolic pathways.

Results: Seventy-two participants were randomized (semaglutide $n=35$; placebo $n=37$), with 75% completing week 16. At baseline, lower HRQoL correlated with greater depressive severity, higher BMI and insulin resistance, and poorer cognitive performance. Semaglutide produced significantly greater HRQoL improvement than placebo (Treatment $\times$ Time $p=0.027$), with an adjusted +11.8-point gain at week 16 versus +4.0 points for placebo ($p=0.015$), exceeding minimal clinically important differences. Improvements were independent of changes in depressive symptoms or weight, indicating a distinct therapeutic signal. Reductions in effort discounting significantly moderated semaglutide's HRQoL effect ($p=0.039$), explaining ~19% of within-group variance. These findings support the interpretation that semaglutide may reduce the perceived effort required for daily activities, improving role fulfillment and functional engagement. Mediation analysis showed that reductions in HbA1c partially mediated HRQoL gains (indirect effect = 5.20, 95% CI 0.71–11.25). This suggests that improvements in chronic glycemic exposure, even within a non-diabetic range, may enhance subjective well-being and vitality.

Conclusions: Adjunctive semaglutide significantly improved HRQoL in adults with MDD and cognitive dysfunction through convergent motivational and metabolic mechanisms. These benefits occurred independently of mood improvement, underscoring therapeutic domains not targeted by conventional antidepressants. Semaglutide may address aspects of day-to-day functioning that are central to recovery and highly valued by patients. This study provides first-in-human evidence supporting GLP-1RAs as mechanistically novel, patient-centered interventions for improving quality of life in mood disorders.

Learning Objective 1: Understand how insulin and glucose metabolism influence neurobiology, physical health, and overall HRQoL in MDD, and how GLP-1 receptor agonists may shape the functional course of depression through these pathways.

Learning Objective 2: Recognize why health-related quality of life (HRQoL) is an essential outcome to measure in future clinical trials and how it captures dimensions of recovery beyond traditional symptom-based endpoints.

Literature References: Badulescu S, Gill H, Shah H, et al. Semaglutide for the treatment of cognitive dysfunction in major depressive disorder: A randomized clinical trial. *Med.* Published online November 2025;100916. doi:10.1016/J.MEDJ.2025.100916

Mansur RB, Ahmed J, Cha DS, et al. Liraglutide promotes improvements in objective measures of cognitive dysfunction in individuals with mood disorders: A pilot, open-label study. *J Affect Disord.* 2017;207:114-120. doi:10.1016/J.JAD.2016.09.056

7:00 p.m. - 8:30 p.m.

Satellite Symposium: Moving Beyond Sleep: The Broader Connection Between the Orexin System and Psychiatric Disorders

MOVING BEYOND SLEEP: THE BROADER CONNECTION BETWEEN THE OREXIN SYSTEM AND PSYCHIATRIC DISORDERS

Emmanuel Mignot, Stanford University School of Medicine

Roger McIntyre, University of Toronto

Overall Abstract: In clinical practice, sleep and psychiatric disorders are still treated as entirely separate issues, leaving the essential biology of both conditions unaddressed. This causes patients to become trapped in ongoing cycles of relapse. In reality, there are multiple factors that continually work together and worsen patient quality of life and outcomes, including the neglected orexin-driven arousal mechanisms, abnormalities in REM sleep structure and architecture, the low use of validated screening tools, and the incomplete differential diagnoses for hypersomnia. Our symposium will help improve clinicians' understanding of the biological link between sleep regulation and mood dysregulation, better known as the orexin system, to support a shift from fragmented, symptom-based management to integrated, mechanism-driven care.

Learning Objective 1: Understand the orexin-mediated mechanisms of arousal, REM regulation, and reward, and how these pathways influence co-occurring sleep disturbances and psychiatric disorders

Learning Objective 2: Evaluate the clinical trial data surrounding safety, efficacy, and adverse event monitoring of new and emerging orexin receptor antagonists

Literature References: Vasudeva S, Wong S, Le GH, Dri CE, Teopiz KM, Ho R, Rhee TG, McIntyre RS. Efficacy and safety profiles of FDA-approved dual orexin receptor antagonists in depression: A systematic review of pre-clinical and clinical studies. *J Psychiatr Res.* 2025 Nov;191:752-769. doi: 10.1016/j.jpsychires.2025.10.001. Epub 2025 Oct 10. PMID: 41109037.

Holguin G, Martin-Fardon R. Modulatory effects of orexin and dynorphin on stress-related alcohol seeking and relapse: pivotal role of the posterior paraventricular nucleus of the thalamus. *Front Pharmacol.* 2026 Jan 26;17:1729040. doi: 10.3389/fphar.2026.1729040. PMID: 41669681; PMCID: PMC12883789.

Thursday, May 28, 2026

6:30 a.m. - 8:00 a.m.

Satellite Symposium: Incorporating Novel Muscarinic Agents for Schizophrenia Into Clinical Practice: Overcoming Clinical Inertia

INCORPORATING NOVEL MUSCARINIC AGENTS FOR SCHIZOPHRENIA INTO CLINICAL PRACTICE: OVERCOMING CLINICAL INERTIA

Jose Rubio, Northwell Health

Sunny Tang, Zucker School of Medicine at Hofstra/Northwell

Megan Good, Beth Israel Deaconess Medical Center

Overall Abstract: This symposium highlights muscarinic antipsychotic therapies for schizophrenia, placing in focus their non-dopaminergic mechanism of action. Topics include the emerging scientific evidence and clinical trial data supporting muscarinic receptor modulation and its role in symptom management. Practical considerations for clinical adoption are also on tap, including how to identify appropriate patients, transition from D2 receptor–blocking agents, and approach titration. Attention then turns to recognizing and managing adverse effects associated with this class. On the whole, this session focuses on translating the latest evidence into practical strategies that can help clinicians confidently integrate these therapies into individualized care for patients with schizophrenia.

Learning Objective 1: Compare muscarinic and dopaminergic pathophysiology and therapeutic mechanisms of action in schizophrenia

Learning Objective 2: Evaluate clinical limitations of D2 receptor–blocking agents in support of muscarinic therapy adoption for patients with schizophrenia

Literature References: Schneider-Thoma J, Zhu Y, Qin M, Dong Y, Guan S, Wang J, Tian J, Lin X, Rodolico A, Siafis S, Bighelli I, Wehner M, Veith C, Kraye F, Scheuring E, Davis JM, Priller J, Nikolakopoulou A, Salanti G, Li C, Leucht S. Comparative efficacy and tolerability of antidopaminergic and muscarinic antipsychotics for acute schizophrenia: a network meta-analysis of randomised controlled trials indexed in international English and Chinese databases. *Lancet*. 2026 Feb 28;407(10531):876-891. doi: 10.1016/S0140-6736(25)02365-7. PMID: 41763745

Kaul I, Claxton A, Sauder C, Patel T, Chaturvedi S, Brown D, Zhu H, Marcus R, Sawchak S, Brannan SK. Long-Term Safety and Efficacy of Xanomeline and Trospium Chloride in Schizophrenia: A 52-Week Open-Label Extension Trial. *Am J Psychiatry*. 2026 Mar 1;183(3):183-192. doi: 10.1176/appi.ajp.20241186. Epub 2026 Feb 4. PMID: 41634905

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

Keynote Plenary: AI Beyond Evil Robots: Ensuring Transformative Means Better

AI BEYOND EVIL ROBOTS: ENSURING TRANSFORMATIVE MEANS BETTER

Tiffany Farchione, US Food and Drug Administration

Roy Perlis, Massachusetts General Hospital

Overall Abstract: The rapid development of modern machine learning methods, and accelerating adoption across medicine, promises to transform the practice of psychiatry as well. This presentation will review some of the less-appreciated promise of these technologies, including clinical decision support, biomarker development, treatment discovery, and delivery of evidence-based psychotherapies. It will also consider the challenges, most notably their potential to adversely impact mental health at the individual and population level. It will emphasize ways in which changes across medicine may have implications for mental health care as well. Finally, the presentation will suggest strategies

that may help to ensure that applications of AI maximize the ability of psychiatrists and other clinicians to deliver high-quality care at scale.

Learning Objective 1: Understand ways in which artificial intelligence may enhance care delivery in psychiatry

Learning Objective 2: Describe potential adverse consequences of increased use of AI in terms of public health as well as individual mental health care.

Literature References: Perlis RH, Differences in psychiatric documentation and management in primary care with artificial intelligence scribe use, JAMA Psychiatry, in press.

Perlis RH, Artificial Intelligence can transform mental health, but not necessarily for the better, JAMA Psychiatry, in press.

9:30 a.m. - 11:30 a.m.

Update from Federal and Other Funding Agencies Plenary

UPDATE FROM FEDERAL AND OTHER FUNDING AGENCIES

Anita Clayton, University of Virginia SOM

Overall Abstract: Continuing with long-standing tradition, this is the much-anticipated 2026 Update From Federal and Other Funding Agencies Plenary. Alphabet soup never tasted so good! Hear updates from NIMH, NIAAA, PCORI, NIDA, DHA, and the VA.

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. Approximately 27.9 million (10%) Americans are diagnosed with AUD each year, resulting in over 178,000 deaths from alcohol-related causes. Alcohol misuse costs American society more than \$249 billion annually. To date, the Food and Drug Administration (FDA) has approved three medications for AUD treatment: disulfiram, acamprosate, and naltrexone, which is available in both oral and long-acting injectable formulations. In addition, several other repurposed compounds have shown efficacy for treating AUD, including nalmefene, baclofen, topiramate, gabapentin, and varenicline. 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: Soyka M, Rösner S. Modern pharmacotherapy guidance for treating alcohol use disorders. *Expert Opin Pharmacother*. 2025 Feb;26(2):147-156. doi: 10.1080/14656566.2024.2445734. Epub 2024 Dec 30. PMID: 39702947.

Litten RZ, Falk DE, Ryan ML, Fertig J, Leggio L. Five priority areas for improving medications development for alcohol use disorder and promoting their routine use in clinical practice. *Alcohol Clin Exp Res*. 2020 Jan;44(1):23-35. doi: 10.1111/acer.14233. Epub 2019 Dec 5. PMID: 31803968.

PATIENT-CENTERED COMPARATIVE EFFECTIVENESS RESEARCH

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

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

Learning 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.

ADVANCING THERAPEUTICS FOR SUBSTANCE USE DISORDERS THROUGH NIDA'S THERAPEUTICS DEVELOPMENT PROGRAM

Ivan Montoya, DHHS/National Institute on Drug Abuse

Abstract: The National Institute on Drug Abuse (NIDA) supports and conducts the research and development of safe and effective therapeutics for Substance Use Disorders (SUDs). These efforts span a broad range of intervention modalities, including pharmacotherapies (small molecules and biologics), therapeutic devices, digital therapeutics, and behavioral interventions.

NIDA's Therapeutics Development Program (TDP) funds a diverse portfolio of preclinical and clinical research projects, encompassing the full development continuum—from identification and optimization of lead compounds, through IND-enabling studies and IND submission, to all phases of clinical trials, including Phase III. The overarching goal of the TDP is to advance promising therapeutics toward U.S. Food and Drug Administration (FDA) approval or acceptance and implementation in clinical practice. The program supports research through both grants and contracts, with the majority of funding provided via cooperative agreement grants. These funding mechanisms are open to for-profit and non-profit organizations at both national and international levels, fostering broad collaboration across sectors. This presentation will provide an overview of the NIDA Therapeutics Development Program and highlight the current pipeline of medications and other therapeutic approaches under investigation for the treatment of SUDs and overdose. Information on current funding opportunities for therapeutics development at NIDA is available at: <https://nida.nih.gov/about-nida/organization/divisions/division-therapeutics-medical-consequences-dtmc/research-programs#PDP>

Learning Objective 1: Describe the scope and structure of the NIDA Therapeutics Development Program for SUDs, including opioid, cocaine, methamphetamine, and cannabis use disorders.

Learning Objective 2: Identify key medications and other therapeutic approaches currently in the development pipeline for the treatment of SUDs and overdose.

Literature References: Montoya ID, Volkow ND. IUPHAR Review: 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.

Sawyer-Morris G, Ulukaya M, Kushmerick-McCune B, Clark KJ, Bruce J, Gatzke S, Walters ST, Taxman FS. Advancing research translation in addiction and pain: A portfolio analysis of the NIH HEAL initiative. *J Clin Transl Sci.* 2025 Apr 14;9(1):e92. doi: 10.1017/cts.2025.68. PMID: 40395395; PMCID: PMC12089859.

UPDATE FROM DEFENSE HEALTH AGENCY PSYCHOLOGICAL HEALTH RESEARCH PORTFOLIO

Fuad Issa, Defense Health Agency

Abstract: Congress allocated \$15 million to Defense Health Agency (DHA) to fund medical research to support military families. It directed DHA to collaborate with institutions of higher education, Federal agencies, and non-profit entities. Six areas of interest were identified: Adverse Childhood Events, Menopause and Midlife Women's Health, Medical Barriers to Growing and Supporting Families, Gender-Specific Health Care, Mental and Behavioral Health, and Substance Use Disorders. This presentation will describe how DHA proceeded with identifying needs and developing a plan for awarding grants to meet the above mandate.

Learning Objective 1: Identify the countermeasures for military community needs and vulnerabilities

Learning Objective 2: Define models of care for efficient and tailored interventions

Literature References: - Awada SR, Song SJ. Children Associated with Armed Forces and Armed Groups: Understanding and Addressing Mental Health Needs. *Psychiatry.* 2025 Fall;88(3):192-206.

- Liu JJW, Nazarov A, Ein N, et al. Treating Posttraumatic Stress Disorder in Military Populations: A Meta-Analysis. *J Clin Psychiatry*. 2025 Mar 24;86(2):24r15571.

UPDATES FROM VETERAN HEALTH ADMINISTRATION (VA) RESEARCH INITIATIVES

Lori Davis, Veterans Affairs Medical Center

Abstract: For 100 years, the Veterans Health Administration (VHA) has been at the forefront of biomedical and behavioral health research, generating discoveries that have transformed the care not only of Veterans but of the broader American public. This presentation provides an update on current VHA research priorities in psychiatry, psychopharmacology, suicide prevention and substance use disorders. The VHA operates one of the largest integrated healthcare research enterprises in the world, serving over 9.1 million enrolled Veterans across 170 medical centers and more than 1,190 outpatient clinics. Mental health conditions—including PTSD, major depression, bipolar disorder, schizophrenia, and substance use disorders—represent among the most prevalent and clinically challenging conditions in this population. Approximately 2.8 million Veterans, representing 14 percent of the total U.S. Veteran population, reported at least one substance use disorder in the past year, underscoring the urgency of continued research investment. This talk will highlight key VHA research infrastructure, including the Mental Illness Research, Education and Clinical Centers (MIRECCs), the PTSD Psychopharmacology Initiative, collaborations with the Department of Defense, and Health Systems Research and Development programs targeting implementation of evidence-based treatments. Emerging areas, including novel pharmacotherapies for PTSD, psychedelic compounds, and opioid safety initiatives, will be discussed. Attendees will gain a current perspective on how this century-old federal research enterprise continues to shape psychiatric practice and CNS drug development.

Learning Objective 1: The participant will be able to broadly describe the current research initiatives supported by the VA on topics of understanding and treating mental health conditions and substance use disorders.

Learning Objective 2: The participant will gain an understanding of the VA research portfolio and mechanism of funding opportunities.

Literature References: Hoffmire CA, Denneson LM, Monteith LL, et al. Accelerating Research on Suicide Risk and Prevention in Women Veterans Through Research-Operations Partnerships. *Med Care*. 2021;59:S11-S16. doi:10.1097/MLR.0000000000001432

Woodward EN, Oliver KA, Drummond KL, et al. Transitioning an implementation research intervention to a sustained clinical service: Telehealth primary care mental health integration implementation in Veterans Health Administration. *Psychol Serv*. 2025;22(4):641-654. doi:10.1037/ser0000903

NIMH UPDATE

Matthew Rudorfer, National Institutes of Health/NIMH

Abstract: In 1946, President Harry S. Truman signed the National Mental Health Act, enabling the founding, three years later, of the National Institute of Mental Health (NIMH). Now one of 27 Institutes and Centers that constitute the National Institutes of Health (NIH),

part of the U.S. Department of Health and Human Services (HHS), the mission of NIMH is to transform the understanding and treatment of mental illnesses through basic and clinical research, paving the way for prevention, recovery, and cure. For the past year, NIMH has been led by Acting Director Andrea Beckel-Mitchener, Ph.D., while a national search for a permanent director is underway. To fulfill its vital public health mission, the Institute is guided by its Strategic Plan for Research, a roadmap for the Institute's priorities, outlining four major goals: Define the brain mechanisms underlying complex behavior, including genomics; examine mental illness trajectories across the lifespan to determine when, where, and how to intervene; strive for prevention and cures, optimizing and personalizing preventive and therapeutic interventions; and advance mental health services to strengthen public health. Over 10% of the NIMH budget supports the intramural research program on the NIH campus in Bethesda, Maryland, site of cutting-edge basic and clinical research, ranging from early-phase treatment development, such as breakthrough studies with intravenous ketamine for severe depression, to genomics and advanced brain imaging. Most NIMH support is directed to universities, research institutions, and small business, for largely investigator-initiated studies, with an overarching goal of transforming research into real-world care. Translational research expanding the contribution of Research Domain Criteria (RDoC) and biomarker development are encouraged, and the experimental therapeutics approach, studying mediators of treatment response, is required in all clinical trials applying for NIMH support. Suicide prevention research remains a priority, including studies of rapidly-acting interventions, including ketamine and potentially other classical and novel treatments. Consistent with the recent ASCP consensus statement on the subject, deprescribing is a growing area of interest to NIMH, given the host of questions in need of systemic research, including the potential role of nonpharmacologic interventions before, during, and after deprescribing, in the interest of reducing inappropriate or excessive medication use. Another priority area is the treatment of first-episode psychosis, led by the Early Psychosis Intervention Network (EPINET), a learning health care system aimed at enhancing coordinated specialty care to improve early identification, diagnosis, clinical assessment, intervention effectiveness, service delivery, and health outcomes for individuals with early psychosis. EPINET now has 8 regional scientific hubs and has enrolled approximately 4,000 participants from more than 100 clinics across 17 states, promoting early intervention and conducting effectiveness research, while making the EPINET Core Assessment Battery available to all early psychosis care clinicians to assess key domains of early psychosis, treatment, and recovery.

Learning Objective 1: At the conclusion of this presentation, attendees will appreciate the four goals of the NIMH Strategic Plan.

Learning Objective 2: At the conclusion of this presentation, attendees will gain an understanding of role of the EPINET project in promoting early identification and coordinated specialty care in the treatment of individuals with early psychosis.

Literature References: George P, Spark TL, Devora A, et al. Structural characteristics of Early Psychosis Intervention Network (EPINET) programs. *Psychiatr Serv.* 2026; Online ahead of print.

doi:10.1176/appi.ps.20250320.

Morris SE, Sanislow CA, Pacheco J, et al. Revisiting the seven pillars of RDoC. *BMC Medicine.* 2022;20(1):220.

1:15 p.m. - 2:45 p.m.

Workshops

***^DURABILITY OUTCOMES IN TREATMENT RESISTANT DEPRESSION**

Scott Aaronson, Sheppard Pratt

Overall Abstract: In major depressive disorder, treatment resistance is associated with reduced probability of achieving short-term benefit from sequential antidepressant interventions and increased probability of relapse if short-term benefit is achieved. This workshop will review existing data and present new findings regarding the durability of benefit of 4 novel interventions for treatment-resistant depression (TRD): transcranial magnetic stimulation (TMS), (es)ketamine (KET), vagus nerve stimulation (VNS) and psychedelics. Dr. Wilson will review existing data on the durability of benefit following response to TMS including new information on frequency, timing and retreatment outcomes in patients who relapsed after responding or remitting in their index TMS course. Dr. Rosenblat will review evidence on the durability of antidepressant response to KET, both with KET discontinuation and as a maintenance strategy. He will present new findings from an extensive database from his program. Dr. Conway will review evidence regarding durability of benefit with VNS and present new findings from the RECOVER trial on clinical outcomes after 2 years of active VNS plus treatment as usual. The findings address durability and late emergence of benefit for symptom severity, daily function, and quality-of-life outcomes. Dr. Suppes will address recent findings for durability of response to psychedelics with a focus on her study in Veterans. To our knowledge, the durability of benefit of treatments for TRD has never been the topic of a scientific symposium at any meeting. Indeed, much attention has focused on the impact of these interventions on the likelihood of short-term response and remission, despite the fact that treatment resistance is strongly linked to risk of relapse. This symposium will address a critical clinical challenge and population-based need, namely optimal long-term care in TRD. By addressing the timing and predictors of relapse/recurrence, this symposium will have implications for mechanistic issues regarding neuroplastic processes that may contribute to sustained benefit.

Learning Objective 1: Participants will be able to identify best practices to capture durability outcomes in treatment resistant depression.

Learning Objective 2: Participants will be able to cite three reasons why durability is key to adopting novel interventions in treatment resistant depression.

Literary References: Conway CR, Rush AJ, Gordon C, Preskorn SH, Sackeim HA, Aaronson ST, McIntyre RS, Lee YL, Shy O, Tran Q, Way J, Bunker MT. An examination of symptoms, function and quality of life as conjoint clinical outcome domains for treatment-resistant depression. *J Mood Anxiety Disord.* 2025 Apr 14;10:100121. doi: 10.1016/j.xjmad.2025.100121. PMID: 40657595; PMCID: PMC12243987.

Ellis S, Bostian C, Donnelly A, Feng W, Eisen K, Lean M, Conlan E, Ostacher M, Aaronson S, Suppes T. Long-term outcomes of single-dose psilocybin for U.S. military Veterans with severe treatment-resistant depression - 12-month data from an open-label pilot study. *J Affect Disord.* 2025 Nov 15;389:119655. doi: 10.1016/j.jad.2025.119655. Epub 2025 Jun 9. PMID: 40499827.

TRANSCRANIAL MAGNETIC STIMULATION: DURABILITY OF ANTI-DEPRESSANT RESPONSE

Saydra Wilson, The University of Minnesota

Individual Abstract: This presentation will summarize a review of the literature outlining the long-term durability of the antidepressant effects of transcranial magnetic stimulation (TMS). Durability data out to 12 months will be discussed for standard TMS protocols. Strategies for relapse prevention including preservation/maintenance TMS and psychopharmacology will be discussed. Additionally, the current level of evidence for the durability of accelerated TMS protocols will be reviewed. The proposed talk will provide a necessary overview of TMS durability and allow for the learner to compare and contrast with other interventions for treatment resistant depression. The talk updates the state of the field for evidence based relapse prevention strategies.

Literature References: Noda, Y., Wada, M., Mimura, Y., Taniguchi, K., Tarumi, R., Moriyama, S., ... and Nakajima, S. Repetitive Transcranial Magnetic Stimulation as Maintenance Treatment of Depression: The MAINT-R Randomized Clinical Trial. *JAMA Network Open*. 2025; 8(6), e2515881-e2515881.

Matsuda, Y., Sakuma, K., Kishi, T., Esaki, K., Kito, S., Shigeta, M., and Iwata, N. Repetitive transcranial magnetic stimulation for preventing relapse in antidepressant treatment-resistant depression: A systematic review and meta-analysis of randomized controlled trials. *Brain Stimulation: Basic, Translational, and Clinical Research in Neuromodulation*. 2023; 16(2), 458-461.

Wilson, S., Croarkin, P. E., Aaronson, S. T., Carpenter, L. L., Cochran, M., Stultz, D. J., and Kozel, F. A. Systematic review of preservation TMS that includes continuation, maintenance, relapse-prevention, and rescue TMS. *Journal of Affective Disorders*. 2022; 296, 79-88.

DURABILITY OF VAGUS NERVE STIMULATION TREATMENT-RESISTANT DEPRESSION: NEW, MORE COMPREHENSIVE FINDINGS FROM THE RECOVER TRIAL

Charles Conway, Washington University in St. Louis

Individual Abstract: Patients with markedly treatment-resistant major depression (TRD) have low likelihood of benefiting from antidepressant treatments and high likelihood of rapid relapse if benefit is obtained. Hence, in the management of markedly treatment-resistant MDD there are two very high thresholds to surmount: obtaining initial acute benefit and sustaining this benefit over time. Vagus Nerve Stimulation (VNS) of the left cervical vagus nerve, using a surgically-implanted pulse generator and electrical lead attached to the vagus nerve, received FDA approval for markedly TRD in 2005. Older studies of VNS demonstrated that patients with TRD who responded to VNS sustained response (60-70%). Subsequent studies using registry data also demonstrated high sustained antidepressant benefit.

Methods: The RECOVER VNS trial is the largest, prospective, device-based trial ever conducted in psychiatry, with 84 sites targeting 500 unipolar and 500 bipolar TRD participants. The goal of RECOVER is to characterize change in depressive symptoms, function, and quality of life (QoL) in a cohort of largely Medicare TRD patients. Here we report on the unipolar cohort, which has completed two years of the trial. Year one is triple-

blinded, with blinded, offsite raters, blinded on site raters, and the patients themselves blinded. After year one, all participants become open-label and all devices were activated.

The focus of this presentation is to report on the durability of benefits in those patients who were assigned to active VNS in year one total time spanning September 2019 to April 2025.

Participants: Adults with moderate-severe MDD with ≥ 4 failed antidepressant trials in the current episode, randomized to blinded, adjunctive VNS for 12 months, who subsequently received open-label, adjunctive VNS for 12 additional months (N=214).

Interventions: VNS and concomitant psychotropic medications and interventional psychiatric modalities (electroconvulsive therapy, transcranial magnetic stimulation, ketamine/esketamine) were characterized over the 12-month extension.

Main Outcomes and Measures: The durability of benefit achieved at 12 months was assessed at 18 and 24 months for depressive symptoms (3 scales), daily function, QoL, a tripartite composite of all 3 domains, and the Clinical Global Impression–Improvement (CGI-I) scale (overall improvement). Loss of benefit and relapse were assessed, along with the emergence of meaningful benefit in patients without benefit at 12 months. Substantial benefit (at least 50% symptom reduction from baseline; CGI-I of 1 or 2; tripartite with at least 2 of 3 subscales evidencing benefit) and meaningful benefit thresholds for symptoms (at least 30% reduction from baseline), function, QoL, CGI-I, and the tripartite measure were set a priori.

Results: Most patients with substantial benefit maintained their benefit (18-month median=78.8%; 24-month median=79.0% across 5 measures), as did patients with at least a meaningful benefit at 12 months (18-month median=83.1%; 24-month median=81.3% across 7 measures). Furthermore, many patients with no meaningful benefit at 12 months achieved it at 18 (median=30.6%) and 24 (median=37.8%) months. The strong maintenance of benefit was not accounted for by changes in psychotropic medications or interventional psychiatry modalities.

Conclusions and Relevance: Depressive symptom, daily function, and QoL benefits obtained after 12 months of adjunctive VNS were sustained in about 80% of patients continuing VNS. Approximately 30% with no meaningful benefit at 12 months accrued increased benefit over the subsequent year. These data add to the literature supporting the long-term durability of benefit of VNS in markedly TRD.

Literature References: McIntyre RS, Alsuwaidan M, Baune BT, et al. Treatment-resistant depression: definition, prevalence, detection, management, and investigational interventions. *World Psychiatry*. Oct 2023;22(3):394–412. doi:10.1002/wps.21120

Sackeim HA, Brannan SK, Rush AJ, George MS, Marangell LB, Allen J. Durability of antidepressant response to vagus nerve stimulation (VNS). *Int J Neuropsychopharmacol*. Dec 2007;10(6):817–26. doi:10.1017/S1461145706007425

BEYOND THE ACUTE COURSE: EXPLORING THE DURABILITY OF KETAMINE'S ANTIDEPRESSANT EFFECTS IN THE MAINTENANCE PHASE OF TREATMENT

Joshua Rosenblat, University of Toronto

Individual Abstract: The acute antidepressant effects of ketamine for treatment resistant depression (TRD) have been well established with rapid reductions in depressive symptom severity observed within hours of a single ketamine infusion. Earlier studies evaluated a

single infusion of ketamine and observed return of depressive symptoms within days to weeks of the single infusion. More recent studies employed an 'acute course' evaluating 4-8 doses over the course of 2-4 weeks. The acute course appeared to have greater antidepressant effects (compared to single dose studies), however, depressive symptoms were still observed to return within weeks of the last ketamine infusion. As such, the current standard of care for off label ketamine for depression typically employs a maintenance phase with 'booster' infusions administered every 2-8 weeks, with the frequency of booster infusions typically customized to individual patients based on the duration of benefits observed, which does appear to have significant variability between patients. A similar phenomenon is seen with nasal esketamine where an acute course consists of 8 doses over 4 weeks, with responders and remitters typically continuing on with maintenance treatments every 1-4 weeks for relapse-prevention. Indeed, phase 3 trials have demonstrated significant benefits for relapse prevention with continuing esketamine doses every 1-2 weeks compared to those stopping (ie randomized to placebo maintenance dosing) suggesting a role for maintenance treatment. Herein we will summarize the data on the durability of antidepressant effects of ketamine and esketamine, with a focus on maintenance ketamine and esketamine TRD studies. After providing an overview, we will present original data on TRD patients receiving maintenance ketamine infusions. We evaluated a cohort of 135 TRD patients (110 with major depressive disorder and 25 with bipolar depression), all of whom responded to an acute course of ketamine infusions and later received maintenance infusions. Linear mixed models found that depression and suicidality scores, as measured by the Quick Inventory of Depressive Symptomatology (QIDS-SR16) assessment, were significantly decreased after an acute course of ketamine infusions, with improvements persisting while patients continued to receive maintenance infusions over several months. Similar observations were seen after analyzing weekly patient-reported clinical global impression scores. Ketamine was determined to be relatively safe, with zero cases of suicidal behaviour and addiction behaviour throughout treatment. One patient diagnosed with bipolar I disorder underwent affective switching, with no further tolerability concerns following stabilization. These results provide preliminary support for the long-term clinical utility of maintenance ketamine infusions. Taken together, real world evidence supports the use of ketamine for relapse-prevention in the maintenance phase of treatment. Additionally, clinical trial evidence support the use of esketamine in the maintenance phase, demonstrating superiority above those switched to placebo after an acute response.

Literature References: Haikazian S, McIntyre RS, Meshkat S, Kratiuk K, Llach CD, Orsini DK, Di Luch SD, Rosenblat JD. Real world effectiveness of maintenance ketamine infusions for treatment-resistant depression in major depressive disorder and bipolar disorder. *Psychiatry Res.* 2025 Oct;352:116691. doi: 10.1016/j.psychres.2025.116691. Epub 2025 Aug 15. PMID: 40834563.

Zaki N, Chen LN, Lane R, Doherty T, Drevets WC, Morrison RL, Sanacora G, Wilkinson ST, Young AH, Lacerda ALT, Paik JW, Popova V, Fu DJ. Safety and efficacy with esketamine in treatment-resistant depression: long-term extension study. *Int J Neuropsychopharmacol.* 2025 Jun 6;28(6):pyaf027. doi: 10.1093/ijnp/pyaf027. PMID: 40319349; PMCID: PMC12143125.

HOW DURABLE ARE ACUTE EFFECTS OF PSILOCYBIN ON TREATMENT-RESISTANT DEPRESSION?

Trisha Suppes, Stanford University

Individual Abstract: Treatment resistant depression (TRD) affects a significant number of patients who experience major depression episodes. When patients experience TRD, even if responsive to treatment, the likelihood of relapse is greater. The use of psilocybin, often referred to as a classic psychedelic because of its action on serotonin receptors, has been studied for the treatment of depression and TRD in a number of pilot studies and more recently in Phase 2 studies with Phase 3 studies ongoing. While early results are promising, few studies have reported observations beyond the acute response to usually single-dose psilocybin treatment. Clinical trials of psilocybin for acute depression in smaller trials both controlled and open report striking acute response rates of 50% or greater response rates at primary outcome. The larger Phase 2 studies are less optimistic but still reporting significant positive impact for acute effects. By contrast few studies to date have followed up patients longer term with only two reporting six-month outcomes (Carhart-Harris et al., 2018; Erritzoe et al., 2024) and two reporting 12-month outcomes (Ellis et al., 2025; Goodwin et al., 2025). Early findings support that those who respond initially to psilocybin with diminished depression symptoms often show improvement in other domains such as anxiety and quality of life, however the persistence of response and remission does not necessarily extend over many months. During the workshop we will review studies on the long-term durability of depression response to psilocybin. We will focus on outcomes in mood as well as other domains such as quality of life.

Literature References: Ellis S, Bostian C, Donnelly A, Feng W, Eisen K, Lean M, Conlan E, Ostacher M, Aaronson S, Suppes

T. Long-term outcomes of single-dose psilocybin for U.S. military Veterans with severe treatment-resistant depression - 12-month data from an open-label pilot study. *J Affect Disord.* 2025 Nov 15;389:119655. doi: 10.1016/j.jad.2025.119655. Epub 2025 Jun 9. PMID: 40499827

Goodwin, G.M., Aaronson, S.T., Alvarez, O., Carhart-Harris, R., Chai-Rees, J., Croal, M., DeBattista, C., Dunlop, B.W., Feifel, D., Hellerstein, D.J., Husain, M.I., Kelly, J.R., Kirlic, N., Licht, R.W., Marwood, L., Meyer, T.D., Mistry, S., Nowakowska, A., P'aleníček, T., Repantis, D., Schoevers, R.A., Simmons, H., Somers, M., Teoh, E., Tsai, J., Wahba, M., Williams, S., Young, A.H., Young, M.B., Zisook, S., Malievskaia, E., 2025. The role of the psychedelic experience in psilocybin treatment for treatment-resistant depression. *J. Affect. Disord.* 372, 523–532. <https://doi.org/10.1016/j.jad.2024.12.061>.

***EVOLVING UNDERSTANDINGS OF PSYCHEDELICS IN CLINICAL RESEARCH**

Francisco Moreno, University of Arizona

Overall Abstract: Over the past 20 years, data from controlled clinical trials with a variety of psychedelic drugs have been collected from more than a thousand patients. While clinical endpoints are typically reported from these trials, little focus has been placed on data that inform the actual participant experience, non-pharmacological variables impacting outcomes, and logistics of administering these novel and highly psychoactive interventions in modern clinical environments. Practical matters like challenges for scalability and access may significantly affect how these compounds can be used in clinical settings. This workshop will cover unique therapeutic opportunities as well as challenges with group delivery formats and provide recommendations for future trials. Questions such as the role of active psychotherapy versus psychological support during psychedelic sessions remains a focus of interest.

Workshop content will include data and discussion on the comparison of evidence-based Trauma Focused Psychotherapy for PTSD vs psychological support in the context of psilocybin administration. Questions about what specific agents may be preferentially utilized in conditions such as PTSD due to the quality of their induced experience merits exploration. Data on the benefits of psilocybin for PTSD will be shared, as well as new data looking at participant-therapist interactions. While using psychological support during psychedelic sessions rather than a formal evidence-based psychotherapy approach, data related to therapeutic alliance and the effect of subjective patient experience during a Phase 2 Treatment Resistant Depression study will be shared and discussed. This workshop will include presentation of data and clinical experiences related to what happens in the setting of investigator-initiated research and large-scale clinical trials with psychedelic agents. Insights shared during the discussion could inform future research directions, and clinical implementation.

Learning Objective 1: Discuss the effects of non-pharmacological variables in quality of experience and clinical outcomes in clinical psychedelic research

Learning Objective 2: Review established understandings of psychedelic drug selection, and the added value of psychotherapy.

Literary References: Seybert C, Schimmers N, Silva L, Brecksema JJ, Veraart J, Bessa BS, d'Orsi D, Schoevers RA, Oliveira-Maia AJ. Quality of reporting on psychological interventions in psychedelic treatments: a systematic review. *Lancet Psychiatry*. 2025 Jan;12(1):54-66. doi: 10.1016/S2215-0366(24)00333-X. Epub 2024 Dec 9. PMID: 39667373.

Kittur ME, Burgos M LA, Jones BDM, Blumberger DM, Mulsant BH, Rosenblat JD, Husain MI. Mapping psilocybin therapy: A systematic review of therapeutic frameworks, adaptations, and standardization across contemporary clinical trials. *J Affect Disord*. 2025 Dec 15;391:119952. doi: 10.1016/j.jad.2025.119952. Epub 2025 Jul 18. PMID: 40684956.

UNDERSTANDING PSILOCYBIN ADMINISTRATION: DOSE, PARTICIPANT CHARACTERISTICS, AND THERAPEUTIC CONTEXT

Namik Kirlic, Compass Pathways

Individual Abstract Background: Psilocybin shows promise for treatment-resistant depression (TRD) and post-traumatic stress disorder (PTSD), yet the interplay between pharmacological dose, individual patient characteristics, and therapeutic context during psilocybin administration warrants ongoing research. Understanding these factors is critical for the scalable and accessible real-world delivery of psilocybin treatment.

Methods: In Study 1, hierarchical regression assessed how pre-treatment participant characteristics and dose (25mg, 10mg, or 1mg COMP360 psilocybin [a proprietary, pharmaceutical-grade synthetic psilocybin formulation, developed by Compass Pathfinder Ltd.]) predicted subjective psychedelic experience in 233 adults with treatment-resistant depression (ClinicalTrials.gov NCT03775200). In a subset of 101 participants from Study 1, Study 2 used natural language processing (NLP) of session transcripts to predict clinical response ($\geq 50\%$ MADRS reduction) from linguistic sentiment, psychedelic experience, and dose. In Study 3, transcripts from 22 participants with PTSD receiving 25 mg COMP360 psilocybin (ClinicalTrials.gov NCT05312151) were analyzed for words-per-minute (WPM) by participant and support provider during preparation, administration, and follow-up sessions to characterize support and engagement patterns.

Results: In Study 1, COMP360 dose was the strongest predictor of subjective psychedelic experience, while the pre-treatment individual characteristics showed only modest associations across experiential domains. In Study 2, linguistic sentiment and participant emotional breakthrough predicted clinical response with 85–88% accuracy, such that the stronger emotional experiences correlated with greater symptom reduction. In Study 3, administration sessions were characterized by 78% silence versus 25–30% in non-administration sessions. Providers' speech density was less variable than that of participants across all sessions, consistent with adherence to standardized training.

Conclusions: Taken together, these findings indicate that the psychedelic experience during psilocybin administration is immersive and internally driven, shaped primarily by the pharmacological dose, and that the consequent strong emotional experience may contribute to positive treatment outcomes. Future research is warranted to confirm the utility of these tools and the current findings.

Literature References: Goodwin GM, Aaronson ST, Alvarez O, et al. Single-dose psilocybin for a treatment-resistant episode of major depression. *New England Journal of Medicine*. 2022;387(18):1637-48.

Dougherty RF, Clarke P, Atli M, et al. Psilocybin therapy for treatment resistant depression: prediction of clinical outcome by natural language processing. *Psychopharmacology*. 2025;242(7):1553-61.

RECRUITING, RETAINING, AND TAILORING PSYCHEDELIC CLINICAL TRIALS FOR VULNERABLE POPULATIONS

Peter Hendricks, The University of Alabama at Birmingham

Individual Abstract: Psychedelic-assisted therapy has shown signals of efficacy for a variety of mental health conditions, but participants in psychedelic clinical trials have not been representative of the broader populations most affected by these conditions. A recent systematic review of 49 primary trials of psychedelics and MDMA for mental health conditions found that only 12% reported participant income and 31% reported educational attainment. In US-based trials that did report these data, participants had markedly higher socioeconomic status than the general population, with 93% having some college education versus 62% nationally. This lack of socioeconomic diversity limits the generalizability of existing findings and raises concerns about equitable access to psychedelic therapies as they move toward clinical implementation. This presentation will draw on three lines of research addressing the recruitment, retention, and tailoring of psychedelic clinical trials for vulnerable populations, with a focus on economically disadvantaged individuals. First, a conceptual framework for evaluating psilocybin-facilitated psychotherapy in vulnerable populations will be discussed, including barriers to participation like logistical constraints, mistrust of medical research, and the need for culturally informed consent procedures. Second, findings from a systematic review documenting the extent of socioeconomic underrepresentation in psychedelic trials will be presented, underscoring the need for standardized socioeconomic data reporting and targeted enrollment strategies. Third, data from a recently completed randomized controlled trial of psilocybin for cocaine use disorder (Hendricks et al., in press) will be shared. This quadruple-blind, placebo-controlled trial enrolled 40 adults with cocaine use disorder at a major medical research center in the Deep South of the US. Participants were predominantly Black (82.5%), male (82.5%), and of lower socioeconomic status (65% annual income at or below \$20,000). Psilocybin recipients had a

significantly higher percentage of cocaine abstinent days, greater likelihood of complete cocaine abstinence, and reduced risk of cocaine lapse through 180 days after end-of-treatment compared to placebo recipients. No serious adverse events occurred. These findings indicate that psychedelic clinical research can be feasibly and safely conducted with underrepresented and vulnerable populations when appropriate considerations are made around recruitment, retention, and therapeutic context. Recommendations for designing more inclusive psychedelic trials will be discussed, along with strategies for addressing the specific needs of economically disadvantaged communities so that the benefits of psychedelic therapies are not limited to those already well-served by the current research enterprise.

Literature References: Ortiz CE, Dourron HM, Sweat NW, Garcia-Romeu A, MacCarthy S, Anderson BT, Hendricks PS. Special considerations for evaluating psilocybin-facilitated psychotherapy in vulnerable populations. *Neuropharmacology*. 2022;214:109127.

Hendricks PS, Grossman DH, Ortiz CE, Lappan SN, Bradley M. A systematic review of income and education reporting in psychedelic clinical trials. *Nature Mental Health*. 2025;3:567–574.

Hendricks PS, et al. Psilocybin in the Treatment of Cocaine Use Disorder: A Randomized Clinical Trial. *JAMA Network Open*.

EVALUATING THE CLINICAL UTILITY OF PSILOCYBIN THERAPY VERSUS OTHER PSYCHEDELIC DRUG INTERVENTIONS FOR THE TREATMENT OF POSTTRAUMATIC STRESS DISORDER

Brandon Weiss, Johns Hopkins University School of Medicine

Individual Abstract: The purpose of the presentation will be to investigate the optimal form of psychedelic therapy for Posttraumatic stress disorder (PTSD), with a focus on three major criteria of clinical utility: efficacy, rapidity, and tolerability/safety. Despite significantly greater research and funding focused on MDMA-assisted therapy's (MDMA-AT) effect on PTSD, recent evidence has pointed to serotonin 2A agonist drugs as a source of potentially greater clinical utility. The clinical utility of psilocybin versus MDMA will be examined in view of data collected from a recent Johns Hopkins pilot clinical trial (N = 20; NCT06407635) that investigated the efficacy, rapidity, and tolerability/safety of Psilocybin Therapy in the treatment of PTSD. This experimental trial randomized participants with PTSD (CAPS-5 score > 34) to two psilocybin drug sessions (25 mg in session 1, 25 mg or 35 mg in session 2) with either standard psychological support (PST condition) or trauma-focused psychotherapy (TFT condition; including elements of Cognitive Processing Therapy and in vivo exposure). In the course of this presentation, psychological mechanisms underlying psilocybin's effect on PTSD will be examined (e.g., is acute trauma-related mental processing necessary for therapeutic response), along with evidence bearing on whether the TFT condition is incrementally beneficial (based on between-condition CAPS-5 score change and therapist ratings). Final results are forthcoming upon completed data collection in January 2026. This inquiry into identifying the best psychedelic therapy approach to treat PTSD is vital for guiding medical and institutional leaders (e.g., VA, DoD, HHS) on the most effective allocation of resources to resolve the longstanding health crisis facing individuals with PTSD.

Literature References: McGowan NM, Rucker JJ, Yehuda R, Agrawal M, Modlin NL, Simmons H, Tofil-Kaluza A, Das S, Goodwin GM. Investigating the safety and tolerability of

single-dose psilocybin for post-traumatic stress disorder: A nonrandomized open-label clinical trial. *Journal of Psychopharmacology*. 2025:02698811251362390.

Mitchell JM, Ot'alora G M, van der Kolk B, Shannon S, Bogenschutz M, Gelfand Y, Paleos C, Nicholas CR, Quevedo S, Balliett B, Hamilton S. MDMA-assisted therapy for moderate to severe PTSD: a randomized, placebo-controlled phase 3 trial. *Nature Medicine*. 2023;29(10):2473-80.

BUILDING COLLABORATIVE CAPACITY IN EARLY CAREER PSYCHOPHARMACOLOGY: STRATEGIES FOR EFFECTIVE PARTNERSHIPS ACROSS ACADEMIA, INDUSTRY, AND CLINICAL PRACTICE

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

Overall Abstract: Developing effective, sustainable collaborations is essential for early career investigators navigating the rapidly evolving landscape of clinical psychopharmacology and translational mental health research. This workshop, organized by the ASCP Early Career Committee, will provide structured, practical guidance to help emerging scientists, clinicians, and clinician-investigators build collaborative networks that accelerate scientific discovery, enhance career development, and support long-term success across diverse professional trajectories. This interactive session will begin with a moderated panel of leaders representing academia, industry, and clinical practice who will share real-world insights into forming, maintaining, and leveraging collaborative relationships. Panelists will discuss the strategic advantages of interdisciplinary partnerships, common barriers faced by early career professionals, and effective approaches for initiating collaborations with mentors, institutions, community partners, and cross-sector stakeholders. Particular attention will be given to navigating collaboration during career transitions, understanding differences in organizational culture, and promoting equitable and inclusive partnerships that amplify the roles of women and members of underrepresented groups. Following the panel, participants will engage in structured breakout groups led by experienced facilitators from academia, industry, and clinical research. These small-group discussions will offer opportunities for connection with leaders in the field, peer networking, and skill-building exercises focused on communication, expectation-setting, conflict resolution, and team science principles. By the end of the workshop, attendees will be equipped with actionable strategies, expanded professional connections, and greater confidence in their ability to form productive collaborations that support scientific advancement, enhance career resiliency, and contribute meaningfully to the broader psychopharmacology community.

Learning Objective 1: Foster mutual understanding, skill development, and practical knowledge of the collaboration process across academia, industry, and clinical practice, including identify and bridge cultural gaps; recognize and address the differing priorities, timelines, and incentives between various sectors.

Learning Objective 2: Develop effective communication and teamwork skills: apply strategies for open, interdisciplinary communication and teamwork to overcome collaboration barriers and foster a culture of mutual respect, information sharing to attain shared goals.

Literary References:

1. Palmer, M. and R. Chaguturu (2017). "Academia–pharma partnerships for novel drug discovery: essential or nice to have?" *Expert Opinion on Drug Discovery* 12(6): 537-540.

2. D'Hooghe, T. (2017). "Transparent collaboration between industry and academia can serve unmet patient need and contribute to reproductive public health." *Hum Reprod* 32(8): 1549-1555.

THE EVOLVING NATURE OF ACADEMIC-INDUSTRY PARTNERSHIPS

Mark Rapaport, American Psychiatric Association

Individual Abstract: The intent of this presentation is to discuss the evolving nature of academic-industry partnerships. This evolution reflects the impact of technological advances on the types of investigations being performed in Psychiatry and mental health. In the 1980s and 1990s these partnerships usually involved investigators serving as sites for trials of new medications, investigator initiated trials usually involving a company's compound, or serving on an expert panel to inform the research direction of a company. With the advent of cloud computing, digital health, machine learning, the electronic medical record, and AI, as well as advances in the development of multi-modal platforms, the relationships between academia and industry have become much more varied and complex. It is leading to new forms of partnerships with networks of academic sites, with at times multi-industry partners working together with academia on projects. As part of the workshop I will discuss a number of these types of partnerships and their implication for young and mid-career investigators.

Literature References: Transparent collaboration between industry and academia can serve unmet patient need and contribute to reproductive public health.

D'Hooghe T. *Hum Reprod*. 2017 Aug 1;32(8):1549-1555. doi: 10.1093/humrep/dex230.

PMCID: PMC5850474

Academia-pharmaceutical industry linkage: An academic perspective.

Mubarak Z, Abbas N, Hashmi FK, Husnain SZ, Bukhari NI.

J Pharm Policy Pract. 2024 Apr 5;17(1):2332872. doi: 10.1080/20523211.2024.2332872.

PMCID: PMC11000613

TAKE-AWAYS FROM MY EXPERIENCE STARTING OUT IN CLINICAL PSYCHOPHARMACOLOGY RESEARCH

Anita Clayton, University of Virginia SOM

Individual Abstract:

Abstract: In my experience as an Early Career Psychopharmacologist, I learned a few things.

1. Say "Yes" to opportunities – you may end up somewhere other than you planned, but it may be better
2. Be enthusiastic
3. Don't hesitate to ask – the worst that can happen is they say "No" and that is almost never the response
4. Build momentum with others
5. Learn what you need to know
6. Attend talks peripheral to your area to expand your thinking

7. Join organizations with your interests – and get involved

8. Start mentoring others – you will learn so much

And then you become a mid-career and ultimately a senior psychopharmacologist!

Literature References: Reference: Kahn CR. Sounding Board: Picking a Research Problem -- The Critical Decision. NEJM. 1994;330(21):1530-1533. DOI: 10.1056/NEJM1994052633021131530 – 1533

WHY DO WE NEED TEAM SCIENCE APPROACHES IN NEUROBIOLOGICAL AND CLINICAL STUDIES

Vilma Gabbay, Miller School of Medicine, University of Miami

Individual Abstract: This talk will highlight the importance of team science and interdisciplinary collaboration. We will discuss both challenges and strategies for fruitful collaboration. We will present examples from five ongoing multidisciplinary studies, including a project investigating the neuroimmunological underpinnings of HIV comorbidity with depression, which brings together experts in infectious diseases, pathology, and psychiatry (Inflammation, BBB disruption, and Reward Function in the Pathogenesis of Depression among PWH). Another example is a center grant focused on developing new therapies for pain and opioid use disorders, involving collaboration across implementation science, general internal and community medicine, pain and substance use specialists, and psychological treatment experts (Integrated Care for Chronic Pain and Opioid Use Disorder: The IMPOWR Research Center at Montefiore/Einstein (IMPOWR-ME)). We will review all stages of collaborative research—from initial aims development and team formation to study execution and manuscript preparation.

Literature References: Gallo L., Bhambhani Y., Lu T., Holzman S., Bao Y., Musicaro R., Roske C., Richard J. T., Delgado G. E., Baker Z., Starrels J., Stotts A., Deng Y., Rodgers C. R. R., Perez H. R., Norton B. T., and Gabbay V. A randomized trial evaluating Acceptance and Commitment Therapy and smart phone care management application to augment buprenorphine therapy for opioid use and chronic pain. Substance Use and Addiction, 2025 Jan;46(1):166-174. doi: 10.1177/29767342241265178. Epub 2024 Aug 22. PMID: 39171416; PMCID: PMC11652247.

Gabbay V., Ely BA., Vileisis J., Petrovic Z., Cicvaric A., Asnis GM., Kim-Schulze S., Radulovic J., Immune and Neural Response to Acute Social Stress in Adolescent Humans and Rodents. Translational Psychiatry, 2024 Jul 25;14(1):306. doi: 10.1038/s41398-024-03008-5. PMID: 39054336; PMCID: PMC11272929.

DEVELOPMENT OF ESKETAMINE. AN ACADEMIC -INDUSTRY DREAM COLLABORATION

Jaskaran Singh, Neurocrine Biosciences

Individual Abstract: The development of esketamine represents a remarkable example of how collaboration between academia and industry can accelerate the translation of basic science into transformative clinical innovation. The story began Yale University and at the National Institutes of Health (NIH), where pioneering academic research first revealed the

rapid antidepressant effects of ketamine, uncovering a completely new mechanism of action distinct from traditional monoaminergic pathways. Building on these foundational discoveries, industry efforts focused on translating this knowledge into a safe, effective, and regulatory-approved therapy for patients with treatment-resistant depression.

What made this journey particularly unique was that ketamine, unlike most investigational compounds, was already available for clinical use during its clinical development. This allowed clinicians and researchers to explore its therapeutic potential in real-world settings even as formal trials of esketamine were underway. Consequently, the development process raised atypical scientific and clinical questions—such as optimal dosing frequency and long-term safety—that could not be addressed solely through conventional pharmacokinetic principles like half-life. Academic investigators played a critical role in shaping these discussions by generating real-world data, exploring mechanisms of action, and advancing understanding of ketamine's enantiomers. In parallel, industry provided the infrastructure for large-scale clinical trials, regulatory engagement, and drug formulation. Together, these complementary efforts established a dynamic feedback loop—academic findings informed industry development, and industry-generated data refined clinical practice. The outcome of this collaboration was the successful approval of the first antidepressant with a novel mechanism of action in over half a century. Beyond its scientific impact, the development of esketamine highlights how open communication, shared curiosity, and joint problem-solving across sectors can overcome traditional barriers in drug discovery. This partnership between academic innovation and industrial development not only transformed the treatment landscape for depression but also set a new precedent for how future neuropsychiatric therapeutics might be discovered and brought to patients.

Literature References: Singh JB, Fedgchin M, Daly EJ, et al. A Double-Blind, Randomized, Placebo-Controlled, Dose-Frequency Study of Intravenous Ketamine in Patients With Treatment-Resistant Depression. *Am J Psychiatry*. 2016;173(8):816-826

Singh JB, Fedgchin M, Daly EJ, Drevets WC. Relapse prevention in treatment-resistant major depressive disorder with rapid-acting antidepressants. *Adv Pharmacol*. 2020;89:237-259.

ARE EARLY CAREER CLINICAL RESEARCHERS IN PSYCHIATRY AN ENDANGERED SPECIES?

Dan Iosifescu, New York University School of Medicine

Individual Abstract: The reduction in funding and training opportunities for early career clinical researchers in neuropsychiatric disorders is a very concerning development. A robust pipeline of trainees and early career researchers is critical for the viability of future development of novel treatments for severe mental illness. This presentation will review, on the basis of the literature and the speaker's personal experience, the challenges of early career clinicians in establishing a career in research in the academia. Specific challenges are faced by trainees with diverse backgrounds or disabilities. Important directions to ensure success will be discussed, including the role of mentoring, strategies for publication and searching funding opportunities, and work-life balance.

Literature References: 1. Sperry SH, Douglas KM, Dean OM, Fries GR, Gomes FA, Hosang GM, Morton E, Sandorffy B, Van Rheen TE, Xu N, Huber RS. Barriers to and facilitators of success for early and Mid-Career professionals focused on bipolar disorder: A

global needs survey by the International Society for Bipolar Disorders. *Bipolar Disord.* 2023 Aug;25(5):379-390.

2. Miller E, Choi YK, Taran M, Huang A, Tadd K, Bampton T, Wilkes F. Reflections on challenges and opportunities in attempting a clinical academic career. *Australas Psychiatry.* 2025 Jun 13:10398562251351505.

THE YOUNG INVESTIGATOR AS A PLURIPOTENT STEM CELL: THE ROLE OF INDUSTRY-ACADEMIC PARTNERSHIPS IN A SUCCESSFUL CAREER

Charles Nemeroff, The University of Texas at Austin

Individual Abstract: The trajectory to success in academic medicine has in recent years become increasingly more difficult, particularly for clinician scientists. A multitude of factors have unfortunately conspired to place obstacles in the pathway to success in academia. These include, but are not limited to, 1) declining extramural funding from the National Institutes of Health (NIH) with a clear bias to fund basic laboratory research rather than clinical research and more specifically treatment trials; 2) declining hospital revenues that previously served as a source of support for academic faculty; 3) declining university support for medical school faculty. Fundamentally the majority of academic faculty must cobble together salary and research support by a combination of clinical service, administrative and/or teaching roles and research funding. Industry offers several potential forms of support for faculty including: serving as site principal investigator in randomized clinical trials, investigator-initiated clinical studies, preclinical laboratory studies, service or data safety monitoring boards (DSMB) and involvement in drug development and clinical trial design. Finally the opportunity to be involved in data analysis from clinical trials and resultant publications is of obvious considerable academic value.

Literature References: Snyder, S. H. (2005). The audacity principle in science. *Proceedings of the American Philosophical Society*, 149(2), 141-158.

Wang G, Aguado M, Spear MA, Alphs L, Chen C, Huang H, Lu XX, Doostzadeh J, Wu S, Wang S, Patel A, Nemeroff CB, Wang Z, Li A, Luo W. 2025. ANK3 as a Novel Genetic Biomarker for Liafensine in Treatment-Resistant Depression: The ENLIGHTEN Randomized Clinical Trial. *JAMA Psychiatry.* doi: 10.1001/jamapsychiatry.2025.2416

^COMMUNICATION AND CONFLICT MANAGEMENT: PRACTICAL TOOLS FOR EFFECTIVE LEADERSHIP IN RESEARCH

*Ynhi Thomas, Baylor College of Medicine and Michael E. DeBakey VA Medical Center
Erica Kaczmarek, University of Toronto*

Nidhi Kulkarni, Centre for Youth Bipolar Disorder, CAMH

Ivan Montoya, DHHS/National Institute on Drug Abuse

Holly Swartz, University of Pittsburgh School of Medicine

Crystal Clark, University of Toronto, Women's College Hospital

Nicholas Murphy, Texas A&M University, Naresh K. Vashisht College of Medicine

Danica Johnson, University of Toronto

Overall Abstract: Effective leadership in psychiatry and behavioral health research requires navigating interpersonal challenges with clarity, empathy, and professionalism.

Miscommunication and unresolved conflict can erode collaboration, morale, and outcomes.

This interactive two-hour workshop will equip participants with evidence-based tools to manage difficult conversations and reframe conflict as an opportunity for growth. The session begins with a brief didactic overview of communication and conflict management frameworks, including active listening, perspective-taking, and negotiation strategies drawn from organizational psychology and medical leadership training. Participants will complete the Thomas-Kilmann Conflict Mode Instrument (TKI®) to identify their individual conflict style and reflect on how these tendencies shape professional interactions. A moderated panel discussion will follow, featuring Drs. Ivan Montoya, Holly Swartz, Mahavir Agarwal, and Alexander Aaronson, who will share experiences navigating challenging situations that required self-advocacy and boundary setting and discuss the communication strategies they used to resolve them. Building on these insights, a didactic segment will introduce reframing techniques and practical communication tools to transform conflict into collaboration. Participants will receive digital “pocket mantras” synthesized from leadership curricula from Harvard Business School and the literature. Small-group breakout sessions will provide opportunities for attendees to apply these strategies to personal scenarios, engage in peer reflection, and set concrete goals for improving communication and conflict management in their professional environments.

Learning Objective 1: Identify their individual conflict management style and describe how it influences professional interactions.

Learning Objective 2: Apply evidence-based communication strategies to reframe conflict, de-escalate tension, and establish professional boundaries.

Literary References:

- 1) Thomas KW, Kilmann RH. Thomas-Kilmann Conflict Mode Instrument. XICOM; 1974.
- 2) Wolfe AD, Hoang KB, Denniston SF. Teaching conflict resolution in medicine: lessons from business, diplomacy, and theatre. *MedEdPORTAL*. 2018;14:10672.

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

Panel Sessions

^ADVANCES IN DEPRESSION RESEARCH: A TRIBUTE TO NOLAN WILLIAMS

Charles Nemeroff, The University of Texas at Austin

Overall Abstract: This panel presentation brings together four investigators who have worked closely with Nolan Williams over the last several years and is meant to present state of the art research relevant to mood disorders for which he was intimately involved and invested. Overall, they comprise four areas: 1. The role of a history of child abuse and neglect in treatment resistance in mood disorders; 2. Understanding the mechanism of action of ketamine with an emphasis on its action at the mu opiate receptor; 3. The use of low frequency focused ultrasound in the treatment of mood and anxiety disorders and 4. The

promise of psychedelic medicines, more specifically ibogaine, in the treatment of traumatic brain injury and other neuropsychiatric disorders. In brief, childhood maltreatment has been conclusively shown to produce reliable long term biological changes in the brain and body that are associated with increased vulnerability to several medical and psychiatric disorders. In addition such patients are relatively treatment resistant to conventional evidence-based treatments for mood disorders and this represents a clear confound in large scale phase II and III clinical trials. There are a number of preclinical studies that have demonstrated that the mu opioid antagonist naltrexone blocks the behavioral effects of ketamine and there are now clinical studies that have clearly shown that naltrexone pretreatment blocks the antidepressant and anti-suicide effects of IV ketamine. One unanswered question has been whether ketamine is acting as a mu opiate receptor agonist or is primarily releasing endogenous opioids that act on the mu opiate receptor. A combination of preclinical and clinical studies suggest the latter to be the case. This raises important questions about the development of opiate agonists in the treatment of treatment resistant major depression. Remarkable advances have occurred in the development of neuromodulation techniques for the treatment of mood disorders, largely transcranial magnetic stimulation, including the SAINT method originated at Stanford. One disadvantage of TMS is its inability to target deep subcortical structures. Low frequency focused ultrasound (FUS) has that capability and a pilot sham controlled study of FUS directed to the left amygdala during fMRI revealed a clear reduction in amygdala and its targets (hippocampal and insular) activity. In an uncontrolled study, 3 weeks of daily treatment resulted in significant reductions in mood and anxiety symptom severity scores with no serious side effects. There has been much recent attention on the potential of various psychedelic medications in the treatment of PTSD and mood disorders. In an open study of 30 male US servicemen with a history of traumatic brain injury (TBI) ibogaine administered with magnesium to mitigate cardiac side effects led to marked improvement of indices of TBI immediately, one month and 12 months later. In addition symptom severity of comorbid depression PTSD and anxiety were similarly improved. Structural brain imaging and resting state EEG measures showed significant post treatment changes. It appears that ibogaine may provide durable long term effects in patients with TBI/PTSD. Taken together, these presentations provide a backdrop for the remarkable contributions that have been promulgated by Nolan Williams and will serve as a partial legacy to his enduring impact on the field.

Learning Objective 1: To understand the remarkable contributions made by Nolan Williams to the field of psychedelics and neuromodulation as evidenced by the trajectory of those two fields.

Learning Objective 2: To understand the recent developments of novel treatments for treatment refractory depression.

Literary References:

1. Teicher MH, Gordon JB, Nemeroff CB. 2022. Recognizing the importance of childhood maltreatment as a critical factor in psychiatric diagnoses, treatment, research, prevention and education. *Mol Psychiatry* 27,1331-1338.
2. Nemeroff CB. 2020. The State of Our Understanding of the Pathophysiology and Optimal Treatment of Depression: Glass Half Full or Half Empty? *Amer J Psychiatry* 177(8) 671-685.

UNDERSTANDING AND HARNESSING THE OPIOID EFFECTS OF KETAMINE

Alan Schatzberg, Stanford Univ. School of Medicine

Individual Abstract: Ketamine has become a more commonly used agent for refractory depressed patients, primarily via intravenous infusion of racemic agent or the intranasally administered esketamine enantiomer. The drug has been largely thought to act via NMDA receptor antagonism; however, our group has argued that the rapid antidepressant effects are mediated through mu-opioid receptor (MOR) agonism. In the first part of the talk, we review the reasoning beyond our hypothesis and describe our study (Williams N et al *Am J Psychiatry* 2018) in which naltrexone or placebo was administered 40 minutes prior to an intravenous ketamine infusion at 0.5mg /kg in a double-blind, random order, crossover design separated by 2-9 weeks. We observed significant reduction in depression in the ketamine plus placebo group that was attenuated by pre-administration of naltrexone. Subsequent to this human experiment, there have been some 9 reports that demonstrated in rodents that the behavioral effects of ketamine were blocked by pre-administration of naltrexone. Our human experiment has recently been replicated by Luke Jelen and colleagues and published in *Nature Medicine* (2025). By combining the basic naltrexone versus placebo protocol with f-MRI, it appeared that the opioid effect preceded the NMDA antagonism and accounted for the rapid antidepressant effect. In the pre-clinical studies one key issue has remained unanswered: namely, is the MOR effect of ketamine due to its relatively weak MOR agonism (similar to its degree of NMDA antagonism) or does it reflect a release of endogenous opioids such as b-endorphin? Using a beta endorphin antibody, Pittenger's group (*Translational Psychiatry* 2024) replicated the naltrexone blockade of ketamine's behavioral effects in rodents, suggesting the drug's MOR effects may largely reflect mu opioid release. The effect of ketamine on MOR may explain why other NMDA antagonists (such as memantine) have not been shown to have antidepressant properties. We have hypothesized that the antidepressant and anti-suicide effects of ketamine could be extended by low doses of buprenorphine, an MOR partial agonist used to treat opioid use disorder. Yovell et al (*Am J Psychiatry* 2016) reported that over 4 weeks, low doses of buprenorphine (0.4-0.8mg per day) in hospitalized borderline personality or unipolar depressed patients reduced suicidal ideation significantly more than did placebo; however, patients still demonstrated considerable suicidal severity. We repeated (Tucciarone J et al, *SoBP Annual Meeting* 2025) the four week low dose buprenorphine trial after giving an open label infusion of ketamine and in unipolar suicidal patients and observed not only significant differences between drug and placebo in reduction of suicidal ideation but overall lower post treatment suicidal ideation than was seen in the Yovell et al study. These data point to potential harnessing of opioid activity to reduce suicidality. After the four weeks, the patients' buprenorphine or placebo was stopped and they were followed blindly to medication treatment for 2 weeks. Transient worsening of suicide and depression ratings was observed in the patients who stopped buprenorphine as compared to placebo. Physical signs or symptoms of opioid withdrawal were not observed. Further studies are needed to understand how long to treat patients with buprenorphine and to determine the optimal withdrawal protocol.

Literature References: Williams NR, Heifets BD, Blasey C, et al. Attenuation of Antidepressant Effects of Ketamine by Opioid Receptor Antagonism. *Am J Psychiatry*, 2018;175(12):1205-1215.

Jelen LA, Lythgoe DJ, Stone JM, et al. Effect of naltrexone pretreatment on ketamine-induced glutamatergic activity and symptoms of depression: a randomized crossover study. *Nature Medicine*, 2025;31:2958–2966.

NON-INVASIVE AMYGDALA NEUROMODULATION IN HUMANS WITH FOCUSED ULTRASOUND: NEUROBIOLOGICAL AND CLINICAL EFFECTS IN MOOD, ANXIETY, AND TRAUMA-RELATED DISORDERS

Gregory Fonzo, The University of Texas at Austin Dell Medical School

Individual Abstract: Mood, anxiety, and trauma-related disorders (MATRDs) are highly prevalent and comorbid. A sizable number of patients do not respond to first-line treatments. The amygdala plays a critical role in reactivity to emotional stimuli, and amygdala hyperactivity is implicated across MATRDs in pathophysiology and treatment response. Non-invasive neuromodulation is a second-line treatment approach, but current methods rely on cortical targets to indirectly modulate subcortical structures, e.g., the amygdala, implicated in MATRDs. Low-intensity transcranial focused ultrasound (tFUS) is a non-invasive technique for direct subcortical neuromodulation, but its safety, feasibility, and promise as a potential treatment is largely unknown. In a target engagement study, magnetic resonance imaging (MRI)-guided tFUS to the left amygdala (was administered during functional MRI (tFUS/fMRI) to test for acute modulation of blood oxygenation level dependent (BOLD) signal in a double-blind, within-subject, sham-controlled design in patients with MATRDs (N= 29) and healthy comparison subjects (N= 23). Participants also completed a resting state scan and an emotional face processing paradigm before and after each active/sham in-scanner sonication to assess acute effects on amygdala intrinsic connectivity and responses to naturalistic emotional stimuli. Then, in an unblinded treatment trial, the same patients then underwent 3-week daily (15 sessions) MRI-guided repetitive tFUS (rtFUS) to the left amygdala to examine safety, feasibility, symptom change, and change in amygdala reactivity to emotional faces. Active vs. sham tFUS/fMRI reduced, on average, left amygdala BOLD signal and produced patient-related differences in hippocampal and insular responses during sonication. Following sonication, active (vs. sham) tFUS induced emotion non-specific attenuated activation in the left amygdala target, as well as right amygdala, bilateral anterior insula, and dorsal anterior cingulate (dACC) (time x session corrected p 's < 0.05). Greater emotion non-specific activation attenuations were observed for MATRD patients in more lateral portions of bilateral amygdala and bilateral mid/posterior insula (group x time x session corrected p 's < 0.05). Active (vs. sham) tFUS attenuated left amygdala intrinsic connectivity with right amygdala (time x session corrected p 's < 0.05) and produced increased left amygdala connectivity with right dACC in the MATRD but not HC group (group x time x session corrected p 's < 0.05). Daily rtFUS treatment was well-tolerated with no serious adverse events. There were significant reductions on the primary outcome (Mood and Anxiety Symptom Questionnaire General Distress subscale; p = 0.001, Cohen's d = 0.77), secondary outcomes (Cohen's d of 0.43–1.50), and amygdala activation to emotional stimuli at post-treatment. Findings provide initial evidence of tFUS capability to rapidly and durably modulate amygdala function, safety and feasibility of rtFUS treatment in MATRDs, and impetus for future double-blind randomized controlled trials to examine efficacy. Additional work is needed to optimize energy delivery to subcortical targets, define optimal sonication parameters for desired effects, and examine durability of benefits beyond the acute treatment phase.

Literature References: Barksdale BR, Enten L, DeMarco A, et al. Low-intensity transcranial focused ultrasound amygdala neuromodulation: a double-blind sham-controlled target engagement study and unblinded single-arm clinical trial. *Mol Psych*. 2025;30(10):4497-4511.

Davidson B, Xhima K, Cosgrove R, et al. A roadmap for focused ultrasound applications in psychiatry: Proceedings of the 2024 symposium on focused ultrasound in psychiatry (FUS-PULSE). *Brain Stimulation*. 2025;18(5):1651-1662.

CLINICAL AND NEURAL OUTCOMES OF MAGNESIUM-IBOGAINE FOR TRAUMATIC BRAIN INJURY IN SPECIAL OPERATIONS FORCES VETERANS

Ian Kratter, Stanford University School of Medicine

Individual Abstract: Chronic sequelae of traumatic brain injury (TBI) can include functional impairments and psychiatric syndromes such as post-traumatic stress disorder (PTSD), depression, and anxiety, and some Veterans with TBI have sought treatment with the onirogen ibogaine. Ibogaine has been associated with fatal cardiac arrhythmias, but coadministration of magnesium may mitigate this risk. As an initial exploration of outcomes and neural mechanisms of ibogaine, we performed a prospective observational study in 30 male Veterans with a history of TBI. Clinically, we assessed changes in the WHODAS 2.0 from baseline to immediately (primary outcome) and 1 month (secondary outcome) after treatment. Additional secondary outcomes included changes in PTSD (CAPS-5), depression (MADRS) and anxiety (HAM-A). We identified significant improvements in functioning both immediately (Cohen's $d = 0.74$) and 1 month ($d = 2.20$) after treatment and in PTSD ($d = 2.54$), depression ($d = 2.80$) and anxiety ($d = 2.13$) at 1 month after treatment. Next, we performed a long-term follow-up study to assess the durability of these findings. 27 of the original 30 participants completed at least one such assessment. Significant reductions in disability and PTSD, depression, and anxiety symptoms were sustained at 12 months post-treatment ($d \geq 2.18$). Similar improvements were observed at 3-, 6-, and 9-month follow-ups ($d \geq 1.81$). Kaplan-Meier survival analyses estimated the probability of sustained remission 12 months after treatment as 84% for PTSD, 66% for depression, and 61%, for anxiety. Biologically, we collected MRI scans and resting-state EEG. Post-hoc pairwise comparisons revealed an estimated marginal mean reduction of 1.3 years between predicted brain age at the baseline and 1-month visits. Regional linear mixed effect (LME) models revealed a significant main effect of study visit on cortical thickness in 13 of 62 examined regions of interest (ROIs) and 8 of 28 subcortical ROIs. Post-hoc testing revealed significant volumetric expansion between the baseline and both post-treatment visits. We also assessed the effects of ibogaine on cortical oscillations and complexity. After treatment, slower oscillations (theta-alpha) increased in power, and power at higher frequencies (beta-gamma) decreased. Accordingly, the theta/beta ratio increased post-treatment, which correlated with improved cognitive inhibition, and peak alpha frequency and neural complexity also were lower. These neurophysiological markers correlated with improved executive function, PTSD, and anxiety. Finally, we assessed the level of mystical experience during the treatment using the MEQ-30. Using LME models, we observed that higher MEQ-30 scores were associated with significantly greater reductions in both the CAPS-5 score and peak alpha frequency. Themes from the narrative accounts portrayed an accelerated, self-directed psychotherapeutic process. Altogether, these findings suggest that magnesium-ibogaine treatment may provide durable symptomatic improvements in veterans with TBI-related sequelae. Potential mechanisms of these improvements include sustained neuroplastic changes in brain morphometry, reduced spatiotemporal complexity of brain activity, 'slowing' of cortical oscillations in the brain at rest, and a mystical self-directed psychotherapeutic experience. Randomized controlled trials with long-term follow-up are needed to validate these initial results.

Literature References: Cherian KN, Keynan JN, Anker L, et al. Magnesium-ibogaine therapy in veterans with traumatic brain injuries. *Nature Medicine*. 2024;30(2):373-381.

Lissemore JI, Chaiken A, Cherian KN, et al. Magnesium-ibogaine therapy effects on cortical oscillations and neural complexity in veterans with traumatic brain injury. *Nature Mental Health*. 2025;3:918–931.

***^PHOTOBIMODULATION WITH NEAR INFRARED LIGHT: A NOVEL TREATMENT FOR PSYCHIATRIC DISORDERS**

Dan Iosifescu, New York University School of Medicine

Overall Abstract: Transcranial photobiomodulation (t-PBM) with near-infrared light penetrates robustly into the cerebral cortex and is absorbed by the mitochondrial enzyme cytochrome c oxidase, stimulating the mitochondrial respiratory chain and leading to increased ATP production. t-PBM also significantly increases cerebral blood flow and oxygenation. Antidepressant effects and pro-cognitive effects of t-PBM have been reported in animal models and in humans. This panel will present new data on the effects of t-PBM in several neuropsychiatric disorders. Dr. Cassano will present data from studies in patients with major depressive disorder (MDD), including a recent study where different parameter combinations of t-PBM resulted in divergent effects on cerebral hemodynamics (measured with fMRI BOLD) and on clinical symptoms of depression. We will additionally present the effects of several doses of t-PBM on brain temperature (measured with ¹H-MRS chemical shift). Dr. Iosifescu will present data on the effects of t-PBM in Alzheimer's disease, including from a recently completed large study. Dr. Almeida will present data from t-PBM studies in subjects with bipolar disorder and cognitive dysfunction. t-PBM significantly improved executive function and attention in individuals with remitted bipolar disorder. Neuroimaging revealed a biphasic cerebral blood flow response, suggesting dynamic neuromodulatory effects. Finally, Dr. Gaggi will synthesize neuroimaging evidence across multiple clinical populations to clarify the neurophysiological mechanisms through which tPBM influences brain activity, highlighting existing studies including data from our group demonstrating that intrinsic brain signals such as the fractional amplitude of low-frequency fluctuation (fALFF) in the fMRI BOLD signal track metabolic responsiveness to tPBM in early Alzheimer's disease and major depressive disorder, with lower baseline metabolism predicting larger neural modulation. In aggregate, these data support the role of t-PBM as a novel neuromodulation technique with unique biological and clinical effects in neuropsychiatric disorders. The panel will also outline how measurable imaging markers integrated with the clinical data can serve to establish dose-dependent neural effects and can guide the development of more precise, mechanism-based interventions such as t-PBM.

Learning Objective 1: The participants will be able to describe the mechanism of transcranial photobiomodulation

Learning Objective 2: The participants will be able to discuss neuropsychiatric disorders where transcranial photobiomodulation has shown preliminary clinical efficacy

Literary References:

1. Gaggi NL, Iosifescu DV. Transcranial photobiomodulation: an emerging therapeutic method to enhance brain bioenergetics. *Neuropsychopharmacology*. 2024; 50(1):314-315.

2. Vieira WF, Iosifescu DV, McEachern KM, Gersten M, Cassano P. Photobiomodulation: An Emerging Treatment Modality for Depression. *Psychiatr Clin North Am.* 2023; 46(2):331-348.

DOSE-DEPENDENT EFFECTS OF TRANSCRANIAL PHOTOBIMODULATION ON BRAIN TEMPERATURE IN PATIENTS WITH MAJOR DEPRESSIVE DISORDER: A SPECTROSCOPY STUDY

Paolo Cassano, Massachusetts General Brigham

Individual Abstract Background: Transcranial photobiomodulation (t-PBM) with near-infrared (NIR) light penetrates the cerebral cortex and is absorbed by the mitochondrial enzyme cytochrome-C oxidase, stimulating the mitochondrial respiratory chain. t-PBM also significantly increases cerebral blood flow and oxygenation. Small-scale studies have reported that t-PBM may effectively treat Major Depressive Disorder (MDD). However, relationships between t-PBM dose and brain temperature effects are unclear. Therefore, possible excess brain warming during t-PBM administration is a concern and must be investigated. In this pilot study, we evaluated the dose-dependent brain temperature effects of t-PBM in subjects with MDD.

Methods: 30 adult subjects (aged 18-65 years) meeting DSM-5 criteria for MDD, not treatment-resistant (0-2 failed antidepressants in the current episode), either unmedicated or on stable doses of antidepressants, with no other significant medical or psychiatric comorbidities, were enrolled. All subjects underwent three t-PBM sessions with different doses (peak irradiance; low: 50, medium: 300, high: 850 mW/cm², low and medium doses were administered in continuous wave mode, high dose in pulsed wave mode) and sham treatment. H-MRS data: using a 3T Siemens Trio MRI scanner, single-voxel MRS was performed with a PRESS sequence (TE/TR = 30ms/2s, dynamic averages = 32x4). A voxel with a volume of 30 mm × 30 mm × 15 mm was placed on the left prefrontal region. Brain temperature (°C) was derived by analyzing the 1H-MRS spectrum chemical shift differences between the water (~4.7 ppm) and N-acetyl aspartate (NAA) (~2.01 ppm) peaks, using jMRUI software's HLSVD method and Zhu et al. formula: $T_{\text{brain}} (^{\circ}\text{C}) = 36 - [103.8 \times (\Delta\text{H}_2\text{O}-\text{NAA} - 2.6759)]$. Pre- and post-irradiation temperature fluctuations for all conditions (active t-PBM and sham) were compared using a two-sample student-paired t-test [all data passed the normality test, Shapiro-Wilk test; $W > 0.95$, $p\text{-value} > 0.23$ ($\alpha=0.05$)]. We also tested for potential differences in the pre-post variability (σ^2) of brain temperature in each group using the respective sample sizes, mean, and standard deviation. Pearson correlation analyses were used to assess the absolute brain temperatures and [H₂O-NAA] frequency difference association. An alpha value (α)=0.05 was considered the threshold for statistical significance. Statistical analyses were performed using GraphPad Prism 9.0.0.

Results: After quality control of the data, the following group numbers were available for both pre- and post-temperature estimations: Sham (n=10), Low (n=11), Medium (n=10), and High (n=8). We did not detect significant temperature differences for any t-PBM-active or sham groups post-irradiation (unpaired t-test; $p\text{-value range } 0.105\text{-}0.781$). We also tested for potential differences in the pre-post variability of brain temperature in each group. As for t-PBM active groups, the lowest fluctuation (variance) was observed for the medium-dose ($\sigma^2=0.29$), followed by the low-dose ($\sigma^2=0.47$), and the highest fluctuation was for the high-dose ($\sigma^2=0.67$). Non-t-PBM sham condition showed the overall lowest fluctuation ($\sigma^2=0.11$).

Conclusion: Our MRS thermometry results show no significant brain temperature elevations during the t-PBM application procedure. The brain temperature variations observed pre- and post-t-PBM sessions were not statistically significant. The lowest temperature variation was observed for the medium dose, while the highest was for the high dose. This study was part of the primary completion of the National Institute of Mental Health (NIMH) study (ClinicalTrials.gov Identifier: NCT04366258).

Literature References: Iosifescu, D. V., Collins, K. A., Hurtado-Puerto, A., et al. Grant Report on the Transcranial near Infrared Radiation and Cerebral Blood Flow in Depression (TRIADE) Study. *Photonics*. 2023; 10(1), 90. <https://doi.org/10.3390/photonics10010090>

Weerasekera A, Coelho DRA, Ratai EM, et. al. Dose-dependent effects of transcranial photobiomodulation on brain temperature in patients with major depressive disorder: a spectroscopy study. *Lasers Med Sci*. 2024 Oct 7;39(1):249. doi: 10.1007/s10103-024-04198-6. PMID: 39370461.

TRANSCRANIAL PHOTOBIMODULATION FOR ALZHEIMER'S DISEASE

Dan Iosifescu, New York University School of Medicine

Individual Abstract: A large body of evidence supports mitochondrial dysfunction as an important pathology in Alzheimer's disease. We will review in this presentation emerging evidence that transcranial photobiomodulation (t-PBM) with near infrared light, which stimulates mitochondrial function, can improve cognitive deficits in subjects with Alzheimer's disease. Most of the earlier data are derived from rodent studies and from small, proof-of-concept clinical trials. However, we will also present recent results from a recently completed larger study in patients with mild cognitive impairment (MCI) and early stage Alzheimer's disease (AD) which enrolled 196 subjects. 78 subjects with current MCI or mild AD were randomized to an 8 week treatment with 3 weekly sessions of active t-PBM (808 nm, 300 mW/cm² irradiance) or sham (total 24 sessions). t-PBM was delivered to the prefrontal cortex, bilaterally. Clinical and neuropsychological testing were done at screen, endpoint, and at the long term follow-up (3 months after the end of randomized treatment) to study the permanence of clinical effects. To evaluate brain mechanisms of t-PBM in this population we tested changes in fMRI Blood-Oxygenation-Level Dependent (BOLD) signal after a single treatment to demonstrate t-PBM-dependent increases in prefrontal cortex blood flow. 68 participants completed all study procedures. 10 subjects (12.8%) terminated the study early. Based on these results, we will discuss the effects of t-PBM on global cognitive functioning and on specific cognitive domains in subjects with AD. We will also highlight the associations between clinical cognitive improvement and hemodynamic changes measured with fMRI BOLD.

Literature References:

1. Iosifescu DV, Song X, Gersten MB, Adib A, Cho Y, Collins KM, Yates KF, Hurtado-Puerto AM, McEachern KM, Osorio RS, Cassano P. Protocol Report on the Transcranial Photobiomodulation for Alzheimer's Disease (TRAP-AD) Study. *Healthcare (Basel)*. 2023; 11(14):2017.
2. Gaggi NL, Collins KA, Gonzalez-Castillo J, Hurtado AM, Castellanos FX, Osorio R, Cassano P, Iosifescu DV. 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.

TRANSCRANIAL INFRARED LASER STIMULATION IMPROVES COGNITIVE PERFORMANCE AND INDUCES A BIPHASIC CEREBRAL PERFUSION RESPONSE IN REMITTED BIPOLAR DISORDER

Jorge Almeida, The University of Texas at Austin

Individual Abstract: Transcranial infrared laser stimulation (TILS) is a novel non-invasive neuromodulation approach under investigation for cognitive enhancement in bipolar disorder (BD). We evaluated the acute and cumulative effects of repeated TILS on neurocognitive performance and cerebral blood flow (CBF) in individuals with remitted BD. In an open-label pilot study, 28 participants with remitted BD received weekly 10-minute TILS sessions (wavelength 1064 nm, power density 250 mW/cm²) over the bilateral prefrontal cortex for 6 weeks. Neurocognitive outcomes were assessed before and after treatment using the Cambridge Neuropsychological Test Automated Battery (CANTAB), focusing on executive and attentional domains. CBF was measured via arterial spin labeling (ASL) MRI at baseline, after the first TILS session (acute effect), and following the final session (cumulative effect). Repeated-measures ANOVAs and MANOVAs evaluated changes over time, with follow-up nonparametric tests for significant multivariate effects. TILS was associated with significant improvements in cognition: participants showed faster response inhibition ($p = 0.036$), improved sustained attention ($p = 0.002$), and greater cognitive flexibility ($p = 0.012$) after the six-week intervention. Neuroimaging results revealed a biphasic CBF response, with acute TILS inducing increased perfusion and cumulative TILS leading to decreased perfusion across key regions implicated in BD pathophysiology, including the prefrontal cortex, amygdala, and ventral striatum. These findings demonstrate that repeated TILS can enhance executive function and attentional control while modulating cerebral hemodynamics in remitted BD, highlighting a promising neuromodulation strategy to address persistent cognitive deficits in this population.

Literature References: Barrett DW, Davis RE, Siegel-Ramsay, JE, et al. Cognitive improvement and prefrontal network interactions in individuals with remitted bipolar disorder after transcranial infrared laser stimulation. *Front Psychiatry*. 2025; 16:1547230

Barrett DW, Gonzalez-Lima F. Transcranial infrared laser stimulation produces beneficial cognitive and emotional effects in humans. *Neuroscience*. 2013; 230:13–23

UNCOVERING MECHANISMS OF PHOTOBIMODULATION BEHIND CLINICAL CHANGES: EVIDENCE FROM NEUROIMAGING

Naomi Gaggi, New York University Grossman School of Medicine

Individual Abstract: The goal of this presentation is to provide mechanistic insight into transcranial photobiomodulation (tPBM)-induced clinical, cognitive, and behavioral changes presented by the other panelists and existing literature. More specifically, it will synthesize findings from tPBM studies (case reports, clinical trials, etc.) that use a variety of neuroimaging modalities, including functional MRI and magnetic resonance spectroscopy, across healthy and psychiatric populations to clarify the neurophysiological mechanisms underlying clinical changes after tPBM. Content will include 1) existing evidence of tPBM-induced neurophysiological changes in both healthy and clinical groups, 2) our team's ongoing work alongside current clinical trials, and 3) future directions for integrating tPBM

into clinical trials based on neuroimaging evidence. While we will discuss a host of findings from our lab and others, we highlight two new studies. Our group's work and clinical trials span multiple populations, including Alzheimer's disease, sleep disorders, depression, bipolar disorder, and traumatic brain injury. We show that intrinsic brain activity, measured with MRI-derived fractional amplitude of low-frequency fluctuations (fALFF), may serve as a marker of bioenergetic change after tPBM. We previously reported the first evidence that tPBM increases fALFF in aging individuals with early Alzheimer's disease (AD) (Gaggi et al., Brain Stim 2024). To further examine metabolic mechanisms, two analyses across three sites assessed whether baseline cerebral metabolism predicts fALFF changes during tPBM in early AD (n=19, mean age 74). Baseline 31P-MRS quantified metabolic status. As shown in prior work, fALFF increased during tPBM in frontal regions irradiated by the laser (e.g., F3: $t=-2.29$, $p=0.03$; F4: $t=-2.78$, $p=0.01$). In the current analysis, fALFF change correlated with PCR/Pi in regions including F3 ($\rho=.762$, $p=.028$), F4 ($\rho=-.833$, $p=.010$), and FP2 ($\rho=-.786$, $p=.036$). Overall, lower baseline metabolism predicted larger tPBM-related fALFF increases in frontal regions. We also explored the effect of tPBM on fALFF in 12 individuals with major depressive disorder (MDD) using concurrent tPBM-MRI (mean age 36, 70% female, 90% non-Hispanic/Latinx), who underwent three different doses of tPBM vs. sham (voxel-wise paired t-tests). Changes in fALFF during the medium dose appeared in the left thalamus and caudate and right medial frontal and temporal regions (cluster size $k > 100$; $t=3.36$, $p < .001$). fALFF was modulated by the three tPBM doses in MDD, with the medium dose showing the strongest effects and no modulation during sham. Overall, these results support the relationship between fALFF and quantitative measures of cerebral metabolism and show that brain activity can be modulated by tPBM in mood and cognitive disorders, particularly in regions with impaired metabolism showing the most robust increases. By integrating imaging-driven mechanistic insights with emerging clinical evidence, this talk aims to outline a roadmap for advancing tPBM as an informed, mechanism-based intervention for brain health. These findings provide some of the first mechanistic evidence linking tPBM-induced changes in intrinsic brain activity to quantitative markers of cerebral metabolism, identifying potential biomarkers of treatment sensitivity and clarifying how impaired metabolic function may shape neural responsiveness across disorders. By establishing measurable imaging markers and demonstrating dose-dependent neural modulation, this work advances the field toward more precise, mechanism-guided tPBM interventions and more targeted clinical trial design.

Literature References: 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.

Gaggi NL, Parincu Z, Peterson A, et al. Enhancing sleep, wakefulness, and cognition with transcranial photobiomodulation: a systematic review. *Front Behav Neurosci.* 2025;19:1542462.

***LESSONS FROM TRANSFORMING THE PSYCHIATRIC HEALTHCARE SYSTEM: HOW TO IMPROVE OUTCOMES?**

Andrew Nierenberg, Massachusetts General Hospital

Overall Abstract: The current psychiatric healthcare system is fragmented, the quality of care is variable, and outcomes are all too frequently suboptimal for our patients. While challenging and difficult, we need to transform the system of care if we aim to improve

outcomes. The purpose of this panel is to discuss lessons learned from ongoing efforts to transform psychiatric care from the perspectives of public policy, the perspective of someone with lived experience, a comprehensive system to improve the care of people who experience their first episode of psychosis, and a learning health network focusing on bipolar disorder. Rebecca Bagley will discuss the ambitious efforts of The Kennedy Forum to reach its 90-90-90 goals, aiming to screen 90% of the public for serious mental illness, provide evidence-based treatment to 90% of those affected, and help 90% of individuals improve. George McAllister will discuss his experience of treatment for bipolar disorder in the current system of care, what worked, and what did not. Lisa Dixon will discuss EPINET and ONTrackNY using a learning health system approach to improve the outcomes of young people with their first psychotic episode. Andrew Nierenberg will discuss the ongoing development of the Bipolar Action Network, a learning health improvement network across multiple healthcare systems designed to improve outcomes across the spectrum of bipolar disorder for all ages. Crystal Clark will discuss the challenges and successes of these efforts to improve care and outcomes.

Learning Objective 1: Identify and compare diverse approaches to transforming psychiatric care—including public-policy initiatives (e.g., the Kennedy Forum’s 90-90-90 goals), lived-experience perspectives, coordinated specialty care for first-episode psychosis (EPINET/OnTrackNY), and learning health networks for bipolar disorder—and evaluate how these models address fragmentation, variability in care quality, and suboptimal outcomes.

Learning Objective 2: Describe actionable strategies for implementing system-level improvements in psychiatric services by integrating lessons learned across policy, lived experience, early psychosis programs, and learning health networks, with the aim of increasing use of evidence-based treatments and improving patient outcomes across populations.

Literary References:

1. <https://www.thekennedyforum.org/approach/alignment-for-progress/90-90-90/>
2. <https://nationalepinet.org/>

ALIGNMENT FOR PROGRESS: A MOVEMENT TO BRING CHANGE

Nathaniel Counts, The Kennedy Forum

Individual Abstract: The current psychiatric healthcare system is fragmented, the quality of care is variable, and outcomes are all too frequently suboptimal for our patients. While challenging and difficult, we need to transform the system of care if we aim to improve outcomes. The purpose of this panel is to discuss lessons learned from ongoing efforts to transform psychiatric care from the perspectives of public policy, the perspective of someone with lived experience, a comprehensive system to improve the care of people who experience their first episode of psychosis, and a learning health network focusing on bipolar disorder. Rebecca Bagley will discuss the ambitious efforts of The Kennedy Forum to reach its 90-90-90 goals, aiming to screen 90% of the public for serious mental illness, provide evidence-based treatment to 90% of those affected, and help 90% of individuals improve. George McAllister will discuss his experience of treatment for bipolar disorder in the current system of care, what worked, and what did not. Lisa Dixon will discuss EPINET and ONTrackNY using a learning health system approach to improve the outcomes of young people with their first psychotic episode. Andrew Nierenberg will discuss the ongoing development of the Bipolar Action Network, a learning health improvement network across multiple healthcare systems designed to improve outcomes across the spectrum of bipolar disorder for all ages.

Crystal Clark will discuss the challenges and successes of these efforts to improve care and outcomes.

Literature References: Vohs JL, Cahill J, Taylor SF, Heckers S, Weiss A, Chaudhry S, Silverstein S, Tso IF, Breitborde NJ, Vinson A, Lapidus A. Forging a learning health system for early psychosis: Insights from the academic community EPINET. *Schizophrenia Research*. 2025 Apr 1;278:109-18.

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 May 1;25(3).

ONE EXPERT BY EXPERIENCE JOURNEY

George McAllister, Bipolar Action Network

Individual Abstract: Living with bipolar disorder has shaped my life in ways I never expected. My days have often swung between deep, immobilizing lows and bursts of energy and confidence that felt unstoppable—until they weren't. For years, I struggled to understand why my emotions shifted so sharply and why my thoughts raced at one moment and slowed to a crawl the next. Coming to terms with the diagnosis was both a relief and a reckoning. Learning to manage bipolar disorder has been a gradual process of self-discovery: recognizing triggers, accepting my limits, and finding treatment that actually helps. Medication, therapy, and support from the people in my life have slowly become anchors. Even so, the disorder remains a daily companion—sometimes quiet, sometimes demanding attention. While the challenges are real, this journey has also taught me resilience, self-awareness, and a deeper compassion for myself. I continue to navigate the highs and lows, working toward stability and embracing the small victories that remind me that living with bipolar disorder is not just about surviving—it's about learning who I am and how I want to move through the world.

Literature References: Aiken, C. *The Depression and Bipolar Workbook*. 2020
Miklowitz, D. *The Bipolar Disorder Survival Guide*. 2019

CHALLENGES OF BUILDING A LEARNING HEALTH SYSTEM FOR EARLY PSYCHOSIS CARE

Lisa B Dixon, College of Physicians and Surgeons, Columbia University/New York State Psychiatry

Individual Abstract: The Early Psychosis Intervention Network (EPINET) is a national initiative designed to advance coordinated specialty care (CSC) for individuals experiencing first-episode psychosis by establishing a learning health system (LHS) infrastructure across diverse clinical sites. EPINET integrates harmonized data collection, stakeholder input, and continuous quality improvement to accelerate the translation of research into practice, thereby improving outcomes for service users. ONTrackNY, a statewide CSC program and EPINET regional hub, delivers evidence-based, multidisciplinary care—including psychopharmacology, cognitive-behavioral interventions, family support, supported employment and education, and peer services—to individuals aged 16–30 with recent-onset nonaffective psychosis. ONTrackNY emphasizes recovery-oriented, person-centered care and

utilizes a centralized data infrastructure to monitor fidelity, inform practice-based research, and support ongoing adaptation of services. Both EPINET and ONTrackNY exemplify the integration of LHS principles in early psychosis care, fostering collaborative learning, standardized outcome measurement, and participatory governance. These approaches have demonstrated significant improvements in treatment engagement, functional recovery, and reduction in hospitalization rates, while also addressing disparities in access and outcomes. The ongoing development of EPINET and ONTrackNY continues to inform best practices and drive innovation in early intervention for psychosis. Challenges have included disrupted funding, high staff turnover, variable agency-level support, gaps in follow-up care, and implementing the model at rural sites.

Literature References: Basaraba CN, Scodes JM, Dambreville R, et al: Prediction tool for individual outcome trajectories across the next year in first-episode psychosis in coordinated specialty care. *JAMA Psychiatry*. 2023;, 80(1):49-56.

van der Ven E, Jones N, Bareis N, et al.: An intersectional approach to ethnoracial disparities in pathways to care among individuals with psychosis in coordinated specialty care. *JAMA Psychiatry*. 2022, 79(8):790-798.

TRANSFORMING THE HEALTHCARE SYSTEM WITH THE BIPOLAR ACTION NETWORK

Andrew Nierenberg, Massachusetts General Hospital

Individual Abstract Background: The system of care for people with bipolar disorder is fragmented and disjointed. Gaps in care are significant: methods of assessment are inconsistent, treatments vary widely and are often not guideline-concordant, and care is poorly coordinated. At a population level, outcomes have not improved in over 20 years, outcomes are not systematically tracked, and patients often have no input in their care design.

Methods: To address these gaps, we designed a Learning Health Network (LHN) for bipolar disorder. LHNs use an organizational architecture that facilitates collaborative, data-driven improvements in population health outcomes. They promote a culture of continuous learning, data sharing, and innovation, with a focus on achieving outcomes that matter to all stakeholders and accelerating the rate of improvement. We used a structured, idealized system co-design process to align diverse stakeholders—patients, families, clinicians, and system leaders—around shared goals and to envision a radically improved future state of care. The Bipolar Action Network design process had four objectives: 1) Build a community by fostering a shared commitment to improving health and well-being among stakeholders, 2) Identify and test changes in care organization to enhance system performance, 3) Develop leaders and cultivate their skills in systems thinking and quality improvement (QI), and 4) Develop a rapid learning system by establishing measures to track the processes and outcomes of bipolar care, and the structures and actions to continuously evaluate and optimize the performance of the system.

Results: We engaged 17 healthcare systems and a design team comprising approximately 50 individuals representing patients, caregivers, clinicians, researchers, and advocacy organizations. The collaborative design processes yielded several outputs: a shared network vision, mission, theory of change documented in Key Driver Diagrams and logic models, an environmental scan of existing evidence and innovations, design concepts, and a patient journey map integrated into a "blueprint" of system changes. Stakeholders prioritized the design concepts based on potential impact and feasibility. We also developed core

governance policies, data capture tools, a registry, an online knowledge repository and an evaluation plan. A dashboard was designed to provide network participants with a “common operating picture”, enabling situational awareness and collaborative decision-making. We also began building systems change capacity through quality improvement (QI) training for prospective clinical site leaders and co-production training for participants.

Conclusion: Through a deliberate design process, we established an LHN organization, encompassing collaborative relationships, design, structures, theories, tools, and measurement systems, to transform the system of care and achieve better outcomes for people living with bipolar disorder. This LHN can serve as a prototype to improve outcomes for people with other serious psychiatric disorders.

Literature References:

1. Considerations in the Development of Learning Health Networks for Mood Disorders. Lipschitz JM, Adler C, Almeida J, et al. Journal of Affective Disorders. 2025.
2. Nierenberg AA, Margolis P, Strakowski S, Trivedi M, Yatham LN, Bipolar Disorder Learning Health N. A Bipolar Learning Health Network: An innovation whose time has come. Bipolar Disord. May 2023;25(3)

***^DEVELOPING TREATMENTS FOR THE NON-MOTOR SYMPTOMS OF PARKINSON'S DISEASE**

Gerard Sanacora, Yale University

Overall Abstract: The non-motor mood symptoms associated with Parkinson's disease (PD) are associated with increased disability and accelerated disease progression. But standard serotonergic-based antidepressants have limited efficacy for PD depression, and there has been little progress in understanding its pathology or evaluation of new treatments. With an increased understanding of the PD-related pathology in mood-related circuitry there is a growing interest in developing plasticity-enhancing interventions such as ketamine and 5HT_{2A} targeting drugs as treatments for the mood and other non-motor symptoms associated with PD. In this panel Shlomi Raz will present data on a Non-hallucinogenic serotonin 5-HT_{2A/2C} receptor agonist AB-300 that was assessed in the tetrabenazine (TBZ) progressive-ratio rodent model, a validated paradigm for probing motivational dysfunction that parallels non-motor symptoms of apathy and depression in Parkinson's disease. TBZ reliably induced a marked reduction in motivated responding, reflected by fewer lever presses and rewards earned. AB-300 significantly reversed these deficits, with the strongest and most consistent improvements seen at 5 mg/kg and particularly within the low-motivation subgroup—an analogue for patients with prominent apathy. Bupropion served as a positive control and confirmed assay sensitivity. These results show that AB-300 restores goal-directed behavior in an established translational model of apathy, supporting its advancement into the Phase Ib PD trial where non-motor symptoms, including apathy and motivational loss, are key readouts alongside motor outcomes. Psilocybin shows early promise for treating mood dysfunction associated with depression, but its potential benefit in PD is unclear, as safety concerns have excluded people with neurodegenerative disease from previous trials. Ellen Bradley will present findings on psilocybin's effects from the first open-label pilot study in PD (NCT04932434). 12 participants with mild to moderate stage PD plus depression and/or anxiety (mean age 63.2 ± 8.2 years, 5 women) received psilocybin (one 10 mg followed by one 25 mg dose) paired with a course of psychotherapy. Tolerability, preliminary efficacy, and changes in emotional and cognitive experience were examined using natural language

processing of psychotherapy session content. The design of a recently initiated randomized placebo controlled trial funded by the Michael J Fox Foundation (MJFF) exploring the efficacy of psilocybin in PD will also be discussed. Measures of synaptic plasticity has been demonstrated to be lower in individuals with PD. Sophie Holmes will present the results of a study demonstrating this using PET imaging and then present newly collected data from a second recently completed MJFF funded study of ketamine treatment of PD. The results of of the 50 person randomized controlled trial will be presented for the first time in a national meeting. The treatment with ketamine demonstrated both statistical and clinically meaningful benefits over placebo on the primary endpoint of week-8 MADRS. Secondary outcome measures also largely favored ketamine treatment over placebo. Overall, the treatment was relatively well tolerated, further suggesting a potential role for ketamine in the treatment of the Parkinson's associated mood symptoms. Lastly, Daniel Weintraub will serve as the discussant helping to provide perspective on the relevant neurobiology, unmet need, and meaningfulness of the data presented.

Learning Objective 1: To familiarize the audience with the prominent non-motor symptoms of Parkinson's disease and the novel treatment approaches being tested for the treatment of non-motor symptoms of Parkinson's disease.

Learning Objective 2: To outline the preclinical and clinical emerging data suggesting possible novel treatment effects of the non-motor symptoms associated with Parkinson's disease.

Literary References: Shi Y, Dobkin R, Weintraub D, Cho HR, Caspell-Garcia C, Bock M, Brown E, Aarsland D, Dahodwala N. Association of Baseline Depression and Anxiety with Longitudinal Health Outcomes in Parkinson's Disease. *Mov Disord Clin Pract*. 2024 Sep;11(9):1103-1112

Bradley ER, Sakai K, Fernandes-Osterhold G, Szigeti B, Ludwig C, Ostrem JL, Tanner CM, Bock MA, Llerena K, Finley PR, O'Donovan A, Zuzuarregui JRP, Busby Z, McKernan A, Penn AD, Wang ACC, Rosen RC, Woolley JD. Psilocybin therapy for mood dysfunction in Parkinson's disease: an open-label pilot trial. *Neuropsychopharmacology*. 2025 Jul;50(8):1200-1209

AB-300, A NOVEL 5-HT_{2A/2C} AGONIST, REVERSES MOTIVATIONAL DEFICITS IN A TETRABENAZINE MODEL OF PARKINSON'S DISEASE APATHY

Daniel Jeffries, Ariadne Bio

Individual Abstract Background: Apathy is one of the most prevalent and debilitating non-motor symptoms (NMS) of Parkinson's Disease (PD), affecting up to 70% of patients. It is characterized by reduced initiative and goal-directed behavior, significantly increasing caregiver burden and predicting cognitive decline. Despite its impact, there are no FDA-approved therapies for PD apathy. While dopaminergic replacement therapies effectively treat motor symptoms, they often fail to improve apathy, and standard treatments like SSRIs can exacerbate it. Emerging neuroimaging evidence suggests that serotonergic degeneration—specifically the loss of 5-HT_{2A} receptor availability—plays a critical role in the pathophysiology of NMS in PD. We investigated the therapeutic potential of AB-300, a novel, non-hallucinogenic 5-HT_{2A/2C} receptor agonist, to reverse motivational deficits in a translational rodent model.

Methods: The efficacy of AB-300 was evaluated in a tetrabenazine (TBZ)-induced model of reduced motivation. Male Long-Evans rats (N=27) were trained on a Progressive Ratio (PR) schedule of reinforcement, where the effort required to obtain a food reward increases exponentially. Once stable performance was achieved, apathy was induced via the administration of the VMAT2 inhibitor TBZ (2.5 mg/kg IP), which depletes monoamines and reliably induces a low-effort bias. In a randomized, counterbalanced, repeated-measures design, animals received AB-300 (5 mg/kg or 10 mg/kg SC) or vehicle 15 minutes prior to testing. Bupropion (20 mg/kg IP) served as a positive control. Primary endpoints included the total number of lever presses and rewards earned (breakpoint).

Results: Administration of TBZ significantly reduced motivational behavior compared to vehicle control, lowering both total lever presses and rewards earned ($p < 0.001$). Treatment with AB-300 significantly attenuated these TBZ-induced deficits. At the 5 mg/kg dose, AB-300 significantly increased the number of rewards earned compared to the TBZ/Vehicle condition ($p < 0.001$). This restorative effect was comparable to that of the positive control, Bupropion ($p < 0.001$). Subgroup analysis revealed that the efficacy of AB-300 was most pronounced in animals with lower baseline motivation ("low performers"), effectively normalizing their effort-based decision-making. The 10 mg/kg dose also improved performance but did not show increased efficacy over the 5 mg/kg dose.

Conclusions: AB-300 demonstrated robust efficacy in reversing experimentally induced motivational deficits driven by monoamine depletion. These data support the hypothesis that 5-HT_{2A/2C} agonism can restore goal-directed behavior in the absence of intact dopaminergic tone. Given the specific serotonergic pathology associated with apathy in human PD, AB-300 represents a promising, novel therapeutic candidate for the treatment of non-motor symptoms in Parkinson's Disease, addressing a significant unmet need where current standard-of-care options are insufficient.

Literature References: 1) Maillet A, Krack P, Lhommée E, et al. The prominent role of serotonergic degeneration in apathy, anxiety and depression in de novo Parkinson's disease. *Brain*. 2016;139(9):2486-2502.

2) Maher S, Yilmaz Z, O'Keane V, et al. Treatment of Apathy in Parkinson's Disease and Implications for Underlying Pathophysiology. *J Clin Med*. 2024;13(8):2216.

PSILOCYBIN THERAPY FOR DEPRESSION IN PARKINSON'S DISEASE

Ellen Bradley, UCSF

Individual Abstract Background: Depression is common in Parkinson's disease (PD), frequently treatment-resistant, and associated with reduced quality of life as well as accelerated physical and cognitive decline. Early evidence suggests that the serotonergic psychedelic psilocybin may be a promising novel intervention for treatment-resistant mood dysfunction in non-PD populations, but no prior psilocybin trials have enrolled participants with PD or any other neurodegenerative illness.

Methods: We aimed investigate the safety, tolerability, and preliminary efficacy of oral synthetic psilocybin paired with psychotherapeutic support for people with PD and comorbid mood dysfunction. In this open-label, single-arm pilot study (NCT04932434), we recruited people aged 40-75 with mild to moderate idiopathic PD (Hoehn and Yahr stages 1-3) who also met criteria for a depressive and and/or anxious disorder and all other inclusion/exclusion criteria. We used a dose escalation protocol where participants first

received a 10 mg safety dose of psilocybin and, if this was well-tolerated, received a 25 mg treatment dose approximately 2 weeks later. Primary outcomes were safety and tolerability measured by the incidence, severity, and treatment-relatedness of adverse events (AEs) elicited through assessments of vital signs, acute subjective drug effects, changes in motor and non-motor symptoms, psychotic symptoms, suicidality, cognitive performance, and care partner distress. The secondary outcome was feasibility measured by recruitment and retention rates as well as treatment satisfaction. We explored preliminary efficacy as well as changes in blood-based markers of inflammatory activity. As this was a pilot study, no formal sample size calculation was performed. We used mixed effects linear models to examine changes in assessment scores from pre- to post-treatment. This study is registered at ClinicalTrials.gov, NCT04932434.

Results: 12 participants (mean age 63.2 [SD 8.2] years, 5 women) enrolled; all completed the full protocol, receiving both doses of psilocybin. There were no serious adverse events and no medications were required to manage acute cardiovascular or psychotomimetic effects of psilocybin. Ten of 12 participants experienced treatment-emergent adverse events; the most frequent were anxiety, nausea, and increased blood pressure during the period of acute psilocybin effects. We observed no worsening of psychotic symptoms or negative effects on cognitive performance. Motor symptoms measured by the Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) improved (Part II: -7.5 ± 0.9 , $p < .001$, $g=1.2$; Part III: -4.6 ± 1.3 , $p=.001$; $g=0.3$), as did performance in select cognitive domains (Paired Associates Learning [-0.44 ± 0.14 , $p=.003$, $g=0.4$], Spatial Working Memory [-0.52 ± 0.17 , $p=.003$, $g=0.7$], and Probabilistic Reversal Learning [2.9 ± 0.9 , $p=.003$, $g=1.3$]). These improvements were sustained until the final safety assessment one month following drug exposure. Depression measured by the Montgomery-Asberg Depression Rating Scale improved post-treatment (-9.3 ± 2.7 , $p=.001$, $g=1.0$); this improvement persisted to the final assessment three months following drug exposure. Analyses of inflammatory markers are in process and anticipated to be finalized prior to this meeting.

Conclusion: This study provides the first data on psilocybin's safety and tolerability in people with PD. Results suggest that randomized clinical trials to examine the effects of psilocybin therapy on mood dysfunction as well as other PD symptoms are warranted.

Literature References: Bradley ER, Sakai K, Fernandes-Osterhold G, et al. "Psilocybin Therapy for Mood Dysfunction in Parkinson's Disease: An Open-Label Pilot Trial." *Neuropsychopharmacology*. 2025; 10.1038/s41386-025-02097.

Weintraub D, Aarsland D, Chaudhuri KR, et al. "The Neuropsychiatry of Parkinson's Disease: Advances and Challenges." *The Lancet Neurology*. 2022; 10.1016/S1474-4422(21)00330-6.

TARGETING SYNAPTIC LOSS IN PARKINSON'S DISEASE DEPRESSION WITH KETAMINE

Sophie Holmes, Yale University

Individual Abstract: Depression is highly prevalent in Parkinson's disease (PD) and contributes to disability, diminished quality of life, and accelerated disease progression. Serotonergic antidepressants show limited efficacy in PD depression, and little progress has been made in clarifying its underlying mechanisms or developing targeted treatments. We hypothesize that PD-related pathology within mood-related circuitry contributes to depression in PD, and that plasticity-enhancing interventions such as ketamine may

effectively target these mechanisms. Synaptic density ([¹¹C]UCB-J PET) and functional network organization (fMRI) were measured in PD participants with depression (n=10), without depression (n=20), and healthy controls (n=18). In a parallel-design randomized clinical trial (n=51), PD participants with depression received six infusions of ketamine or placebo. A mechanistic imaging subset (13 per arm) completed pre- and post-treatment [¹¹C]UCB-J PET and fMRI. The trial database was locked on November 18, 2025, and unblinding has only just occurred. Full analyses are now underway, and complete clinical and mechanistic results will be presented in May 2026. Synaptic density was significantly reduced in mood-related regions—including the dlPFC, ACC, amygdala, and hippocampus—in PD depression compared with both PD without depression and healthy controls (all $p < 0.05$). Lower synaptic density in the dlPFC, amygdala, and hippocampus correlated with greater depression severity (all $p < 0.05$). Functional connectivity was reduced within default mode and fronto-limbic networks in PD depression. We observed a significant difference on the primary outcome—change in MADRS from baseline to post-treatment ($p = 0.0063$). Participants in the placebo group showed a mean reduction of –10 points, whereas those receiving ketamine demonstrated a –16-point reduction. Ketamine was well tolerated, with no serious adverse events reported. These convergent clinical and mechanistic findings suggest that synaptic and network abnormalities represent a key pathway in PD depression—one that ketamine may be well positioned to target. With unblinding now complete, this trial provides the first randomized, controlled efficacy data for ketamine in a neurodegenerative disease. The results may support ketamine as a mechanism-informed therapeutic option for PD depression and help guide broader strategies to treat neuropsychiatric symptoms in neurodegeneration.

Literature References: The neuropsychiatry of Parkinson's disease: advances and challenges Weintraub, D et al. The Lancet Neurology, Volume 21, Issue 1, 89 - 102

Duman, R.S., Aghajanian, G.K., Sanacora, G. and Krystal, J.H., 2016. Synaptic plasticity and depression: new insights from stress and rapid-acting antidepressants. Nature medicine, 22(3), pp.238-249.

4:30 p.m. - 6:00 p.m.

Plenary Panel: Artificial Intelligence: Understanding the Present and Anticipating the Future

ARTIFICIAL INTELLIGENCE: UNDERSTANDING THE PRESENT AND ANTICIPATING THE FUTURE

Valentina Mantua, Center for Drug Evaluation and Research, Food and Drug Administration

Overall Abstract: Artificial intelligence is fundamentally transforming psychiatric practice across multiple domains, from accelerating drug discovery and development, to advancing digital therapeutics and enhancing clinical decision support systems. These technological advances hold unprecedented promise for improving diagnostic accuracy, personalizing treatment approaches, and expanding access to mental health care. However, these innovations bring significant challenges that must be carefully navigated, including algorithmic bias that may perpetuate health disparities, privacy vulnerabilities in sensitive mental health data, model hallucinations that could provide inaccurate clinical information, automation complacency among healthcare providers, performance drift as models encounter

new populations, lack of transparency in algorithmic decision-making, and ambiguous accountability frameworks when AI systems influence patient care. This conference plenary session will feature three presentations followed by a panel of experts that explore the current landscape, emerging opportunities, and critical challenges facing AI implementation in psychiatry. The first speaker will provide a comprehensive overview of AI technologies currently being deployed in psychiatric settings, examining their applications across clinical research and practice while addressing both the technical capabilities and practical limitations of these systems. The second speaker will examine the rapidly emerging role of LLMs and AI chatbots in psychiatric care, exploring their therapeutic potential and clinical risks, while critically evaluating implementation considerations, including safety protocols, risk simulation, benchmarking, therapeutic boundaries, and integration with traditional care models. While the talk will primarily focus on chatbots for care purposes, the clinical role of LLMs and AI for diagnostic and clinical decision support will also be considered. The third speaker will present practical, real-world examples of AI applications in clinical trial analyses, demonstrating how machine learning algorithms, natural language processing, and predictive modeling are advancing psychiatric research methodologies, improving patient recruitment and retention, and accelerating the translation of research findings into clinical practice. The session will conclude with an expert panel discussion addressing regulatory considerations, ethical frameworks, and strategies for responsible AI implementation that prioritizes patient safety and therapeutic benefit while fostering continued innovation in psychiatric care.

USING ARTIFICIAL INTELLIGENCE AND SOCIAL MEDIA DATA FOR POPULATION MENTAL HEALTH SURVEILLANCE

Yulin Hswen, Artificial Intelligence Interdisciplinary Institute at Maryland Computer, Mathematics and Natural Sciences Epidemiology and Biostatistics, School of Public Health University of Maryland

Abstract: Digital technologies have transformed how individuals express psychological distress, seek support, and interact with mental health information. Advances in artificial intelligence (AI) have enabled the analysis of large scale unstructured data sources such as social media, search queries, and digital text to detect early signals of mental health risk at the population level. This plenary will examine how computational psychiatry and digital mental health methods can complement traditional clinical models by enabling real time surveillance of depression, anxiety, and substance use. Drawing on empirical examples from large scale social media and multimodal data studies, this talk will highlight how natural language processing, computer vision, and machine learning can identify patterns of distress, risk escalation, and exposure to harmful content before individuals present to clinical care. The presentation will also address ethical considerations including privacy, algorithmic harm, representativeness, and the risk of reinforcing stigma or inequities through digital systems.

Learning Objective 1: Describe how artificial intelligence methods applied to social media and digital text data can be used to monitor population level mental health risks in real time.

Learning Objective 2: Evaluate the ethical, clinical, and equity considerations involved in integrating digital mental health surveillance tools into psychiatric research and practice.

Literature References: Chancellor, S., and De Choudhury, M. (2020). Methods in predictive techniques for mental health status on social media: a critical review. *NPJ digital medicine*, 3(1), 43.

Insel, T. R. (2017). Digital phenotyping: technology for a new science of behavior. *Jama*, 318(13), 1215-1216.

ASSESSING AI FOR CLINICAL CARE AND RESEARCH

John Torous, Beth Israel Deaconess Med. Ctr. and Harvard Medical School

Abstract: While advances in AI technology abound, there is a growing concern that a lack of standards and safety protocols for the use of AI in both care and research is now the chief barrier to progress. While no single technology company, regulator, organization, or hospital holds the solution, the need for some consensus and ground rules has become self-evident. This talk will review efforts towards this goal with a focus on selected efforts, such as that in the UK by the MHRA, in the US by NAMI, and broadly across the published literature/public internet.

Learning Objective 1: Assess the state of AI regulation both in the United States as well as abroad.

Learning Objective 2: Identify common themes around safety and rigor across various AI regulation or guidance systems

Literature References: Dwyer B, Flathers M, Sano A, Dempsey A, Cipriani A, Gazi AH, Hill B, Gorban C, Rodriguez CI, Stromeyer IV C, King D. Mindbench. ai: an actionable platform to evaluate the profile and performance of large language models in a mental healthcare context. *NPP—Digital Psychiatry and Neuroscience*. 2025 Nov 14;3(1):28.

Torous J, Cipriani A. A Paradigm Shift in Progress: Generative AI's Evolving Role in Mental Health Care. *JMIR Mental Health*. 2025 Dec 17;12:e82369.

BRIDGING AI INNOVATION AND CLINICAL TRIAL DATA IN PSYCHIATRY: MATHEMATICAL LIMITS AND CLINICAL CONSEQUENCES

Joseph Geraci, NetraMark Holdings

Abstract: Artificial intelligence is fundamentally transforming psychiatric practice across multiple domains, from accelerating drug discovery and development, to advancing digital therapeutics and enhancing clinical decision support systems. These technological advances hold unprecedented promise for improving diagnostic accuracy, personalizing treatment approaches, and expanding access to mental health care. However, these innovations bring significant challenges that must be carefully navigated, including algorithmic bias that may perpetuate health disparities, privacy vulnerabilities in sensitive mental health data, model hallucinations that could provide inaccurate clinical information, automation complacency among healthcare providers, performance drift as models encounter new populations, lack of transparency in algorithmic decision-making, and ambiguous accountability frameworks when AI systems influence patient care. This conference plenary session will feature three presentations followed by a panel of experts that explore the current landscape, emerging opportunities, and critical challenges facing AI implementation in psychiatry. The first speaker will provide a comprehensive overview of AI technologies currently being deployed in psychiatric settings, examining their applications across clinical research and practice while addressing both the technical capabilities and practical limitations of these systems. The second speaker will examine the rapidly emerging role of LLMs and AI chatbots in psychiatric care, exploring their therapeutic potential, while critically evaluating implementation considerations including safety protocols, therapeutic boundaries, and

integration with traditional care models. The third speaker will present practical, real-world examples of AI applications in psychiatric clinical trial analyses, illustrating both where machine learning, natural language processing, and predictive modeling add value and where they encounter fundamental limits in typically sized, heterogeneous datasets, with implications for study design, patient stratification, and the responsible translation of research findings into clinical practice. The session will conclude with an expert panel discussion addressing regulatory considerations, ethical frameworks, and strategies for responsible AI implementation that prioritizes patient safety and therapeutic benefit while fostering continued innovation in psychiatric care.

Learning Objective 1: Understand why modern AI systems, including large language models, face fundamental limits when applied to typically sized, heterogeneous psychiatric clinical trial datasets, and how these limits affect reliability, reproducibility, and interpretation of results.

Learning Objective 2: Learn how augmented AI approaches can work within these limits to support clinical trial design, patient stratification, and evidence generation—without conflating statistical artifacts with true treatment effects.

Literature References: Geraci, J., Qorri, B., Tsay, M. et al. Explainable AI-driven precision clinical trial enrichment: demonstration of the NetraAI platform with a phase II depression trial. *npj Digit. Med.* 8, 749 (2025). <https://doi.org/10.1038/s41746-025-02143-7>

Geraci, J., Rao, P., Grandinetti, C., Qorri, B., Nadolny, P., Ayalew, K., Bregnhøj, L., Edwards, L., Hofmann, K., Khozin, S., Schaltenbrand, N., Stemmler, T., Yeomans, A., Zambas, D. and Khin, N., (2025) “Current Opportunities for the Integration and Use of Artificial Intelligence and Machine Learning in Clinical Trials: Good Clinical Practice Perspectives”, *Journal of the Society for Clinical Data Management* 5(2). doi: <https://doi.org/10.47912/jscdm.426>

Friday, May 29, 2026

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

Panel Sessions

***WHAT TO KNOW ABOUT KETAMINE SAFETY: PATIENT MONITORING, NEUROTOXICITY, AND CONSIDERATIONS FOR SPECIAL PATIENT POPULATIONS**

Benjamin Brody, Weill Cornell Medical College

Overall Abstract: Twenty-five years have passed since the publication of the initial report that ketamine hydrochloride has rapid acting antidepressant properties. While initially established as a treatment for refractory depression, ketamine therapy has emerged as a promising intervention for a diverse range of psychiatric conditions, including obsessive-compulsive disorder (OCD), substance use disorders, anxiety disorders, post-traumatic stress disorder among others. Unlike esketamine, racemic ketamine is not regulated by a Risk Evaluation and Mitigation (REMS) program, leaving clinicians far more latitude to use ketamine in varied formulations and settings with limited outcome data to inform their practices. The laissez faire regulatory environment for racemic ketamine also leaves

clinicians with limited practical guidance to weight when considering ketamine therapy. In this symposium, clinician investigators with experience leading ketamine services and research groups summarize emerging safety considerations. They will review FDA guidance about unmonitored ketamine use, published and unpublished safety data from their own work, and illustrative case examples that highlight safety risks and opportunities. Dr. Benjamin Brody, Service Chief for Acute Care Services at Weill Cornell Medicine / Psychiatry and founding chief of the ketamine service in the department of Psychiatry, will discuss adverse reactions during ketamine therapy including acute dysphoria, hypertensive urgency, risks associated with unmonitored or remote monitoring of ketamine use, and considerations for individuals with substance use disorders. Dr. Samuel Wilkinson, Medical Director of the Yale Depression Research Program, will review evidence of the potential for neurotoxicity with long term ketamine exposure from both preclinical and human studies, highlighting risks associated with frequent or high-dose use. These studies underscore 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 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. Dr. Joshua Rosenblat, a staff psychiatrist and clinician-researcher at the Mood Disorders Psychopharmacology Unit at Toronto Western Hospital, will review risks associated with ketamine therapy in special populations including patients with co-occurring depression and PTSD, borderline personality disorder, and older adults and end-of-life cancer. Dr. Cristina Cusin will serve as discussant, contextualizing the issues and emphasizing the importance of team-based collaborative care to prevent burnout and optimize outcomes when taking care of patients with medically and psychiatrically complex, who are at chronic high risk for suicide. Dr. Cusin is the director and founder of the Massachusetts General Hospital Ketamine clinic for treatment-resistant depression, and is involved in numerous research studies on ketamine in treatment-resistant mood disorders at MGH.

Learning Objective 1: Participants will describe the potential for acute and long-term side effects and adverse outcomes associated with ketamine therapy to inform ketamine referrals and informed consent discussions.

Learning Objective 2: Participants will describe psychiatric and general medical comorbidities and concomitant therapies such as PTSD, substance use disorders, personality disorders, hypertension, use of benzodiazepines or naltrexone that should contextualize a decision to refer a patient for ketamine therapy.

Literary References:

1. Brody, B. D., Popeo, D. M., Smetana, R. W., and Kanellopoulos, D. (2025). How Do We Get Ketamine Safety Right? Three Questions From a Clinical Service. *The Journal of clinical psychiatry*, 86(3), 25com15946.
2. Li, S. W., Kumpf, K. T., Urrutia, J., Krystal, J. H., Sanacora, G., and Wilkinson, S. T. (2025). Ketamine for depression, but at what cost? a review of ketamine's neurotoxic effects from preclinical and human studies. *American Journal of Psychiatry*, 182(10), 903-912.

RACEMIC KETAMINE SIDE EFFECTS, ADVERSE REACTIONS, AND MONITORING

Benjamin Brody, Weill Cornell Medical College

Individual Abstract: Racemic ketamine is not governed by a Risk Evaluation and Mitigation (REMS) program, giving practitioners broad latitude to prescribe varying doses, frequencies and formulations with few restrictions. This limited regulatory oversight posed few concerns in the early years of psychotropic ketamine use, when the route of administration was primarily intravenous and thus by necessity administered by a healthcare professional. The wide adoption of telehealth during the covid pandemic paired with compounding pharmacies capable of dispensing lozenges or nasal sprays directly to consumers has moved ketamine therapy into a higher-risk landscape. Ketamine clinics, telehealth practices and individual providers now offer ketamine in oral, intranasal and intramuscular routes along with varying levels of supervision including in-person, remote, or none at all. In 2022 and 2023, the FDA issued a series of warnings about compounded ketamine products. This guidance highlighted the lack of data to guide appropriate dosing of compounded ketamine products and three specific risks of ketamine in unmonitored settings: vital sign abnormalities, sedation, and dissociation. This lecture will review this guidance, the safety advantages of in-person monitoring for ketamine treatment, and highlight several strengths of intravenous infusion over 40 minutes. These include 100% bioavailability, precise weight-based dosing to achieve therapeutic sub-anesthetic blood levels, and the ability to pause or discontinue a partially-completed infusion if patients experience serious adverse reactions. Ketamine's dissociative properties can cause a spectrum of affective responses, from euphoria to acute dysphoria complicated by suicidal ideation. Case examples and preliminary data from the Weill Cornell Medicine / Psychiatry ketamine infusion service will highlight these risks. A final risk of unmonitored, direct to consumer ketamine prescription is that there is no mechanism to prevent diversion, or self-escalation of a substance with known addiction potential. Rates of ketamine use disorder remain low but may be rising in western countries, and preliminary evidence supports a possible role for ketamine-assisted psychotherapy in substance use disorders. Nevertheless, patients with a history of substance use disorders and those requesting higher-than standard frequency or dosing may warrant additional counselling, or referral for alternate treatments to reduce the risks of development and sequela of ketamine use disorder such as overdose, ketamine-induced cystitis, or neurotoxic effects, which will be focus of the second lecture.

Literature References: Brody, B. D., Popeo, D. M., Smetana, R. W., and Kanellopoulos, D. (2025). How Do We Get Ketamine Safety Right? Three Questions From a Clinical Service. *The Journal of clinical psychiatry*, 86(3), 25com15946.

Brody, B. D., Park, N., Christian, A., Shaffer, C. W., Smetana, R., Kotbi, N., ... and Kanellopoulos, D. (2024). Ketamine for major depressive disorder during an inpatient psychiatric admission: Effectiveness, adverse events, and lessons learned. *Journal of Affective Disorders*, 351, 293-298.

KETAMINE FOR DEPRESSION, BUT AT WHAT COST? EVIDENCE FOR NEUROTOXICITY FROM HUMAN AND ANIMAL STUDIES

Samuel Wilkinson, Yale School of Medicine

Individual Abstract: This presentation examines ketamine's neurotoxic potential across preclinical and clinical studies, then integrated findings from human clinical trials of esketamine and observational studies in recreational users. Animal studies have found that repeated or high-dose subanesthetic ketamine administration results in consistent excitotoxic neuronal damage and lasting cognitive deficits, especially in perinatal animals. Infrequently administered relatively low and moderate subanesthetic doses (< 1 mg/kg approximate human intravenous equivalent) do not yield overt histopathology in rat and nonhuman primate models. In humans, observational studies in frequent high-dose (> 1 g/day) ketamine users show memory and executive function impairments. In contrast, a large clinical trial found that intranasal esketamine at doses up to 84 mg, administered weekly or every other week for several years, is associated with maintained or slightly improved cognitive function in adults with major depression. Lower cognitive function (attention, processing speed) showed some potential worsening among elderly patients; the clinical significance of this is unknown. Direct comparisons of esketamine and off-label racemic ketamine at higher doses have not been done. These studies underscore 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 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.

Literature References:

1. Brody, B. D., Popeo, D. M., Smetana, R. W., and Kanellopoulos, D. (2025). How Do We Get Ketamine Safety Right? Three Questions From a Clinical Service. *The Journal of clinical psychiatry*, 86(3), 25com15946.
2. Li, S. W., Kumpf, K. T., Urrutia, J., Krystal, J. H., Sanacora, G., and Wilkinson, S. T. (2025). Ketamine for depression, but at what cost? a review of ketamine's neurotoxic effects from preclinical and human studies. *American Journal of Psychiatry*, 182(10), 903-912.

USE OF KETAMINE FOR DEPRESSION IN SPECIAL POPULATIONS

Joshua Rosenblat, University of Toronto

Individual Abstract: Replicated randomized controlled clinical trials (RCTs) have demonstrated rapid and robust antidepressant effects with ketamine for treatment resistant depression (TRD). Safety and tolerability of ketamine infused at 0.5-1 mg/kg over 40 minutes has been established in RCTs and real world effectiveness (RWE) studies, however, many RCTs excluded more complex patient presentations raising questions about the safety and effectiveness of ketamine in these specific subgroups that have been under represented in clinical trials. The present session will review existing evidence and present original data from our group evaluating the clinical utility and safety of ketamine for TRD in older adults, medically ill patients near end of life, patients with comorbid borderline personality disorder (BPD) and bipolar disorder. In all of these subgroups, we observed comparable antidepressant effectiveness, however, this presentation will focus specifically on safety and tolerability in these groups. Older Adults: In an RWE study (NCT04209296), we treated fifty-three older adults (Mage = 67, SD = 6; 57% female [n = 30]) with an acute course of 4 ketamine infusions. Thirty-six participants (69%) experienced treatment-emergent

hypertension during at least 1 infusion, and 10 (19%) required intervention with an antihypertensive. Drowsiness was the most commonly reported adverse event (50% of infusions; n = 73). End of Life: We conducted a single-arm, open-label phase II trial in participants with advanced cancer with moderate to severe MDD received three flexible doses of intranasal (IN) ketamine (50–150 mg) over a one-week period (NCT03410446). Mean MADRS scores decreased significantly from baseline (mean MADRS of 31, standard deviation 7.6) to Day 8 (11 +/- 7.4) with an overall decrease of 20 points (p < 0.001). Common adverse effects included fatigue, dissociation, nausea, dysgeusia and headaches; almost all adverse effects were mild and transient, resolving within 2 h of each ketamine dose with one dropout related to adverse effects (negative dissociative episode). TRD with comorbid BPD: In a TRD population with comorbid BPD (N=100; n=50 BPD-positive compared with n=50 BPD-negative), an acute course of 4 ketamine infusions was administered (NCT04209296). Both BPD-positive and BPD-negative groups improved significantly on the QIDS-SR16, QIDS-SR16 suicide ideation item, anxiety, and functionality scales with large effect sizes. There was no significant difference between groups with regards to side effects or drop out. No treatment-emergent suicidality was observed. There was a trend for greater dissociative symptoms during infusions that did not reach statistical significance. Treatment Resistant Bipolar Depression (TRBD): We conducted a randomized, midazolam-controlled clinical trial in 69 TRBD patients receiving an acute course of 4 ketamine or 4 midazolam infusions over 2-weeks (NCT05004896). Safety and tolerability were comparable to previous studies in major depressive disorder (MDD). We closely monitored for any treatment emergent mania, hypomania or psychosis on a daily basis during the trial. No evidence of treatment emergent mania or psychosis were observed in either arm, however, 1 participant in each arm developed mixed features, suggesting of a 2-3% risk of treatment emergent mixed features with ketamine or midazolam. This estimate aligns with previous RWE studies and single dose ketamine trials in bipolar disorder, suggesting risk of mania or hypomania is relatively low. Taken together, the safety and tolerability of ketamine in more complex patient populations appears promising with comparable side effects as observed in MDD RCTs that often excluded these individuals.

Literature References: Kevork Danayan, Noah Chisamore, Nelson B. Rodrigues, Joshua D. Di Vincenzo, Shakila Meshkat, Zoe Doyle, Rodrigo Mansur, Lee Phan, Farhan Fancy, Edmond Chau, Anika Tabassum, Kevin Kratiuk, Anil Arekapudi, Kayla M. Teopiz, Roger S. McIntyre, Joshua D. Rosenblatt,

Real world effectiveness of repeated ketamine infusions for treatment-resistant depression with comorbid borderline personality disorder, *Psychiatry Research*, Volume 323, 2023, 115133, <https://doi.org/10.1016/j.psychres.2023.115133>.

Orly Lipsitz, Joshua D. Di Vincenzo, Nelson B. Rodrigues, Danielle S. Cha, Yena Lee, David Greenberg, Kayla M. Teopiz, Roger C. Ho, Bing Cao, Kangguang Lin, Mehala Subramaniapillai, Alastair J. Flint, Kevin Kratiuk, Roger S. McIntyre, Joshua D. Rosenblatt, Safety, Tolerability, and Real-World Effectiveness of Intravenous Ketamine in Older Adults With Treatment-Resistant Depression: A Case Series, *The American Journal of Geriatric Psychiatry*, Volume 29, Issue 9, 2021, Pages 899-913, <https://doi.org/10.1016/j.jagp.2020.12.032>.

***^THE DISCOVERY AND CLINICAL DEVELOPMENT OF (2R,6R)-HYDROXYNORKETAMINE FOR DEPRESSION AND PAIN**

Todd Gould, University of Maryland School of Medicine

Overall Abstract: This symposium will present the translational development of (2R,6R)-hydroxynorketamine (2R6R), a ketamine metabolite, which is currently in human phase II trials for treatment resistant depression, obsessive compulsive disorder, and neuropathic pain. The session brings together the teams responsible for the discovery, IND-enabling work, and early-phase clinical studies across two therapeutic indications, providing attendees with an end-to-end view of a novel psychopharmacologic agent advancing through the development pipeline. Dr. Todd Gould from the University of Maryland School of Medicine will describe the preclinical discovery of 2R6R's efficacy in depression models, including mechanistic studies, pharmacology, and translational biomarkers supporting its advancement into development. He will highlight how understanding stereoisomer-specific activity and non-NMDA receptor mechanisms informed selection of 2R6R as a drug candidate with a potentially improved safety and tolerability profile relative to ketamine. Dr. Craig Thomas from the NIH National Center for Advancing Translational Sciences will detail the IND-enabling program, including synthesis and formulation, PK/PD modeling, and preclinical safety findings that guided first-in-human dosing and risk-mitigation strategies. Dr. Carlos Zarate (NIH National Institute of Mental Health) will present key findings from the first-in-human Phase I study, summarizing safety, tolerability, PK parameters, and early biomarker signals relevant to antidepressant activity, as well as the design, rationale, and progress of the treatment resistant depression Phase II trial including clinical endpoints, biomarker strategy, and anticipated next steps. Dr. Robert McCarthy, Rush University Medical Center, will present data demonstrating analgesic activity in preclinical pain models and describe the design and status of the Phase II study evaluating analgesic efficacy, durability of response, and comparative outcomes for a single infusion of 2R6R versus ketamine or saline in individuals with neuropathic extremity pain. The discussant (Dr. Dawn Ionescu, Johnson and Johnson Innovative Medicine) will integrate themes across presentations, emphasizing the translational decision-making that enabled forward progression from mechanistic discovery to human studies across two indications. The panel will address scientific, regulatory, and methodological challenges unique to developing a stereoisomeric metabolite as a therapeutic agent, including the complexities of advancing an academic and NIH intramural-led program in the absence of traditional industry sponsorship and the associated implications for scalability, regulatory interaction, and trial design. Attendees will gain an integrated understanding of how mechanistic neuroscience, biomarker-driven strategy, and rigorous clinical methodology can facilitate development of novel psychopharmacologic agents. This symposium will also underscore how coordinated collaboration among academic investigators, federal research institutes, and clinical trial centers can efficiently advance innovative therapeutics addressing substantial unmet need in both mood disorders and chronic pain. This session will be of broad interest to investigators focused on drug development in mood disorders, pain and their comorbidity as well as translational neuroscience more broadly.

Learning Objective 1: Describe the mechanistic, translational, and preclinical evidence supporting the development of (2R,6R)-hydroxynorketamine as a therapeutic candidate for depression and pain.

Learning Objective 2: Identify key clinical, regulatory, and methodological considerations in advancing (2R,6R)-hydroxynorketamine from Phase I to Phase II trials across multiple indications, including biomarker and trial-design strategies.

Literary References: Zanos P, Moaddel R, Morris PJ, Georgiou P, Fischell J, Elmer GI, Alkondon M, Yuan P, Pribut HJ, Singh NS, Dossou KSS, Fang Y, Huang XP, Mayo CL,

Wainer IW, Albuquerque EX, Thompson SM, Thomas CJ, Zarate CA Jr., Gould TD (2016) NMDAR-independent antidepressant actions of ketamine metabolites. *Nature*. 533, 481-486.

Raja SM, Guptill JT, Mack M, Peterson M, Byard S, Twieg R, Jordan L, Rich N, Castledine R, Bourne S, Wilmschurst M, Oxendine S, Avula SGC, Zuleta H, Quigley P, Lawson S, McQuaker SJ, Ahmadkhaniha R, Appelbaum LG, Kowalski K, Chineta T, Barksdale K, Gufford B, Awan A, Sancho AR, Moore MC, Berrada, Cogan GB, DeLaRosa J, Radcliffe J, Pao M, Kennedy M, Lawrence Q, Goldfeder L, Amanfo L, Zanos P, Gilbert JR, Morris PJ, Moaddel R, Gould TD, Zarate, Jr. CA, Thomas CJ (2024) A Phase 1 assessment of the safety, tolerability, pharmacokinetics and pharmacodynamics of (2R,6R)-hydroxynorketamine in healthy volunteers. *Clinical Pharmacology and Therapeutics*. 116, 1314-1324.

FROM KETAMINE METABOLITE TO CANDIDATE THERAPEUTIC: PRECLINICAL DISCOVERY OF (2R,6R)-HNK RELEVANCE TO DEPRESSION TREATMENT

Todd Gould, University of Maryland School of Medicine

Individual Abstract: Rapid-acting ketamine-based therapies have reshaped antidepressant drug development, yet their dissociative side effects, abuse liability, and challenges with repeat dosing underscore the need for pharmacologically distinct alternatives. Hydroxynorketamines (HNKs) are formed in vivo after ketamine administration and the 12 HNK stereoisomers are distinguished by the position of cyclohexyl ring hydroxylation (at the 4, 5, or 6 position) and their unique stereochemistry at two stereocenters. Although HNKs were initially classified as inactive metabolites because of their lack of anesthetic effects, a series of studies have identified (2R,6R)-HNK (2R6R) as a potential mediator of the antidepressant actions of ketamine. 2R6R preserves the therapeutic potential of ketamine while exhibiting minimal NMDAR antagonism, no dissociative or anesthetic activity, and no measurable abuse liability in preclinical models. I will discuss how these preclinical data—spanning behavior, synaptic physiology, pharmacology, and translational biomarkers—led to the selection of 2R6R as a drug development candidate supporting the ongoing clinical program of 2R6R in treatment-resistant depression and other neuropsychiatric indications. Using rodent behavioral paradigms of stress- and depression-relevant phenotypes, we demonstrated that 2R6R produces rapid and sustained antidepressant-like responses at doses devoid of the locomotor, dissociative-like or anesthetic and intravenous self-administration effects typical of ketamine. Mechanistic studies revealed that 2R6R enhances AMPAR-mediated synaptic transmission and up-regulates synaptic plasticity biomarkers in hippocampal and prefrontal regions. Hippocampal Schaffer-collateral CA1 synapses are rapidly potentiated in vitro following 2R6R application, and are persistently primed to support enhanced long-term potentiation long after drug wash-out both in vivo and in vitro mediated in a mTORC1, BDNF/TrkB, IP3R, and L-type calcium channel dependent manner. Stereoisomer-specific pharmacology—including the 2R6R isomer rather than the 2S6S or racemic HNK was guided by differential efficacy in rodent models and a more favorable safety/tolerability profile. Our recent unpublished studies have assessed stereoisomer-specific synaptic effects of all 12 naturally produced HNKs identifying robust differences in pharmacodynamic properties indicating how HNK structure mediates pharmacological activity. Overall, this talk will illustrate how mechanistic neuroscience, translational pharmacology and biomarker-driven decision-making converged to move forward 2R6R from bench to clinic. Attendees will gain insight into how academic-NIH collaborations can

chart a path for novel molecules in neuropsychiatric indications — expanding the therapeutic toolkit beyond traditional monoaminergic treatments and ketamine itself.

Literature References: Riggs LM, Aronson S, Mou TCM, Pereira EFR, Thompson SM, Gould TD (2025). Bioactive ketamine metabolite exerts in vivo neuroplastogenic effects to improve hippocampal function in a treatment-resistant depression model. *Cell Reports*. 44, 115743.

(2025) Rapid hippocampal synaptic potentiation induced by ketamine metabolite (2R,6R)-hydroxynorketamine persistently primes synaptic plasticity. *Neuropsychopharmacology*. 50, 928-940.

PRECLINICAL DEVELOPMENT OF (2R,6R)-HYDROXYNORKETAMINE FOR HUMAN CLINICAL EVALUATION

Craig Thomas, NCATS, NIH

Individual Abstract: Dissociative and psychedelic agents are ushering in a new era of therapy options for a variety of mental health disorders including treatment resistant depression. While promising, the expanded access to these drugs of abuse is worrisome given our ongoing struggles containing the opioid epidemic that began with expanded use of opioid-based pain therapies. The discovery of (2R,6R)-Hydroxynorketamine as an agent that possesses ketamine-like activity in key models of depressive behavior without the dissociative and additive properties has excited the mental health community. Prior to conducting human clinical studies in key patient populations, a series of IND-enabling studies was conducted to set a clinical path for the evaluation of (2R,6R)-Hydroxynorketamine in healthy volunteers. This presentation is intended to describe the planning, methods and outcomes of these studies that led to the subsequent evaluation of (2R,6R)-Hydroxynorketamine in a phase 1 setting.

Literature References: Morris P, Moaddel R, Zanos P, Moore C, Gould TD, Zarate C, Thomas C (2017) Synthesis and NMDA receptor activity of ketamine metabolites. *Organic Letters*. 19, 4572-4575.

Morris PJ, Burke RD, Singh A, Sharna AK, Lynch DC, Lemke-Boutcher LE, Mathew S, Elayan I, Rao DB, Gould TD, Zarate CA, Zanos P, Moaddel R, Thomas CJ (2021) A comparison of the pharmacokinetics and NMDAR antagonism-associated neurotoxicity of ketamine, (2R,6R)-hydroxynorketamine, and MK-801. *Neurotoxicology and Teratology*. 106993.

CLINICAL DEVELOPMENT OF (2R,6R)-HYDROXYNORKETAMINE: ONGOING TRIALS IN TRD AND OCD AND PHASE 1 SAFETY, TOLERABILITY, AND PK/PD RESULTS IN HEALTHY VOLUNTEERS

Carlos Zarate, National Institute of Mental Health

Individual Abstract: (R,S)-Ketamine is a dissociative anesthetic with analgesic and antidepressant effects, but its dissociative adverse effects and misuse liability limit broader use despite promising efficacy. (2R,6R)-hydroxynorketamine (RR-HNK), a ketamine metabolite, lacks anesthetic and dissociative properties in preclinical models while retaining antidepressant and analgesic activity. We report the safety, tolerability, pharmacokinetics

(PK), and pharmacodynamics (PD) of RR-HNK from a Phase 1 study in healthy volunteers. The trial comprised a six-level single-ascending-dose (SAD; 0.1–4 mg/kg) and a two-level multiple-ascending-dose (MAD; 1 and 2 mg/kg) design, each administered as 40-minute intravenous infusions to mirror common ketamine dosing for depression. RR-HNK was well tolerated across all dose levels, with no serious adverse events. Measures of dissociation and sedation showed no anesthetic or dissociative effects within the examined range. PK analyses in both SAD and MAD parts demonstrated dose-proportional increases in exposure. As a PD measure—motivated by preclinical findings and ketamine’s known effects on gamma-band oscillations—quantitative EEG showed increases in gamma power in some participants at lower to mid doses. Cerebrospinal fluid sampling confirmed central nervous system exposure. RR-HNK is being investigated for treatment-resistant depression (TRD), pain, and obsessive-compulsive disorder (OCD). Ongoing studies include: (1) an OCD trial with 1:1:1 randomization to 0.25 mg/kg RR-HNK, 0.5 mg/kg RR-HNK, or placebo (IV saline), with change in OCD severity measured by the Yale–Brown Obsessive-Compulsive Scale (Y-BOCS); and (2) a single-site, randomized, double-blind, placebo-controlled, crossover study in TRD evaluating two weeks of IV RR-HNK (0.25–2.0 mg/kg), an enhancer of synaptic glutamate release. Exploratory biomarkers include gamma oscillatory power and other spectral metrics with MEG, resting-state and task-based functional connectivity with fMRI, and prefrontal glutamate and other metabolites measured using 7T ¹H-MRS. These Phase 1 findings and ongoing trials support further evaluation of RR-HNK as a non-dissociative candidate therapy for TRD, pain, and OCD.

Literature References: Highland JN, Zanos P, Riggs LM, Georgiou P, Clark SM, Morris PJ, Moaddel R, Thomas CJ, Zarate CA Jr, Pereira EFR, Gould TD. (2021) Hydroxynorketamines: pharmacology and potential therapeutic applications. *Pharmacological Reviews*. 73, 763-791.

Raja SM, Guptill JT, Mack M, et al. A phase 1 assessment of the safety, tolerability, pharmacokinetics and pharmacodynamics of (2R,6R)-hydroxynorketamine in healthy volunteers. *Clin Pharmacol Ther*. 2024;116(5):1314-1324. doi:10.1002/cpt.3391.

EVALUATION OF THE (2R,6R)-HYDROXYNORKETAMINE AS A POTENTIAL CLINICAL USEFUL ANALGESIC AGENT: TRANSLATIONAL EXPERIENCE FROM PRECLINICAL TO HUMAN STUDY

Robert McCarthy, Rush University Medical Center

Individual Abstract: Ketamine is rapidly metabolized into over twenty characterized metabolites including the active metabolite (2R,6R)-Hydroxynorketamine (HNK). Preclinical studies indicate that hydroxynorketamines exert antidepressant-relevant behavioral actions and may also have analgesic, anti-inflammatory, and other physiological effects that are relevant for the treatment of a variety of human diseases. In this presentation I will review our translational experience with (2R,6R)-HNK in murine models of clinical pain, culminating in an ongoing clinical trial under an FDA research IND in patients with neuropathic pain. Preclinical studies: We have shown (2R,6R)-HNK has analgesic properties best quantified by reduction in mechanical hyperalgesia in murine models of pain (plantar incision, peripheral nerve injury, tibial fracture and casting, and discogenic pain low-back pain). Evidence of analgesic efficacy was greater with established pain compared to those seen in naive animals. Common to findings in these models was that a brain penetrating □-amino-3-hydroxy-5-methyl-4-isoxazolepropionic (AMPA) acid receptor blocker abolished

analgesic behaviors. Consistent hippocampal protein changes in (2R,6R)-HNK treated animals compared to saline controls were increases in the ratios of GluA1, GluA2 and Kv2.1 but decreased the BDNF to GADPH ratio. Spinal cord and dorsal root ganglion protein changes have also been investigated in some of the models. No significant adverse events were identified in (2R,6R)-HNK treated animals with animals continuing to gain weight throughout the study periods. More recently, we have demonstrated that (2R,6R)-HNK has less effect on motor coordination, balance and endurance than pregabalin at equianalgesic doses and delays the development of morphine tolerance when co-administered. Clinical study: Based on our preclinical experience we proposed a clinical trial of a single dose of (2R,6R)-HNK to obtain clinical evidence of effectiveness in the treatment of neuropathic pain. The study was funded by the Department of Defense Fiscal Year 2022 Chronic Pain Management Research Program (CPMRP) Clinical Exploration Award. The study design was a randomized double blind three way (1:1:1) cross over clinical trial to evaluate the effectiveness and duration of analgesic of a single infusion of (2R,6R)-HNK 0.5mg/kg compared with ketamine 0.5mg/kg and saline with a 5-week interval between treatments on pain, pain qualities, physical function, pain interference, sleep disturbance and quality of life in subjects with neuropathic pain of the extremities. Specific aims of the trial include AIM 1 - To determine if (2R,6R)-HNK will decrease the sensory dimension (intensity) of pain as assessed by the area under the NRS pain scores by time curve, as well as the affective dimension (unpleasantness) of NP (allodynia, hyperalgesia, burning, aching, tingling, lancinating). AIM 2 - To determine if (2R,6R)-HNK will improve physical function, sleep quality and quantity, decrease pain interference and improve quality of life in subjects with NP. AIM 3 - To evaluate the duration of effectiveness of a single (2R,6R)-HNK 0.5 mg/kg infusion administered over 45 minutes on pain, physical function, pain interference and quality of life. We will longitudinally evaluate all subjects daily for 35 days following drug administration for pain intensity and pain qualities. I will review the progress of this study and current status at the time of the presentation.

Literature References: Das V, Basovich MB, Thomas CJ, et al. A Pharmacological Evaluation of the Analgesic Effect and Hippocampal Protein Modulation of the Ketamine Metabolite (2R,6R)-Hydroxynorketamine in Murine Pain Models. *Anesth Analg*. 2024; 138:1094-1106.

Das V, Milejczyk I, Basovich MB, et al. Behavioral and biochemical changes associated with the analgesic effects of (2R,6R)-hydroxynorketamine alone and in combination with meloxicam following disk puncture in mice. *Front Pain Res (Lausanne)*. 2025 ;6:1574474.

***^NEW AND ANTICIPATED INTERVENTIONS FOR PERINATAL DEPRESSION**

Anita Clayton, University of Virginia SOM

Overall Abstract: The incidence of depression during the perinatal time-period is approximately 15% and is the leading contributor to maternal morbidity and mortality. If unrecognized or untreated, many women continue to experience symptoms for 3-5 years, continuing the negative impact on mother and child. Currently SSRIs and SNRIs are first line treatments for perinatal depression, but these medications are frequently underdosed or ineffective and patients and families are concerned about their use during pregnancy or lactation. During this panel, presentations will: 1) describe the incidence of symptoms and the potential pathophysiology of perinatal depression, 2) address the potential for epigenetic biomarkers to identify who is at risk for postpartum depression (PPD) and who is likely to respond to conventional antidepressants, 3) describe current approved treatments for PPD

[Neuroactive steroid (NAS) GABA-A receptor positive allosteric modulators (PAMs)], and the promise of psilocin for PPD, and 4) describe the comorbidity of PPD and substance use disorders (SUD) and the acceptance and unrealized effectiveness of neuromodulatory interventions (TMS) in pregnant women. We hope a robust audience discussion about these issues will further our understanding of the state and future interventions in perinatal depression.

Learning Objective 1: Articulate unmet needs in perinatal depression such as early identification and intervention, management of co-morbid substance abuse, and potential response to treatments with new MOAs.

Learning Objective 2: Understand the potential promise of epigenetic biomarkers that identify who is at risk of PPD, will likely to respond to treatment with standard of care antidepressants, or indicate risk of postpartum psychosis; treatments with unique MOAs such as neuroactive steroid GABA-A receptor positive allosteric modulators and/or psychedelics like psilocin (5-HT 2A agonist); and neuromodulation in management of co-morbid substance abuse in pregnancy.

Literary References:

1. Dama MH, et al. Perinatal Depression: A Guide to Detection and Management in Primary Care. J Am Board Fam Med. 2024;36(6):1071-1086
2. Wisner KL, et al. Onset Timing, Thoughts of Self-harm, and Diagnoses in Postpartum Women with Screen-Positive Depression Findings. JAMA Psychiatry. 2013;70(5):490-498

PATHOPHYSIOLOGICAL MECHANISMS OF PERINATAL DEPRESSION

Kristina Deligiannidis, Zucker Hillside Hospital

Individual Abstract: Major depressive disorder with peripartum onset, commonly referred to as perinatal depression, affects 10-20% of childbearing women, representing one of the most common complications of pregnancy. Risk factors include previous psychiatric history, childhood trauma, low socioeconomic status, intimate partner violence, and lack of social support. Perinatal depression is associated with maternal morbidity and mortality in the first-year postpartum, impaired maternal-infant bonding, disrupted child neurodevelopment, and increased healthcare costs exceeding \$32.5 billion annually in the United States. Despite recommendations for universal screening, perinatal depression remains significantly underdiagnosed and undertreated. This presentation examines the clinical features, prevalence patterns, and emerging understanding of the pathophysiology underlying this critical condition. The clinical presentation of perinatal depression includes core depressive symptoms alongside perinatal-specific features such as anxious intrusive thoughts about infant harm, anxiety about infant wellbeing, and guilt regarding maternal capabilities. Evidence suggests heterogeneity in symptom severity, time of onset and in symptom cluster profiles. The pathophysiology of perinatal depression involves complex interactions between multiple biological systems. Dramatic fluctuations in neuroactive steroids, particularly allopregnanolone, modulate GABAergic neurotransmission throughout pregnancy and precipitously decline postpartum. These changes correlate with altered brain connectivity patterns, including increased default mode network connectivity and disrupted GABAergic signaling in mood-regulating regions. Additional neuroimaging studies reveal perinatal depression specific alterations including reduced hippocampal volume, increased cortical thickness in frontal regions and white matter microstructural changes. The hypothalamic-

pituitary-adrenal axis undergoes profound adaptations during pregnancy, with placental CRH driving cortisol elevations that peak at parturition before rapidly declining, potentially contributing to postpartum vulnerability in susceptible individuals. Inflammatory markers, including elevated IL-6 and TNF- α , suggest immune dysregulation as an additional contributing factor. Recent breakthrough treatments targeting some of these mechanisms have emerged, with future novel therapeutics in development, some aimed at new targets. Brexanolone, an intravenous formulation of allopregnanolone, demonstrated rapid antidepressant effects within 60 hours in clinical trials, leading to FDA approval in 2019. Subsequently, zuranolone, an oral neuroactive steroid, showed significant improvement in depressive symptoms within day 15 of treatment, with effects sustained through 45 days post-treatment. These novel therapeutics represent a paradigm shift from traditional antidepressants, offering rapid symptom relief through direct modulation of GABAergic systems and a shift to the development of rapid-acting pharmacotherapies for perinatal depression.

Literature References: Longoria KD, Nguyen TC, Franco-Rocha O, Garcia SR, Lewis KA, Gandra S, Cates F, Wright ML. A sum of its parts: A systematic review evaluating biopsychosocial and behavioral determinants of perinatal depression. PLoS ONE. 2024;19(7): e0290059.

Wenzel ES, Frye, R, Roberson-Nay R, Payne JL. The neurobiology of postpartum depression. Trends in Neurosciences, 2025; 48(7):469-482.

EPIGENETIC BIOMARKERS IN POSTPARTUM DEPRESSION AND POSTPARTUM PSYCHOSIS

Jennifer Payne, University of Virginia

Individual Abstract: We previously identified epigenetic biomarker patterns at genes that are predictive of "reproductive" mood disorders including postpartum depression (PPD) and premenstrual dysphoric disorder (PMDD). We originally investigated estrogen mediated epigenetic reprogramming events in the hippocampus and risk for PPD using a cross species translational design. We identified two genetic loci, HP1BP3 and TTC9B, which were modified by estrogen exposure in the rodent model and were also prospectively predictive of PPD in antenatal blood in pregnant women who later developed PPD. These same epigenetic biomarkers were also found to be present in women with PMDD who were also responsive to selective serotonin reuptake inhibitors. Postpartum psychosis (PP) is another reproductive mood disorder which presents with manic, depressive or mixed symptoms with psychosis shortly after delivery. We investigated whether our epigenetic biomarkers were also found in women with PP and conducted an epigenome-wide association study (EWAS) to assess whether epigenetic changes were predictive of either type of psychiatric symptoms or recurrence of psychiatric illness outside of the postpartum time period. We found that our previously identified epigenetic biomarkers were NOT associated with PP, indicating that PPD and PP have separate underlying biological mechanisms. We also identified multiple (912) epigenetic changes statistically associated with depressive symptoms, but no epigenetic changes were statistically associated with either manic or psychotic symptoms. We also identified epigenetic changes that were associated with future psychiatric relapse outside of the postpartum time period, though the follow-up period was limited to 4 years. Future research will include identifying the underlying pathophysiology of central nervous system sensitivity to reproductive hormone change as well as further developing the identified

epigenetic changes associated with psychiatric relapse outside of the postpartum time-period in women with PP by extending the length of follow-up. Development of blood tests that are predictive of a future mental illness or future course of psychiatric illness has the potential to move psychiatry from a reactive approach to a preventative one and to reduce stigma surrounding mental illness in general.

Literature References: Guintivano J, Arad M, Gould TD, Payne JL, Kaminsky ZA. Antenatal prediction of postpartum depression with blood DNA methylation biomarkers. *Mol Psychiatry*. 2014; 19(5):633.

Payne JL, Osborne LM, Cox O, et al. DNA methylation biomarkers prospectively predict both antenatal and postpartum depression. *Psychiatry Res*. 2020; 285:112711.

APPROVED AND POTENTIAL TREATMENTS FOR PPD

Anita Clayton, University of Virginia SOM

Individual Abstract: SSRI antidepressants represent first-line treatment for perinatal depression during both pregnancy and postpartum. As with other major depressive episodes, about 50% of those treated with adequate doses for an adequate duration respond to treatment, with onset of response in 4-6 weeks, although higher doses may be needed later in pregnancy due to increased drug metabolism and volume of distribution. The first FDA-approved antidepressant for treatment of PPD is zuranolone, an oral neuroactive steroid (NAS) GABA-A receptor positive allosteric modulator (PAM), which is a synthetic allopregnanolone, demonstrated superiority of 50 mg/d dose vs. placebo x 14 days (time-limited treatment) with rapid onset and extended maintenance of effect in women with moderate to severe PPD. It may be used as an initial treatment in PPD for severe symptoms and/or suicide risk, or postpartum after failure of a monoamine antidepressant during pregnancy. Another potential treatment for PPD is RE104, the prodrug of 4-OH-DiPT, an analogue of psilosin, but with shorter (2-3 hour) duration of psychedelic effect. This serotonin receptor (5-HT_{2A}) agonist may produce psychedelic effects, disrupt brain networks and reduce activity in the Default Mode Network, thus increasing connectivity. Positive topline results from the Reunion Neuroscience RECONNECT Phase 2 clinical trial evaluated a single 30 mg subcutaneous injection of RE104 vs active control arm using 1.5 mg dose, in adult female patients with moderate-to severe PPD. Primary endpoint was met with the 30mg dose demonstrating a statistically significant reduction from baseline on the MADRS total score of 23.0 points on Day 7, as compared to a reduction of 17.2 points in patients treated in the 1.5 mg active control arm (difference of 5.80; p=0.0094). Clinically meaningful reductions were observed for RE104 30mg on Day 1 following administration and maintained through Day 28. Safety and tolerability were reassuring. There is potential for drugs with new MOAs to expand therapeutic options in the treatment of PPD.

Literature References: Deligiannidis KM, Meltzer-Brody S, Maximos B, et al. Zuranolone for the treatment of Postpartum Depression. *Am J Psychiatry* 2023;180(9):668-675.

Clayton A, Hoffman MC, Hendricks P, et al. RE104: A Novel Serotonergic Psychedelic 4-OH-DiPT Prodrug for the Treatment of Postpartum Depression. Presentation at the 64th Annual Meeting of the American College of Neuropsychopharmacology, January 12-15, 2026, Nassau, Bahamas

ADDICTION AND NEUROMODULATION IN PREGNANCY

Rana Jawish, University of Utah School of Medicine

Individual Abstract: Substance use disorders (SUDs)—particularly stimulant and nicotine use—remain major drivers of maternal morbidity and mortality in the United States, with limited evidence-based treatment options available during pregnancy. Pharmacologic interventions for stimulant use disorder lack safety data in pregnant populations, while behavioral treatments alone often produce insufficient reductions in use or relapse risk. Transcranial magnetic stimulation (TMS), a noninvasive neuromodulation modality with a robust safety profile in nonpregnant adults, is now emerging as a promising therapeutic approach for addressing addiction and co-occurring psychiatric disorders during pregnancy. The purpose of this presentation is to provide an integrated overview of the current landscape of addiction in pregnancy, synthesize emerging clinical and neurobiological evidence for TMS as a potential treatment modality, and present new feasibility, acceptability, and preliminary outcome data from pilot work that evaluates TMS safety and clinical response in pregnant patients with stimulant use disorder. This presentation will review (1) epidemiologic trends in stimulant use disorder during pregnancy; (2) neurocircuitry of addiction relevant to perinatal neurobiology; and (3) rationale for neuromodulation as a mechanistically targeted intervention. Methodology from an ongoing mixed-methods feasibility study will be discussed, including development of pregnancy-specific TMS treatment parameters, implementation of dual-target (left DLPFC and bilateral mPFC) and accelerated protocols, maternal safety monitoring, and integration of fetal ultrasound surveillance. Preliminary findings demonstrate high treatment acceptability, strong maternal engagement, and meaningful reductions in craving and depressive symptoms across the treatment course, with no observed maternal or fetal adverse events. Qualitative data further highlight perceived improvements in emotional regulation, motivation for change, and recovery-oriented behaviors. These findings represent the first prospective evidence describing TMS feasibility and therapeutic potential for stimulant use disorder in pregnancy and underscore the urgent need for safe, mechanism-based treatments for this high-risk population. The presentation will conclude with a discussion of clinical implications, ethical considerations, and key research directions—including scalable trial designs, biomarker-driven treatment personalization, and integration of neuromodulation within perinatal addiction care systems. Together, this work aims to advance the field by establishing neuromodulation as a promising and potentially transformative intervention for addressing addiction and psychiatric comorbidity during pregnancy.

Literature References:

1. Trends and Adverse Pregnancy and Birth Outcomes Associated With Stimulant-Related Disorder Diagnosis. Pippard NS, Bandoli G, Baer RJ. *Addiction* (Abingdon, England). 2024;119(11):2006-2014. doi:10.1111/add.16636.
2. Beyond the Efficacy of Transcranial Magnetic Stimulation in Peripartum Depression: A Systematic Review Exploring Perinatal Safety for Newborns. Miuli A, Pettorruso M, Stefanelli G, et al. *Psychiatry Research*. 2023;326:115251. doi:10.1016/j.psychres.2023.115251.

THE FUTURE DSM: DESIGNING A SCIENTIFIC, INCLUSIVE, AND PRACTICAL DIAGNOSTIC MANUAL FOR MODERN PSYCHIATRY

Nitin Gogtay, American Psychiatric Association

Overall Abstract: The DSM has long served as the foundational diagnostic manual for mental health worldwide, shaping clinical practice, research, training, and policy. Yet the rapid evolution of neuroscience, clinical research, population health, and data science has created a gap between contemporary scientific knowledge and the static structure of a diagnostic system updated only once per decade. This symposium, grounded in the work of the APA's future DSM strategic committee and its subcommittees, presents a comprehensive overview of the challenges facing psychiatric diagnosis today and highlights key directions for rethinking the DSM. (Dr. Nitin Gogtay/Maria Oquendo/Jonathan Alpert) will serve as Chair and coordinate discussion. Dr. Nitin Gogtay/Maria Oquendo/Jonathan Alpert) will open the session by reviewing the historical trajectory of the DSM, the scientific and practical reasons for current reevaluation, and the overarching framework guiding the committee's efforts. This introduction will highlight challenges and the need for a system that can more flexibly incorporate new discoveries. Dr. Dost Öngür will then present a new diagnostic model that reconceptualizes how psychiatric disorders are categorized. He will describe proposed structural model aimed at improving validity, enhancing cross-diagnostic coherence, and fostering stronger alignment with the underlying biology of mental disorders and contextual factors influencing the diagnoses. Dr. Anissa Abi-Dargham will discuss the efforts of the Biomarker Subcommittee, which will evaluate the readiness and role of biological markers in future DSM development. She will outline the evidentiary standards proposed for the inclusion of such biological factors, highlighting promising candidates, and address methodological, ethical, and implementation considerations. In closing, the first speaker will also outline potential next steps for evolving the DSM—including governance structures, integration strategies, and stakeholder engagement. It will also introduce the vision of transitioning toward a more dynamic, continuously updated DSM—one that functions as a truly living document capable of incorporating scientific advances in real time.

Learning Objective 1: Learn about new proposed model for the next DSM

Learning Objective 2: Learn how future DSM plans to address emerging biomarkers and biological factors

Literary References:

1. Regier DA, Kuhl EA, Kupfer DJ. The DSM-5: Classification and criteria changes. *World Psychiatry*. 2013 Jun;12(2):92-8. doi: 10.1002/wps.20050. PMID: 23737408; PMCID: PMC3683251
2. First, M. B., Erlich, M. D., Adler, D. A., Leong, S., Dixon, L. B., Oslin, D. W., Goldman, B., Koh, S., Levine, B., Berlant, J. L., and Siris, S. G. (2019). How the DSM Is Used in Clinical Practice. *The Journal of nervous and mental disease*, 207(3), 157–161. <https://doi.org/10.1097/NMD.0000000000000953>

THE FUTURE DSM: DESIGNING A SCIENTIFIC, INCLUSIVE, AND PRACTICAL DIAGNOSTIC MANUAL FOR MODERN PSYCHIATRY

Jonathan Alpert, Albert Einstein College of Medicine

Individual Abstract: The DSM has long served as the foundational diagnostic manual for mental health worldwide, shaping clinical practice, research, training, and policy. Yet the rapid evolution of neuroscience, clinical research, population health, and data science has created a gap between contemporary scientific knowledge and the static structure of a

diagnostic system updated only once per decade. This symposium, grounded in the work of the APA's future DSM strategic committee and its subcommittees, presents a comprehensive overview of the challenges facing psychiatric diagnosis today and highlights key directions for rethinking the DSM. Dr. Maria Oquendo, Chair of the Future DSM Strategic Committee, will serve as Session Chair. Dr. Jonathan Alpert (Vice Chair of the Future DSM Strategic Committee) will review the historical trajectory of the DSM, the scientific and practical reasons for current reevaluation, and the overarching framework guiding the committee's efforts. He will also highlight challenges and the need for a system that can more flexibly incorporate new discoveries. He will outline potential next steps for evolving the DSM—including governance structures, integration strategies, and stakeholder engagement, and will also introduce the vision of transitioning toward a more dynamic, continuously updated DSM—one that functions as a truly living document capable of incorporating scientific advances in real time. Dr. Dost Öngür (Chair of the Future DSM Structure and Dimensions Subcommittee) will then present a new diagnostic model that reconceptualizes how psychiatric disorders are categorized. He will describe proposed structural model aimed at improving validity, enhancing cross-diagnostic coherence, and fostering stronger alignment with the underlying biology of mental disorders and contextual factors influencing the diagnoses. Dr. Anissa Abi-Dargham (Chair of the Future DSM Biomarker Subcommittee) will discuss the efforts of the Biomarker Subcommittee, which will evaluate the readiness and role of biological markers in future DSM development. She will outline the evidentiary standards proposed for the inclusion of such biological factors, highlighting promising candidates, and address methodological, ethical, and implementation considerations. Dr. Nitin Gogtay (Vice Chair of the Future DSM Strategic Committee), Session Discussant, will summarize themes and moderate the discussion.

Literature References: Oquendo MA, Abi-Dargham A, Alpert JE, Benton TD, Clarke DE, Compton WM, Drexler K, Fung KP, Kas MJH, Malaspina D, O'Keefe V, Öngür D, Wainberg ML, Yonkers KA, Yousif L, Gogtay N, Initial Strategy for The Future of The Diagnostic and Statistical Manual (DSM). *Am J Psychiatry*, in press

Öngür D, Abi-Dargham A, Clarke DE, Compton WM, Cuthbert B, Fung KP, Gogtay N, Kas MJH, Kumar A, Malaspina D, O'Keefe VM, Oquendo MA, Wainberg ML, Yonkers KA, Yousif L, Alpert JE The Future of DSM: A Report from the Structure and Dimensions Subcommittee. *Am J Psychiatry*, in press.

STRUCTURE AND DIMENSIONS SUBCOMMITTEE

Dost Ongur, Harvard Medical School/McLean Hospital

Individual Abstract: This presentation will review the activities of the Structure and Dimensions Subcommittee of the Future DSM Committee and the recommendations arising from this work to date. We will review a diagnostic construction model proposed by our committee and the implications for modifications to the existing DSM.

Literature References:

1. The Future of DSM: A Report from the Structure and Dimensions Subcommittee. Dost Öngür, Anissa Abi-Dargham, Diana E. Clarke, Wilson M. Compton, Bruce Cuthbert, Kenneth P. Fung, Nitin Gogtay, Martien J. H. Kas, Anand Kumar, Dolores Malaspina, Victoria M. O'Keefe, Maria A. Oquendo, Milton L. Wainberg, Kimberly A. Yonkers, Lamyaa Yousif, Jonathan E. Alpert

2. Initial Strategy for The Future of The Diagnostic and Statistical Manual (DSM). María A. Oquendo, Anissa Abi-Dargham, Jonathan E. Alpert, Tami D. Benton, Diana E. Clarke, Wilson M. Compton, Karen Drexler, Kenneth P. Fung, Martien J. H. Kas, Dolores Malaspina, Victoria M.O'Keefe, Dost Öngür, Milton L. Wainberg, Kimberly A. Yonkers, Lamyaa Yousif, Nitin Gogtay

THE DSM SUBCOMMITTEE ON CANDIDATE BIOMARKERS AND BIOLOGICAL FACTORS

Anissa Abi Dargham, State University of New York at Stony Brook

Individual Abstract: Psychiatry remains one of the few medical fields where clinical practice relies almost entirely on interviews and historical information rather than laboratory tests or imaging to guide diagnosis, predict outcomes, select treatments, and anticipate response. Despite decades of research advancing our understanding of brain biology across DSM categories, these insights have yet to be fully integrated into clinical care. A key challenge for future iterations of the DSM is to incorporate biological knowledge in a way that reflects both its current breadth and inherent limitations, while establishing a framework for ongoing evolution. In this session, we will review the work of the DSM subcommittee on candidate biomarkers and biological factors and invite an interactive discussion to gather input and raise awareness on this critical topic.

Literature References: Abi-Dargham A, Horga G. The search for imaging biomarkers in psychiatric disorders. *Nat Med.* 2016 Nov; 22(11):1248-1255.

Abi-Dargham A, Moeller SJ, Ali F, DeLorenzo C, Domschke K, Horga G, Jutla A, Kotov R, Paulus MP, Rubio JM, Sanacora G, Veenstra-VanderWeele J, Krystal JH. Candidate biomarkers in psychiatric disorders: state of the field. *World Psychiatry.* 2023 Jun;22(2):236-262. PMID: 37159365.

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

Regulatory Challenges: Ask the Experts

REGULATORY CHALLENGES: ASK THE EXPERTS

Tiffany Farchione, US Food and Drug Administration

Valentina Mantua, Center for Drug Evaluation and Research, Food and Drug Administration

Bernard Fischer, U.S. Food and Drug Administration

Overall Abstract: This session is intended to facilitate dialogue between expert regulators from the US Food and Drug Administration and conference participants with an interest in drug development and clinical research in psychopharmacology. There will be no pre-submitted questions, but rather regulators will take questions directly from the audience.

Learning Objective 1: Participants will be able to ask questions to a panel of FDA representatives.

Learning Objective 2: Participants will learn from regulators how to improve quality of clinical research.

Wednesday, May 27, 2026

Poster Session I with Lunch

W1. THE PHASE 2/3 GAIN TRIAL OF THE FIRST-GENERATION P. GINGIVALIS GINGIPAIN INHIBITOR ATUZAGINSTAT IN MILD-TO-MODERATE PROBABLE ALZHEIMER'S DISEASE: NEW CEREBROSPINAL FLUID BIOMARKER DATA

Michael Detke^{*1}, Marwan Sabbagh², Joanna Bolger¹, Mark Ryder³, Craig Mallinckrodt⁴, Florian Ermini¹, Casey Lynch¹, Stephen Dominy¹

¹Lighthouse Pharma, ²Barrow Neurological Institute, ³UCSF, ⁴Pentara Corporation

Abstract Background: Porphyromonas gingivalis (Pg), best known for its role as a keystone pathogen in chronic periodontitis, has emerged as a promising target in the treatment of Alzheimer's disease (AD) through epidemiological, pathological, and mechanistic preclinical studies. We developed an orally bioavailable investigational small-molecule, COR388 (atuzaginstat), that specifically targets and inhibits lysine-gingipain (Kgp), the major protease virulence factor of Pg. We tested atuzaginstat in the GAIN trial, a randomized, double-blind, placebo-controlled phase 2/3 trial (NCT03823404) of a low-dose and high-dose over 48 weeks in participants with mild-moderate AD (N = 643). The primary ITT prespecified cognitive endpoint, ADAS-Cog11 was not met. However, in a prespecified subgroup analysis, Pg detected in saliva (PG-DS), both doses of atuzaginstat engaged the Kgp target and demonstrated a dose-dependent effect on ADAS-Cog11, slowing cognitive decline in participants with Pg-positive saliva (n = 244) in the high-dose group by 57% (p = 0.020). In the low-dose group, cognitive decline was slowed by 42% (p = 0.066).

Here, we present CSF AD biomarker data from the GAIN study that shows a disease-modifying effect of atuzaginstat on CSF p-tau181. This finding informed the design of the Phase 2 study of LHP588, a second-generation Kgp inhibitor with an improved liver safety profile. The LHP588 study in Pg-positive mild-moderate AD, known as the SPRING Trial (NCT06847321), is ongoing after receiving \$49.2M in funding from the National Institute on Aging (NIA).

Methods: The GAIN trial SAP prespecified an exploratory analysis of CSF A β -42/40 ratio, p-tau181 concentration, and total tau concentration. CSF was collected at baseline (N = 491) and end of study. Using ELISA assays, the mean percent change from baseline at Week 48 was analyzed separately for each biomarker using ANCOVA with fixed effects of treatment group, ApoE4 status, acetylcholinesterase inhibitor and/or memantine usage, site-country, and baseline value for each biomarker as a covariate for the ITT population and prespecified PG-DS subgroup.

Results: P-tau181 levels were observed to increase in both the ITT and Pg-positive-saliva placebo groups from baseline to week 48. In the ITT group, the p-tau181 increase was significantly inhibited in the atuzaginstat 40 mg BID arm (p = 0.048, n = 79), and there was a statistical trend of the 40 mg BID dose to inhibit the p-tau181 increase in the Pg-positive-saliva subgroup (p = 0.083, n = 34). The atuzaginstat 80 mg BID treatment arms had fewer evaluable

subjects and did not reach statistical significance in the ITT group ($p = 0.174$, $n = 65$) or the Pg-positive-saliva subgroup ($p = 0.778$, $n = 20$).

Conclusions: Longitudinal p-tau181 levels were observed to increase in CSF from baseline to week 48 in both the ITT and PG-DS placebo groups, while no significant longitudinal changes were detected for A β -42/A β 40 or total tau. This pattern of longitudinal increase in CSF p-tau181 levels during cognitive decline without a concomitant change in A β 42 or total tau has been previously reported. The data suggest that Pg infection was driving the increase in CSF p-tau181 levels during the length of the GAIN trial. Based on these results, in the phase 2 study of LHP588 in Pg-positive mild-moderate AD, inclusion criteria include Pg-positive saliva, but also high plasma p-tau-217 levels that will allow us to test the hypothesis that p-tau217 may be a pharmacodynamic biomarker of LHP588 activity.

W2. GALANTAMINE-MEMANTINE COMBINATION REGULATING THE KYNURENINE PATHWAY METABOLISM IN THE TREATMENT OF POST-STROKE DEPRESSION AND POST-STROKE COGNITIVE IMPAIRMENTS AND PREVENTION OF STROKE

Anne Khodarkovskaya^{*1}, Kwame Amonu², Bruno Pillari², Yaxel Levin-Carrion², Maju Koola³

¹Cooper Medical School of Rowan University, ²Rutgers New Jersey Medical School, ³George Washington University School of Medicine and Health Sciences

Abstract: Stroke is currently a leading cause of mortality and disability worldwide, often resulting in debilitating neuropsychiatric sequelae, such as poststroke depression (PSD) and poststroke cognitive impairments (PSCI). Despite advances in acute stroke care, effective therapeutic options for these complications and their effect on functional recovery and quality of life remain limited as there are no FDA-approved treatments for PSD and PSCI. The kynurenine pathway (KP), the principal route of tryptophan metabolism, is a promising target for novel therapeutic strategies. KP produces metabolites, such as kynurenine, 3-hydroxykynurenine, and quinolinic acid, which act with various effects on neuroinflammation, excitotoxicity, and neuroplasticity. Disruption of KP has been increasingly implicated in the pathophysiology of both stroke and its neuropsychiatric aftermath. Factors leading to stroke enhance the activity of KP, leading to imbalances between neuroprotective and neurotoxic metabolites which cause cognitive impairments and diversion of tryptophan metabolism away from serotonin. Medications which target KP, such as galantamine and memantine, can work synergistically to restore balance between KP metabolites, reducing recurrent stroke risk in addition to mitigating PSD and PSCI. This review aims to elucidate the role of modulation of KP in stroke survivors, specifically with the galantamine-memantine combination, highlighting evidence and therapeutic prospects in prevention of stroke and its neuropsychiatric sequelae.

W3. DYNAMIC CAUSAL MODELING OF TRIPLE-NETWORK CONNECTIVITY VARIES BY SUICIDE ATTEMPT HISTORY

*Benjamin Chandler*¹, Carlos Cortes¹, Hiroe Hu¹, Brady Greene¹, Adam Fijtman¹, Carlos Zarate¹, Elizabeth Ballard¹, Jessica Gilbert¹*

¹Division Intramural Research Program, National Institute of Mental Health

Abstract Background: The triple-network model of psychopathology implicates dysregulated interactions among salience, default mode, and executive control networks in mood disorders and suicidal behavior. We examined whether suicide attempt (SA) history in major depressive disorder (MDD) or bipolar disorder (BD) is associated with altered triple-network effective connectivity using resting-state magnetoencephalography (MEG).

Methods: Adults with unipolar or bipolar depression (n=37; 29 MDD, 8 BD) completed resting-state MEG (275-channel CTF). Participants were grouped by lifetime SA history (SA+ n=13; SA- n=24). Regions of interest were selected a priori as canonical triple-network nodes: posterior cingulate cortex (PCC; default mode), bilateral anterior insula (AI; salience), and bilateral lateral prefrontal cortex (LPFC; executive control). Source time series were analyzed using Dynamic Causal Modeling (SPM12). Four biologically plausible effective connectivity architectures were compared using Bayesian model selection (BMS). Parametric Empirical Bayes tested for parameters differentiating SA+ and SA- [posterior probability (Pp) > 0.95].

Results: BMS favored the model architecture comprising reciprocal connections between all three nodes. Relative to SA-, SA+ participants showed reduced backward AI-to-PCC connectivity ($E_p = -0.46$; $P_p = 1$). SA+ participants also exhibited reduced PCC excitatory synaptic gain ($E_p = -0.35$; $P_p = 1$) and reduced PCC intrinsic self-coupling ($E_p = -0.49$; $P_p = 1$).

Discussion: Suicide attempt history was associated with altered salience-to-default mode feedback and altered PCC intrinsic dynamics, consistent with the triple-network model of psychopathology. These findings support a circuit-level account of suicidal behavior in mood disorders and motivate evaluation of effective connectivity markers in larger samples.

W4. A REVIEW OF EVIDENCE AND AN ALGORITHM FOR USE OF PSYCHOPHARMACOLOGY IN THE TREATMENT OF TOBACCO USE DISORDER IN BEHAVIORAL HEALTH SETTINGS

*Afrah Mohammad*¹, David Osser²*

¹VA Boston Healthcare System/Harvard Medical School, ²VA Boston Healthcare System,

Abstract: Tobacco Use Disorder (TUD) represents a major and persistent public health problem and is disproportionately prevalent among individuals with psychiatric illness. Despite its substantial contribution to morbidity and mortality, TUD is frequently under-addressed in behavioral health settings, in part due to clinician uncertainty regarding psychopharmacologic complexity, psychiatric safety, and treatment sequencing. This presentation introduces a new, evidence-derived psychopharmacology algorithm for the treatment of TUD developed through the Psychopharmacology Algorithm Project at the Harvard South Shore Program. The purpose of this presentation is to provide psychopharmacologists and psychiatric clinicians with a

structured, clinically actionable framework for medication-based treatment of TUD that integrates efficacy, safety, comorbidity-specific considerations, and treatment resistance. The content synthesizes findings from randomized controlled trials, meta-analyses, systematic reviews, and previously published algorithms to support rational pharmacologic decision-making in complex behavioral health populations. Methodologically, the algorithm was developed through a targeted PubMed literature review of English-language pharmacotherapy studies, including efficacy and safety trials, followed by qualitative expert consensus and iterative refinement through blinded peer review. The algorithm is intended as a heuristic to guide clinical judgment rather than a rigid guideline. After confirmation of TUD and readiness for pharmacotherapy, the algorithm prioritizes evaluation of comorbid conditions that may alter medication selection, including major depressive disorder, bipolar disorder, other serious mental illnesses, posttraumatic stress disorder, alcohol use disorder, cardiovascular disease, seizure risk, and concerns regarding post-cessation weight gain. Key findings to be presented include evidence supporting consideration of bupropion as an initial treatment option in patients with comorbid depression, while generally avoiding antidepressants in bipolar disorder and exercising caution or avoidance in individuals with seizure risk. In the main treatment pathway for cigarette smoking, varenicline is established as the most effective first-line pharmacotherapy, with combined nicotine replacement therapy as a second-line consideration when varenicline is contraindicated or declined. Criteria for adequate varenicline trials, dose adjustments, side-effect management, and evidence-informed augmentation strategies, including bupropion, are detailed. The role of combination therapy, such as varenicline plus nicotine replacement, is reviewed in the context of mixed and limited evidence. For users of smokeless tobacco, available data also support varenicline as the preferred first-line agent. Management of common adverse effects across pharmacotherapies is addressed. The presentation concludes with a discussion of emerging and investigational treatments with less established evidence but potential future promise. The clinical importance of this work lies in equipping behavioral health clinicians with a coherent psychopharmacologic roadmap that supports ownership of TUD treatment, improves cessation outcomes, and reduces tobacco-related morbidity and mortality among patients with mental illness.

W5. EVIDENCE FROM RANDOMIZED CONTROLLED TRIALS IN SUBSTANCE USE DISORDERS WITH MEMANTINE, GALANTAMINE, N-ACETYLCYSTEINE, AND DOXAZOSIN/PRAZOSIN

Kristine Hawkins^{*1}, *Elizabeth G. Varghese*², *Sajoy P. Varghese, MD*³, *Maju Mathew Koola, MD*⁴

¹*Cooper Medical School of Rowan University*, ²*Niles West High School*, ³*VISN 23, Clinical Resource Hub, Minneapolis VA Medical Center*, and *University of California, Davis*, ⁴*George Washington University School of Medicine and Health Sciences*

Abstract Background: Substance use disorders (SUDs) remain a major public health challenge, with high relapse rates and limited pharmacologic options across most substances. There have been no novel treatments developed for SUDs since 2006. While existing treatments target isolated components of neurobiological pathways, addiction is increasingly recognized as a disorder involving dysregulation across multiple neurotransmitter systems, including NMDA,

nicotinic, and noradrenergic signaling. This complexity suggests monotherapy approaches are likely to be insufficient. Repurposing FDA-approved medications with complementary mechanisms represents a promising strategy to expand treatment options.

Methods: We conducted a review of randomized controlled trials (RCTs) and meta-analyses which evaluated five repurposed pharmacologic agents (galantamine, memantine, N-acetylcysteine, prazosin, and doxazosin) for the treatment of SUDs. A literature search was conducted using PubMed, Google Scholar, ClinicalTrials.gov, SCOPUS, and the Cochrane Library. Eligible studies included RCTs and meta-analyses assessing outcomes such as substance use, abstinence, craving, relapse, or treatment retention across alcohol, tobacco, opioid, cannabis, cocaine, and methamphetamine use disorders. Study characteristics and outcomes were extracted and synthesized into charts with quantitative and qualitative data for analysis.

Results: Across trials, efficacy varied by medication, substance, and patient subgroup. Galantamine (8 RCTs, N=700) demonstrated benefits in tobacco (TUD), alcohol (AUD), cocaine (CocUD) and cannabis (CUD) use disorder, with reductions in cigarette consumption, biochemical markers, and cocaine-positive urine samples. Memantine (17 RCTs, N=1,210) showed limited efficacy as monotherapy but improved outcomes when combined with established treatments such as naltrexone or buprenorphine, particularly for AUD and opioid use disorder (OUD) and had some efficacy signal in TUD and CocUD. NAC (17 RCTs, N=1,715) demonstrated efficacy signals in AUD, OUD, CocUD, CUD and was the only medication to show clinical benefit in methamphetamine use disorder. It's strongest effects in specific subgroups, including individuals with prior abstinence, moderate to severe AUD, adolescents and young adults, and stimulant use disorders, suggesting a role in relapse prevention. Prazosin (10 RCTs, N=1,521) consistently reduced stress induced craving and drinking outcomes in AUD, particularly among individuals with heightened withdrawal severity or comorbid posttraumatic stress disorder. Doxazosin (7 RCTs, N=377) demonstrated robust effects in CocUD, especially with rapid titration and in genetically defined subgroups, in addition to efficacy signal in TUD and AUD.

Conclusion: Collectively, these findings highlight the limitations of single mechanism treatment approaches for SUDs and support a multidimensional treatment framework. The complementary mechanisms and favorable safety profiles of these agents highlight their potential utility in combination pharmacotherapy strategies. Future research should prioritize study designs to evaluate synergistic effects, optimize patient selection, and advance treatment approaches for SUDs.

W6. CHANGES IN SMOKING-RELATED OUTCOMES WITH TIRZEPATIDE IN INDIVIDUALS WITH METHAMPHETAMINE USE DISORDER WHO SMOKE

Nandini Jha^{*1}, Amrita Ghose¹, Manish Jha¹, Abu Minhajuddin¹, Christian Hendershot²

¹The University of Texas Southwestern Medical Center, ²Keck School of Medicine University of Southern California

Background: Glucagon-like peptide-1 receptor agonists (GLP-1RAs) have emerged as novel candidate drugs for treating a range of substance use disorders. In a recent systematic review, we found 9 trials that were registered in clinicaltrials.gov to evaluate smoking-related outcomes in

individuals with tobacco use disorder. Furthermore, only two prior reports have evaluated the efficacy of GLP-1RAs along with additional smoking cessation treatments (Yammine et al. 2021 and Lengsfeld et al. 2023) and neither found significant medication effects for reducing smoking. However, the effects of these medications on smoking outcomes in the context of another substance use disorder remains poorly understood. In a recent report, Hendershot et al. found that semaglutide, a GLP-1RA administered once weekly as subcutaneous injection, resulted in greater reduction in cigarettes smoked per day as compared to placebo in individuals with moderate-to-severe alcohol use disorder. However, effects of tirzepatide, a dual GLP-1 and glucose-dependent insulintropic polypeptide (GIP) receptor agonist on smoking-related outcomes remain poorly understood. Here, we present changes in smoking-related outcomes from the first study of tirzepatide in individuals with methamphetamine use disorder (MtUD).

Methods: Participants with moderate-to-severe MtUD who received 32 weeks of treatment with tirzepatide (administered weekly, per prescribing label) for a weight-related indication were included (NCT06745128). Number of cigarettes smoked per day (CPD) was obtained for 30 days preceding informed consent at baseline, and for each day of study participation using the timeline followback (TLFB) procedure. Additionally, worst craving for nicotine in the past week was assessed using a visual analog scale (VAS) at baseline (pre-first dose of tirzepatide), and at weekly interval for 32 weeks. Repeated measures mixed model analyses were used to measure changes in CPD and VAS.

Results: Of 35 individuals enrolled, 20 reported smoking cigarettes [14 females/6 males; mean (standard deviation, SD) age = 46.7 (7.1) years]. At baseline, mean (SD) values of CPD and VAS were 11.7 (6.0) and 77.4 (23.8), respectively. After 32 weeks of treatment with tirzepatide, there were significant reductions in CPD [estimate(β)= -2.76, standard error (SE)= 0.56, $p < 0.0001$] and VAS for nicotine (β = -25.1, SE= 4.99, $p < 0.0001$).

Conclusions: This first study of a GLP-1RA in individuals with MtUD who smoke found preliminary evidence for significant reduction in smoking-related outcomes, including numbers of cigarettes smoke and craving symptoms. Larger placebo-controlled randomized controlled trials are needed to validate these findings.

W7. CHANGES IN DEPRESSIVE SYMPTOMS WITH TIRZEPATIDE IN INDIVIDUALS WITH MODERATE-TO-SEVERE METHAMPHETAMINE USE DISORDER

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Abstract Background: Individuals with moderate-to-severe methamphetamine use disorder (MtUD) often report depressive symptoms. In a recent publication (Jha et al. 2025 Journal of Clinical Psychiatry), we found that over 75% of individuals with MtUD enrolled in an RCT experienced mild-to-moderate severity of depression. Furthermore, improvement of depressive symptoms were associated with greater likelihood of subsequent reduction in methamphetamine use. Here, we evaluate the change in depressive symptoms with tirzepatide, a dual agonist of glucagon-like peptide 1 receptor (GLP-1R) and glucose-dependent insulintropic peptide

receptor (GIPR), in individuals with moderate-to-severe MtUD. With the emerging interest in tirzepatide and similar medications as potential treatments for substance use disorders, findings of this report may inform their broader effect on mental health-related outcomes in individuals with MtUD.

Methods: Individuals with moderate-to-severe MtUD who participated in an open-label trial of 32-week-long treatment with tirzepatide for a weight-related indication (NCT06745128) were included. Self-report symptoms of depression were assessed with the 16-item Quick Inventory of Depressive Symptomatology Self-Report version (QIDS-SR) at baseline (i.e., prior to first injection) and weekly thereafter during the 32-week treatment period. Repeated measures mixed model analyses were used to measure changes in QIDS-SR domains.

Results: Of the 35 individuals enrolled, 25 had a QIDS-SR score > 5 (indicating mild or greater symptoms severity) and were included in this report [16 females/9 males; mean (standard deviation, SD) age = 44.6 (8.2) years]. Mean (SD) QIDS-SR score at baseline was 10.2 (3.55). There was a significant reduction in depressive symptoms (Bonferroni adjusted $p < 0.05$) after 5 weeks of treatment [estimate(β) = -4.5, standard error (SE) = 1.11, $p < 0.0001$] which persisted during the entirety of treatment period. Numerically maximal improvement was noted after 20 weeks of treatment (β = -6.0, SE = 1.14, $p < 0.0001$). At week 20, 48% of those with a baseline QIDS-SR score of > 5 met criteria for both response (defined by at least a 50% score reduction) and remission (defined by attaining a score of five or lower). In addition, 8% of individuals met criteria for remission but not response, and 8% of individuals met criteria for response but not remission.

Conclusions: In this first study of a dual GLP-1R/GIPR agonist in individuals with moderate-to-severe MtUD, we observed marked reduction in depressive symptoms with 5 mg/week or higher doses of tirzepatide. These improvements persisted for the entirety of treatment period and were observed before meaningful weight reductions were observed. Future placebo-controlled trials are needed to validate these findings.

W8. SAFETY AND TOLERABILITY OF 32-WEEK-LONG TREATMENT WITH TIRZEPATIDE IN INDIVIDUALS WITH MODERATE-TO-SEVERE METHAMPHETAMINE USE DISORDER

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Abstract Background: Preclinical studies and data from electronic health records suggest potential therapeutic utility of glucagon-like peptide 1 (GLP-1) receptor (R) agonists (GLP-1RAs) for individuals with stimulant (such as methamphetamine) use disorder. Yet, the safety and tolerability of this new class of medication in individuals with methamphetamine use disorder (MtUD) has not been assessed previously. In this first study of tirzepatide, a dual agonist of GLP-1R and glucose-dependent insulinotropic peptide (GIP) receptor, for methamphetamine use disorder, safety and tolerability were evaluated after 32 weeks of treatment.

Method: 35 adults with moderate to severe methamphetamine use disorder, with obesity or overweight with a comorbid weight condition, were enrolled into the study and treated for up to 32 weeks with tirzepatide according to the FDA label. Tirzepatide was initiated at 2.5 mg/week for 4 weeks and dose increased by 2.5 mg/week in four-week intervals up to 15 mg/week or maximally tolerated dose. A priori, feasibility as a secondary outcome was defined as the number of participants who received at least 5mg/week for at least four weeks. Any spontaneously reported adverse events (AEs) were captured at each weekly visit. The Gastrointestinal Symptom Rating Scale (GSRS) was collected at baseline and each weekly visit to measure symptoms of abdominal pain, constipation, diarrhea, indigestion and reflux. Repeated measures mixed model analyses were used to analyze changes in GSRS scores.

Results: Of the 35 participants who were enrolled and received the first injection of tirzepatide, 32 (91.4%) met the feasibility outcome. Three participants dropped out due to side effects, two were incarcerated before they could finish treatment, one was discontinued from the study due to excessive weight loss, one lost contact, and one was discontinued from the study due to a positive urine pregnancy test. Including those participants who dropped out of the study, the total treatment exposure was 82.4%, with 923 of the planned 1,120 injections administered. A total of 326 AEs were reported with 205, 116, and 4 classified as mild, moderate, and severe, respectively. Most adverse events were GI-related side effects, comprising 52.8% of all AEs. One serious adverse event of hospitalization for influenza occurred which was deemed as unrelated to the treatment. There was a transient, non-significant ($p > 0.05$) increase across all GSRS domains during the first four weeks of treatment, which resolved by the sixth week of treatment.

Discussion: These Results support good feasibility of using tirzepatide in individuals with moderate-to-severe MtUD. Gastrointestinal symptoms were the most commonly reported side effects, and were predominantly mild-to-moderate in severity. Larger multi-site placebo-controlled randomized controlled trials are needed to further characterize the safety and tolerability of tirzepatide as a potential treatment for MtUD.

W9. FIRST DOSE TREATMENT EFFECTS WITH INJECTABLE WEEKLY AND MONTHLY BUPRENORPHINE (CAM2038) AND THE RELATIONSHIP BETWEEN BUPRENORPHINE PLASMA CONCENTRATIONS AND WITHDRAWAL SUPPRESSION IN PARTICIPANTS WITH OPIOID USE DISORDER

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Abstract Introduction: Early research examining the relationship between buprenorphine plasma concentrations and opioid withdrawal in patients with opioid use disorder (OUD) reported an association between higher plasma concentrations and withdrawal suppression and

suggested that plasma concentrations of 0.7 to 1.0 ng/mL were needed to control withdrawal (Kuhlman et al 1998; Greenwald et al 2007). More recent research, however, indicates that withdrawal is effectively suppressed in most patients at lower plasma concentrations (Laffont et al 2022; Walsh et al 2024). CAM2038 is a weekly and monthly injectable buprenorphine medication approved for the treatment of moderate-to-severe OUD and, in clinical studies, has demonstrated withdrawal suppression and reductions in illicit opioid use.

Methods: An open-label, single-dose, pharmacokinetic (PK) study evaluated participants with moderate-to-severe OUD randomized to either CAM2038 32 mg weekly or 128 mg monthly. During the 2-week period preceding CAM2038 administration (Day -13 to Day 1), participants were assessed for self-reported illicit drug use using timeline follow back (TLFB). Prior to CAM2038 administration on Day 1, Clinical Opiate Withdrawal Scale (COWS) scores (mild = 5–12; moderate = 13–24; moderately severe = 25–36; severe = > 36) were also collected. Following CAM2038 administration, participants remained inpatient for 5 days (Day 2 to Day 6) and returned for outpatient visits at Day 8 (last visit for CAM2038 weekly group), Day 15, Day 22, and Day 29. PK samples and COWS scores were collected each inpatient day and at subsequent outpatient visits. Illicit drug use was assessed using TLFB at each outpatient visit. A post-hoc analysis (N=110) evaluated the effect of single-dose CAM2038 32 mg weekly and 128 mg monthly on opioid withdrawal and self-reported illicit drug use throughout the dosing interval and the association between buprenorphine plasma concentrations and withdrawal suppression (defined as COWS < 5).

Results: The mean baseline COWS score on Day 1 was 13 (no participants with COWS scores < 5), which declined to 5 and 7 (53% and 32% with COWS scores < 5) by Day 2 and to 3 and 5 (68% and 61% with COWS scores < 5) by Day 3 in the CAM2038 weekly and monthly groups, respectively. At the end of the weekly and monthly dosing intervals (Day 8 and Day 29), the CAM2038 32 mg weekly group had a mean COWS score of 2 (91% with COWS score < 5) and the CAM2038 128 mg monthly group had a mean COWS score of 1 (95% with COWS score < 5). Among PK samples collected with buprenorphine plasma concentrations < 0.5 ng/mL, 92% co-occurred with COWS scores < 5. No meaningful association was found between plasma concentrations and withdrawal suppression across study time points. Prior to CAM2038 administration, 94% of participants reported use of illicit opioids. When reassessed at the end of the weekly and monthly dosing intervals (Day 8 and Day 29), self-reported illicit opioid use had declined to 14% in the CAM2038 32 mg weekly group and to 18% in the CAM2038 128 mg monthly group. Self-reported use of other illicit drugs was also found to decrease following administration of weekly and monthly CAM2038.

Conclusions: Rapid and sustained withdrawal suppression was observed in participants with OUD treated with weekly and monthly CAM2038. COWS scores < 5 were consistently recorded in participants with the lowest observed buprenorphine plasma concentrations. Rates of self-reported illicit opioid use substantially declined across weekly and monthly dosing intervals. These findings reinforce known treatment effects of weekly and monthly CAM2038 and indicate that very low buprenorphine plasma concentrations (< 0.5 ng/mL) effectively suppress withdrawal.

W10. A NEW DAWN FOR SOCIAL ANXIETY TREATMENT: CLINICAL ADVANCEMENT OF THE NOVEL V1aR ANTAGONIST, NTX-1472

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Abstract Background: NTX-1472 is a potent and selective vasopressin 1a receptor (V1aR) antagonist that has been studied in two completed Phase 1 clinical trials. Currently, NTX-1472 is in clinical development by Newleos Therapeutics, Inc. for the treatment of Social Anxiety Disorder. The disease includes 2 subtypes, generalized (SAD-g) and performance-only (SAD-p). SAD-g is characterized by marked fear or anxiety about various social situations. These situations are avoided or endured with intense discomfort, leading to significant impairment and decreased quality of life (Kessler et al., 2005; Stein and Stein, 2008). The Social Anxiety Reduction (SOAR) study (NTX-1472-201) is an ongoing, Phase 2, proof-of-concept study that aims to assess the safety, tolerability, and efficacy of NTX-1472 compared to placebo (PLC) in adults with SAD-g.

Methods: The first clinical trial of NTX-1472 (Study BP41695) was a 3-part study that assessed the safety, tolerability and pharmacokinetics (PK) of single- and multiple-ascending doses of NTX-1472 (Part 1: single-ascending dose and food effect [n=48], Part 2: multiple-ascending dose [n=24]; Part 3: midazolam drug-drug-interaction [n=16]). The second clinical trial (Study BP43293) was an open-label, 2-period study to investigate the effect of repeat doses of itraconazole on the PK of a single dose of NTX-1472 (n=16).

The SOAR study has a double-blind, placebo (PLC)-controlled, parallel-arm study design. Participants must be between 18 and 65 years of age (inclusive) and have a diagnosis of SAD-g as defined by the Diagnostic and Statistical Manual of Mental Disorders 5th Edition and confirmed by the Structured Clinical Interview for DSM-5 Disorders. Participants are randomized, stratified by sex, to receive either NTX-1472 (single dose level, n=50) or PLC (n=50) daily for 8 weeks. The study duration is 99 days for each participant, including a Screening Period of up to 30 days, a Treatment Period of up to 59 days, and a Follow-up Period of up to 10 days.

Results: NTX-1472 has been administered to a total of 86 healthy participants in 2 completed Phase I studies. NTX-1472 was rapidly absorbed with Tmax achieved at 1-3 hours (h) post-dose. Food increased the Cmax of NTX-1472 but had no effect on the AUC, and the half-life was about 5-7 h. NTX-1472 given daily had no effect on the PK of midazolam, a CYP3A4 substrate. Multiple doses of the strong CYP3A4 inhibitor itraconazole increased the AUCinf of NTX-1472 by 2.5-fold. Across both studies, NTX-1472 was well tolerated, as all treatment-emergent adverse events (TEAEs) were non-serious and not dose-limiting. Building on the Phase 1 program, the SOAR study is currently enrolling in 11 sites across the United States, with planned completion in early 2027. The primary endpoint is incidence and severity of TEAEs. Key secondary endpoints include change in the clinician-administered Liebowitz Social Anxiety Scale (LSAS) and the Clinical Global Impression – Severity (CGI-S) scale.

Conclusion: In humans, V1aR antagonists have been shown to decrease amygdala activation to threatening social cues (Lee et al., 2013) and to reduce anxiety-potentiated startle, a biomarker

associated with treatment response in SAD (Hoge et al., 2024; Lago et al., 2021). These, as well as other, findings support the development of NTX-1472, a novel V1aR antagonist, for the treatment of anxiety disorders. The ongoing Phase 2 study will help determine the therapeutic potential of NTX-1472 in SAD-g.

W11. TREATMENT PATTERNS AMONG INCIDENT AND PERSISTENT PATIENTS WITH GENERALIZED ANXIETY DISORDER (GAD)

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Abstract Introduction: Generalized anxiety disorder (GAD) is a chronic and debilitating disorder characterized by excessive worry and distress. Despite its prevalence, real-world treatment patterns and unmet needs remain incompletely characterized. This retrospective analysis examined real-world treatment patterns to identify unmet needs among patients with GAD.

Methods: A retrospective analysis was performed utilizing Komodo Healthcare Map™, a longitudinal, deidentified, US pharmacy and medical claims database. Patients were adults with continuous enrollment for two years before and after their index GAD diagnosis. Two cohorts were defined: 1) Incident GAD with no GAD diagnosis in the two years preceding index diagnosis and 2) Persistent GAD with a GAD diagnosis in the 1-year lookback period, or both GAD-related treatment in the 1-year lookback period and a GAD diagnosis in the 2-year lookback period. Treatment patterns were analyzed for a subset of patients within each cohort that received treatment and had 24-month follow-up data.

Results: A total of 259,158 incident GAD patients (cohort 1) and 1,018,288 persistent GAD patients (cohort 2) met inclusion criteria. Within 12 months of diagnosis, 76% of incident patients received GAD-related pharmacotherapy, as opposed to 98% within the persistent cohort. Treatment rates were similar across cohorts: selective serotonin reuptake inhibitors (SSRIs) were the most frequently prescribed drug medications, followed by benzodiazepines and atypical antidepressants. Treatment patterns were analyzed at the drug-class level in incident (n=59,275) and persistent (n=86,920) sub-cohorts. In the first 12 months after treatment initiation, incident patients had lower rates of persistence (18% vs 31%) and higher rates of discontinuation (58% vs 16%). The persistent cohort had higher rates of treatment changes (switching or combining therapies) at 53% as opposed to 24% within the incident cohort. Within the incident cohort, patients experienced a shorter median time to discontinuation (87 days) relative to the persistent cohort (121 days). Transition to combination therapy (54 days vs 32 days) and treatment switching (35 days vs 48 days) also varied in the incident and persistent groups, respectively. Among the 24% of incident patients who experienced ≥1 treatment change, 76% had an additional modification (switch, combine, or discontinue treatment) within the 24-month study period. Of the 53% of persistent patients who experienced ≥1 treatment change, 94% experienced another therapy change during study follow-up.

Discussion: This real-world claims analysis identifies frequent medication changes (e.g., early discontinuation, switching), highlighting gaps in the effectiveness of the current standard of care for both patients with newly diagnosed and persistent GAD. Within the incident GAD cohort, there were high rates of treatment attrition, with a large proportion of patients discontinuing therapy following brief exposure. While patients within the persistent cohort had lower discontinuation rates, they experienced frequent treatment modification. These findings underscore the need for more effective and better tolerated therapies for GAD.

W12. THE IMPACT OF COMORBID PSYCHIATRIC DISORDERS ON MISCONDUCTS AMONG INCARCERATED INDIVIDUALS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: A PRELIMINARY STUDY

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Abstract Background: Approximately 25% of inmates meet criteria for ADHD, making this disorder prevalent in prison environments. ADHD is associated with alcohol/substance use disorders, complicating diagnosis and treatment in prison settings. Research has demonstrated that inmates with ADHD tend to engage in more violent and non-violent infractions. Thus, this study aims to examine the impact of comorbid disorders and psychostimulant treatment on misconducts among inmates with ADHD.

Methods: This sample consisted of inmates with ADHD placed at Central North Correctional Centre (CNCC) in Canada (n = 35). The number of misconducts were compared before psychostimulant treatment (2006-2011) to after (2012-2017).

Results: Inmates with comorbid alcohol use disorder (M = 0.82, SD = 1.19) displayed significantly more non-violent misconducts ($t(33) = -2.23$, $p = 0.016$) than non-comorbid inmates (M = 0.17, SD = 0.38). However, after psychostimulants were introduced, there were no group differences observed. Inmates with comorbid cannabis use disorder (M = 0.55, SD = 0.69) committed significantly more violent misconducts ($t(33) = -1.81$, $p = 0.040$) than non-comorbid inmates (M = 0.21, SD = 0.41). This remained consistent after psychostimulant treatment. No significant group differences were found regarding misconducts and cocaine use disorder across periods.

Discussion: Inmates diagnosed with comorbid alcohol/cannabis use disorder displayed significantly more misconducts, alluding to a worsening in behavioral regulation with the use of such substances. Interestingly, psychostimulant treatment appeared to maintain or mitigate the severity of misconducts, suggesting potential benefits from the use of psychostimulants among inmates with ADHD and comorbid alcohol/cannabis use disorder.

W13. THE NEUROCHEMICAL AND ANXIOLYTIC-LIKE EFFECTS OF CENTANAFADINE IN PRECLINICAL ASSAYS IN THE RAT AND MOUSE

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Abstract Background: Centanafadine is a norepinephrine (NE), dopamine (DA), and serotonin (5-HT) reuptake inhibitor (NDSRI) currently in clinical development. Overall, it has been shown to possess a favorable efficacy and safety profile in Phase 3 trials in adults, children, and adolescents with ADHD. Emerging clinical and nonclinical data suggest that the pharmacological profile of centanafadine may extend beyond core ADHD symptoms to associated features, including emotional dysregulation, executive dysfunction, and common psychiatric comorbidities such as anxiety. Anxiety-related disorders are frequently associated with dysregulation of monoaminergic neurotransmission. The objective of this study was to further characterize the neurochemical and behavioral effects of centanafadine in this regard using in vivo microdialysis and established preclinical models of anxiety-related behavior.

Methods: The neurochemical and behavioral effects of centanafadine were evaluated using microdialysis and established preclinical models of anxiety. Neurotransmitter levels were quantified in the rat prefrontal cortex (PFC) and ventral striatum (vSTR) following dosing of centanafadine (3, 10, and 30 mg/kg, orally). In mice, anxiety-like behavior was assessed using the marble burying test. Male mice received centanafadine (3, 10, 30, and 40 mg/kg, orally) or chlordiazepoxide (15 mg/kg, intraperitoneally) 60 or 30 mins prior to testing, respectively. Endpoints included the number of marbles buried and total distance traveled. In rats, anxiety-related behavior was evaluated 1h after centanafadine dosing (3, 10 and 30 mg/kg, oral) using the elevated plus maze (EPM) and contextual fear conditioning (CFC) paradigms. For the EPM, endpoints included % time in the open arms, % open arm entries, and total arm entries. In the CFC, rats underwent a conditioning session followed by a test session conducted 24h later, with freezing behavior assessed during the test session.

Results: In this investigation centanafadine significantly increased levels of DA, NE, and 5-HT in the PFC, and 5-HT and DA in the vSTR of rats. At 30 mg/kg, peak increases in the PFC were: 5-HT 1638%, NE 739%, and DA 302%; in the vSTR: 5-HT 1590% and DA 219%. In mice, centanafadine significantly reduced the number of marbles buried following dosing at 30 and 40 mg/kg compared with vehicle-dosed animals without significantly affecting distance traveled. In rats, centanafadine increased open arm exploration in the EPM at the 30-mg/kg dose, including % time in the open arms, % open arm entries, and total arm entries compared with vehicle-dosed animals. In the CFC, centanafadine reduced freezing behavior at the 30-mg/kg dose when compared to vehicle-dosed animals.

Conclusions: In this investigation, centanafadine significantly increased levels of DA, NE and 5-HT in the PFC and 5-HT and DA in the vSTR of rats. Centanafadine demonstrated an anxiolytic-like profile across several well-established mouse and rat assays. Notably, the efficacious dose range between species and assays was remarkably consistent and aligned with the microdialysis data, demonstrating centanafadine as an NDSRI in vivo.

W14. GROWING TREND OF STIMULANT USE IN YOUNG PATIENTS MISDIAGNOSED WITH ADHD: A CASE-BASED SYSTEMATIC REVIEW

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Abstract Objective: The rise in pediatric ADHD diagnoses and stimulant prescribing has raised concerns about misdiagnosis, inappropriate treatment, and psychiatric harm. This systematic review examines pediatric and adolescent case reports of stimulant-associated psychiatric and behavioral adverse effects, with attention to prolonged exposure or potential ADHD misdiagnosis, and presents a novel case of an adolescent female with long-term stimulant treatment and comorbid depression who presented with intentional overdose and psychotic features.

Methods: Data Sources: A database search of PubMed, PsycINFO, and Embase was conducted for pediatric and adolescent case reports published through October 1, 2025, using keywords related to attention-deficit/hyperactivity disorder, stimulant medications, and psychiatric adverse effects.

Study Selection: Of 312 records identified, 42 articles were screened, and 10 were selected for full-text review. Publications not available in English, review articles, and reports lacking accessible full text were excluded.

Data Extraction: Relevant data were extracted and summarized in a clinically oriented manner, including sex, age, primary diagnosis, medication exposure, and associated psychiatric or behavioral adverse effects; no quantitative analyses were conducted.

Case Presentation: An 18-year-old female was brought to the emergency department (ED) on a mental health crisis hold following an intentional overdose of bupropion, amphetamine-dextroamphetamine, fluoxetine, and alcohol. In the interview, the patient appeared guarded and was reluctant to provide details. She reported initiation of amphetamine-dextroamphetamine at 5 years of age, with intermittent discontinuation periods throughout childhood and adolescence. The patient herself recalled developing depressive symptoms around 6 years of age, approximately one year after starting stimulant therapy. Despite this history, she was resistant to considering the possibility that long-term amphetamine-dextroamphetamine use may have contributed to her mood symptoms. During the encounter, the patient exhibited psychotic features, including suspicion and paranoia. She refused trainee presence, consenting only to the attending, and repeatedly asked, "Are they talking about me?" suggesting persecutory ideation. The patient was counseled on the potential psychotic effects of stimulant medications, particularly in individuals without a definitive ADHD diagnosis, and was ultimately receptive. The patient was admitted for medical monitoring, with plans to resume fluoxetine and discontinue amphetamine-dextroamphetamine. Referral to child and adolescent psychiatry was recommended for further evaluation and management.

Results: A total of 10 pediatric and adolescent case reports were identified and 1 novel case presented, describing stimulant-associated psychiatric and behavioral adverse effects, including psychosis, mania, depression, aggression, trichotillomania, paradoxical sedation, and suicidality,

often occurring in the context of early stimulant initiation, prolonged exposure, dose escalation, comorbid neurodevelopmental or psychiatric conditions, or suspected ADHD misdiagnosis.

Conclusions: This case and prior pediatric reports highlight the need for developmentally informed ADHD diagnosis, cautious stimulant prescribing, and close psychiatric monitoring to balance therapeutic benefit against potential long-term neurobehavioral risk in children and adolescents.

W15. EMOTIONAL DYSREGULATION SYMPTOM OUTCOMES IN ADULTS WITH ADHD TREATED WITH CENTANAFADINE: A POOLED POST HOC ANALYSIS OF TWO PHASE 3 TRIALS

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Abstract Background: Attention-deficit/hyperactivity disorder (ADHD) in adults frequently includes symptoms of emotional dysregulation, such as affective lability, emotional overreactivity, frustration tolerance, and anger outbursts. This pooled post hoc analysis of two phase 3 trials evaluated the effect of centanafadine (CTN)—a norepinephrine, dopamine, serotonin reuptake inhibitor—on patient-reported assessment of emotional dysregulation using the adult ADHD Self-Report Scale (ASRS) Expanded Version after 6 weeks of treatment in adults with ADHD.

Methods: Data from two identically designed phase 3 trials were pooled. Eligible patients (aged 18–55 years) with a primary ADHD diagnosis per DSM-5 were randomized to receive CTN 200 or 400mg/day or placebo. Exploratory endpoints included changes from baseline in the Emotional Dyscontrol (ED) subscale score and individual ED line items from the ASRS Expanded Version at Week 6. The ASRS Expanded Version is a validated, self-administered questionnaire that includes 4 items assessing aspects of emotional dysregulation, with responses rated on a 5-point Likert scale (0=never to 4=very often). Endpoints were analyzed using a mixed-effects model for repeated measure without adjusting for multiplicity.

Results: A total of 744 adults were included in the efficacy sample (CTN 200mg, n=242; 400mg, n=241; placebo, n=261). At Week 6, adults treated with CTN reported improvements from baseline in the ASRS ED subscale compared with placebo, reflecting reductions in the frequency of specific patient-reported emotional dysregulation dimensions assessed by the scale (200mg: -0.9, P=0.0023; 400mg: -0.9, P=0.0006). Effect sizes (Cohen's D) for the ASRS ED subscale were 0.27 for CTN 200mg and 0.31 for 400mg. Consistent with the subscale-level findings, improvements from baseline vs placebo were observed across individual Aitems items at Week 6, including those related to affective lability, emotional overreactivity, and anger outbursts.

Conclusions: In this pooled post hoc analysis, CTN was associated with improvements in patient-reported emotional dysregulation in adults with ADHD, as assessed by the ASRS Expanded Version. Improvements were observed across ED items capturing externally expressed, behavioral dimensions of emotional dysregulation, including affective lability,

emotional over reactivity, and anger outbursts, with improvements of similar magnitude to those observed for core ADHD symptom domains.

W16. THE PERSISTENCE OF NEUROEPITHELIAL PROGENITORS IN NEOCORTICAL ORGANOID: IMPEDING ACCURATE MODELS FOR DRUG SCREENING IN NEURODEVELOPMENTAL DISORDERS

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Abstract Human induced pluripotent stem cell (hiPSC)-derived brain organoids represent a human, druggable model system with growing potential for neuropsychiatric disease modeling and pharmacologic screening. Because organoids can be generated in high throughput, they offer a scalable platform to test compounds across diverse genetic backgrounds. However, the fidelity of drug responses depends critically on whether organoids accurately reproduce the cellular composition and maturation trajectories of the human brain. In organoids and also in fetal development, neocortical neurons arise from neuroepithelial progenitors, which differentiate into radial glia (stem cells of the neural cortex) before taking on terminal neuronal cell fates of the laminar cortex. Using hiPSCs from 5 unique donors, we differentiated our stem cells using a 3D neocortical organoid protocol and using snRNA-sequencing to profile the cells at 5 points in time (i.e. Day 10, Day 20, Day 35, Day 50, Day 90) spanning early neuroepithelial induction to neuronal differentiation. Unexpectedly, we identified a large population of early neuroepithelial progenitors that persist through Day 90—well beyond their disappearance in the corresponding in vivo developmental window, when radial glia should dominate the progenitor pool. Using palantir trajectory analysis, we computed fate transition probabilities for each cell and defined a “stalling probability” representing the likelihood of maintaining one’s progenitor identity. Across multiple cell classes, we identified distinct “stalling” and “non-stalling” subpopulations, each with unique molecular signatures. Then, using differential gene expression testing within each cell class, we identified key molecular regulators that drive “stalling” or that permit differentiation. Consistent with prior literature, MAPK signaling emerged as a regulator of stalling in radial glia. Our analysis implicated previously undescribed roles for canonical and non-canonical Wnt pathway in early and mature neuroepithelium stalling. These findings highlight intrinsic regulatory mechanisms that may limit maturation in brain organoids, thereby constraining their translational utility for pharmacologic testing. Ongoing experiments are assessing how pharmacologic modulation of Wnt signaling alters early and mature neuroepithelial persistence and overall cell-type diversity. By improving the fidelity of cortical organoid differentiation, we aim to generate models that better recapitulate in vivo developmental trajectories and enhance the reliability of high-throughput drug screening for psychiatric and neurologic disorders.

W17. LONG-TERM SAFETY AND TOLERABILITY OF CARIPRAZINE IN PEDIATRIC PATIENTS WITH AUTISM SPECTRUM DISORDER, BIPOLAR I DISORDER OR SCHIZOPHRENIA: FINAL RESULTS FROM AN OPEN-LABEL STUDY

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Abstract Background: Guidelines recommend atypical antipsychotics (AAs) as a first-line treatment option for early-onset bipolar I disorder (BP-I) and schizophrenia (SCZ). AAs are also used to treat irritability and aggression in children with autism spectrum disorders (ASD). However, fewer AAs are approved for pediatric use than for adults, and children may be more susceptible to antipsychotic-associated side effects (eg, weight gain, sedation, and extrapyramidal symptoms). Cariprazine, a dopamine D3-preferring D3/D2 receptor and serotonin 5-HT1A receptor partial agonist, is approved to treat both depressive and manic/mixed episodes of BP-I as well as SCZ in adults, and more recently approved to treat BP-I manic/mixed episodes and SCZ in children aged 10-17 and 13-17 years, respectively. Although cariprazine has a well-established risk-benefit profile in adults, it has yet to be fully characterized in pediatric patients. This study evaluated the long-term safety and tolerability of cariprazine for pediatric patients with ASD, BP-I or SCZ.

Methods: Patients aged 5-17 years with ASD, 10-17 years with BP-I, or 13-17 years with SCZ were enrolled in a 52-week, multicenter, open-label, flexible-dose phase 3 study (NCT04578756). Dosing was individualized by diagnosis, age, and body weight and ranged from 0.75 to 4.5 mg/d. Safety parameters included adverse events (AEs), extrapyramidal symptom scales (eg, the Barnes Akathisia Rating Scale [BARS] and Simpson–Angus Scale [SAS]), clinical laboratory measures, vital signs, electrocardiogram (ECG), and suicidality measures (via the Columbia-Suicide Severity Rating Scale [C-SSRS]). Data were analyzed using descriptive statistics.

Results: The safety population included 306 patients (ASD, n=139; BP-I, n=146; SCZ, n=21). Of these, 44% discontinued during the open-label treatment period, most commonly due to withdrawal by a parent/guardian (19%); approximately 8% discontinued due to an AE. Treatment-emergent AE (TEAEs) occurred in 67% of patients and were mostly mild or moderate. Serious TEAEs were reported by 4% of patients overall, and 40% of TEAEs were considered treatment-related by the investigator. Common TEAEs (≥5% for any indication) included weight increase (14%), headache (10%), somnolence (10%), nausea (9%), fatigue (7%), vomiting (7%), agitation (5%), akathisia (5%), insomnia (4%), anxiety (4%), salivary hypersecretion (2%) and dysmenorrhoea (2%). No clinically meaningful changes from baseline were observed in laboratory tests, vital signs or ECGs. A small, clinically nonsignificant increase in age- and gender-adjusted body weight was observed (mean z-score change=0.1). No increased suicidality was reported on the C-SSRS.

Conclusions: Long-term cariprazine treatment in pediatric patients was generally well tolerated with no new signals. Safety outcomes were largely similar across indications, supporting generalizability of the data across pediatric populations.

W18. E2086, A SELECTIVE OREXIN RECEPTOR-2 AGONIST: STUDY FOR PROMOTING WAKEFULNESS IN PATIENTS WITH NARCOLEPSY TYPE 1

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Abstract Objective: To report results from the first clinical study of E2086, a novel, selective orexin receptor-2 (OX2R) agonist, in patients with narcolepsy type-1 (NT1).

Background: E2086 is hypothesized to regulate the sleep/wake cycle by supporting wakefulness through the orexin neuronal pathway; its preclinical profile showed strong dose-dependent efficacy in promoting wakefulness and mitigating cataplexy.

Design/Methods: E2086-A001-101, a multicenter, randomized, double-blind, double-dummy, single-dose, N-of-1, five-period crossover study, evaluated the efficacy, safety, and tolerability of E2086 (5 mg, 10 mg, 25 mg) compared with placebo (PBO) and modafinil 200 mg in adult participants with NT1. Male and female participants with verified diagnoses of NT1 were randomized to receive study drug within an hour of waketime following an overnight polysomnogram. Forty-minute maintenance of wakefulness tests (MWTs) were commenced 2 hours after waketime and continued every 2 hours until ~7 hours postdose (4 total). The Karolinska Sleepiness Scale (KSS) was administered at the end of each MWT. Safety data were collected.

Results: Twenty-two subjects were randomized; 19 subjects were completers (received all 5 treatments and had data from all 4 MWTs). In the safety analysis set (n=21; all randomized subjects who received ≥ 1 dose of study treatment), 12 (57.1%) subjects were male; mean (SD) age was 35.6 (11.8) years. At baseline, the mean (SD) of sleep latency tests was 3.0 (2.7) minutes. Mean (SD) baseline Epworth Sleepiness Scale score was 17.2 (3.5). Least squares (LS) mean sleep latencies (MSLs; 95% confidence interval [CI]) for E2086 5 mg (25.73 [21.67, 29.78] min), 10 mg (34.69 [30.64, 38.75] min), and 25 mg (37.94 [33.88, 41.99] min) were longer and statistically significant compared with PBO (6.46 [2.39, 10.52] min) and modafinil (15.92 [11.88, 19.96] min). MSL with modafinil was also significantly longer versus PBO, establishing assay sensitivity. E2086 10 mg and 25 mg sustained wakefulness for ≥ 30 minutes during each MWT; E2086 5 mg sustained wakefulness for greater than 19 minutes throughout each MWT trial. LS mean (95% CI) KSS scores for E2086 5 mg (4.51 [3.85, 5.18]), 10 mg (3.31 [2.65, 3.98]), and 25 mg (3.25 [2.58, 3.92]) were smaller and statistically significant versus PBO (6.61 [5.94, 7.28]); E2086 10 mg and 25 mg scores were smaller and statistically significant versus modafinil (5.35 [4.68, 6.01]). The effect of E2086 on daytime alertness was durable, with participants maintaining significantly greater alertness with E2086 (all doses) versus PBO and with E2086 (10 mg and 25 mg doses) versus modafinil for each KSS assessment. E2086 was generally well tolerated, with most treatment-emergent adverse events being mild to moderate in severity.

Conclusions: These data demonstrate that E2086 has the potential to improve daytime wakefulness in patients with NT1. The efficacy/safety profile supports continued investigation of E2086 in the narcolepsy patient population.

W19. THE COMPLEX MULTI-SYSTEM SYMPTOM INVENTORY (COMSS): A NEW INSTRUMENT TO ASSESS SYMPTOM FREQUENCY, IMPACT, AND POSTURAL DEPENDENCE ACROSS MULTIPLE CENTRAL AND PERIPHERAL AUTONOMIC SYMPTOM DOMAINS

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Abstract Background: Patients with mental health diagnoses often experience a high burden of cognitive and somatic symptoms alongside concurrent traditional psychiatric symptoms. Many of these can be captured by self-report measures that focus on symptoms commonly experienced by individuals with autonomic nervous system dysregulation. However, available symptom inventories were primarily developed for other applications (e.g., the COMPASS-31), focus on a subset of symptoms (e.g. orthostatic hypotension), and/or have anchor points that can be challenging to compare across patients or across time (e.g., the MALMO). Here, we report on the development and validation of a new 18-item self-report measure with 4 subdomains, designed for both clinical and research use in patients with complex, multi-system symptoms.

Methods: Development started by identifying 31 commonly occurring symptoms reported during autonomic testing and clinic visits at the University of Washington Autonomic Neurology Clinic. These 31 symptoms included central (e.g., problems with concentration or sleep) and peripheral (e.g., gastrointestinal, cardiovascular) symptom areas. Using a two-week lookback, symptoms were scored for frequency ranging from monthly or less (0) to multiple times daily (4). Symptoms occurring with a frequency of weekly or greater were additionally scored for bothersomeness, and a subset of commonly postural items scored for postural dependence. The questionnaire was implemented in Qualtrics as part of an existing clinical study and initial subject responses were gathered from January 2022-April 2024; this larger study also included 11 existing validated instruments, and assessed the presence or absence of 12 commonly occurring diagnoses with complex symptoms.

Results: The analyzed data set included 342 completed questionnaires (average age 45.7 + 13.3 years, 72% female). Prior to item-reduction, Cronbach's alpha (0.95), item-to-item correlations, and item-to-total correlations suggested strong internal validity and moderate item redundancy. Following iterative correlation analysis and linear modeling to eliminate redundant items, an 18-item measure that included both frequency and postural-dependence but no bothersomeness items was used to create the final CoMSS measure. Factor analysis of the final measure revealed a 4 factor structure, with factors roughly corresponding to postural symptoms (similar to core symptoms of postural orthostatic tachycardia syndrome [POTS]); symptoms of low energy, sleep and joint/muscle pain (similar to core symptoms of fibromyalgia and/or ME/CFS); gastrointestinal symptoms (similar to core symptoms of irritable bowel syndrome); and vasomotor, nightmares and anxiety symptoms (similar to a subset of core PTSD symptoms).

Convergent validity for each factor and with concurrently administered validated instruments found Pearson's coefficients ranging from 0.3-0.6, suggesting that the CoMSS is related to, but not redundant with, existing measures.

Conclusions: The novel CoMSS self-report instrument for complex, multi-system symptoms demonstrates strong psychometric properties, and reveals an underlying factor structure potentially similar to existing syndromic diagnostic categorizations.

W20. STATIC AND DYNAMIC DISRUPTIONS OF SALIENCE-NETWORK FLEXIBILITY IN VETERANS WITH COMORBID MILD TBI AND ALCOHOL USE DISORDER

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Abstract Mild traumatic brain injury (mTBI) and alcohol use disorder (AUD) commonly co-occur in Veterans, a comorbidity marked by poor outcomes and resistance to standard pharmacotherapy. Both conditions disrupt the salience network (SN), which coordinates transitions between default mode network (DMN) self-referential processing and cognitive control network (CCN) top-down engagement. When this switching mechanism fails, individuals may become stuck in internally-focused states that sustain rumination, impair cognitive flexibility, and amplify craving. Characterizing how mTBI+AUD jointly alter salience-network dynamics may reveal mechanistic targets for more precise pharmacological and neuromodulatory intervention in this treatment-refractory population. Here, we examine static and dynamic SN interactions in 44 Veterans (22 mTBI+AUD; 22 age- and sex-matched controls) who completed 20 minutes of resting-state fMRI (TR=555 ms) and a post-scan Penn Alcohol Craving Scale. Data were preprocessed in CONN. Static functional connectivity was quantified as time-averaged coupling between the SN-CN and SN-DMN, using six a priori internetwork pairs per hemisphere derived from the Yeo-17 atlas. SN-bias was summarized using a network orientation index (θ), defined as the inverse tangent of SN-CN relative to SN-DMN connectivity across the scan. To capture transient regulatory states, we applied seed-based co-activation pattern (CAP) analysis using a right anterior insula seed (a key SN node), identifying recurring SN-linked brain states and quantifying state persistence and entry frequency. CAP spatial maps were labeled by overlap with canonical Yeo-17 networks using the Dice coefficient. Group differences and craving effects across all subjects were tested using linear mixed-effects models with subject-level random intercepts, with FDR-correction applied. Compared with controls, Veterans with mTBI+AUD exhibited DMN-dominant salience network coupling: reduced SN-CN connectivity ($p=0.009$), increased SN-DMN connectivity ($p=0.014$), and lower network orientation values ($p=0.005$), indicating DMN-SN coupling dominance. Higher alcohol craving was independently associated with this same DMN-biased profile across all participants (all $p < 0.05$). Dynamic CAP analysis identified four reproducible recurring states across all subjects: DMN-SN, SN-dominant, SN-CN, and visual network configurations. The mTBI+AUD group persisted significantly longer in the DMN-SN state ($\beta=3.54s$, $p < 0.001$) and showed fewer state transitions overall ($p < 0.05$). A craving-by-state interaction linked higher craving to prolonged DMN-SN state persistence ($\beta=1.58s$, $p < 0.001$), independent of group. Together, these preliminary findings show that Veterans with mTBI+AUD exhibit convergent

static and dynamic disruptions in SN regulation, marked by a trait-like bias toward DMN-dominant connectivity and prolonged occupancy of DMN-centered brain states. The alignment of time-averaged connectivity biases with reduced moment-to-moment state switching suggests that mTBI+AUD may amplify impairments in SN-driven regulatory flexibility. Clinically, this may help explain why craving-related thoughts become overly salient and difficult to disengage from. Because SN interactions with the DMN and CN are known targets of pharmacologic and neuromodulatory interventions across addiction and mood disorders, these findings nominate specific circuit-level processes for future study. In particular, SN–DMN coupling and SN-DMN-state persistence emerge as testable neural markers that may inform precision treatment development in this high-risk, underserved comorbid Veteran population.

W21. SUCCESSFUL EARLY TREATMENT OF ANTI-N-METHYL-D-ASPARTATE RECEPTOR ENCEPHALITIS ASSOCIATED WITH SMALL CELL LUNG CANCER IN AN ELDERLY MALE PATIENT: A CASE REPORT

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Abstract Background: Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis, a type of autoimmune encephalitis, is characterized by acute onset neuropsychiatric symptoms, predominantly affects young females and is often associated with ovarian teratomas. While small cell lung cancer (SCLC) is a known cause of paraneoplastic encephalitis, its association with anti-NMDAR encephalitis is rare and often carries a poor prognosis because of limited response to immunotherapy.

Case presentation: An 80-year-old male with no psychiatric history presented with flu-like symptoms and subsequently developed acute-onset neuropsychiatric symptoms, including pressured speech, agitation, memory impairment, and abnormal behavior. Autoimmune encephalitis was suspected due to a mildly elevated cerebrospinal fluid (CSF) white cell count and a mass in the right upper lung detected by whole-body computed tomography (CT) on Day 1 of hospitalization. High-dose intravenous corticosteroids were administered on Day 1, with prompt and sustained improvement in symptoms. CSF was subsequently confirmed positive for anti-NMDAR antibodies, and bronchoscopy-guided biopsy of the pulmonary mass confirmed SCLC. The patient recovered without neurological deficits and was discharged in stable condition on hospital Day 30.

Conclusion: We report a rare case of anti-NMDAR encephalitis associated with SCLC in an elderly male patient. Diagnosis in elderly individuals is often challenging because of atypical presentations and lower tumor association. Nonetheless, timely initiation of intervention may lead to favorable outcomes. Clinicians should consider autoimmune encephalitis, including anti-NMDAR encephalitis, when evaluating acute-onset neuropsychiatric symptoms in elderly individuals, and should initiate early immunotherapy alongside tumor screening.

W22. GH001 EFFICACY IS INDEPENDENT OF PRIOR ANTIDEPRESSANT TREATMENT FAILURES IN TREATMENT-RESISTANT DEPRESSION: A POST HOC ANALYSIS OF A PHASE 2B RANDOMIZED CONTROLLED TRIAL

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Abstract Background: Treatment-resistant depression (TRD) affects approximately 30% of patients treated for major depressive disorder and is associated with significant morbidity and mortality. The landmark STAR*D study established that remission rates decline progressively with each antidepressant treatment failure for that current episode (37%, 31%, 14%, and 13% after the first, second, third, and fourth trial, respectively), a pattern that represents a persistent clinical challenge. We recently reported that a single-day individualized dosing regimen (IDR) of GH001, a synthetic form of mebufotenin for pulmonary inhalation, produced ultra-rapid and significant improvements in depressive symptoms versus placebo in patients with TRD (least square mean difference, -15.5; effect size, -2.0; 57.5% remission at Day 8 vs 0% placebo). Here we report a post hoc analysis examining whether GH001 efficacy varied by number of prior lifetime treatment failures.

Methods: Details of the Phase 2b GH001-TRD-201 trial (NCT05800860) have been previously presented. Briefly, 81 patients with TRD (nonresponse to 2-5 prior antidepressant treatments for the current major depressive episode) were randomized 1:1 to receive GH001 IDR (up to three escalating doses of 6, 12, and 18 mg) or placebo on a single day. The current analysis included all 40 GH001-treated patients, who had documented 2-7 prior lifetime antidepressant treatment lines (mean, 3.65). This trial was conducted under the supervision of qualified healthcare professionals, providing psychological support per standard-of-care, but without any planned psychotherapeutic intervention before, during, or after dosing. Spearman rank correlations between number of prior lifetime treatment failures and change in Montgomery-Åsberg Depression Rating Scale (MADRS) score from baseline were calculated at two timepoints: Day 8 of the acute response phase (n=40) and Month 6 of the durable response phase (n=31 of the original 40), among patients who completed the 6-month open-label extension (OLE). Remission rates (MADRS total score ≤10) were calculated by subgroup (2, 3, 4, or ≥5 prior lifetime failures).

Results: There was no meaningful correlation between number of prior lifetime treatment failures and MADRS improvement at Day 8 or at Month 6 (Spearman rank correlations were weak and non-significant at both timepoints). Day 8 remission rates were consistent across subgroups (ranging from 54% to 64% regardless of number of prior lifetime failures). Remission rate at Month 6 among those who completed the OLE remained stable across subgroups. This contrasts sharply with the progressive attenuation observed in STAR*D which reflected the sequential prospective treatment failures within the same episode.

Conclusion: GH001 efficacy is independent of prior lifetime treatment history, directly contrasting the progressive decline observed with conventional antidepressants. To our knowledge, this is the first demonstration in a controlled trial of an investigational antidepressant

agent achieving rapid and durable remission rates that appear independent of prior antidepressant treatment burden in patients with TRD. These findings support the potential of GH001 as a novel treatment for TRD, suggesting a therapeutic effect that is not attenuated by increasing prior treatment exposure.

W23. EXAMINING THE IMPACT OF PATIENT-CENTERED APPROACHES ON THE ASSESSMENT AND MANAGEMENT OF COGNITIVE IMPAIRMENT IN MAJOR DEPRESSIVE DISORDER

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Abstract Introduction: Cognitive impairment affects nearly two-thirds of patients with major depressive disorder (MDD), may persist despite depressive episode remission, may worsen with repeated episodes of depression, and is associated with an increased risk of neurodegenerative disorders. Identifying and addressing cognitive impairment therefore should be a key goal of management to optimize long-term outcomes in MDD.

Methods: Between May 2024 and December 2025, clinicians and patients from five US-based psychiatry and behavioral health clinics participated in a quality improvement initiative. A steering committee comprised of patients and clinicians developed a point of care guide aimed at supporting conversations and shared decision-making around cognitive symptoms. Surveys were administered to patients with MDD (n=118) and their providers (n=74) before and after using the guide. Clinics participated in audit-feedback sessions to evaluate real-world data, identify gaps in evidence-based assessment and management, and develop action plans. Follow-up surveys of patients (n=96) and providers (n=48) were collected 3 months later to assess long-term impact.

Discussion: At baseline, 75% of patients had cognitive symptoms and more than half said that they had a high impact on their quality of life (QoL; Likert 4/5). Only 40% of patients were satisfied with their depression therapy (Likert 4/5) and 42% were not taking any therapy for depression. While 70% of clinicians assessed for cognitive impairment at most appointments, only 48% of patients said the same (Likert 4/5) and 25% of patients were never asked. Following guide integration, patients' confidence in discussing cognitive symptoms increased from 56% to 75%, and 86% felt satisfied with the care decisions (both Likert 4/5). Clinicians set action plans aimed at increasing awareness of cognitive impairment with patients, engaging patients to take part in decision-making, and staying current on emerging evidence. The longitudinal survey revealed lasting changes in treatment for most patients; 44% of patients reported changes in MDD therapy and an additional 33% reported changes in management not related to therapy. Most patients reported improvements in cognitive health (70%) and increased confidence (74%) and involvement (81%) in decision-making. Most clinicians assessed cognitive impairment more frequently (70%) and invited patients to take part in care decisions (77%) as a result of the guide. These findings suggest that building frameworks to evaluate and manage cognitive impairment in MDD such as the collection of patient-reported outcomes and engagement in care planning

through a point of care guide can help to uncover unmet needs in cognitive health and facilitate lasting improvements in care.

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W24. SELTOREXANT VERSUS QUETIAPINE EXTENDED RELEASE AS ADJUNCTIVE TREATMENT IN MAJOR DEPRESSIVE DISORDER WITH INSOMNIA SYMPTOMS: PHASE 3 TRIAL

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Abstract Background: Seltorexant, a first-in-class, selective, orexin-2 receptor antagonist, normalizes hyperarousal and promotes physiological sleep. Significant antidepressant effects and a favorable safety profile of adjunctive seltorexant versus placebo were shown in a phase 3, 6-week study in major depressive disorder with insomnia symptoms (MDDIS;NCT04533529). Here we present results of a trial comparing adjunctive seltorexant versus adjunctive quetiapine extended release(XR) as comparator in MDDIS (NCT04513912).

Methods: This 26-week, international, active-controlled study enrolled participants 18-74 years with DSM-5 diagnosis of MDD without psychotic features, with moderate-to-severe insomnia symptoms and inadequate response to 1-2 antidepressants. Participants were randomized 1:1 to seltorexant 20mg or quetiapineXR (labeled dosage) while continuing their background SSRI/SNRI. The primary endpoint was response rate ($\geq 50\%$ improvement from baseline in Montgomery-Åsberg Depression Rating Scale [MADRS] score) at Week26. Secondary endpoints included change from baseline to Week26 in body weight (key) and in MADRS score. Safety was assessed.

Results: Of 757 participants randomized, 756 received ≥ 1 dose of study intervention(seltorexant:n=366;quetiapineXR:n=390). Week26 response rate was 57.4%(201/350) for seltorexant and 53.4%(194/363) for quetiapineXR; %difference:4.0(95%CI:-3.3,11.3). Mean change from baseline to Week26 in body weight(kg) was 0.5(SD:2.89,n=268) seltorexant and 2.1(SD:3.93,n=263) quetiapineXR (least squares[LS] mean difference:-1.7[95%CI:-2.23,-1.09]), and mean change in MADRS score was -23.0(SD:10.12,n=272) seltorexant and -22.7(SD:9.54,n=263) quetiapineXR (LS mean difference:-0.2[95%CI:-1.77,1.35]). Lower incidences of somnolence(6.3%[23/366];24.1%[94/390]) and adverse events leading to study intervention discontinuation(5.7%[21/366];11.3%[44/390]) were observed with seltorexant versus quetiapineXR.

Conclusions: Treatment arms demonstrated comparable robust response rates, without a statistical difference between groups. Safety findings support the better tolerability of seltorexant as long-term adjunctive treatment for MDDIS.

W25. BENEFITS OF ADJUNCTIVE VAGUS NERVE STIMULATION IN DIFFICULT-TO-TREAT DEPRESSION: OUTCOMES OF A NATURALISTIC EUROPEAN COHORT (RESTORE-LIFE) COMPARED TO THE USA RECOVER RANDOMIZED CONTROLLED TRIAL

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Abstract: Major depressive disorder (MDD) which proves difficult-to-treat (difficult-to-treat depression: DTD) is associated with chronic and/or recurrent depressive symptoms and severe impairments in quality of life (QoL) and functioning. Vagus nerve stimulation (VNS) is an approved, long-term adjunctive treatment for patients with DTD. Its effectiveness in improving QoL and functioning has recently been supported by the US-based RECOVER, randomized, triple-blind, sham-controlled trial. This enrolled adults with moderate-to-severe MDD depressive episodes, randomized 1:1 to receive adjunctive active or sham VNS for 12 months. RESTORE-LIFE is a European prospective, observational, multicenter, post-marketing study assessing the efficacy and effectiveness of VNS therapy in adults with DTD, reflecting the naturalistic clinical practice of VNS in these patients. Inclusion criteria were minimal: a documented diagnosis of chronic (> 2 years) or recurrent (two or more prior episodes) major depressive episode with unsatisfactory response to antidepressant treatments. Here we present the 12-month effectiveness data of VNS therapy in RESTORE-LIFE and compare the findings to those published for RECOVER (NCT03887715) (1,2). In the interim RESTORE-LIFE dataset (n=147), 25.9% of participants had bipolar disorder: RECOVER (n=493) included exclusively patients with MDD (a bipolar RECOVER study is ongoing). At baseline severity of depression (mean [SD] Montgomery-Åsberg Depression Rating Scale [MADRS] score) was slightly higher in RECOVER (34.2 [4.9]) versus RESTORE-LIFE (30.2 [8.4]). Participants had similar QoL; the mean (SD) Mini Quality of Life Enjoyment and Satisfaction Questionnaire (Mini-Q-LES-Q) scores were 15.4 (5.2) in RESTORE-LIFE and 15.0 (4.1) in RECOVER. Both studies included participants with severe DTD, with the mean (SD) number of lifetime failed antidepressant treatments (medications, ECT, TMS and psychotherapies) being 13.3 (8.4) in RECOVER and 15.6 (10.7) in RESTORE-LIFE. Participants in RESTORE-LIFE had a greater mean number of lifetime psychiatric hospitalizations (8.6 vs 2.2) and a greater proportion had received prior electroconvulsive therapy (85.2% vs 45.3%) compared to those in RECOVER (possibly reflecting differences in health care provision). The effectiveness of VNS therapy was similar across both studies. The mean percent time in partial response, response, and remission over 12 months on the clinician-rated MADRS was 41.1%, 24.5%, and 14.7% in RESTORE-LIFE and 32.9%, 18.9%, and 9.5% in RECOVER. Similar results were observed on the patient-rated Quick

Inventory of Depressive Symptomatology–Self-Report, with slightly greater proportions in RECOVER versus RESTORE-LIFE for partial response (40.5% vs 29.3%), response (25.2% vs 18.4%), and remission (12.4% vs 14.3%). Mean percent time in clinically meaningful benefit in the Mini-Q-LES-Q ($\geq 11.89\%$ increase from baseline) was 32.0% in RESTORE-LIFE and 45.4% in RECOVER. Safety of VNS was also evaluated in RESTORE-LIFE and compared to that in RECOVER. These data support the conclusion that the benefits in symptoms and QoL with VNS in participants with marked DTD seen in a randomized clinical trial in the United States are generalizable to patients treated naturalistically in a different, European, health care setting.

W26. POOLED INDIVIDUAL PATIENT DATA ANALYSIS OF THREE PHASE 2 TRIALS SUPPORTS VASOPRESSIN V1B RECEPTOR ANTAGONISM (BH-200 250 MG BID) AS AN ANTIDEPRESSANT MECHANISM FOR THE TREATMENT OF MAJOR DEPRESSIVE DISORDER (MDD)

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Abstract Background: Lack of novel pharmacological mechanisms to address symptoms of MDD, is the main reason behind the unmet medical need in those clinical populations showing suboptimal response to existing treatments. Vasopressin V1b receptor antagonism as a modulator of the HPA stress axis has a therapeutic potential, but clinical evidence across studies has been inconsistent. We conducted a pooled, individual patient data (IPD) analysis across all three randomized, double-blind, placebo-controlled Phase II trials that had a similar design, to estimate overall efficacy and evaluate consistency across studies for BH-200 250 mg BID. Two of the trials demonstrated a separation between patients treated with BH-200 and patients treated with placebo at Week 8, with $p < 0.05$, while the third trial showed no separation.

Methods: Individual Patient Data (IPD) from three Phase II studies (DFI 5878, DFI 5879, and OLIVE) were pooled in an ITT framework (randomized participants with ≥ 1 post-baseline assessment). The endpoint was the change from baseline to Week 8 in Hamilton Depression Scale total score (HAMD-17). A mixed model for repeated measures (MMRM) included baseline, visit, treatment, study, visit-by-treatment, visit-by-study, and treatment-by-study, with covariates (sex, age, baseline BMI) and random effects for country and subject-level visit slope/intercept. Primary estimates focused on the overall treatment effect at Week 8 and assessment of heterogeneity via treatment-by-study interaction.

Results: The pooled dataset included N=610 participants (BH-200 n=362; placebo n=249). BH-200 demonstrated robust improvement versus placebo with a separation starting in Week 2 and increasing over time until Week 8. The least-squares mean difference (BH-200 – placebo) was -2.47 HAMD-17 points ($p=0.000063$). Treatment effects were directionally consistent across studies, with non-significant treatment-by-study heterogeneity (treatment-by-study interaction not significant). A follow-up assessment four weeks after the end of treatment demonstrated a sustained treatment effect for BH-200. Liver enzyme elevations (ALT or AST $\geq 3 \times$ ULN) were

seen, and the pooled absolute risk was 5.9%, varying across studies. Overall adverse event rates appeared comparable between placebo and BH-200, with a generally benign tolerability profile.

Conclusions: In a pooled IPD analysis across three phase 2 trials, BH-200 showed statistically robust and clinically meaningful antidepressant efficacy versus placebo, supporting vasopressin V1b receptor antagonism as a viable antidepressant mechanism in MDD and justifying further evaluation in harder-to-treat populations such as TRD. The benefit/risk ratio remains favorable, with transient and reversible liver enzyme elevations being observed.

W27. GENETICALLY DEFINED SUBGROUP ANALYSIS REVEALS DIFFERENTIAL RESPONSE TO VASOPRESSIN V1B ANTAGONISM IN PATIENTS WITH MDD PRE-EXPOSED TO ANTIDEPRESSANT IN THE CURRENT EPISODE: POST-HOC ANALYSIS OF THE PHASE 2 OLIVE TRIAL

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Abstract Background: Treatment-resistant depression (TRD), a subtype of Major Depressive Disorder (MDD) defined by suboptimal response to antidepressant treatment, represents a significant unmet medical need. Vasopressin V1b receptor modulation has emerged as a potential mechanism relevant to stress-system dysregulation in MDD. BH-200, a selective V1b receptor antagonist, was evaluated in a Phase II randomized, double-blind, placebo-controlled trial (OLIVE, CTIS: 2024-513104-34-00) in adults with MDD. The estimated mean improvement from baseline to Week 8 in the mITT population (N=331) was larger in the BH-200-treated arm than in the placebo arm ($\Delta = -2.98$, $p = 0.0003$). To evaluate BH-200's potential for use in TRD, a post-hoc subgroup analysis was performed in OLIVE's MDD patients who had not responded to at least one adequate course of antidepressant treatment in their current depressive episode prior to enrolling into the trial. This subgroup is defined here as pre-exposed MDD. To test whether variation in V1b-related biology identifies likely responders, we applied a refined polygenic classification retrospectively to the pre-exposed MDD subjects.

Objectives: This analysis aimed to determine the antidepressant efficacy of BH-200 compared with placebo in pre-exposed MDD participants and evaluate whether the polygenic classification is associated with efficacy of BH-200, in the pre-exposed MDD cohort. In addition, we aimed to assess the consistency of findings across HAM-D17 and MADRS outcomes.

Methods: Data were obtained from the randomized, double-blind, placebo-controlled OLIVE trial (mITT N=331), including a pre-exposed MDD subset defined by non-response to at least one antidepressant treatment (n=171). The target endpoint for this analysis was HAM-D17 change from baseline to Week 8. Mixed-model repeated measures (MMRM) analyses were applied. The polygenic classification tool, trained post-hoc using repeated nested cross-validation in the OLIVE dataset to predict BH-200 treatment response, was applied to compute test-positive and test-negative strata.

Results: A total of 171 pre-exposed MDD participants were included. BH-200 showed greater improvement versus placebo in LS mean change from baseline on HAM-D17 in pre-exposed MDD cohort. The treatment difference at Week 6 was -2.00 ($p=0.029$), and at Week 8 it was -1.45 ($p=0.17$). In the genetically defined test-positives ($n=46$), at Week 6, LS mean change over placebo was -5.65 ($p=0.00040$), and at Week 8, was -6.03 ($p=0.00079$). Findings were broadly consistent across HAM-D17 and MADRS outcomes.

Discussion and Conclusion: BH-200 demonstrated a clinically meaningful signal in pre-exposed MDD participants without application of genetic classification. Use of the polygenic classification tool improved signal detection in the test-positive group underlining its potential utility for precision psychiatry approaches in future BH-200 studies. Consistent findings across HAM-D17 and MADRS strengthen confidence in the clinical relevance of V1b pathway modulation for the treatment of depression. Further trials using biomarker-based enrichment are warranted.

W28. CHARACTERISTICS OF DEPRESSION EPISODES TO INFORM REAL-WORLD HEALTH STATES FOR MAJOR DEPRESSIVE DISORDER AND TREATMENT-RESISTANT DEPRESSION

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Abstract Background: Major depressive disorder (MDD) is a chronic disorder characterized by alternating periods of symptoms and remission. Most claims-based studies, however, treat MDD as a chronic illness without multi-episode dynamics. Treatment-resistant depression (TRD) is defined by a depressive episode that fails to respond to ≥ 2 antidepressant (AD) trials of adequate dose and duration. To better depict healthcare utilization and health economics of depression, this study sought to evaluate criteria for the start and end of depressive episodes using claims data and characterize the resulting patient depression courses as a series of depressive episodes of varying treatment-responsiveness alternating with periods of stability.

Methods: Adults with MDD aged 18-64 years were identified in the Merative™ MarketScan® Commercial Database (1/1/2019–9/30/2024). Stable periods (treated or untreated) were defined by ≥ 180 days without any depressive episode events (initiation, augmentation, switch, or dose escalation of an AD; exacerbation (mental health-related emergency department or inpatient visits, suicide attempts, self-harm, psychiatric rehabilitation), or receipt of interventional psychiatry). Following a stable period, the start of a new depressive episode was defined by a depressive episode event following a stable period. An AD was deemed a failure if followed by medication switch/addition, acute exacerbation, or interventional psychiatry treatment. Episodes with ≥ 2 failed ADs of adequate dose and duration, or receipt of interventional psychiatry were classified as treatment-resistant episodes (TREs). Episodes with ≥ 2 failed ADs but of inadequate dose or duration were classified as inadequate treatment episodes (ITEs). Episodes that did not meet TRE or ITE criteria were classified as non-TREs. Individuals were categorized as having ≥ 1 TRE (TRD), ≥ 1 ITE and no TRE (ITD), or only non-TREs (non-TRD).

Results: Among 307,134 individuals (mean age 36.5 ± 12.9 years; 66.3% female), 42% had ≥ 1 episode, 3.5% had ≥ 1 TRE, 8.1% had ≥ 1 ITE, and 88.5% did not experience a TRE. Among patients with an initial non-TRE, 1.2% later developed a TRE during observed follow-up. Anxiety (31.5%) was the most common psychiatric comorbidity. Exacerbations occurred in 17.7% of TRD (6.62 per 100 person-years (PY)), 17.5% of ITD (7.63 per 100 PY), and 4.0% of non-TRD individuals (1.94 per 100 PY). Among TRD individuals, 53.5% met TRD criteria within 180 days of their first episode and 10.1% received interventional treatment. Across all groups there were 11,033 TREs, 26,474 ITEs, and 487,330 non-TREs of which 18,309 included exacerbations. Mean episode duration was longest for TREs (395 ± 229 days), followed by ITEs (271 ± 164 days) and non-TREs (67 ± 100 days). Antipsychotics were observed in 26.7%, 18.4%, and 2.7% and mood stabilizers in 9.7%, 5.7%, and 0.9% of TREs, ITEs, and non-TREs, respectively.

Conclusions: These study results support the feasibility of an episodic framework in real-world claims data. A higher disease burden and exacerbation risk was observed in TRD and ITD patients. The low observed prevalence of TRD may reflect the strict definition applied in this study compared to other real-world studies and the higher prevalence of ITD may suggest suboptimal care in real world. Only half of TRD patients had observed psychiatrist visits and 10% received interventional therapies, highlighting gaps in specialty care. Individuals with TREs and I-TREs warrant further evaluation to reduce subsequent treatment failures and exacerbations.

W29. LONGITUDINAL PROFILING OF TREATMENT TRAJECTORIES IN SSRI-ANCHORED MDD USING AGENTIC AI

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Abstract Background: The longitudinal characterization of treatment trajectories in Major Depressive Disorder (MDD) is critical for navigating the clinical heterogeneity of SSRI-anchored populations¹, yet conventional metrics often fail to capture the dynamics of patient response. This gap results in discordance, where residual deficits in sleep, energy, and executive function persist despite standard-of-care intervention². Traditional episodic clinical assessments lack the temporal resolution to capture these dynamics. This longitudinal population study leverages Headlamp Health's Lumos AITM agentic platform, to identify multi-factorial biomarker signatures of responders and non-responders.

Objective: To identify clinically relevant patient phenotypes in an SSRI-anchored MDD cohort using a Lumos AITM analysis of longitudinal patient-reported outcome and medication data.

Methods: This observational study utilized the Headlamp Health platform, Lumos AITM, to evaluate behavioral trajectories in patients with a SSRI backbone. From an initial cohort of 705 patients with verified medication continuity, 360 met the analytical threshold of ≥ 6 days of active behavioral data. The Lumos AI temporal correlation engine defined "treatment episodes" by identifying continuous usage, where gaps of ≥ 30 days were classified as treatment cessation. By analyzing these episodes, the engine identified seven discrete response patterns, which were aggregated into four clinical phenotypes: Energy and Mood Responders, Worsening from a

Good Baseline, Stable Functioning with Emotional Dampening, and Cognition Rebound with Sleep Disruption. These phenotypes were then linked to more than 22,000 available patient biomarker data points.

Results: Lumos AI™ consolidated patient trajectories into four distinct phenotypes: Energy/Mood phenotype exhibited significant energy and mood gains with stable cognition; Worsening Baseline phenotypes showed a systemic decline in energy, mood, and cognitive efficiency; Stable/Dampened phenotype saw functional improvements in energy, sleep, and cognition paired with declining pleasantness; and Cognitive Rebound phenotype featured sharp cognitive restoration alongside acute sleep disruption with stagnant mood/energy. Analysis showed that outcomes were gated by the patient's biosignature profile rather than diagnosis alone. In younger, low-inflammation cohorts the Aminoketone Advantage leverages a receptive neuro-receptor environment to drive therapeutic gains. Conversely, CNS Stimulant Failure in older cohorts hit a metabolic ceiling where elevated CRP suggested pro-inflammatory cytokines can desensitize receptors, blunting drug efficacy. These two phenotypes with similar diagnoses, baseline characteristics, and an SSRI backbone showed different outcomes, suggesting that direct catecholaminergic stimulation in this subgroup may contribute to diminishing benefit over time.

Conclusions: This population-scale analysis demonstrates that longitudinal patient phenotyping can resolve distinct treatment trajectories in MDD that are not apparent from diagnosis alone. Utilizing Lumos AI™ to synthesize real-world medication episodes, we identified divergent outcomes between CNS stimulant and aminoketone associated biotypes. This analysis suggests that pro-inflammatory baseline states may be associated with reduced treatment effects under direct stimulation, with tolerability varying by age and baseline characteristics. Lumos AI identified baseline cognition and inflammatory markers as high-fidelity biomarkers for characterizing response variability in SSRI-anchored regimens.

W30. DIMENSIONS OF PSYCHEDELIC EXPERIENCE PREDICTING ANTIDEPRESSANT RESPONSE TO PSILOCYBIN ACROSS DIAGNOSES

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Abstract Introduction: Psilocybin therapy has demonstrated efficacy for Major Depressive Disorder (MDD) and Bipolar Depression, yet the mechanisms predicting therapeutic response remain under investigation. We examined whether features of the psychedelic experience, according to the 5 dimensions of Altered States of Consciousness (5D-ASC), predict antidepressant outcomes across a transdiagnostic cohort.

Methods: Adults (N=45) with MDD with severe treatment resistance, Bipolar II Depression, or MDD with chronic Suicidal Ideation received a single 25mg dose of psilocybin across arms of an open-label trial. Depression severity was assessed using the Montgomery-Åsberg Depression Rating Scale (MADRS) at Baseline and Week 3. The 5D-ASC was administered immediately post-dosing. Pearson correlations assessed associations between 5D-ASC dimensions and the change in MADRS scores.

Results: An overall significant association was found between the Oceanic Boundlessness (OB) dimension and reduction in depression severity ($r = -0.34$, $p = 0.02$). Visionary Restructuralization (VR) showed a trend toward significance ($r = -0.29$, $p = 0.054$). Baseline depression severity and other ASC dimensions (Anxious Ego Dissolution, Auditory Alterations) were not predictive of outcome.

Conclusion: These findings suggest that the dimension of "Oceanic Boundlessness" during psychedelic experience predicts therapeutic response to psilocybin for depression, independent of baseline symptom severity and regardless of primary mood disorder. Future controlled trials should further explore this relationship to optimize patient selection and dosing strategies.

W31. ANXIOUS DEPRESSION AS PREDICTOR OF CLINICAL OUTCOMES IN TREATMENT-RESISTANT DEPRESSION (ASCERTAIN-TRD)

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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 in some subsets of patients. Anxious depression, a subtype characterized by the co-occurrence of anxiety symptoms, accounts for approximately 46–53% of patients with MDD and is associated with insufficient symptom improvement, regardless of the type of antidepressant used. The present study investigated the relationship between the presence of anxious depression features and clinical outcomes in patients with MDD enrolled in ASCERTAIN-TRD trial (NCT02977299).

Methods: This is a secondary data analysis investigating the relationship between anxiety subtype 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). Baseline anxious depression was defined using the Hamilton Depression Rating Scale Anxiety and Somatization Subscale (HAMD-AS). Subjects with HAMD-AS score ≥ 7 classified as the anxious depressive subtype. 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 253 (91%) had at least one post-baseline MADRS score and 136 (48.9%) were identified with anxious subtype (65 in the aripiprazole augmentation group, 46 in the rTMS augmentation group, and 71 in the venlafaxine/duloxetine switch group). The presence of anxious depression was not significantly associated with changes in MADRS scores ($p=0.89$, aripiprazole augmentation group; $p=0.53$, rTMS group; $p=0.88$, venlafaxine/duloxetine switch group). Moreover, no significant difference in treatment response between the aripiprazole augmentation and venlafaxine/duloxetine switching groups was found based on anxious depression status ($p=0.57$). Similarly, the comparison between rTMS augmentation and the venlafaxine/duloxetine switching strategy revealed no statistically significant difference in treatment response with respect to anxious depression status ($p=0.70$).

Conclusion: Although anxious depression has been associated with increased symptom severity and greater functional impairment, our findings indicate that it does not function as a reliable moderator or predictor of treatment response within the context of TRD. These findings may be a useful guidance for clinicians, suggesting that standard TRD treatments remain applicable in the anxious MDD subtype.

W32. NEUROACTIVE STEROID CHANGES PRE- AND POST-KETAMINE DURING A DOUBLE-BLIND, CROSSOVER CLINICAL TRIAL: AN EXPLORATORY STUDY

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Abstract Background: Neuroactive steroids such as allopregnanolone, pregnenolone, and dehydroepiandrosterone (DHEA) modulate GABAergic and glutamatergic signaling and are implicated in mood regulation and rapid-acting antidepressant mechanisms. Although effective in treatment-resistant depression (TRD), ketamine's effects on endogenous neurosteroid dynamics remain underexplored. Conversely, how neurosteroid dynamics contribute to ketamine's antidepressant mechanisms also remains unknown.

Methods: In this double-blind, placebo-controlled, crossover study, 32 unmedicated adults with TRD received a single intravenous infusion of ketamine (0.5 mg/kg) or saline placebo, with crossover after a seven-day washout. Plasma concentrations of allopregnanolone, pregnenolone, DHEA, cortisol, adrenocorticotrophic hormone (ACTH), and brain-derived neurotrophic factor (BDNF) were measured at four timepoints relative to infusion: -60 min, +230 min, +24 hr, and +72 hr. Depression severity was assessed using the Montgomery-Åsberg Depression Rating Scale (MADRS). Linear mixed-effects models examined biomarker trajectories and associations with antidepressant response. A random intercept cross-lagged panel model (RI-CLPM) was applied to test temporal directionality and within-person dynamics among select biomarkers.

Results: Compared to placebo, pregnenolone levels significantly declined over time following ketamine infusion ($p=0.043$). No significant group-level changes were observed for allopregnanolone, DHEA, or other biomarkers. Higher cortisol levels at early post-infusion timepoints were associated with less reduction in MADRS scores over time ($p=0.021$), suggesting blunted antidepressant response. Neurosteroid levels were not significantly predictive of treatment outcome. Longitudinal modeling revealed that allopregnanolone levels remained relatively stable across timepoints within individuals, in contrast to other neurosteroids—suggesting it may reflect a more trait-like biological signature. Interestingly, higher baseline BDNF levels were significantly associated with lower post-ketamine allopregnanolone levels ($\beta = -0.19$, $p = 0.004$); this effect was observed only when adjusting for covariates. No directional associations emerged between pregnenolone and its downstream metabolites across time.

Conclusions: Ketamine selectively modulated upstream neurosteroidogenesis, particularly pregnenolone, without robust downstream changes. Allopregnanolone's within-subject stability may indicate a trait biomarker rather than a dynamic state marker. The inverse association between BDNF and allopregnanolone highlights a potentially reciprocal relationship in neuroplasticity and neurosteroid signaling following ketamine. Given the overlapping therapeutic relevance of both ketamine and synthetic neurosteroids (e.g., in postpartum depression), the neuroactive steroid system represents a promising translational target for future mechanistic and clinical investigation.

W33. ASSOCIATION OF MAJOR DEPRESSIVE DISORDER WITH INSOMNIA SYMPTOMS WITH HEALTHCARE RESOURCE USE AND CARDIOVASCULAR AND METABOLIC CONDITIONS – ANALYSIS OF NATIONAL HEALTH AND NUTRITION EXAMINATION SURVEY

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¹Johnson and Johnson

Abstract Background: Insomnia is one of the key symptoms of major depressive disorder (MDD). MDD with insomnia symptoms is associated with increased risk of relapse and poor health-related quality of life.^{1,2} To better characterize the burden of MDD with insomnia symptoms, we examined their association with healthcare resource utilization, and cardiovascular and metabolic (CVM) conditions using nationally representative data from the National Health and Nutrition Examination Survey (NHANES).

Methods: In this cross-sectional study, adults (age ≥ 18 years) with MDD (defined as Patient Health Questionnaire-9 [PHQ-9] score ≥ 10) were identified from the NHANES database (2013-2018). MDD with insomnia symptoms (MDDIS) was defined as having MDD and reporting trouble sleeping to a healthcare professional; MDD w/o IS was defined as not having reported trouble sleeping. Adults with missing information for PHQ-9 and the sleep question were excluded. Study outcomes included healthcare resource utilization (inpatient stay, office visits [all-cause]), work productivity, and CVM conditions (such as hypertension, diabetes, and obesity). MDDIS and MDD w/o IS were balanced using propensity score-based inverse probability of treatment weighting (IPTW), controlling for baseline demographics. Study

outcomes were compared between MDDIS and MDD w/o IS using descriptive statistics and weighted (IPTW and sample weights) logistic regression models. The findings reported here include sample counts and weighted percentages.

Results: From a sample of 15,574 adults, 1,383 (8.2%) had MDD (PHQ-9 ≥ 10) and 853 (5.4%) had MDDIS. Among patients with MDD, 853 (66%) were MDDIS and 530 (34%) were MDD w/o IS. MDDIS versus MDD w/o IS patients were older (mean, 49.0 vs 43.3 years), White (68.3% vs 53.5%), married (39.5% vs 29.8%) and college educated (17.1% vs 13.4). Results from weighted logistic regression analyses found that MDDIS patients had significantly ($p < 0.05$) higher odds than MDD w/o IS for ≥ 3 office visits (67.8% vs 38.9%, odds ratio [OR]: 3.30), hospitalization (21.1% vs 12.2%, OR: 1.93), mental health professional visit (40.0% vs 20.9%, OR: 2.52) and inability to work due to health reasons (57.7% vs 36.4%, OR: 2.38). For CVM conditions, patients with MDDIS versus MDD w/o IS had significantly higher ($p < 0.05$) odds for heart attack (7.4% vs 4.3%, OR: 1.76) and hypertension (64.7% vs 46.6%, OR: 2.10). Findings for obesity (54.4% vs. 44.4%; OR: 1.50) and diabetes (21.7% vs. 17.6%; OR: 1.29) were not statistically significant but showed a similar trend.

Conclusion: MDDIS was associated with higher healthcare resource utilization, reduced work productivity, and poorer CVM health. Study findings indicate that burden of MDDIS extends beyond mental health, contributing to broader clinical and societal impacts. There remains a critical need for therapies that effectively address both depressive and insomnia symptoms in patients with MDD.

Sponsorship: Johnson and Johnson.

W34. ESMETHADONE (REL-1017) IN PATIENTS WITH ANTIDEPRESSANT TACHYPHYLAXIS: A POST HOC EFFICACY ANALYSIS IN A PRE-RANDOMIZATION-DEFINED SUBGROUP

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Abstract Background: Antidepressant tolerance/tachyphylaxis (AT) is defined as initial response ($\geq 50\%$ improvement) to antidepressant treatment followed by relapse while maintained on the same adequate dose. Research on the prevalence, mechanisms and treatment options for AT remains limited. In a prior phase 3 trial (REL-1017-301; NCT04688164), esmethadone (REL-1017) showed favorable results in a subgroup of patients with AT that was independently adjudicated pre-randomization.

Methods: In a phase 3, double-blind, randomized, placebo-controlled, two-arm trial (REL-1017-302; NCT04855747), REL-1017 (75 mg Day 1; 25 mg Days 2–28) or matching placebo was administered to adult outpatients with MDD and inadequate response to first-line antidepressants. Consistent with prior methods used in REL-1017-301, AT was independently

assessed pre-randomization by clinicians from the Massachusetts General Hospital (MGH) Clinical Trials Network and Institute using the MGH Antidepressant Treatment Response Questionnaire (ATRQ). Data were analyzed using mean difference (MD) in Montgomery-Åsberg Depression Rating Scale (MADRS) total score from baseline to Day 7 (key secondary endpoint) and Day 28 (primary endpoint). Although AT status was determined pre-randomization, efficacy analyses within this subgroup were conducted post hoc. A planned interim analysis (IA) was conducted by an independent Data Monitoring Committee (DMC) at approximately 75% enrollment.

Results: At IA, the DMC recommended early study termination due to low conditional power. The intent-to-treat (ITT) population included 236 randomized patients. In the ITT analysis, statistical significance was reached at Day 7; however, the study did not meet its Day 28 primary endpoint. The AT population, independently adjudicated pre-randomization, included 46 randomized patients. While statistical significance in the AT population was achieved only at Day 7 and was not maintained at later time points, Cohen's effect sizes (ES) remained in the moderate range at all assessed time points. In both populations, ITT and AT, loss of statistical significance at later time points reflected increased placebo response and not loss of REL-1017 efficacy.

ITT population (actual visits)

In the ITT population (REL-1017 n=119; placebo n=117), REL-1017 produced a greater reduction in MADRS total score than placebo at Day 7 (mean [SD]: -9.7 [8.23] vs -6.9 [8.58]; mean difference -2.80 [8.41]; Cohen's d=0.33; p=0.0133). At Days 14, 21, and 28, between-group differences were smaller and not statistically significant: Day 14 (-11.8 [9.90] vs -10.9 [9.67]; d=0.10; p=0.4823), Day 21 (-13.8 [10.41] vs -12.9 [10.85]; d=0.08; p=0.5541), and Day 28 (-15.2 [10.99] vs -14.5 [10.46]; d=0.07; p=0.6037).

AT population (actual visits)

In the AT population (REL-1017 n=25; placebo n=21), REL-1017 demonstrated consistently moderate effect sizes across all time points. At Day 7, REL-1017 was associated with a significantly greater MADRS reduction than placebo (-13.5 [9.54] vs -7.4 [8.09]; mean difference -6.11 [8.91]; Cohen's d=0.69; p=0.0288). At Day 14, the between-group difference approached statistical significance (-15.0 [11.59] vs -9.2 [6.60]; d=0.59; p=0.0527). Moderate effect sizes persisted at Day 21 (-14.3 [11.28] vs -10.0 [9.07]; d=0.42; p=0.1810) and Day 28 (-17.0 [11.09] vs -12.8 [7.84]; d=0.42; p=0.2004), despite loss of statistical significance.

Conclusions: While this post hoc analysis included only 46 subjects, AT subjects were independently adjudicated pre-randomization and moderate ES were observed across time points. These analyses further suggest that REL-1017 may represent a promising rapid-acting adjunctive treatment for patients with AT.

W35. PRECLINICAL BEHAVIORAL AND PHARMACOLOGICAL CHARACTERISTICS OF TN-001, A NOVEL, NON-HALLUCINOGENIC NEUROPLASTOGEN FOR THE TREATMENT OF MAJOR DEPRESSIVE DISORDER

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Abstract Background: Psychedelics have recently demonstrated significant clinical promise for the treatment of psychiatric illnesses including major depressive disorder (MDD) and post-traumatic stress disorder (PTSD) [1,2]. However, their hallucinogenic and cardiotoxic properties present unique challenges in the clinical setting that may limit their widespread use.

Neuroplastogens are an emerging class of compounds that promote neuroplasticity, similar to psychedelics, without inducing hallucinations. Here we present data on TN-001, a novel neuroplastogen for the treatment of MDD.

Methods: Agonist and antagonist activity of TN-001 was assessed using PI hydrolysis and PathHunter® β -arrestin2 assays, and responses were normalized to serotonin. For receptor occupancy studies, C57BL/6J mice received intraperitoneal (i.p.) injections of vehicle, psilocybin, or TN-001 and cortical membranes were prepared after 60 minutes. 5-HT_{2A} occupancy was determined using [³H]Cimbi-36. Neural plasticity was assessed using primary culture of mature cortical neurons from Wistar rat embryos, which were incubated with vehicle, psilocin, BDNF, or TN-001 on Day 11 of culture for 3 days. Cells were fixed on Day 14 and immunostained for synaptophysin (SYN), postsynaptic density protein 95 (PSD-95), and microtubule-associated protein 2 (MAP-2). Images were captured using Operetta® CLS (PerkinElmer) and analyzed using Harmony™ software (PerkinElmer).

Behavioral assays were performed in C57BL/6J mice. For head twitch response (HTR) and locomotor activity assays, mice received an i.p. injection of vehicle, psilocybin, or TN-001. HTRs were scored by a blinded experimenter and locomotor activity was recorded as distance moved in cm using Ethovision® (Noldus). In the forced swim test (FST), mice were placed into a cylinder of water 1 hour or 24 hours following i.p. injection with vehicle, fluoxetine, or TN-001, and immobility time was measured using video tracking software.

Results: TN-001 is a Gq-biased partial agonist of human 5-HT_{2A} receptor with an EC₅₀ of 68 nM and E_{max} of 67% (relative to serotonin response) and an antagonist of human 5-HT_{2B} receptor with an IC₅₀ of 142nM and I_{max} of 97%. Similar potency was observed for mouse 5-HT_{2A} receptor (106 nM, 45%). In ex vivo occupancy studies, TN-001 showed robust occupancy of cortical 5-HT_{2A} receptors which exceeded that of psilocin at the same doses. TN-001 showed comparable binding affinities for both mouse and human cortical 5-HT_{2A} receptors (55 nM and 79 nM, respectively). TN-001 induced significant dose-dependent increases in the number of MAP-2 positive neurons, number of MAP-2 positive neurites in μm , and overlap in SYN/PSD-95/MAP-2 staining in μm^2 . These observations represent increases in the number of neurons, total neurite network, and number/area of synapses, respectively. In vivo, TN-001 does not induce HTR and does not impair locomotor activity at relevant doses. In FST, TN-001 significantly reduced immobility time compared to vehicle.

Conclusion: TN-001 is a potent dual 5-HT_{2A} partial agonist and 5-HT_{2B} antagonist that demonstrates structural neuroplasticity ex vivo and antidepressant-like activity in mice without inducing HTR or locomotor impairments. While agonism of 5-HT_{2B} is a common off-target activity among many 5-HT_{2A} agonists, and confers significant risk of cardiac valvular hypertrophy, TN-001 is an antagonist at 5-HT_{2B} receptors and therefore is unlikely to carry this risk. These results provide a promising avenue toward the safe application of 5-HT_{2A}-mediated neuroplasticity to treat MDD and other neuropsychiatric conditions.

TN-001 is an investigational compound and not approved by the Food and Drug Administration for human use.

W36. METABOLIC PROFILE OF ADJUNCTIVE LUMATEPERONE 42 MG IN MAJOR DEPRESSIVE DISORDER: A POOLED ANALYSIS OF 2 RANDOMIZED, PLACEBO-CONTROLLED TRIALS

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Abstract Background: Lumateperone is an atypical antipsychotic indicated for: treatment of schizophrenia in adults; treatment of depressive episodes associated with bipolar I or II disorder (bipolar depression) in adults, as monotherapy and as adjunctive therapy with lithium or valproate; and treatment of major depressive disorder (MDD) in adults as adjunct to antidepressant therapy (ADT). Two Phase 3, randomized, double-blind, placebo-controlled studies (501 [NCT04985942]; 502 [NCT05061706]) demonstrated efficacy and safety of lumateperone 42mg+ADT in patients with MDD with inadequate ADT response. A pooled analysis of these studies evaluated the metabolic profile associated with adjunctive lumateperone 42mg.

Methods: Data were pooled for Studies 501/502, which enrolled adults (18-65y) meeting DSM-5 criteria for MDD with inadequate response to 1-2 ADTs in the current depressive episode. Patients with Montgomery-Asberg Depression Rating Scale Total score ≥ 24 , Clinical Global Impression-Severity score ≥ 4 , and Quick Inventory of Depressive Symptomatology-Self Report-16 item score ≥ 14 were randomized to 6-week lumateperone 42mg+ADT or placebo+ADT. Assessments included changes in weight, body mass index (BMI), waist circumference, cardiometabolic laboratory parameters (cholesterol [total, high-density lipoprotein, low-density lipoprotein], triglycerides, glucose, insulin), and prolactin levels. Subgroups were analyzed by baseline BMI category (normal weight: ≥ 18.5 to $< 25\text{kg/m}^2$; overweight: ≥ 25 to $< 30\text{kg/m}^2$; obese: $\geq 30\text{kg/m}^2$).

Results: The safety population comprised 964 patients (lumateperone+ADT, n=483; placebo+ADT, n=481). Changes from baseline to end of treatment (EOT) were minimal with lumateperone+ADT vs placebo+ADT for weight (-0.1kg vs $+0.0\text{kg}$), BMI (-0.0kg/m^2 vs $+0.0\text{kg/m}^2$), and waist circumference (-0.2cm vs -0.3cm). Potentially clinically significant (PCS) weight increase ($\geq 7\%$ from baseline) was rare during treatment (lumateperone+ADT, 0.4%; placebo+ADT, 1.3%). There were no clinically meaningful changes in cardiometabolic parameters or prolactin levels. At baseline, proportions of patients across BMI categories were similar: normal weight (lumateperone+ADT, 32.3% vs placebo+ADT, 34.3%), overweight (38.5% vs 31.8%), and obese (29.2% vs 33.9%). Changes at EOT were minimal across BMI subgroups and treatment groups for weight (-0.3kg to $+0.3\text{kg}$), BMI (-0.1kg/m^2 to $+0.1\text{kg/m}^2$), and waist circumference (-0.6cm to $+0.1\text{cm}$). PCS weight increase was rare with lumateperone+ADT vs placebo+ADT (normal weight: 0.7% vs 1.2%; overweight: 0.6% vs 0%; obese: 0% vs 2.5%). Changes in cardiometabolic parameters and prolactin levels at EOT were not clinically relevant across BMI subgroups and treatment groups. Most patients remained in

their BMI category by EOT (normal weight: lumateperone+ADT, 91.0% vs placebo+ADT, 95.2%; overweight: 89.8% vs 86.9%; obese: 91.5% vs 94.5%).

Conclusion: Lumateperone+ADT had a favorable safety profile with minimal changes in metabolic parameters across BMI subgroups, indicating that lumateperone may be a well-tolerated adjunctive treatment for patients with MDD with inadequate ADT response.

W37. LUMATEPERONE 42 MG IN MAJOR DEPRESSIVE DISORDER: DEMOGRAPHIC AND CLINICAL SUBGROUPS EFFICACY ANALYSIS IN A PHASE 3 RANDOMIZED PLACEBO-CONTROLLED TRIAL

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Abstract Background: Lumateperone is an atypical antipsychotic indicated for: treatment of schizophrenia in adults; treatment of depressive episodes associated with bipolar I or II disorder (bipolar depression) in adults, as monotherapy and as adjunctive therapy with lithium or valproate; and treatment of major depressive disorder (MDD) in adults as adjunct to antidepressant therapy (ADT). The Phase 3, randomized, double-blind, placebo-controlled Study 502 (NCT05061706) demonstrated the efficacy and safety of lumateperone 42mg+ADT in patients with MDD with inadequate ADT response. To assess consistency of treatment effect with adjunctive lumateperone, this analysis evaluated the efficacy of lumateperone 42mg+ADT in demographic and clinical subgroups of patients in Study 502.

Methods: Eligible patients (18-65 years) met DSM-5 criteria for MDD with inadequate response to 1-2 ADT courses and had Montgomery-Åsberg Depression Rating Scale (MADRS) Total score ≥ 24 , Clinical Global Impression-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. Efficacy was assessed in the overall population and in patient subgroups by demographic and baseline disease characteristics, using a mixed-effects model for repeated measures.

Results: The modified intent-to-treat (mITT) population comprised 469 patients (lumateperone+ADT, n=232; placebo+ADT, n=237). At Day 43 vs placebo+ADT, lumateperone+ADT significantly improved MADRS Total score (least squares mean difference [LSMD]=-4.5; $P < .0001$), CGI-S score (LSMD=-0.5; $P < .0001$), and QIDS-SR-16 Total score (ITT population: LSMD=-2.2; $P < .0001$).

Lumateperone+ADT significantly improved MADRS Total score from baseline to Day 43 in demographic subgroups vs placebo+ADT: age (≤ 40 y: LSMD=-4.3; $P < .01$; > 40 y: LSMD=-4.6; $P < .0001$), sex (male: LSMD=-4.0; $P < .01$; female: LSMD=-4.8; $P < .0001$), region (US: LSMD=-3.5; $P < .05$; non-US: LSMD=-4.8; $P < .0001$). Treatment effect did not reach statistical significance for race (White: LSMD=-4.5; $P < .0001$; non-White: LSMD=-0.7; $P=.8717$) and ethnicity (Hispanic/Latino: LSMD=-2.9; $P=.1468$; not Hispanic/Latino: LSMD=-4.8; $P < .0001$) subgroups. MADRS Total score significantly improved from baseline to Day 43 with lumateperone+ADT irrespective of baseline disease severity (MADRS score < 32 : LSMD=-4.6; $P < .0001$; MADRS score ≥ 32 : LSMD=-4.4; $P < .001$), type of ADT (SSRI:

LSMD=-4.3; $P < .0001$; SNRI and other: LSMD=-4.6; $P < .001$), number of ADT failures in the current episode (1 ADT failure: LSMD=-4.4; $P < .0001$; 2 ADT failures: LSMD=-5.1; $P < .05$), and presence of anxious distress (yes: LSMD=-4.7; $P < .001$; no: LSMD=-4.4; $P < .0001$). Lumateperone+ADT significantly improved ($P < .05$) CGI-S and QIDS-SR-16 Total scores from baseline to Day 43 vs placebo+ADT across most subgroups.

Conclusion: Lumateperone+ADT demonstrated robust efficacy vs placebo+ADT in subgroups of patients with MDD, supporting the drug as a promising adjunctive treatment option for patients with MDD with inadequate ADT response.

W38. EFFICACY OF LUMATEPERONE 42 MG FOR THE TREATMENT OF MAJOR DEPRESSIVE DISORDER: ANALYSIS OF DEMOGRAPHIC AND CLINICAL SUBGROUPS IN A PHASE 3 RANDOMIZED PLACEBO-CONTROLLED TRIAL

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Abstract Background: Lumateperone is an FDA-approved antipsychotic to treat schizophrenia and depressive episodes associated with bipolar I or bipolar II disorder, and adjunct to antidepressant therapy (ADT) for major depressive disorder (MDD). Efficacy and safety of lumateperone 42 mg + ADT was demonstrated in a Phase 3, randomized, double-blind, placebo-controlled study (Study 501 [NCT04985942]) in patients with MDD with inadequate ADT response. To investigate consistency of treatment effect, this analysis of Study 501 evaluated the efficacy of lumateperone 42 mg + ADT in demographic and clinical subgroups of patients with MDD with inadequate ADT response.

Methods: Adults (18-65 years) had DSM-5 criteria for MDD with inadequate response to 1-2 courses of ADT in the current depressive episode, and Montgomery-Asberg Depression Rating Scale (MADRS) Total score ≥ 24 , Clinical Global Impression-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 42 mg or placebo adjunctive to ADT. Efficacy was evaluated in the overall population and in patient subgroups by demographic and baseline disease characteristics, using a mixed-effects model for repeated measures or analysis of covariance.

Results: The modified intent-to-treat (mITT) population comprised 481 patients (lumateperone + ADT, n=239; placebo + ADT, n=242). At Day 43, lumateperone + ADT significantly improved MADRS Total score (least squares mean difference vs placebo [LSMD], -4.9; effect size [ES], -0.61; $P < .0001$), CGI-S score (LSMD, -0.7; ES, -0.67; $P < .0001$), and QIDS-SR-16 Total score (LSMD, -2.4; $P < .0001$) vs placebo + ADT. Improvements in MADRS Total score were significant from baseline to Day 43 in demographic subgroups with lumateperone + ADT vs placebo + ADT: younger (≤ 40 y: LSMD, -4.6; ES, -0.57; $P < .001$), older (> 40 y: LSMD, -5.1; ES, -0.64; $P < .0001$), male (LSMD, -4.3; ES, -0.54; $P < .001$), female (LSMD, -5.2; ES, -0.65; $P < .0001$), White (LSMD, -5.5; ES, -0.69; $P < .0001$), non-White (LSMD, -3.1; ES, -0.39; $P < .05$), Hispanic/Latino (LSMD, -9.8; ES, -1.23; $P < .01$), not Hispanic/Latino (LSMD,

–4.5; ES, –0.57; $P < .0001$), US (LSMD, –5.7; ES, –0.71; $P < .0001$), and non-US (LSMD, –4.3; ES, –0.54; $P < .0001$). Lumateperone + ADT significantly improved MADRS Total score from baseline to Day 43 irrespective of baseline disease severity (MADRS Total score < 32 : LSMD, –4.5; ES, –0.56; $P < .0001$; MADRS Total score ≥ 32 : LSMD, –5.7; ES, –0.71; $P < .0001$), type of ADT (SSRI: LSMD, –5.3; ES, –0.66; $P < .0001$; SNRI/other: LSMD, –4.0; ES, –0.51; $P < .01$), number of ADT failures in the current episode (1 failure: LSMD, –4.5; ES, –0.56; $P < .0001$; 2 failures: LSMD, –7.5; ES, –0.94; $P < .001$), and presence of anxious distress (yes: LSMD, –6.8; ES, –0.85; $P < .0001$; no: LSMD, –3.5; ES, –0.44; $P < .001$). Significant improvements ($P < .05$) in CGI-S score occurred with lumateperone + ADT vs placebo + ADT from baseline to Day 43 in all patient subgroups. Lumateperone + ADT significantly improved ($P < .05$) QIDS-SR-16 Total score at Day 43 vs placebo + ADT in all patient subgroups, except for race (White, $P < .0001$; non-White, $P = .5011$).

Conclusion: Lumateperone 42 mg adjunctive to ADT demonstrated robust efficacy over placebo adjunctive to ADT in subgroups of patients with MDD based on demographic and clinical features. These results indicate lumateperone as a promising adjunctive treatment option for patients with MDD with inadequate ADT response.

W39. PSYCHOPHARMACOLOGY OF ENX-104: A POTENT DOPAMINE (DA) D2/D3 RECEPTOR ANTAGONIST FOR THE TREATMENT OF NEUROPSYCHIATRIC DISORDERS ASSOCIATED WITH ANHEDONIA

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Abstract Background: ENX-104 is a potent dopamine (DA) D2/D3 receptor antagonist that enhances dopaminergic neurotransmission at low doses, representing a potential new therapeutic modality for the treatment of neuropsychiatric disorders associated with anhedonia. Preclinically, ENX-104 has demonstrated a favorable pharmacokinetic (PK) and safety profile, increased DA levels in the reward circuitry, and enhanced reward responsiveness at low doses preferentially blocking presynaptic D2/D3 autoreceptors. Additionally, its high selectivity and potent D2/D3 activity suggests relatively lower risk of off-target effects compared with (a)typical antipsychotics. The objective of this First-in-Human study was to evaluate the safety, tolerability, PK and pharmacodynamic (PD) profiles of single ascending oral doses of ENX-104 in healthy participants.

Methods: This was a randomized, double-blind, placebo-controlled, single ascending dose study. Of a total of 46 healthy male and female participants, 11 received placebo and 35 received ENX-104 across 5 dose levels orally while in-clinic for a period of 3 days. Safety measures included adverse events (AE), labs, vital signs, physical exams, electrocardiograms (ECGs), and extrapyramidal symptoms scales. Blood samples for plasma PK analysis were collected pre-dose through 48h. PK parameters for ENX-104 and its primary metabolites were determined by non-compartmental analysis. Central nervous system target engagement was measured using the NeuroCart test battery analyzed by mixed model analyses of covariance. This battery assessed

saccadic peak velocity, subjective alertness as measured by the Bond and Lader visual analogue scale, visuomotor coordination and attention as measured by adaptive tracking, psychomotor function as measured by body sway, and fine motor skills as measured by alternate side tapping. Peripheral target engagement was measured by analyzing serum prolactin levels.

Results: ENX-104 was safe and well tolerated at all doses tested with no serious or severe AEs reported. 62.9% of participants on ENX-104 experienced at least one AE vs 81.8% on placebo; > 97% of AEs were mild in intensity. No clinically meaningful trends in labs, vital signs, physical exams, ECGs or extrapyramidal symptoms scales were observed. Plasma exposure increased dose-proportionally, with low to moderate variability. ENX-104 demonstrated dose-related decreases in adaptive tracking that were sustained ≥ 48 h. No systematic dose-related changes in saccadic peak velocity, body sway, or finger tapping were noted, indicating little to no impairment in arousal or psychomotor function. Consistent with peripheral postsynaptic D2/D3 receptor antagonism and short plasma half-life, transient, dose-related increases in serum prolactin were observed.

Conclusion: Single oral doses of ENX-104 were safe and well tolerated and demonstrated a favorable PK profile with a short plasma half-life. Consistent with preclinical findings, evidence for sustained central target engagement was demonstrated by decreases in adaptive tracking and peripheral target engagement was evidenced by increases in prolactin.

W40. IMPACT OF GH001 ON DEPRESSIVE SYMPTOMS, ANXIETY, AND QUALITY OF LIFE IN TREATMENT-RESISTANT DEPRESSION: RESULTS FROM A PHASE 2B TRIAL

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Abstract Background: Treatment-resistant depression (TRD) is associated with persistent symptoms of depression, anxiety, and reduced quality of life, despite a limited number of treatments being available. There is a need for novel, rapid-acting, safe treatments. GH001, a synthetic form of 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT) for pulmonary inhalation, has demonstrated potential to reduce depressive symptoms in patients with TRD. This abstract reports efficacy data from a Phase 2b trial assessing GH001 on key depression, illness severity, anxiety, and quality of life measures.

Methods: This multicenter trial (NCT05800860) included a 7-day, randomized, double-blind, placebo-controlled part (Part 1) and a 6-month open-label extension (OLE; Part 2). In Part 1, patients with TRD were randomized 1:1 to receive an individualized dosing regimen (IDR) of up to three escalating doses of GH001 (6, 12, and 18 mg) or placebo IDR on a single day, with a 1-hour interval between doses. The second or third dose of the IDR was administered if the previous dose was well tolerated according to the trial physician's judgement (based on vital signs and adverse events) and if the patient did not achieve an intense psychoactive effect (defined as a mean score of ≥ 75 on the Peak Experience Scale) following the previous dose. In Part 2, patients could receive up to five GH001 IDR treatments as needed based on the patients'

Montgomery-Åsberg Depression Rating Scale (MADRS) score, and safety and tolerability of previous dose(s). This trial was conducted under the supervision of qualified healthcare professionals, providing psychological support per standard-of-care, but without any planned psychotherapeutic intervention before, during, or after dosing. Efficacy was assessed using MADRS (primary endpoint), Clinical Global Impression-Severity (CGI-S), Hamilton Anxiety Rating Scale (HAM-A), and Quality of Life Enjoyment and Satisfaction Questionnaire-Short Form (Q-LES-Q-SF) on Day 1 (baseline and 2 hours post-dose), Day 2, Day 8, and all scheduled OLE visits (Day 15 and monthly up to Month 6/end of treatment). Clinician rated assessments were completed by an independent blinded rater. Efficacy results were summarized descriptively.

Results: Eighty-one patients were randomized (GH001 IDR, n=40; placebo IDR, n=41). In Part 1, change in MADRS total score from baseline to Day 8 was significantly greater with GH001 versus placebo (least-squares [LS] mean difference [SE], -15.5 [1.7]; $P < 0.0001$). This was accompanied by significant improvements in secondary endpoints: LS mean (SE) differences for CGI-S (-2.5 [0.3]), HAM-A (-10.0 [1.4]), and Q-LES-Q-SF (21.4 [2.4]; all $P < 0.0001$). All 81 patients transitioned directly to the OLE and 63 patients (77.8%) completed the OLE. At Month 6, remission (MADRS ≤ 10) was achieved by 73.0% of completers, accompanied by significant improvements across secondary efficacy endpoints: mean (SD) change from baseline for CGI-S (-3.0 [1.4]), HAM-A (-13.3 [7.2]), and Q-LES-Q-SF (24.8 [14.1]; all $P < 0.0001$). Patients received a mean of four GH001 IDR treatments over the trial.

Conclusion: GH001 demonstrated rapid efficacy in reducing depressive symptoms, illness severity, and anxiety symptoms while improving quality of life in patients with TRD in Part 1, with durable responses maintained at 6 months with infrequent retreatments. These findings support further investigation of GH001 for TRD.

W41. RAPID AND SUSTAINED IMPROVEMENT IN ANHEDONIA FOLLOWING INHALED MEBUFOTENIN (GH001) TREATMENT IN PATIENTS WITH TREATMENT-RESISTANT DEPRESSION

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Abstract Background: Anhedonia, a lack of interest or ability to feel pleasure in activities and experiences, is associated with suicide risk, functional impairment, and treatment resistance in patients with major depressive disorder (MDD). Improvement in anhedonia symptoms in patients with MDD has been associated with improvements in quality of life and physical, psychological and social functioning. GH001, a synthetic formulation of mebufotenin (5-MeO-DMT) administered via pulmonary inhalation, was evaluated for efficacy and safety in a Phase 2b clinical trial (NCT05800860) in patients with treatment-resistant depression (TRD). The trial consisted of a 7-day, randomized, double-blind, placebo-controlled part (Part 1) and a 6-month open-label extension (OLE, Part 2). GH001 showed rapid reductions in Montgomery-Åsberg

Depression Rating Scale (MADRS) total scores, with a least squares mean difference of -15.5 points vs placebo at Day 8 ($P < 0.001$). GH001 was well tolerated. This post hoc analysis investigates GH001's impact on anhedonia in patients with TRD.

Methods: In Part 1, patients were randomized 1:1 to receive a single-day individualized dosing regimen (IDR) of GH001 (6, 12, and 18 mg) or placebo via pulmonary inhalation. In the OLE (Part 2), up to five GH001 IDR treatments were administered, based on the patients' MADRS score, and safety and tolerability of previous dose(s). This trial was conducted under the supervision of qualified healthcare professionals, providing psychological support per standard-of-care, but without any planned psychotherapeutic intervention before, during, or after dosing. MADRS assessments were performed at Day 1 (baseline and 2 hours post-dose), Day 2, Day 8, and all scheduled OLE visits (Day 15 and monthly up to Month 6/end of treatment). Anhedonia was assessed using the MADRS 5-item anhedonia subscale (items 1: apparent sadness; 2: reported sadness; 6: concentration difficulties; 7: lassitude; 8: inability to feel; score range: 0-30, with lower scores indicating less severe anhedonia). Clinically meaningful improvement was defined using a published minimal clinically important change (MCIC) threshold of -4.6 to -5.5 points for patients with MDD. This post hoc analysis summarizes anhedonia subscale scores descriptively (mean [SD] changes from baseline).

Results: Eighty-one patients were randomized in the double-blind part (GH001: $n=40$; placebo: $n=41$). Mean (SD) total MADRS scores at baseline were 29.0 (5.4) for GH001 and 28.2 (4.6) for placebo. Baseline anhedonia subscale scores were 17.6 (3.2) for GH001 and 17.4 (2.6) for placebo, and changes from baseline at Day 8 were -9.9 (6.6) and 0.0 (2.3), respectively. For GH001, mean changes exceeded the MCIC threshold at all post-dose time points (2 hours, Day 2, and Day 8), indicating clinically meaningful improvements. In contrast, placebo changes did not exceed the MCIC at any time point. For the OLE completers ($n=63$), change from baseline in MADRS anhedonia subscale score was -12.2 (4.9) at Month 6 ($P < 0.001$) suggesting a clinically meaningful improvement in MADRS anhedonia score was maintained at 6 months.

Conclusion: Patients with TRD receiving GH001 in Part 1 achieved rapid reductions in MADRS anhedonia subscale scores that exceeded the MCIC at all assessed time points, with sustained improvements observed in the OLE at 6 months. These findings suggest GH001 enhance patients' ability to experience pleasure and improve overall functioning.

W42. EFFECTS OF DEXTROMETHORPHAN-BUPROPION (45MG/105MG) IN PARTICIPANTS WITH MAJOR DEPRESSIVE DISORDER AND ANXIOUS DISTRESS

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Abstract Background: Anxiety is a prevalent feature of major depressive disorder (MDD), with anxious distress reported in 45-78% of patients. The DSM-5 'with anxious distress' specifier requires ≥ 2 of 5 symptoms during a depressive episode: feeling keyed up or tense, feeling unusually restless, difficulty concentrating due to worry, fear that something awful may happen, and feeling that one might lose control. Anxiety symptoms in MDD are associated with a decreased response to traditional antidepressant treatments. Dextromethorphan-bupropion (45

mg/105 mg) (DM-BUP; Auvelity®) is an NMDA receptor antagonist, sigma-1 receptor agonist, and CYP2D6 inhibitor approved for the treatment of MDD in adults. Here, we examine the antidepressant efficacy of DM-BUP in people with MDD and anxious distress.

Methods: This post-hoc subgroup analysis used data from the 6-week, Phase 3, double-blind, randomized GEMINI trial evaluating DM-BUP versus placebo in adults (18-65 years) with MDD (MADRS ≥ 25). The primary endpoint was change from baseline in MADRS total score at Week 6; other prespecified endpoints included MADRS response ($\geq 50\%$ reduction) and MADRS remission (≤ 10). Participants with anxiety were eligible provided anxiety had not been the primary clinical concern within 6 months before screening. Anxious distress (proxy definition) required meeting at ≥ 2 of the following: MADRS Concentration Difficulties ≥ 3 with QIDS Concentration Difficulties ≥ 2 ; MADRS Inner Tension ≥ 3 ; QIDS Restlessness ≥ 2 . Continuous outcomes were analyzed using mixed models for repeated measures and categorical outcomes via chi-square tests; P-values were nominal. Safety assessments included TEAEs ($\geq 5\%$ incidence) and discontinuations.

Results: Among participants with anxious distress (DM BUP n=115/156; placebo n=102/161), DM-BUP produced greater reductions in MADRS total score versus placebo at all timepoints, with least squares mean ($\pm$ SE) differences of -3.20 ± 0.99 , -4.08 ± 1.23 , -5.21 ± 1.34 , -5.82 ± 1.39 , and -5.12 ± 1.56 at Weeks 1, 2, 3, 4, and 6, respectively (all $P \leq 0.001$). DM-BUP treatment resulted in higher response rates at all visits ($\geq 50\%$ reduction in MADRS total score; all $P < 0.05$) and higher remission rates from Week 2 onward (MADRS total score ≤ 10 ; all $P < 0.01$). CGI-S scores improved from Week 1 onward with DM-BUP versus placebo (all $P < 0.01$), along with higher CGI-I improvement rates at Weeks 1-4 (all $P < 0.05$). DM-BUP was associated with improvement in patient-reported outcomes, including Q-LES-Q and SDS at all timepoints. A greater proportion of participants reported being Much/Very Much Better on the PGI-I with DM-BUP versus placebo at all visits (Week 6: 39.1% vs 26.5%; $P = 0.048$). Across participants in the GEMINI trial, the most common TEAEs were dizziness, nausea, headache, diarrhea, somnolence, and dry mouth. Anxiety-related TEAEs were uncommon (4.3% DM-BUP vs 1.2% placebo), and discontinuations due to anxiety were low (1.9% vs 0%).

Conclusions: DM-BUP demonstrated robust antidepressant efficacy in participants with MDD and anxious distress, showing improvements in MADRS severity, response, and remission compared to placebo. Clinician-rated global impressions and patient-reported outcomes also showed improvements. DM-BUP was generally well-tolerated, with low rates of anxiety-related discontinuations. Overall, these findings support DM-BUP as a clinically meaningful and well-tolerated treatment option for patients with MDD and anxious distress.

W43. HJ-006: A NON-HALLUCINOGENIC SYNAPTOGENIC COMPOUND WITH RAPID AND SUSTAINED ANTIDEPRESSANT EFFICACY

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Abstract Introduction: Current antidepressants (SSRIs/SNRIs) face limitations including delayed onset (4–6 weeks) and modest efficacy (~50% response rates), while serotonergic

psychedelics show rapid antidepressant potential via 5-HT_{2A} agonism and synaptic plasticity but are hindered by hallucinogenic activity and 5-HT_{2B}-mediated cardiotoxicity.

Objectives: To address these challenges, we characterize HJ-006, a novel synaptogenic agent, designed to promote neuroplasticity without hallucinogenic or safety liabilities, and antidepressant efficacy.

Methods: Antidepressant-like efficacy was evaluated using established in vivo models, including the forced swim test (FST), tail suspension test (TST), and sucrose preference test (SPT) in chronic unpredictable mild stress (CUMS) and corticosterone-induced depression paradigms. Neuroplasticity-related effects were assessed using neurite outgrowth and synaptogenesis assays, as well as multielectrode array (MEA) recordings in corticosterone-damaged hippocampal neurons. Safety and liability assessments included the head twitch response (HTR), conditioned place preference (CPP), and cardiovascular monitoring by non-human primate ECG. Pharmacokinetic properties were characterized by in vivo PK profiling.

Results: HJ-006 is an orally active, brain-penetrant, small molecule. In vitro, HJ-006 showed significant effects on neurite-outgrowth and synaptogenesis in primary cultures of rat cortical neurons. It demonstrated rapid (30 min post-single dose) FST antidepressant effects in corticosterone-induced depression and reversed CUMS-induced deficits in FST, TST, and SPT, with efficacy sustained ≥ 8 days, with no hallucinogenic behavior (HTR-negative). Safety profiles included no CPP rewarding effects, enhanced dendritogenesis/synaptogenesis in cortical neurons, rescued CORT-impaired hippocampal activity (30 nM, 15 min post-treatment), 5-HT_{2B} antagonist activity ($K_i=2.18$ nM, $IC_{50}=272.8$ nM), favorable brain penetration, CYP3A4 metabolism, no cardiovascular signals in primates, and a 40 $\times$ safety margin in 14-day toxicity studies.

Conclusions: HJ-006 is a first-in-class non-hallucinogenic neuroplastogen with rapid, sustained antidepressant-like efficacy and improved safety, supporting its potential as a transformative depression treatment.

W44. PATIENT REPORTED OUTCOME RESPONSE FOLLOWING TREATMENT WITH LIAFENSINE IN ANK3 BIOMARKER POSITIVE PATIENTS WITH TREATMENT RESISTANT DEPRESSION

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Abstract Background: Liafensine, a triple monoamine reuptake inhibitor, has demonstrated antidepressant efficacy in patients with treatment-resistant depression (TRD) who are positive for an ANK3 genetic biomarker. While clinician-reported measures are commonly used to assess treatment response, they may not fully capture patients' lived experiences of symptom burden and functional impairment. Patient-reported outcome measures may provide complementary and clinically meaningful information regarding treatment benefit.

Methods: This post hoc analysis evaluated patient-reported outcomes from a randomized, double-blind, placebo-controlled study of liafensine (1 mg or 2 mg daily) in adults with moderate-to-severe ANK3-positive TRD. Patient-Reported Depression Functioning (PRDF) total and domain scores, assessing symptom frequency and functional impact across nine symptom

groupings, were analyzed in 188 participants (liafensine, n = 124; placebo, n = 64). Changes from baseline through Days 7 and 42 were assessed using mixed-effects models for repeated measures. Effect sizes were calculated, and correlations with clinician-reported measures were examined.

Results: Compared with placebo, liafensine produced statistically significant improvements in PRDF total frequency, functional impact, and global impact scores as early as Day 7, with effects sustained through Day 42. Improvements were observed across all PRDF symptom domains, including mood, anxiety, cognition, energy, social functioning, and suicidality, despite relatively low baseline severity in some domains. Effect sizes were generally in the medium range and comparable to those observed for clinician-reported outcomes. PRDF impact scores demonstrated sustained functional improvement over time and were sensitive to treatment-related changes consistent with improvements on the Sheehan Disability Scale.

Conclusions: In ANK3-positive patients with treatment-resistant depression, liafensine demonstrated early, sustained, and multidimensional therapeutic benefit from the patient perspective. The PRDF sensitively captured improvements in both symptom burden and functional impact, supporting its utility as a complementary endpoint alongside clinician-reported measures in biomarker-defined clinical trials.

W45. PSYCHOMOTOR DISTURBANCE AS A PREDICTOR OF TREATMENT RESPONSE IN MOOD DISORDERS: A SYSTEMATIC REVIEW

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Abstract Background: Psychomotor disturbance (PMD) is a discrete symptom domain of mood disorders such as major depressive disorder (MDD) and bipolar disorder (BD). Despite PMD's association with greater depressive symptom severity, its potential utility as a clinical biomarker for therapeutic efficacy remains underinvestigated. Herein, we aim to evaluate whether scale-based assessments of PMD are associated with clinical efficacy across pharmacological and non-pharmacological interventions for mood disorders.

Methods: Following PRISMA guidelines, a systematic search was conducted from inception to July 2025 on Ovid and PubMed databases to retrieve randomized controlled trials, open-label trials, and observational studies reporting treatment efficacy and scale-based assessments of PMD. Studies were screened, methodological quality was assessed, and data extraction was conducted by three independent reviewers.

Results: A total of 29 studies were included, evaluating antidepressants (monoaminergic and glutamate modulators), electroconvulsive therapy (ECT), repetitive transcranial magnetic stimulation (rTMS), OnabotulinumtoxinA (OnA), and psychotherapy. Findings from this study indicate that PMD, specifically psychomotor retardation (PmR), was consistently associated with improved treatment response for ECT. PMD was shown to predict worse clinical efficacy or no difference in clinical efficacy to SSRIs. Mixed results were found for TCAs, with limited results found for other evaluated interventions, including rTMS, OnA, and psychotherapy.

Conclusions: To our knowledge, this is the first systematic review to comprehensively and critically evaluate PMD as a predictor of response, remission, and relapse to various interventions in persons with MDD and bipolar depression. Although studies were largely confined to smaller sample sizes and MDD populations, PMD appears to be a promising, low-cost clinical marker underutilized in precision psychiatry. Integrating PMD into multimodal predictive models remains a scalable approach that, if properly validated with prospective studies, holds hope advancing personalized and optimized treatment approaches to navigate the complex heterogeneity of mood disorders.

W46. THE MONOTHERAPY ANTIDEPRESSANT PIPELINE PROBLEM: ONLY 8 APPROVALS OUT OF 28 ATTEMPTS IN THE LAST 25 YEARS

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Abstract Introduction: Although more than twenty-five antidepressants are currently available for clinical use, most were developed serendipitously over the past seven decades and are based on a limited set of mechanisms, including monoamine oxidase inhibition, serotonergic reuptake modulation, and more recently, N-methyl-D-aspartate (NMDA) receptor activity. We postulated that advances in chemistry and improvements in clinical trial methodology would lead to development of newer mechanisms. However, such progress has not materialized over the past twenty-five years. Using reporting requirements mandated under the U.S. Food and Drug Administration Modernization Act, we examined registered monotherapy clinical trials on ClinicalTrials.gov conducted between 2000 and 2025.

Methods: We searched ClinicalTrials.gov using the following criteria: “Major Depressive Disorder,” “Completed Studies,” “Phase 2, 3,” “Interventional Studies,” “Studies with **Results**,” and “Funded by Industry” from January 1, 2000 to December 12, 2025. Clinical trial data for gepirone were obtained from the FDA AccessData database after it was not identified in the initial search. We excluded pediatric trials, non placebo controlled studies, adjunctive therapies, contraindicated conditions, antidepressants approved before 2000, and trials without MADRS or HAM-D as the primary endpoint. From eligible trials, we extracted data on drug name, trial duration, primary endpoint, year of approval or current development status, baseline and change in MADRS or HAM-D scores, and number of trial participants. To quantify the effectiveness of investigational antidepressants, standardized changes in depression rating scale scores were summarized using standardized mean differences expressed as Cohen’s d.

Results: Our review identified twenty-eight new antidepressant development programs initiated by large pharmaceutical companies during this period. Our initial search identified 235 clinical trials. After eligibility screening, 50 trials met inclusion criteria and were included in the analysis. We identified 28 antidepressant development programs, of which eight resulted in FDA-approved antidepressants; their years of approval and mean effect sizes are: escitalopram (2002, 0.15), vortioxetine (2013, 0.26), desvenlafaxine succinate sustained release (2008, 0.15), vilazodone (2011), levomilnacipran extended release (2013, 0.27), intranasal esketamine (2019, 0.49), and gepirone (2023, 0.24), dextromethorphan-bupropion (2022, 0.34). Approved

medications were significantly more likely to have trials enrolling ≥ 100 participants per treatment arm compared with non-approved medications ($\chi^2 = 15.2$, $df = 1$, $p < 0.0001$).

Discussion: All approved antidepressants act through well-established mechanisms of action and were supported by adequately powered clinical trials demonstrating significant improvements in depressive symptoms. In contrast, the remaining development programs generally enrolled smaller sample sizes and pursued novel therapeutic targets that failed to demonstrate sufficient efficacy during clinical testing. Six exploratory programs achieved an effect size ≥ 0.3 but did not reach the market due to insufficient efficacy or corporate decisions ($n = 3$), while the remaining programs remain under investigation ($n = 3$). In this context, relapse-prevention trial designs and alternative therapeutic modalities, including medium- to large-molecule approaches adapted from treatments for diabetes and obesity, may represent the most promising avenues for future development, potentially benefiting from similar elements of serendipity.

W47. EARLY RESPONSE TO PSILOCYBIN IN ADULTS WITH TREATMENT-RESISTANT DEPRESSION AS A PREDICTOR FOR ANTIDEPRESSANT EFFICACY

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Abstract Background: Psilocybin-assisted psychotherapy (PAP) has emerged as a novel intervention for treatment-resistant depression (TRD). TRD is associated with a lower probability of achieving remission with conventional antidepressant treatments, decreased quality of life, and increased risk of suicidality and all-cause mortality. Early symptom improvement with conventional antidepressants is a strong predictor of antidepressant efficacy, however, the predictive utility of early improvements with psilocybin has not been evaluated.

Objective: To evaluate if 24-hour post-treatment effects of psilocybin on depression symptoms are a predictor of changes in depressive symptoms at 2-8 weeks post-dose in adults with TRD.

Methods: Participants ($n=30$) received one 25 mg dose of psilocybin with supportive psychotherapy (psilocybin-assisted psychotherapy [PAP]) as part of a phase 2 randomized, waitlist-controlled, open-label clinical trial (NCT0502946). The primary outcome of the trial was the change in depression severity using the Montgomery-Åsberg Depression Rating Scale (MADRS) over the Week 2 primary endpoint period and up to 8 weeks of follow-up post-dose. Linear regression analyses were used to determine if participants who had reductions in depression symptoms at Day 1 post-dose (“early responders”) were more likely to have depressive symptom reductions at weeks 2, 4, 6 and 8.

Results: The linear regressions indicate that change in MADRS Day 1 post-dose significantly predicted change in MADRS at week 2, $F(2, 26)=14.789$, $p < 0.001$, week 4, $F(2, 25)=16.867$, $p < 0.001$, week 6, $F(2, 23)=6.878$, $p=0.005$ and week 8, $F(2, 23) = 8.277$, $p=0.002$. Large effect sizes were observed when converting the adjusted R^2 value to Cohen’s f^2 for Day 1 change predicting change in MADRS at weeks 2 ($R^2=0.496$), 4 ($R^2=0.540$), 6, ($R^2=0.320$) and 8 ($R^2=0.368$). The beta coefficient for change in MADRS score at Day 1 as a predictor of change at subsequent weeks was as follows: week 2, 0.765 ($p < 0.001$), week 4, 0.797 ($p < 0.001$), week 6, 0.639 ($p=0.001$) and week 8, 0.680 ($p < 0.001$). In total, 25 out of 30 (83.3%) participants had

a lower MADRS score at Day 1 post-dose compared to Baseline with a mean reduction of 35.9% (-11.21). Five (16.7%) participants had an increase in their MADRS scores from Baseline to Day 1, and did not have marked improvement in their MADRS thereafter. Baseline MADRS score did not significantly predict change in MADRS score at weeks 2-8. Change in MADRS at Day 1 was predictive of change in MADRS from weeks 2-8 when controlling for sex and age as covariates.

Conclusion: Participants who had a rapid improvement in depressive symptoms the day after receiving psilocybin were more likely to have continued antidepressant benefit after 2-8 weeks. These findings enhance our understanding of the clinical characteristics associated with “early responders” to psilocybin. The ability to communicate to patients that early symptom improvement is associated with antidepressant benefits may enhance expectancy effects and help clinicians evaluate treatment trajectories. Further research is needed to explore the underlying pathophysiological mechanisms related to early antidepressant benefit to psilocybin.

Future Directions: Building on these findings, data from an ongoing federally funded, triple-blind, randomized, placebo-controlled trial (NCT06341426) will provide a larger, well-controlled sample (n=90) to evaluate how early changes in depression symptoms can predict more prolonged antidepressant effects with 6-months of follow-up.

W48. EARLY MOTIVATIONAL AND HEDONIC RESPONSES TO ANTIDEPRESSANTS IN MAJOR DEPRESSIVE DISORDER: A REAL-WORLD EVIDENCE STUDY

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Abstract Background: Loss of interest or pleasure is a hallmark of major depressive disorder (MDD) and typically eases before other depressive symptoms once treatment is initiated.^{1, 2} This study examined changes in depressive and anhedonic symptoms in adults with MDD receiving commonly prescribed antidepressants (ADs), focusing on early rebound of motivation and age-related variations in response patterns.

Methods: Adults with MDD and receiving AD therapy participated in online interviews using the Ad-Infer EVAL system, a tool designed for positive and differential AI diagnosis assessment and data collection. Wave 1 (W1) ran from May 2024 to October 2024. Wave 2 (W2) spanned September 2024 to March 2025, achieving a follow-up rate of 56.4%. In the adjusted sample, participants were assigned to 1 of 3 medication groups: fluoxetine or paroxetine (GR1, n=75), bupropion (GR2, n=44), or vortioxetine (GR3, n=40); they were then stratified into 3 age groups (< 35, 35-54, and ≥55 years [y]). Differences in proportions of MDD prevalence, depressive symptoms, or anhedonic symptoms were compared between 2 timepoints within groups with McNemar test or between groups with Bonferroni-corrected chi-square test.

Results: Most participants were female (GR1, 81.0%; GR2, 54.5%; GR3, 77.5%); 19% were aged < 35 y, 51% were between 35-54 y, and 30% were aged ≥55 y. By W2, MDD prevalence dropped by 14% in GR1, 30.1% in GR2 and 20% in GR3. Relapse was markedly higher in GR1 (87%) than in GR2 (50%) or GR3 (51%; $P < .01$). Across treatment groups, participants showed significant improvement in motivation (GR2, $P=.003$; GR3, $P=.05$), social satisfaction (GR1, $P < .001$; GR3, $P=.001$), and cognitive functioning (GR1, $P=.0045$; GR2, $P=.005$; GR3, $P=.05$); similar improvements were observed for each medication group across the 3 age subgroups. GR3 experienced a rise in motivation for the participants aged < 35 and 35-54 y, with gains hovering between 23.6% ($P=.002$) and 13.6%, respectively. Both GR2 and GR3 exhibited reductions in anhedonia, shifting from 77.8% to 38.8% ($P < .001$) and from 60.9% to 44.4% ($P=.030$), respectively. While the reduction was significant for younger and middle-aged adults for GR1, a reduction in anhedonia was observed in GR3 only among adults aged ≥55 y, with prevalence decreasing from 42.9% to 15.4% ($P=.0004$). Significant improvements in cognitive function were observed across treatment groups ranging from 17.5% (GR3, $P=.05$) to 30.4% (GR2, $P=.005$) gains. A noteworthy dip in psychomotor retardation was observed, especially within the GR1 and GR2 cohorts: from 64.8% to 41.5% in GR1 ($P=.004$) and from 43.2% to 9.8% in GR2 ($P < .001$).

Conclusion: Results of this real-world study suggest that early response in motivation symptoms and anhedonia is a frequent phenomenon in AD treatment arguing for the clinical usefulness of being an early predictor symptom in MDD. Different response profiles were seen by medication class, where bupropion and vortioxetine exhibited lower relapse rates and more reductions in anhedonia compared with SSRIs. There was some age-related variation in responses; younger and middle-aged adults may have experienced particularly selective benefits of vortioxetine, whereas older adults may have had the strongest anhedonia reduction. Collectively, these findings underscore the clinical importance of monitoring motivational and anhedonic symptoms during early treatment and suggest that AD strategies should be based on symptom profiles rather than solely on depression severity.

W49. REAL-WORLD EVIDENCE OF THE CLINICAL AND PREFERENCE IMPACT OF A PRESCRIPTION DIGITAL THERAPEUTIC FOR MAJOR DEPRESSIVE DISORDER: AN ONGOING PROSPECTIVE STUDY IN AN ACADEMIC HEALTH SYSTEM

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Abstract Purpose: This presentation details the implementation of a prescription digital therapeutic (PDT) as an adjunct to pharmacotherapy for Major Depressive Disorder (MDD). The study aims to move beyond controlled trial data to evaluate how PDTs perform within the complex workflows of a large academic health system, specifically focusing on clinician-patient preferences and real-world engagement patterns.

Methodology: Conducted at the University of Utah's Huntsman Mental Health Institute (HMHI), this prospective pilot study identifies patients via routine clinical judgment. Data

collection integrates: Patient/Clinician Surveys: Assessing baseline attitudes and acceptability. Clinical Outcomes: PHQ-9 scores at baseline and six months. Platform Analytics: Real-time engagement and adherence metrics. EMR Extraction: Longitudinal healthcare utilization data. Interim Findings and Content: The presentation will share critical interim data regarding the recruitment and initiation phase: Recruitment Feasibility: Analysis of the "clinical judgment" model for identifying PDT candidates, including enrollment rates and barriers encountered within the academic workflow. Baseline Preference Profiles: Specific findings on clinician and patient expectations versus early-stage engagement (first 30 days). Implementation Friction: Identification of technical or systemic hurdles in linking PDT platform data with Electronic Medical Records (EMR). Importance for the Field: These findings advance the field by testing the "last mile" of digital medicine. While the efficacy of PDTs is established, their utility is often bottlenecked by implementation barriers in routine practice. This presentation argues that the success of digital psychiatry depends less on the therapeutic software itself and more on the alignment of technology with existing clinical workflows and provider-patient preferences. This RWE provides a blueprint for academic centers to transition digital tools from experimental adjuncts to standardized components of MDD care.

W50. ANXIOLYTIC EFFECTS OF DEXTROMETHORPHAN-BUPROPION (45MG/105MG): POST HOC ANALYSES ACROSS TRIALS IN MAJOR DEPRESSIVE DISORDER

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Abstract Background: Anxiety is common in major depressive disorder (MDD), with anxious distress reported in 45-78% of patients and associated with poorer outcomes. Dextromethorphan-bupropion (45mg/105mg) is an NMDA receptor antagonist and sigma-1 agonist approved for MDD in adults. Here we evaluate anxiolytic efficacy of dextromethorphan-bupropion across trials performed in patients with MDD.

Methods: Post hoc analyses were conducted using data from 4 clinical trials of dextromethorphan-bupropion: ASCEND and GEMINI (6-week, double-blind, randomized controlled trials [RCTs] vs bupropion or placebo) and COMET and EVOLVE (open-label studies up to 15 months). Anxiety symptoms were assessed via the Hamilton Anxiety Rating Scale (HAM-A) (EVOLVE) and the Montgomery-Åsberg Depression Rating Scale (MADRS) Inner Tension item (all studies), as well as a MADRS anxiety and vegetative symptoms subscale (comprised of the Inner Tension, Concentration Difficulties, Reduced Sleep, and Reduced Appetite items) capturing interconnected features of MDD. Anxiety treatment-emergent adverse events (TEAEs) were examined.

Results: In EVOLVE, dextromethorphan-bupropion significantly reduced HAM-A scores from baseline (15.6) by 3.4 ± 5.34 (mean $\pm$ SD) and 10.2 ± 6.33 at Week 1 and Month 12 ($P < 0.001$). Remission of anxiety symptoms occurred in 78.3% of participants at Month 12. HAM-A correlated with Inner Tension ($p=0.57-0.62$). Open-label studies showed significant mean reductions in Inner Tension (EVOLVE: $-0.86, -2.48$; COMET: $-0.83, -2.10$ at Week 1 and Month 12; all $P < 0.001$), as well as the anxiety and vegetative subscale (EVOLVE: $-2.96,$

−9.46; COMET: −2.84, −9.28 at Week 1 and Month 12, respectively; all $P < 0.001$). In RCTs, dextromethorphan-bupropion significantly improved Inner Tension versus control groups at Week 6 (GEMINI: $\Delta=0.37$; ASCEND: $\Delta=1.19$); the anxiety and vegetative subscale also showed significant improvement (GEMINI: $\Delta=1.41$; ASCEND: $\Delta=2.22$)(all $P < 0.05$). Anxiety TEAEs were infrequent, with an absolute prevalence of 0.9-2.1% across groups, and were generally transient (median duration: 4-44 days), with few discontinuations.

Conclusions: In this post hoc analysis, dextromethorphan-bupropion was associated with clinically meaningful, sustained improvement in anxiety symptoms in adults with MDD. Anxiety-related TEAEs were infrequent. These findings are supportive of dextromethorphan-bupropion use in patients with MDD and anxiety symptoms.

W51. MULTIMODAL IDENTIFICATION OF NEUROBIOLOGICAL SUBTYPES ASSOCIATED WITH KETAMINE RESPONSE IN TREATMENT-RESISTANT DEPRESSION USING NETRAAI

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Abstract Background: Ketamine has demonstrated rapid antidepressant effects in treatment-resistant depression (TRD), but its psychoactive properties complicate blinding and obscure identification of true biological response. Integrating multimodal clinical and neurobiological data may help resolve response heterogeneity and clarify ketamine's mechanisms of action.

Methods: We reanalyzed data from a small, randomized, double-blind, placebo-controlled crossover Phase II trial of intravenous racemic ketamine (0.5 mg/kg) versus saline placebo in TRD (NCT00088699; n=33). NetraAI, an explainable AI/ML framework designed to identify low-dimensional human-interpretable feature sets, was used to analyze and integrate baseline clinical symptom scales (e.g., MADRS, HAM-A, HAMD-17, BDI), physiological measures (e.g., BMI), volumetric structural MRI features, and resting-state MEG recordings. Due to the crossover design, participant data from both infusion sessions were pooled, yielding 63 analyzable cases (3 incomplete subject datasets were excluded). Pooling was performed to increase statistical power while preserving within-subject treatment labels; analyses focused on identifying stable subgroup structure rather than independent observations. Treatment response was defined as a $\geq 40\%$ reduction in MADRS scores at Day 7. The NetraAI framework partitions the patient population into explainable and unexplainable subpopulations, focusing on identifying compact (2-4 variable), multimodal feature sets defining biologically coherent Model-Derived Subgroups (MDS).

Results: Multimodal integration revealed multiple internally consistent reproducible ketamine responder MDS characterized by convergent clinical, anatomical, and functional signatures. One MDS ($p=0.028$, Cohen's $d=2.11$) integrated elevated emotional reactivity with reduced posterior cingulate and inferior parietal white matter volumes, implicating default mode network and emotional regulation circuitry consistent with ketamine's glutamatergic modulation of large-scale networks. Another MDS ($p=0.047$, Cohen's $d=1.33$) combined cardiovascular anxiety symptoms with elevated isthmus cingulate and lingual grey matter volumes, suggesting altered

interoceptive and autonomic processing within salience-related networks. The large effect sizes of these MDS indicate clinically meaningful separation of strong ketamine responders. Additional MDS incorporating MEG-derived variables were also identified.

Conclusions: Integrating clinical symptoms, physiological measures, structural neuroanatomy, and functional network dynamics identifies distinct neurobiological pathways associated with ketamine response in TRD. These findings demonstrate how NetraAI's multimodal data integration can link symptom dimensions to brain circuitry, support biomarker-informed patient stratification and improve interpretability of ketamine trials. Findings should be interpreted in the context of modest sample size and crossover design but collectively support the potential of explainable multimodal approaches to advance precision psychopharmacology and trial enrichment strategies in neuropsychiatric drug development.

W52. OREXIN 2 RECEPTOR AGONISTS AS A POTENTIAL THERAPEUTIC APPROACH TO THE TREATMENT OF SLEEP-WAKE DISTURBANCE, FATIGUE, AND COGNITIVE DEFICIT IN NEUROPSYCHIATRIC DISEASE

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Abstract: Sleep disorders are among the most prevalent and impairing health conditions globally. These conditions frequently co-occur with psychiatric disorders, especially among individuals with mood, anxiety, psychotic, and neurodevelopmental disorders, leading to some of the most common comorbidities in clinical practice. Orexin neuropeptides, which signal through orexin receptor 1 (OX1R) and 2 (OX2R), are regulators of sleep-wake behavior and stabilize wakefulness through activation of downstream arousal neurocircuitry, including histamine, serotonin, dopamine, acetylcholine, and norepinephrine circuits. OX2R agonists have recently emerged as potentially transformative treatment options for patients with central disorders of hypersomnolence, including narcolepsy. Alixorexton, a highly potent, selective OX2R agonist, has been shown to normalize daytime sleepiness (i.e., achievement of mean sleep latency on the Maintenance of Wakefulness Test > 20 minutes) in a phase 2 study (Vibrance-1; NCT06358950) of patients with narcolepsy type 1 (NT1), where the pathophysiology involves loss of orexin-producing neurons. Furthermore, the study showed clinically meaningful improvements across a multitude of NT1 symptoms that are often inadequately treated with current therapies, including cataplexy and more recently recognized symptoms related to cognitive impairment and fatigue. Alixorexton also demonstrated clinically meaningful improvements in measures of wakefulness, cognitive impairment, and fatigue in a phase 2 study (Vibrance-2; NCT06555783) of patients with narcolepsy type 2 (NT2), a population that typically has preserved cerebrospinal orexin levels and a less well defined disease pathophysiology. Achieving clinical effects with an OX2R agonist across multiple symptoms, including cognitive impairment and fatigue, in a population with central disorders of hypersomnolence indicates that it is plausible to target improvement in the lives of patients in

areas other than sleepiness by targeting the orexin pathway. Two other OX2R agonist molecules are currently being evaluated in healthy volunteers, with plans for clinical testing in patients with attention deficit and hyperactivity disorder (ADHD) and patients with fatigue associated with multiple sclerosis or Parkinson's disease, respectively, later this year. This presentation will highlight the key data supporting the utility of alixorexton across sleep-wake disturbance, fatigue, and cognition, and discuss ongoing product development plans.

W53. A NOVEL DISEASE-MODIFYING STRATEGY FOR NARCOLEPSY TYPE 1 – PRECLINICAL RATIONALE AND DEVELOPMENT ROADMAP FOR THE DOXA PLATFORM

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Abstract: Narcolepsy type 1 (NT1) is a chronic, orphan neurological disorder caused by autoimmune-mediated destruction of orexin-producing neurons in the lateral hypothalamus, leading to profound orexin deficiency (CSF orexin-A ≤ 110 pg/mL), cataplexy, excessive daytime sleepiness (EDS), REM sleep dysregulation, and fragmented sleep-wake cycles. Current therapies, including OX2R-selective agonists (TAK-861, ALKS-2680, ORX750), provide symptomatic relief but suffer from receptor desensitization, high insomnia rates (up to 65%), incomplete REM control, and no impact on the underlying neurodegeneration. DOXA (Dual Orexin Receptor Agonists) platform—introduces first-in-class non-sulfonamide compounds (AEX-41, AEX-2) that restore orexin signaling more physiologically than OX2R-only molecules. Preclinical data in the ORX-KO mouse model demonstrate that AEX compounds (e.g. AEX-41 at 40 mg/kg PO) achieves 90.9% cataplexy reduction ($p < 0.001$), 73% wakefulness increase over 60 min ($p < 0.005$), and significant sleep architecture improvement (REM duration –10%, SWS transitions –15%, $p < 0.05$). These preclinical results outperform OX2R-selective benchmarks in animal models and support dual agonist OX1R/OX2R as a superior symptomatic strategy. To address the core neurodegenerative pathology, we propose proof-of-concept (PoC) studies in Parkinson's disease (PD) and amyotrophic lateral sclerosis (ALS) models. In α -synuclein A53T transgenic mice (PD model), we plan to evaluate whether Cathepsin H (CTSH) of AEX-41 inhibitory activity can enhance α -synuclein clearance. In the B6-hTDP43wt $\times$ A315T transgenic model (Thy1-driven human TDP-43 WT/A315T mutation, ALS model), we aim to explore potential modulation of TDP-43 pathology, neuroinflammation, and motor neuron survival. These studies are proposed PoC investigations and have not yet been performed. Succinctly, a hybrid pharmacology approach combining DOXA (dual OX1R/OX2R agonist with CTSH inhibition) with regenerative cell therapy (e.g., AstroRx – hESC-derived astrocytes) could be explored in ALS models: DOXA would enhance neuronal signaling and reduce inflammation, while AstroRx would provide trophic support and glutamate clearance,

potentially offering synergistic neuroprotection. These hybrid concepts are at the hypothesis stage and will be tested in future preclinical work.

The development roadmap includes:

1. Formulation optimization of AEX-41 and AEX-2 to achieve robust oral bioavailability (> 70%) and support chronic daily dosing in NT1 patients, with focus on solubility enhancement, metabolic stability, and CNS penetration.
2. Proposed PoC studies in Parkinson's disease (PD) models using α -synuclein A53T transgenic mice to explore the neuroprotective effects of AEX-41, including reduction of α -synuclein aggregation, and motor/non-motor symptom amelioration via CTSH inhibition and dual orexin signaling.
3. Proposed PoC studies in amyotrophic lateral sclerosis (ALS) models using the B6-hTDP43wt $\times$ A315T transgenic model (Thy1-driven human TDP-43 WT/A315T mutation) to investigate the potential of AEX compounds (e.g., AEX-2) to modulate TDP-43 pathology, reduce neuroinflammation, and slow motor neuron loss.
4. Diabetes PoC Study Plan – db/db and STZ-Induced Mouse models, using AEX-2 and AEX-24 to evaluate insulin sensitization, β -cell rescue, glucose tolerance, and metabolic recovery in type 2 diabetes models.
5. Advancement of the Next-Gen AEX series (e.g., AEX-635, AEX-609, AEX-23, AEX-24) for broader CNS applications, including enhanced CTSH inhibition, sigma-1 receptor modulation, and improved selectivity profiles for NT1, PD, ALS, and other neurodegenerative conditions.
6. Comprehensive ADME-Tox profiling (absorption, distribution, metabolism, excretion, and toxicity) in multiple species, including CYP inhibition assessment, reactive metabolite screening, and GLP-compliant toxicology to support future clinical development.

This DOXA strategy represents a potential paradigm shift from purely symptomatic to neuroprotective treatment, offering both rapid symptom relief and the prospect of slowing neurodegeneration in NT1, PD, ALS, and metabolic disorders. Early clinical translation of this approach could significantly improve long-term outcomes for patients with narcolepsy type 1 and related neurodegenerative conditions.

W54. TARGETED ELIGIBILITY REVIEW CAN DECREASE THE NUMBER OF INAPPROPRIATE PARTICIPANTS ENROLLED IN CLINICAL TRIALS

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Abstract Background: Ensuring enrolled participants meet all the inclusion criteria and none of the exclusion criteria is critical to the success of any clinical trial. Regulatory agencies have historically deferred to the investigators' determinations on whether a patient is appropriate for a clinical study; however, with the rise of clinics specializing in research rather than patient care, investigators' motivations for enrolling participants may not always align with the best interest of science. Additionally, there are increasing examples of patients enrolled into trials where standard protocol defined screening procedures and review alone were not enough to ensure the

quality of patients enrolled. The complexity of study designs and more robust eligibility criteria have created an environment where more sponsors are looking for additional oversight measures to ensure quality patients are enrolled. To mitigate and reduce the impact of the above-mentioned points, targeted eligibility review utilizing independent medical reviewers has started to become more common in clinical trials.

Objective: To evaluate the impact of targeted eligibility review on participant enrollment in psychiatric trials over the past four years and to analyze the reasons for screen failure.

Methods: Retrospective review of internal study enrollment trackers and targeted eligibility submissions across multiple psychiatric indications was done for over 1000 participants whom sites intended to randomize. Analysis was done comparing all patients who passed the first set of protocol defined screening criteria, as determined by the site, to those patients who were subsequently determined not to meet targeted eligibility criteria.

Results: We reviewed targeted eligibility data for 1332 participants across multiple trials and psychiatry indications. Since these participants' screening information had already been reviewed by the investigators, and the investigators determined they were eligible to be randomized, all of the participants should have been able to proceed to Baseline. Upon further targeted eligibility review, 156 participants (11.7%) were determined to be screen failures prior to becoming randomized. While the combined analysis revealed an impact of ~12% more participants being screen failed after passing the investigators' initial screening, this quality impact was observed to be as high as 38% in one individual study where the enrollment criteria were more complex. The overall impact of screen failing these additional patients was at its simplest a proactive reduction in protocol deviations. Additionally, targeted eligibility review may have potentially reduced a negative impact to the statistical analyses of these trials since these participants would have likely needed to be removed from ITT power calculations.

Conclusion: Incorporating targeted eligibility review in psychiatry clinical trials can reduce the risk of enrollment deviations. Further analysis is needed to determine the full impact on data quality.

W55. IMPACT-EXT: EVALUATING THE DURABILITY AND REDOSING OF TSND-201 (METHYLONE) FOR THE TREATMENT OF PTSD

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Abstract Background: TSND-201 (methylone) is under clinical investigation as a treatment for post-traumatic stress disorder (PTSD), a debilitating psychiatric condition affecting an estimated 12 million adults in the US each year. Current therapies have limited efficacy, highlighting the need for novel treatment approaches. Non-hallucinogenic compounds that provide rapid and sustained therapeutic effects could offer practical advantages over classical psychedelics. TSND-201 is a selective, fast-acting neuroplastogen that promotes neuroplasticity by releasing serotonin, norepinephrine, and dopamine. Consistent with its lack of direct activity at serotonin (5-HT)_{2A} receptors, TSND-201 is non-hallucinogenic in both humans and preclinical models. Preclinical studies show that TSND-201 produces rapid, robust, and durable improvements in

models of PTSD, depression, and anxiety. In a prior Phase 2 randomized, placebo-controlled trial (IMPACT-1), TSND-201 demonstrated rapid and sustained reductions in PTSD symptoms as measured by the CAPS-5. These promising results led to FDA Breakthrough Therapy Designation. In the present study, we assess the durability of TSND-201's effects and evaluate the impact of redosing in participants who completed IMPACT-1.

Methods: The IMPACT-EXT study was a multicenter open-label extension clinical trial evaluating the durability and redosing of TSND-201. Participants were completers from the IMPACT-1 phase 2 clinical trial evaluating safety and efficacy of TSND-201 for PTSD who chose to enroll in the open-label extension trial. Participants of the IMPACT-1 trial were adults with PTSD and a CAPS-5 total score ≥ 35 who had tried at least one prior treatment (pharmacotherapy and/or psychotherapy) for PTSD. A total of 44 of 59 completers from IMPACT-1 enrolled (21 from the prior-TSND-201 arm and 23 from the prior placebo arm). Overall, CAPS-5 scores at the end of IMPACT-1 among those who enrolled in this extension study were notably higher than the average of all who completed IMPACT-1 (i.e., participants with more severe illness enrolled into the extension study). Participants attended monthly visits and were followed for up to 12 months. Treatment with a course of open-label TSND-201 (4 weekly doses) could occur upon two consecutive visits with a CAPS-5 score ≥ 28 .

Results: Participants who received TSND-201 in the IMPACT-1 study and had a meaningful response (≥ 10 -point improvement on CAPS-5) demonstrated sustained efficacy through Week 14 (-22.5 point change from IMPACT-1 baseline) and Week 18 (-17.4 point change from baseline). After an additional course of open-label treatment (e.g., one course in IMPACT-1 and one course in this study), participants experienced significant improvement in CAPS-5 scores lasting up to 16 weeks after the second treatment. There were no new safety findings after repeat treatment with TSND-201.

Conclusion: These results show that TSND-201 maintains therapeutic effects for about four months, informing redosing strategies and future Phase 3 study design. This study supports the development of TSND-201 as a treatment for PTSD.

W56. SAFETY, PHARMACOKINETICS, AND PHARMACODYNAMICS OF MSD-001 AFTER SINGLE DOSING IN HEALTHY ADULTS: A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY

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Abstract Background: MSD-001 (5-MeO-MiPT) is an orally bioavailable tryptamine primarily targeting 5-HT1A, 5-HT7, and 5-HT1D receptors. Its selection was guided by AI-based analysis linking biochemical properties to large-scale subjective experience data to select a compound that produces mild psychoactive effects without inducing strongly altered or disorienting experiences. This clinical evaluation aims to support future combination strategies for selectively inducing therapeutically relevant mental states. This single ascending dose study evaluated the

safety, pharmacokinetic (PK), and pharmacodynamic (PD) profiles of MSD-001 (0.5–10mg) in healthy male and female participants.

Methods: In this randomized, double-blind, placebo-controlled study, healthy participants received a single dose of MSD-001 or placebo. Participants were stratified by cytochrome P450 (CYP) 2D6 activity status: intermediate/extensive metabolizers (IM/EM) received 0.5, 1, 3, 6, or 10 mg MSD-001, while poor metabolizers (PM) received 0.5 or 3 mg MSD-001. Safety was assessed via adverse events (AEs), vital signs, ECGs, laboratory tests, and physical and psychiatric evaluation. Plasma and urine PK were analyzed noncompartmentally. PD outcomes included subjective measures such as the Real-Time Intensity (RTI) scale, the 5-Dimensional Altered States of Consciousness (5D-ASC) questionnaire and a Visual Analogue Scale (VAS), as well as electroencephalography (EEG), functional magnetic resonance imaging (fMRI) and NeuroCart, a validated central nervous system test battery. PD endpoints were analyzed using mixed-effects models and ANOVA.

Results: 47 (40 IM/EM, 7 PM) participants were randomized. Single-dose MSD-001 was safe and well tolerated, with no serious AEs. Most AEs were mild, self-limiting and transient. A dose-related increase in AEs was observed. The most common AEs for MSD-001 were sensory processing disorder (e.g., visual effects; 50%), euphoric mood (33.3%), and feeling of relaxation (33%), and for placebo sensory processing disorder (40%), euphoric mood (20%), disturbance in attention (20%), and hyperhidrosis (20%). No clinically meaningful cardiovascular, laboratory, physical, or psychiatric abnormalities were observed. In IM/EM participants, MSD-001 was rapidly absorbed (median T_{max} 1–2 h; median $t_{1/2}$ ~2–3 h) with generally dose-related exposure, although C_{max} and AUC were similar at 6 and 10 mg. In PMs, median C_{max} increased ~1.6–1.8-fold and $t_{1/2}$ ~2-fold relative to IM/EMs. MSD-001 produced dose-related PD effects compared with placebo, with minimal changes at 0.5–1 mg and the most consistent effects at 6–10 mg. Effects typically emerged within 30 min, peaked at 2–3 h, and resolved by 6 h. Subjective effect measures showed visual, bodily, and emotional/metacognitive effects on the RTI, along with increases in total altered state of consciousness, mood and calmness on the 5D-ASC and VAS, without effects on anxiety or cognitive control. EEG analyses showed reduced delta and theta power and increased gamma power, suggesting a shift toward increased cortical activation and altered information processing, while fMRI changes were minimal. NeuroCart evaluation showed inconsistent effects on saccadic peak velocity, saccadic reaction time, and smooth pursuit.

Conclusions: Single oral doses of MSD-001 up to 10 mg were safe and generally well tolerated in healthy male and female participants, with rapid absorption and dose-related exposure influenced by CYP2D6 activity status. MSD-001 produced dose-dependent subjective drug effects without inducing anxiety. Effects peaked within 2–3 h and resolved by 6 h post-dose. The findings support 6–10 mg as the target dose range in future trials.

W57. BLINDING INTEGRITY IN PSYCHEDELIC RANDOMIZED CONTROLLED TRIALS: A SYSTEMATIC REVIEW

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Abstract Importance: Psychedelic drugs possess acute psychoactive effects that can compromise blinding integrity in randomized controlled trials (RCTs). Functional unblinding, when participants or raters correctly identify treatment allocation based on subjective effects, may bias outcomes through expectancy effects, challenging the validity of efficacy estimates and regulatory acceptance.

Objective: To systematically quantify the prevalence of blinding integrity assessment and the extent of functional unblinding in psychedelic RCTs for psychiatric disorders.

Evidence Review: A systematic review was conducted in accordance with PRISMA guidelines across OVID Medline, Embase, and APA PsycInfo (January 2020–July 2025), supplemented by manual searches of three prior reviews for studies prior to January 2020. Eligible studies included all RCTs investigating psychedelics as psychiatric interventions. Data extracted included blinding integrity assessment methods and results for participants and raters.

Findings: Of 105 RCTs (psilocybin n=10, lysergic acid diethylamide (LSD) n=7, ketamine n=73, 3,4-Methylenedioxymethamphetamine (MDMA) n=10, ayahuasca n=2, N,N-Dimethyltryptamine (DMT) n=2, noribogaine n=1), only 29.5% (n=31) evaluated blinding integrity, yet 58.1% (n=61) cited blinding as a limitation. Functional unblinding was substantial: psilocybin, LSD, and ayahuasca studies frequently reported blinding failure values of > 90% among participants and raters; inert placebo controlled MDMA trials exceeded 85%; ketamine trials rarely assessed blinding (17.8%) but showed improved preservation with midazolam versus saline controls. No control strategy consistently achieved ideal blinding.

Conclusions and Relevance: This first evaluation of blinding integrity in psychedelic RCTs indicates functional unblinding is pervasive among participants and raters raising concerns about the validity of efficacy findings. Few trials assess blinding or expectancy, highlighting the need for standardized, validated measures and innovative designs to separate true pharmacological effects from expectancy-driven responses.

W58. UNLOCKING MEDICINES FOR NEUROPSYCHIATRY BY ENHANCING ORAL ABSORPTION USING A LYMPHATIC-TARGETING PRODRUG TECHNOLOGY

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Abstract Introduction: Depression and anxiety are disabling mental health conditions with a significant need for new treatment options. The Glyph™ platform, a lymphatic-targeting prodrug technology, can be applied to overcome limitations such as high first-pass metabolism, low oral bioavailability, and/or side effects, which may otherwise present barriers to patient use. The platform reversibly conjugates a drug of interest to a dietary fat molecule using proprietary chemistry, shifting absorption toward intestinal lymphatics to avoid first-pass hepatic metabolism and enhance oral bioavailability while reducing dose. GlyphAllo™ (SPT-300 or Glyph Allopregnanolone), an oral prodrug of allopregnanolone, is designed to overcome allopregnanolone's poor oral bioavailability from substantial first-pass hepatic metabolism. Allopregnanolone is an endogenous neurosteroid that has been clinically validated as a rapidly

acting antidepressant with anxiolytic and sleep-promoting effects through its pharmacology as a GABAA receptor positive allosteric modulator. Here, we discuss how GlyphAllo was developed using the Glyph platform and present initial proof-of-concept and safety results from phase 1 and phase 2a clinical trials in healthy volunteers.

Methods: A series of lymphatic-targeting allopregnanolone prodrugs was evaluated by screening for in vitro plasma release and assessing plasma levels after oral administration across species. GlyphAllo was evaluated in a multipart phase 1 clinical trial (NCT05129865) of healthy volunteers including single and multiple ascending dose components. Safety, pharmacokinetic data, and pharmacodynamic assessments, including the Stanford Sleepiness Scale (SSS), quantitative EEG (qEEG), and video-oculography for saccadic eye velocity (SEV), were collected. GlyphAllo's potential to reduce physiological stress in healthy volunteers was evaluated in an initial proof-of-concept phase 2a (NCT05129865) pharmacodynamic trial using the Trier Social Stress Test (TSST), a clinical validated model of anxiety.

Results: Based on the discovery and preclinical screening methods, GlyphAllo (SPT-300) was selected as the lead development candidate. In a phase 1 clinical trial in healthy volunteers, oral dosing of GlyphAllo was generally well-tolerated and resulted in a > nine-fold increase in allopregnanolone plasma levels compared to previously reported bioavailability of oral allopregnanolone. Peak allopregnanolone plasma levels and pharmacodynamic markers, including increased beta EEG power and reduced SEV, were observed 3-5 hours post-dose. GlyphAllo demonstrated initial proof-of-concept in a phase 2a TSST clinical trial, significantly blunting the salivary cortisol stress response compared to placebo in healthy volunteers ($p=0.0001$). No treatment-related severe or serious adverse events were reported. The most common adverse event was somnolence, which was mild or moderate and transient in all cases. SSS scores returned to baseline by six hours post dose.

Conclusion: These data validate the Glyph platform's ability to enhance oral bioavailability and confirm that the pharmacodynamic activity of GlyphAllo is consistent with the pharmacology of allopregnanolone. A phase 2b, placebo-controlled trial (BUOY-1) is currently underway to evaluate the efficacy and safety of GlyphAllo in patients with major depressive disorder, with or without anxious distress (NCT07065240). GlyphAllo's development and demonstration of enhanced oral bioavailability provides an initial proof-of-concept supporting the wider applicability of the lymphatic-targeting prodrug approach to therapeutic molecules with previous limitations.

W59. A RANDOMIZED, PLACEBO-CONTROLLED TRIAL OF THE FATTY ACID AMIDE HYDROLASE INHIBITOR PALMITOYLETHANOLAMIDE IN BIPOLAR DEPRESSION

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Abstract: There is growing interest in the endocannabinoid system (ECS) as an alternative signaling pathway involved in mood disorders. In response to stressors such as mood episodes, the breakdown of endocannabinoids by the Fatty Acid Amide Hydrolase (FAAH), a degrading enzyme located in the somatodendritic compartments of neurons, reduces endocannabinoid levels and increases HPA stress and inflammation. Higher FAAH breakdown has been described in subjects with depression, PTSD, and suicide ideation. Thus, FAAH inhibition may also represent a unique, valuable target in the therapeutics of Bipolar Depression. Palmitoylethanolamide (PEA) is an FAAH inhibitor, a member of the extended endocannabinoid family. PEA significantly increases the levels of key endocannabinoids (ECs), such as anandamide (AEA), and, through the so-called entourage effect, indirectly activates CB1 receptors. PEA also has shown potent anti-inflammatory and antioxidant effects in humans. Lower PEA levels were observed in depression, inversely associated with depressed mood, diminished interest/pleasure, and psychomotor retardation. In Depression, the first clinical trial examining the antidepressant effects of PEA (600 mg twice daily for six weeks, double-blind, placebo-controlled design) showed a significant improvement in depression scores compared to placebo. The PEA group showed a rapid onset and significantly greater improvements in depressive symptoms score from week 2 compared to the placebo group. The objective of this 6-week, double-blind, placebo-controlled study is to evaluate the antidepressant efficacy of the PEA in Bipolar Depression and the association between antidepressant response with endogenous cannabinoids and cytokines (PEA, AEA, 2-AG, OEA; TNF, IL2, 4, 6, 10, 12). Outpatients with BD in a depressive episode will be followed up for six weeks, with baseline, week 2, 4, and endpoint (post-treatment) assessments. Two groups will be randomized: treatment as usual (TAU, mood stabilizer) plus placebo (n=25) versus TAU plus PEA (600mg/day bid) (n=25). Overall, PEA showed a significant improvement of depressive symptoms in 6 weeks, but not statistically different from placebo. Further studies are warranted.

W60. EFFICACY, SAFETY AND TOLERABILITY OF LYSERGIC ACID DIETHYLAMIDE FOR THE TREATMENT OF DEPRESSIVE SYMPTOMS: A META-ANALYSIS AND SYSTEMATIC REVIEW

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Abstract Background: Since the Food and Drug Administration designated lysergic acid diethylamide (LSD) as a “breakthrough” treatment for generalized anxiety disorder, accumulating randomized clinical trials (RCTs) evaluating LSD’s anxiolytic effects have also reported improved depression symptoms. Given the co-occurrence of anxiety and depression, evaluating the safety and efficacy of LSD in treating depression symptoms is warranted.

Methods: MEDLINE/PubMED, Embase, and PsychINFO were searched from inception to December 9, 2025. RCTs evaluating efficacy of LSD on depression symptoms in adults with mental disorders were included. Cochrane Risk of Bias Tool 2.0 and X2 and I2 tests were used to measure quality and heterogeneity. This review was preregistered on PROSPERO (CRD420251063539).

Results: Of 465 screened studies, five RCTs met selection criteria (N = 227). Our synthesis and random-effects meta-analysis demonstrated that LSD treatment significantly reduced depression symptoms compared to the comparator (SMD = -0.65; 95% CI: -0.92 to -0.38, p = 0.000002). Studies varied in design and three of the included studies administered LSD with psychological support, although study-level heterogeneity was not significant (I² = 0%, p = 0.54). Three studies had low risk of bias. All-cause discontinuation demonstrated reasonable acceptability of LSD treatment. Severe adverse events possibly related to study parameters included hospitalizations (N = 3) and acute anxiety/delusions (N = 1).

Conclusion: Our findings suggest that LSD, with and without psychological support, reduces depression scores in clinical populations. This review is limited by small sample size. Future well-designed RCTs are needed to establish the efficacy and safety of LSD in managing depression.

W61. BEYOND MOOD: BROADER PSYCHOLOGICAL BENEFITS OF IV KETAMINE FOR MAJOR DEPRESSIVE DISORDER

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Abstract Background: Intravenous ketamine has demonstrated efficacy in treating treatment-resistant depression (TRD), yet the accompanying psychological changes during treatment remain inadequately characterized.

Methods: We examined psychological measures in adults with treatment-resistant major depressive disorder receiving IV ketamine. Assessment instruments included the Adverse Childhood Experiences (ACE) questionnaire, Quick Inventory of Depressive Symptomatology Self-Rated 16-item (QIDS-SR16), Life Orientation Test-Revised (LOT-R), Brief Resilience Scale (BRS), Brief Resilient Coping Scale (BRCS), Cognitive Flexibility Scale (CFS), and Perceived Stress Scale (PSS). Participants were stratified into two cohorts: those completing baseline measures before initiating ketamine (pre-treatment), and those completing measures during ongoing treatment (mid-treatment). Follow-up assessments were administered at participants' convenience. Treatment response was operationalized as ≥50% reduction in QIDS-SR16 scores. Paired comparisons utilized Wilcoxon signed-rank tests. For the pre-treatment cohort, linear regression examined whether ACE scores predicted depression score changes, while logistic regression evaluated ACE effects on response rates.

Results: The combined cohort (n=27) had a median age of 52 years (22 females, 5 males). Among pre-treatment participants (n=12), 75% (9/12) achieved treatment response. Wilcoxon signed-rank testing demonstrated significant post-treatment reductions in QIDS-SR16 scores (median difference=11, 95% CI [7.5, 14.5], p=0.003). Significant improvements were observed in LOT-R scores (median difference=3.0, 95% CI [1.0, 5.0], p=0.02) and BRCS scores (median difference=4.0, 95% CI [1.0, 7.0], p=0.008). Changes in BRS (median difference=1.1, 95% CI [-0.2, 2.1], p=0.09) and CFS (median difference=8.4, 95% CI [-0.5, 18], p=0.06) approached but did not reach statistical significance. PSS scores decreased significantly (median difference=11.2, 95% CI [3.0, 20.0], p=0.02). In the mid-treatment cohort (n=15), none of the psychological measures (LOT-R, BRS, BRCS, CFS, PSS) showed significant changes. Median

intervals between assessments were 7.2 months (pre-treatment) and 11.7 months (mid-treatment). Neither linear nor logistic regression analyses revealed significant associations between ACE scores and treatment outcomes.

Conclusions: Patients initiating IV ketamine for treatment-resistant MDD demonstrated significant improvements in optimism, resilient coping capacity, and perceived stress levels. Near-significant trends emerged for cognitive flexibility and resilience. Conversely, patients receiving maintenance ketamine showed no significant psychological changes, suggesting no attenuation of initial treatment benefits during long-term therapy. Childhood adversity did not influence acute antidepressant response or remission rates. Study limitations include small sample size and exclusive use of self-report instruments.

W62. THE COMPLEX DIAGNOSTIC PROFILE OF PSYCHIATRIC OUTPATIENTS PRESENTING FOR THE TREATMENT OF BIPOLAR DEPRESSION

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Abstract Objectives: To examine the prevalence of current comorbid disorders in outpatients presenting for the treatment of bipolar depression and determine the significance of comorbidity by examining whether patients want treatment to address the comorbid disorder and whether comorbidity is associated with prolonged unemployment.

Methods: One hundred thirty-one psychiatric outpatients with bipolar depression were interviewed with the Structured Clinical Interview for DSM-IV (SCID) and the borderline personality disorder section of the Structured Interview for DSM-IV Personality. At the end of each SCID module patients were asked if the symptoms of the disorder were a reason for coming for treatment. The interview also included the item from the Schedule for Affective Disorders and Schizophrenia assessing the amount of time missed from work due to psychiatric reasons during the past 5 years.

Results: Nearly 80% of the patients were diagnosed with at least 1 comorbid disorder (n=104, 79.4%), more than 60% were diagnosed with 2 or more comorbid disorders (n=82, 62.6%), and almost half were diagnosed with 3 or more disorders (n=60, 45.8%). More than two-thirds of all patients wanted their treatment to also address a comorbid disorder (n=89, 67.9%). For each anxiety disorder except specific phobia more than three-quarters of the patients with the disorder wanted treatment to address the comorbid anxiety disorder. More than 90% of the patients with attention deficit disorder desired treatment for the comorbidity. By contrast, patients were least interested in having treatment for a comorbid substance use disorder. Patients with 2 or more comorbid disorders were more than 3 times more likely to be chronically unemployed than patients who were not diagnosed with 2 or more disorders.

Conclusion: Most patients presenting for the treatment of bipolar depression have a comorbid psychiatric disorder and they usually want their treatment to also address their comorbid conditions.

W63. SODIUM-GLUCOSE COTRANSPORTER-2 INHIBITORS REDUCE SUICIDALITY, ALL-CAUSE MORTALITY, AND HOSPITALIZATION IN BIPOLAR DISORDER: A COHORT STUDY OF 1.23 MILLION ADULTS

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Abstract Background: Sodium-glucose cotransporter-2 inhibitors (SGLT2is) have demonstrated promising neuropsychiatric properties in animal research.

Aims: We aimed to examine whether SGLT2i exposure is associated with reduced incidence of suicidality, all-cause mortality, and hospitalization in bipolar disorder (BD).

Method: This cohort study utilized the TriNetX network (2008–2025) to identify 1,230,821 adults with BD, including 36,092 SGLT2i users and 1,194,729 non-users. The outcomes were incident suicidality, all-cause mortality, and hospitalization over 5-years of follow-up. Adjusted hazard ratios (aHRs) were estimated using Cox proportional hazards models, with additional 1:1 propensity score matching (PSM) for survival analysis conducted to control for confounding. Subgroup analyses stratified results by sex, race/ethnicity, concurrent mood stabilizer use, and somatic comorbidities.

Results: SGLT2i exposure was associated with significantly reduced risk of suicidality (aHR 0.75, 95% CI 0.71–0.79), all-cause mortality (aHR 0.55, 95% CI 0.52–0.57), and hospitalization (aHR 0.71, 95% CI 0.69–0.72). Protective associations remained consistent across subgroups, including patients receiving lithium, lamotrigine, or valproate. After PSM (31,001 matched pairs), five-year outcomes favored SGLT2i users: suicidality-free survival 94.51% versus 93.56%, overall survival 88.99% versus 79.57%, and hospitalization-free survival 72.39% versus 66.72% (all $p < 0.001$).

Conclusions: In this large cohort of over 1.2 million adults with BD, SGLT2i therapy was associated with substantially lower risks of suicidality, hospitalization, and all-cause mortality, with consistent benefits across demographic and clinical subgroups. These findings suggest SGLT2is may represent a promising therapeutic strategy to improve psychiatric and survival outcomes in BD. Prospective RCTs are warranted to evaluate long-term safety and efficacy.

W64. PRECLINICAL EFFICACY OF CONCOMITANT ADMINISTRATION OF NOVEL GSK3 β INHIBITOR 4MT-A AND LITHIUM OROTATE

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Abstract Background and Purpose: Lithium's effects in bipolar disorder may be due to Glycogen synthase kinase 3 beta (GSK3 β) inhibition. Prolonged clinical use of lithium carbonate at 1,200 mg/day (226 mg of elemental lithium) has significant renal toxicity, while 4MT-A, a novel ATP-competitive GSK3 β inhibitor, and low doses of lithium orotate (LiOr) have each

shown preclinical efficacy without kidney toxicity in animal safety studies. Concomitant administration of 4MT-A and LiOr was examined in a validated model of positive affective state, amphetamine-induced positive appetitive ultrasonic vocalizations (USVs). The LiOr dose corresponded to ~15 mg elemental lithium in humans. The 4MT-A dose was substantially below the no-adverse-effect level from GLP (good laboratory practice) animal safety studies. The purpose was to determine whether a low dose of LiOr could enhance 4MT-A efficacy.

Methods: Adult male Wistar rats were treated in 5 groups (n=10 per group): saline, dextro-amphetamine (AMP), or AMP preceded by lithium orotate (LiOr) 1.25 mg/kg, 4MT-A 6 mg/kg, or the concomitant administration of 4MT-A 6 mg/kg and LiOr 1.25 mg/kg. Each treatment was given by intraperitoneal injection 60 minutes before AMP. USVs (> 50 kHz, appetitive curved upward) were recorded over 120 minutes in 21 sequential 5-minute intervals. A machine learning method (DeepSqueak) was implemented to automatically detect, segment, and analyze the USVs over time, with statistical comparison between groups performed using a repeated-measures ANOVA.

Results: The mean (+/- SEM) numbers of USVs per 5 minutes were 38 (+/- 37), 288 (+/- 72), 287 (+/- 56), 218 (+/- 61), and 151 (+/- 47), respectively, with saline, AMP, and administration of AMP preceded by LiOr, 4MT-A 6 mg/kg, and concomitant administration of both agents. AMP increased USVs compared to saline by 756% ($p < 0.0001$). The mean number of USVs observed with AMP alone was reduced by < 1% ($p=0.95$), 25% ($p=0.003$), and 48% ($p < 0.0001$), when AMP was preceded by LiOr 1.25 mg/kg, 4MT-A 6 mg/kg, and concomitant administration of 4MT-A and LiOr. Administered together, 4-MT-A and LiOr reduced USVs more than either individual component ($p < 0.001$ for each comparison).

Conclusions: Novel GSK3 β inhibitor 4MT-A (6 mg/kg) and a low dose of LiOr reduced amphetamine-induced positive appetitive ultrasonic vocalizations more when they were used together than when either was used alone. The potential synergy between these compounds may be further explored to optimize therapeutic GSK3 β inhibition.

W65. THE NEUROBIOLOGICAL EFFECTS OF PSILOCYBIN IN TREATMENT RESISTANT BIPOLAR DEPRESSION: PROTOCOL AND INTERIM ANALYSIS OF CLINICAL OUTCOMES

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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=12 enrolled to date) with an expected recruitment rate of 2 participants per month. Interim analyses of participants who have completed the trial to date revealed a significant reduction in MADRS scores from baseline ($30.6 \pm \text{SD } 6.8$) to primary endpoint at Week 1 ($15.1 \pm \text{SD } 11.9$), with a mean difference of -15.5 ($\text{SD } 9.52$) points ($p < 0.001$). Improvements were sustained through to secondary endpoint at Week 4, with a mean difference of -16.6 ($\text{SD } 9.0$) points ($p < 0.001$). No treatment emergent mania, hypomania or psychosis was observed. An updated 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 up to that point.

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.

W66. EFFECT OF CARIPRAZINE TREATMENT ON SLEEP AND MOOD SYMPTOMS IN PATIENTS WITH BIPOLAR I DEPRESSION AND BASELINE SLEEP DISTURBANCE: POST HOC ANALYSIS OF THREE RANDOMIZED PLACEBO-CONTROLLED CLINICAL TRIALS

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Abstract Introduction: Sleep disturbance is a core feature of bipolar I disorder (BP-I) and is associated with greater disease severity and worse outcomes, including increased rates of relapse and suicide attempts. Cariprazine (CAR), a dopamine D3-preferring D3/D2 and serotonin 5-HT1A receptor partial agonist, is approved for the treatment of manic, mixed, and depressive episodes associated with BP-I. In previous post hoc analyses of three phase 2 or 3, randomized, double-blind, placebo-controlled studies of adults with BP-I depression, CAR demonstrated broad efficacy in treating core depressive symptoms, including a potential benefit for sleep. The

present post hoc analysis aimed to further assess the effects of CAR on sleep and mood symptoms in a subset of patients with BP-I depression and reduced sleep at baseline.

Methods: Data were pooled from three randomized, double-blind, placebo-controlled, phase 2 or 3 clinical trials (NCT01396447, NCT02670538, NCT02670551) evaluating CAR 1.5 and 3 mg/d in adults with BP-I depression. To enrich for moderate/severe sleep disturbance, analyses were conducted in patients with a Montgomery–Åsberg Depression Rating Scale (MADRS) item 4 (“Reduced sleep”) score ≥ 4 at baseline. Effects on sleep, depression, and anxiety symptoms were assessed by change from baseline to week 6 in MADRS item 4, MADRS total score, and Hamilton Depression Rating Scale (HAM-D) anxiety/somatization factor scores, respectively. Additional outcomes included the proportion of patients achieving sleep response (≥ 2 -point decrease in MADRS item 4), MADRS response ($\geq 50\%$ reduction in MADRS total score), and MADRS remission (MADRS total score ≤ 10) at week 6. For change from baseline outcomes, a mixed-effect model for repeated measures was used to estimate least-square mean (LSM) changes, along with P values corresponding to the between-treatment difference vs placebo. For categorical outcomes, a logistic regression model was used to assess P values vs placebo. Analyses were conducted for individual dose groups (1.5 mg/d, 3 mg/d) and the pooled CAR dose group (combined 1.5-3 mg/d).

Results: At baseline, 984 patients (71.1% of the pooled intent-to-treat population) had moderate or severe sleep disturbance (1.5 mg/d: n=327; 3 mg/d: n=326; placebo: n=331) and were included in the analysis population. At week 6, LSM change from baseline in MADRS item 4 score was significantly $>$ placebo (-1.6) for CAR 3 mg/d (-2.0; $P < .01$) and the combined 1.5-3 mg/d dose group (-1.9; $P < .05$), but not for 1.5 mg/d (-1.9; $P > .05$). A significantly greater proportion of patients treated with CAR 3 mg/d vs placebo achieved sleep response (57.1% vs 48.3%; $P < .05$). LSM changes in MADRS total score were significantly greater across CAR dose groups (-15.5 to -15.4) vs placebo (-12.3; all $P < .001$). Significantly more CAR-treated than placebo-treated patients achieved MADRS response (45.6% to 47.9% vs 36.6%; all $P < .05$) and MADRS remission (30.4% to 31.5% vs 20.8%; all $P < .01$). CAR was also associated with significantly greater LSM reductions vs placebo in HAM-D anxiety/somatization factor score across dose groups (-3.6 to -3.3 vs -2.7; all $P < .01$).

Conclusions: In this post hoc analysis, CAR treatment was associated with improvements in sleep and mood symptoms at week 6 among patients with BP-I depression and baseline sleep disturbance. Overall, these results suggest that CAR may be an effective treatment option for this patient population.

W67. AN OPEN-LABEL, TWO-ARM STUDY OF KETAMINE’S EFFECTS ON FLUID COGNITION IN MOOD DISORDERS WITH AND WITHOUT PSYCHOSIS

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Abstract Background: Individuals with mood disorders, including major depressive disorder (MDD) and bipolar disorder (BD), frequently exhibit neurocognitive deficits; however, no pharmacological treatments effectively target cognition. Cognitive dysfunction is especially

prominent in individuals with prior psychotic symptoms. Ketamine, an N-methyl-D-aspartate receptor antagonist, has rapid antidepressant and anti-suicidal ideation effects in unipolar and bipolar depression and may improve cognition through glutamate-mediated synaptic plasticity. Emerging evidence suggests that ketamine can enhance fluid cognition (ability to reason, learn and solve novel problems without relying on prior knowledge) within hours to days, sometimes independently of mood improvement. This study evaluates baseline fluid cognition by psychosis history, ketamine-related cognitive improvement, differential response by psychosis status, and safety in individuals with prior psychotic experiences.

Methods: Twenty subjects (age = 41.05 ± 13.85 ; 11 female; 13 with MDD, 7 with BD) were included by convenience sampling. Prior psychotic experience was assessed at baseline using the Questionnaire for Psychotic Experiences or a clinical interview. Ten subjects received up to five open-label ketamine infusions (0.5 mg/kg over 40 minutes) over three weeks; the remaining subjects comprised a no-intervention group for comparison purposes. Participants who received ketamine had a lifetime history of suicidal ideation but were not in an active suicide crisis. The NIH Toolbox Fluid Cognition Composite and the Montgomery–Åsberg Depression Rating Scale (MADRS) were assessed at baseline, after the first infusion (or a comparable time point for the no-intervention group), and after the final infusion. Adverse events were recorded using MedDRA on the days following the first and last infusions. Independent-samples t-tests assessed baseline Fluid Cognition differences by psychosis history. Linear mixed-effects models examined changes in MADRS and Fluid Cognition across condition (baseline, no-intervention, post-infusion 1, and post-infusion 5) and by psychosis status, controlling for diagnosis and including random intercepts for subjects. Adverse events were summarized descriptively.

Results: No subjects had a primary psychotic disorder or psychotic symptoms within two weeks prior to study inclusion. Six participants had prior psychotic experiences. Baseline Fluid Cognition did not differ by psychosis history (98.5 ± 11.6 vs. 98.8 ± 13.7 ; $t = 0.04$, $p = 0.96$). Ketamine reduced MADRS scores across conditions [$F(3, 23.27) = 4.68$, $p = 0.011$], with no effect of psychosis history [$F(1, 16.67) = 0.07$, $p = 0.79$]. Ketamine was also associated with improvement in cognition across conditions [$F(3, 18.45) = 16.73$, $p < 0.001$], again with no effect of psychosis history [$F(1, 16.89) = 0.04$, $p = 0.85$]. Participants with prior psychotic experiences reported only mild, transient adverse events (e.g., gastrointestinal symptoms, muscle pain), with no hallucinations or psychotic symptoms observed.

Conclusion: Ketamine was well tolerated and was associated with improvements in depressive symptoms and fluid cognition in individuals with mood disorders, regardless of prior psychotic experiences. No psychotic symptoms persisted on the days following the infusions. These findings suggest that repeated ketamine infusions may be a safe and effective intervention to enhance mood and cognition in mood disorders, including in individuals with a history of psychosis. Further studies with larger samples are needed to confirm these findings and to evaluate long-term safety and efficacy.

W68. TIRZEPATIDE PRECIPITATING ACUTE LITHIUM TOXICITY IN STABLE BIPOLAR I DISORDER

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Abstract Background: Lithium is the most efficacious treatment for bipolar disorder, yet remains underprescribed due to concerns regarding its narrow therapeutic window and primary dependence on renal elimination. Glucagon-like peptide-1 (GLP-1) and dual GLP-1/glucose-dependent insulintropic polypeptide (GIP) receptor agonists are frequently prescribed for weight loss but have been identified as potential causes of acute kidney injury (AKI), particularly in association with severe gastrointestinal symptoms. Data suggest lithium toxicity can occur following initiation of semaglutide, and the prescribing information for tirzepatide explicitly warns against concurrent administration with narrow-therapeutic-index medications, including lithium. We describe a case of lithium toxicity developed following tirzepatide initiation in a patient on stable lithium therapy for a decade.

Case Presentation: We present a 55-year-old male with bipolar I disorder, multiple psychiatric hospitalizations, and suicide attempts. Comorbidities include obesity and essential tremor. After trials of multiple psychotropics including lamotrigine, valproate, and antipsychotics, he was treated with lithium for almost a decade (600–1,200 mg/day), remaining stable. Over eight years, lithium levels were within, or slightly below, the therapeutic range (0.3–1.2 mEq/L), and serum creatinine remained between 1.0–1.3 mg/dL, with no evidence of kidney disease. Tirzepatide 2.5 mg weekly was started three months before presentation and increased to 5 mg weekly three weeks prior. After this dose increase, he developed hyporexia, nausea, and vomiting, leading to poor oral intake. He maintained lithium adherence; levels were not monitored. As the intensity of his gastrointestinal symptoms escalated, he developed new and progressively worsening cognitive deficits, odd behaviors, and worsening tremor, prompting emergency department evaluation. At an outside hospital, he was dehydrated with AKI (creatinine 2.51 mg/dL, eGFR 29) and lithium 4.1 mEq/L. After IV hydration, he transferred to our center with lithium 2.4 mEq/L and creatinine 1.5 mg/dL at admission. He was confused with impairments in attention, short-term memory, and orientation. He underwent three hemodialysis sessions over 48 hours. Lithium concentrations decreased progressively, falling to 0.3 mEq/L after the third session, and creatinine normalized. His confusion gradually diminished and overall cognitive function showed ongoing improvement. EEG showed nonspecific diffuse slowing; neuroimaging was unremarkable. Lithium was held during hospitalization.

Conclusion: This case highlights the risk of acute severe AKI and lithium toxicity associated with GLP-1/GIP receptor agonists. The unmonitored use of GLP-1 and GLP-1/GIP agonists in patients with bipolar disorder and other mental health conditions underscores the urgent need to educate prescribers of these agents and to develop clear guidance on lithium dose reduction, adjustment, and monitoring when these medications, especially long-acting formulations such as semaglutide and tirzepatide, are initiated. Such guidance is essential to prevent toxicity while preserving appropriate use of lithium as an effective mood stabilizer. As proposed by our group, several mechanisms may contribute to lithium toxicity in this context: delayed gastric emptying with altered lithium absorption, potential direct effects on renal function, and, most plausibly in this case, gastrointestinal adverse effects leading to poor oral intake, volume depletion, AKI, and reduced lithium clearance.

W69. EFFECTS OF CARIPRAZINE ON SYMPTOMS OF ANXIETY: A POOLED POST HOC ANALYSIS OF DOUBLE-BLIND CLINICAL TRIALS IN PATIENTS WITH DEPRESSION

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Abstract Introduction: Anxiety is a common and burdensome co-occurring symptom in both bipolar and unipolar depression. Cariprazine (CAR) is a dopamine D3-preferring D3/D2 and serotonin 5-HT1A receptor partial agonist approved for the treatment of manic/mixed and depressive episodes of bipolar I disorder (BP-I) and the adjunctive treatment of major depressive disorder (aMDD). Separate analyses of BP-I depression and aMDD clinical trials have suggested that CAR has effects on anxiety; however, the assessment of anxiety may be confounded by treatment-emergent adverse events (AEs) that can mimic or mask anxiety symptoms (e.g., akathisia or sedation). This pooled post hoc analysis of BP-I depression and aMDD clinical trials evaluated the effect of CAR on anxiety across indications, including adjustments for the presence of AEs to determine their impact on anxiety scores.

Methods: Data from 2 BP-I depression trials (NCT02670538 and NCT02670551) and 1 aMDD trial (NCT03738215) were pooled and analyzed by treatment groups (placebo [PBO], CAR 1.5 mg/d, and CAR 3 mg/d). The change from baseline to Week 6 in Hamilton Anxiety Rating Scale (HAM-A) total score was evaluated using a mixed model for repeated measures, with treatment group, visit, baseline HAM-A score, treatment-group-by-visit, baseline-by-visit, study, indication (aMDD vs BP-I), and treatment-group-by-indication as covariates. Additional models adjusted for the presence of AEs of akathisia (pooled terms: akathisia, restlessness) or the presence of AEs of sedation (terms: sedation, somnolence, hypersomnolence). Least squares mean differences (LSMDs), 95% CIs, and P values vs PBO were determined in the pooled intent-to-treat (ITT) population (patients who took ≥ 1 dose of study drug and had ≥ 1 post-baseline assessment). Adjustments were also repeated in individual indications as a sensitivity analysis.

Results: The pooled ITT population consisted of 952 patients from the 2 BP-I clinical trials and 751 from the aMDD clinical trial, for a total of 1,703 patients (PBO, n=568; CAR 1.5 mg/d, n=566; CAR 3 mg/d, n=569). Baseline HAM-A total scores indicated moderate anxiety on average: PBO=19.5, CAR 1.5 mg/d=20.0, CAR 3 mg/d=20.0. Without AE-related adjustments, anxiety improvements based on HAM-A total score were significantly greater at Week 6 with both CAR doses vs PBO (LSMD [95% CI]: 1.5 mg/d, -1.3 [-1.9, -0.7], $P < .001$; 3 mg/d, -0.7 [-1.3, -0.1], $P < .05$). In AE-adjusted models, change from baseline in HAM-A total score for both CAR doses vs PBO indicated similar treatment effect sizes and significance levels after adjusting for akathisia (1.5 mg/d, -1.3 [-2.0, -0.7], $P < .001$; 3 mg/d, -0.8 [-1.4, -0.1], $P < .05$) and sedation (1.5 mg/d, -1.3 [-1.9, -0.7], $P < .001$; 3 mg/d, -0.7 [-1.3, -0.1], $P < .05$). In sensitivity analyses of separate indications, results with and without adjustment were consistent for CAR 1.5 mg/d; however, CAR 3 mg/d did not reach statistical significance vs PBO.

Conclusions: CAR was associated with improvements in anxiety in pooled analyses of BP-I depression and aMDD trials. These improvements were observed even after adjusting for potentially confounding effects of treatment-emergent akathisia or sedation; however, analyses

were limited by small sample size of patients with AEs due to relatively infrequent incidence rates. Overall, these results suggest that CAR has effects on anxiety across mood disorders, which may be independent of AEs.

W70. REAL-WORLD IMPACT ON ANXIETY SYMPTOMS OF CARIPRAZINE AS ADJUNCTIVE TREATMENT IN MAJOR DEPRESSIVE DISORDER OR MONOTHERAPY IN BIPOLAR I DISORDER

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Abstract Introduction: Patients with major depressive disorder (MDD) or bipolar I disorder (BP-I) commonly experience anxiety symptoms. Cariprazine (CAR) is a dopamine D3-preferring D3/D2 and serotonin 5-HT1A receptor partial agonist approved for the treatment of manic/mixed and depressive episodes of BP-I and for the adjunctive treatment of MDD. This real-world study aimed to evaluate changes in anxiety symptoms over a 12-month period in patients diagnosed with MDD or BP-I prescribed CAR.

Methods: This retrospective cohort study analyzed electronic health records from NeuroBlu Data (1/1/2019 to 12/31/2024) to select adults with ≥ 2 diagnoses for either MDD or BP-I who were prescribed CAR (1st prescription=index date). Adjunctive CAR was required for patients with MDD, including both ≥ 1 prescription for antidepressant therapy (ADT) in the 12-months pre-index and co-prescription of ADT with CAR for ≥ 14 days post-index and the full duration of CAR exposure. Patients were required to have a Generalized Anxiety Disorder 7-item (GAD-7) score ≥ 10 (moderate to severe anxiety) ≤ 30 days pre-index (baseline) and ≥ 1 follow-up GAD-7 measure ≤ 12 months post-index, prior to the occurrence of any censoring event. Patients were excluded if they had a prior CAR prescription or schizophrenia diagnosis within 12 months pre-index, concomitant antipsychotic use at index, or absence of MDD/BP-I diagnosis within 12 months pre-index. Follow-up was censored upon CAR discontinuation, new antipsychotic exposure, schizophrenia diagnosis, or the end of the study period. Outcomes included mean GAD-7 scores and mean change from baseline to 0-2, 2-6, and 6-12 months after index and were only evaluated for patients with data available during each time window. Lower scores indicate less severe anxiety. Responses to the 7 individual GAD-7 items were also analyzed in a subpopulation where item level data were available. Each item requires patients to indicate how frequently over the last 2 weeks they have experienced a particular symptom: “not at all,” “several days,” “more than half the days,” and “nearly every day.” Categorical variables were reported as proportions, while continuous variables were presented as means with 95% CIs.

Results: The final cohort included 252 patients at baseline (MDD, n=99; BP-I, n=153); the mean (SD) age was 39.5 (13.4) years and 76% were female. Mean GAD-7 scores improved from baseline for all time windows analyzed. From baseline, mean GAD-7 scores decreased from 16.3 to 12.7 at 0-2 months (n=190, mean change from baseline [95% CI]: -3.7 [-4.5, -2.8]); from 16.4 to 12.1 at 2-6 months (n=110, mean change [95% CI]: -4.3 [-5.5, -3.1]); and from 15.9 to 11.8 at 6-12 months (n=52, mean change [95% CI]: -4.1 [-5.8, -2.4]). For patients with item-level scores available (0-2 months: n=59, 2-6 months: n=40, and 6-12 months: n=22) the proportion of

patients reporting symptoms on “more than half the days” or “nearly every day” decreased from baseline for all items at 0-2 and 2-6 months; although the sample size at 6-12 months was smaller, a decrease was still seen on all items except for the ‘feeling afraid’ item, which increased slightly.

Conclusions: In real-world clinical practice, patients with MDD or BP-I prescribed CAR showed improvements from baseline in mean GAD-7 total scores at 0-2, 2-6, and 6-12 months. These findings suggest that CAR may be associated with improved anxiety symptoms when prescribed as adjunctive therapy in MDD or as monotherapy in BP-I.

W71. ANTIPSYCHOTIC SWITCHING AMONG PATIENTS WITH BIPOLAR I DEPRESSION AFTER INITIATING CARIPRAZINE VS LUMATEPERONE: A REAL-WORLD CLAIMS-BASED STUDY

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Abstract Introduction: Switching between atypical antipsychotics (AAs) is common in patients with bipolar I disorder (BP-I), and is associated with an increased risk of relapse and hospitalization. Understanding real-world patterns of AA switching could inform prescribing practices to potentially improve clinical and economic outcomes. This study compared real-world AA switch rates in patients with BP-I depression initiating cariprazine versus those initiating lumateperone.

Methods: Commercially insured adults with BP-I depression who initiated cariprazine or lumateperone (first dispensing=index date) were identified using claims data from the Komodo Research Database (12/20/2020–11/30/2024). Patients were required to have ≥ 12 months of continuous health insurance coverage preindex (baseline period), ≥ 2 pharmacy claims for the index AA, and ≥ 3 months of follow-up postindex. Exclusion criteria included administration of a long-acting injectable antipsychotic within 3 months preindex, dispensing of an antidepressant or mood stabilizer on the index date, dispensing of a nonindex AA from 14 days preindex to 30 days postindex, or a primary diagnosis of schizophrenia during the baseline period or on the index date. Baseline demographic and clinical characteristics of AA cohorts were balanced using inverse probability of treatment weighting based on propensity scores. Rates of switching within 3, 6, 9, or 12 months postindex were calculated from the weighted cohorts, where a switch was defined as ≥ 2 postindex dispensings of a nonindex AA (or ≥ 1 such dispensing in a separate sensitivity analysis). Logistic regression models compared switch rates between cohorts using odds ratios (ORs), 95% CIs, and P values.

Results: The analysis included patients who initiated cariprazine (n=2330) or lumateperone (n=571). At each time point considered, the proportion of patients who switched to a different AA was lower among those who initiated cariprazine relative to those who initiated lumateperone; switch rates among cariprazine and lumateperone cohorts were 12.7% and 19.2% at 3 months, 20.0% and 28.1% at 6 months, 26.2% and 31.6% at 9 months, and 28.7% and 38.6% at 12 months, respectively. Compared to patients who initiated lumateperone, those who

initiated cariprazine were 39% less likely to switch by 3 months (OR [95% CI]=0.61 [0.48, 0.78], $P < .001$), 36% less likely by 6 months (0.64 [0.51, 0.80], $P < .001$), 23% less likely by 9 months (0.77 [0.60, 0.98], $P < .05$), and 36% less likely by 12 months (0.64 [0.49, 0.83], $P < .001$). ORs were also significantly in favor of cariprazine at 3, 6, and 12 months in a sensitivity analysis which relaxed the definition of a switch to ≥ 1 dispensing of a nonindex AA postindex. Patients switched to a variety of AAs, most commonly ($\geq 5\%$ for either cohort) aripiprazole (cariprazine cohort: 4.5%; lumateperone cohort: 7.0%), lurasidone (4.2%; 5.4%), and olanzapine (3.6%; 5.8%). Numerically more patients switched from lumateperone to cariprazine (4.7%) than from cariprazine to lumateperone (2.5%).

Conclusions: Among patients with BP-I depression, those who began cariprazine were significantly less likely to switch to a different AA at 3, 6, 9, and 12 months from treatment initiation compared to those who began lumateperone.

W72. COMPARATIVE EFFICACY OF BUPROPION VS SELECTIVE SEROTONIN REUPTAKE INHIBITORS IN ANTIDEPRESSANT-NAIVE, OBESE PATIENTS WITH MAJOR DEPRESSIVE DISORDER

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Abstract Background: Antidepressant drug selection in patients with co-morbid obesity is not well-studied. Observational and secondary analyses of clinical trials evaluating efficacy of antidepressants suggest that medications with noradrenergic and dopaminergic mechanisms of action may be more effective in managing symptoms of major depressive disorder (MDD) in obese patients than medications that are purely serotonergic. Bupropion, a dopamine and noradrenergic reuptake inhibitor, indicated for MDD also induces weight loss and has demonstrated efficacy in inducing remission when added to an SSRI in obese patients in secondary analyses.

Objective: The purpose of this study is to compare the efficacy of bupropion versus SSRIs in antidepressant-naïve, obese patients with major depressive disorder.

Methods: This was a retrospective observational study utilizing a global cohort of 169 Health Care Organizations grouped into a network within the TriNetX database. Adults aged 18 or over with a diagnosis of a major depressive episode and obesity were grouped into two cohorts: 1) exposure to bupropion (n=166,271) and 2) exposure to SSRIs (n=1,016,277). In both cohorts, pregnant patients given antidepressants prior to their initial MDD diagnosis were excluded. Patients who received antidepressants prior to their first exposure to bupropion or SSRI were also excluded. Both cohorts were propensity matched based on 16 covariates including demographics, comorbid conditions such as anxiety disorders, and medication use such as antipsychotic use. The primary outcome was remission of a major depressive episode. Secondary outcomes included evaluating socioeconomic and psychosocial differences between the groups. Outcomes were observed up to five years after an initial intersectional history of MDD, obesity, and antidepressant intervention.

Results: After propensity matching, each cohort yielded 165,629 patients. The primary endpoint analysis indicated a small but statistically significant difference in MDD remission rates in favor of bupropion with an absolute risk rate of 8.5% compared to 7.9% in the SSRI group (Risk Ratio [RR] 1.07, 95% CI 1.05-1.10, $p < 0.0001$). A small but statistically significant difference was observed in the secondary composite outcome of socioeconomic and psychosocial health hazards, with a higher incidence among individuals receiving SSRIs compared with those receiving bupropion with absolute risk of 6.8% and 5.8%, respectively (RR 0.86, 95% CI 0.84-0.88, log-rank $p < 0.0001$). Kaplan-Maier analysis showed that patients receiving bupropion achieved MDD remission 15% faster than those on SSRIs (Hazard Ratio [HR] 1.15, 95% CI 1.12-1.18, $p < 0.0001$).

Conclusion: In this large, propensity-matched retrospective observational cohort study of antidepressant-naïve adults with obesity and major depressive disorder, bupropion monotherapy was associated with a small but statistically significant higher rate of remission compared with SSRIs. Additionally, SSRI treatment was associated with a slightly higher incidence of socioeconomic and psychosocial health hazards. Further prospective investigation is needed to assess the clinical significance of these differences in conjunction with other objective remission indicators.

W73. EFFECT OF PSYCHEDELIC THERAPIES ON SLEEP IN PSYCHIATRIC DISORDERS: A SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMIZED CLINICAL TRIALS

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Abstract Background: Disturbances in sleep are implicated in most psychiatric disorders and are a substantial source of disability and distress. As randomized controlled trials (RCTs) of psychedelic therapies for psychiatric disorders expand, the effects of these novel interventions on sleep outcomes are yet to be systematically delineated.

Objective: This systematic review aims to synthesize the current data on changes in sleep outcomes from RCTs involving adults with psychiatric disorders following administration of serotonergic psychedelics or MDMA.

Methods: We systematically searched MEDLINE, EMBASE, Cochrane Central, PsycINFO, WHO ICTRP, Web of Science, and ClinicalTrials.gov for RCTs investigating psychedelics in psychiatric populations (search conducted 18 July 2025). Studies were included if they involved adults with a psychiatric diagnosis being administered a psychedelic (with or without therapy) in an RCT, defined as: psilocybin, lysergic acid diethylamide (LSD), DMT, 5-MeO-DMT, mescaline, or MDMA, with ≥ 1 sleep outcome at baseline and post-administration (e.g. embedded sleep item/subscale or objective measure). Data requests were sent to authors for outcomes embedded within psychiatric scales when sleep items were not reported in the literature. Effect sizes were calculated as Hedges' g for change-from-baseline to each study's primary endpoint; SD(change) used assumed $r=0.5$, and multiple within-trial sleep outcomes were combined to a

single study-level effect assuming within-study correlation ($\rho=0.5$; sensitivity varied r , ρ). Review followed PRISMA 2020 guidelines and risk of bias was assessed with ROB-2.

RESULTS: Seven RCTs (N=233 participants contributed to analysis) administering psilocybin, ayahuasca, and LSD contributed previously unreported sleep outcomes via data sharing. No eligible MDMA, DMT, 5-MeO-DMT, or mescaline RCTs contributed sleep outcome data. All outcomes were reported as embedded sleep items/subscales across 9 parent psychiatric scales rather than dedicated sleep instruments. Random-effects (REML) pooled analysis at each trial's primary endpoint demonstrated a small improvement in sleep disturbances following psychedelic administration (Hedges $g = -0.26$, 95% CI -0.49 to -0.02 ; $p=0.031$; $I^2=17.3\%$), with negative values indicating improved sleep. Sensitivity analyses were significant in 8/9 r - ρ specifications (non-significant only at $r=0.3$, $\rho=0.7$).

Discussion: Serotonergic psychedelics were associated with a small but significant improvement in sleep outcomes. Conclusions are moderated by high clinical and methodological variability across trials and low author response to data requests (7/44, 16%). Future RCTs should include dedicated sleep instruments (e.g., PSQI) to assess sleep outcomes.

W74. IMPACT OF SELTOREXANT ON COGNITIVE PERFORMANCE OF ADULTS WITH MAJOR DEPRESSIVE DISORDER WITH INSOMNIA SYMPTOMS

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Abstract Background: Many individuals with major depressive disorder (MDD) experience inadequate response to standard therapies and have residual symptoms, such as insomnia, and/or subsequent deficits in cognitive function. Cognitive deficits may contribute to negative short- and long-term functional outcomes in MDD¹. Here we evaluated cognitive performance using a novel iPad-administered cognitive test battery in adults with MDD and insomnia symptoms (MDDIS). Data are from a 26-week randomized, double-blind study comparing adjunctive treatment with the selective orexin-2 receptor antagonist, seltorexant, versus quetiapine XR in adults with MDDIS with an inadequate response to current standard antidepressant therapy.

Methods: Participants with MDDIS received either seltorexant (20 mg; n=366) or flexibly dosed quetiapine XR (150/300 mg; n=390) administered adjunctively to their standard antidepressant (SSRI/SNRI) regimen. Cognition was evaluated using the ReVeRe.D cognitive test battery, based on classical neuropsychological tests spanning cognitive domains impacted in MDD²: Symbol Sorting Test (SST), Digit Span Forward Test (DSFT), Digit Span Backward Test (DSBT), Word List Recall Test (WLRT), Visuospatial Block Recall Test (VBRT), Symbol Digit Matching Test (SDMaT), Trail Making Test (TMT-B), and the Block Maze Test (BMT). For each test, a Reliable Change Index (RCI) was derived to distinguish clinical change from measurement error and to determine the percentage of participants exhibiting a meaningful improvement ($RCI > 1.96$) or meaningful decline ($RCI < -1.96$) at 26 weeks by treatment group. Nominal p-values were generated post-hoc to assess statistical significance, uncontrolled

for multiplicity. P-values were derived from a generalized Cochran-Mantel-Haenszel (CMH) test for general association, adjusting for region, age group, and baseline rumination level.

Results: Participants in the seltorexant group had numerically greater improvements in executive functioning, verbal learning, and processing speed. On the SST number of categories completed (executive functioning), 12.4% of seltorexant participants showed meaningful improvement versus 6.5% for quetiapine XR ($p=0.04$), while meaningful decline occurred in 2.8% and 4.7% of patients ($p=0.37$), respectively. For SST perseverative errors, meaningful improvement was exhibited by 7.6% and 4.7% of the seltorexant and quetiapine XR groups ($p=0.18$), respectively. On the WLRT assessment (verbal learning) meaningful improvement was similar for seltorexant (1.7%) and quetiapine XR (1.4%; $p=0.77$). Lastly, on the SMDaT (processing speed), clinically meaningful improvement was noted in 21.1% of seltorexant- vs. 14.5% of quetiapine XR-treated participants ($p=0.07$).

Conclusions: RCI analyses support that the larger numerical gains in executive function observed at Week 26 with seltorexant compared with quetiapine XR were clinically meaningful and statistically significant. Similarly, seltorexant demonstrated clinically meaningful improvements in processing speed, with effects trending toward statistical significance. Meaningful decline was observed less frequently in each treatment group, with numeric differences in executive function favoring seltorexant. These data suggest that long-term improvements noted with seltorexant treatment in patients with MDDIS may have clinical relevance for functional cognitive impairments observed in MDDIS populations.

W75. INTERMITTENT WHITE LIGHT AT 60 HZ AS A POTENTIAL NEUROSTIMULATION APPROACH FOR DEPRESSION: EFFECTS ON EEG ACTIVITY AND SAFETY IN HEALTHY HUMAN VOLUNTEERS

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Abstract: In addition to pharmacological treatments, non-invasive brain stimulation (NIBS) represents an option for the treatment of psychiatric diseases including major depressive disorder (MDD). Intermittent white light delivered at a specified frequency is currently being investigated as a novel NIBS intervention. We have previously shown that 60-Hz white light stimulation in mice induces brain entrainment, microglia-mediated remodelling of the perineuronal net, and reactivation of juvenile-like plasticity (ref. 1). These findings suggest a potential application in MDD and warrant further investigation in humans. This study was aimed to (1) characterize neural entrainment and synchrony induced by repeated 60-Hz flickering light using EEG, and (2) evaluate the safety and tolerability of this intervention in healthy volunteers. Ethical approval was obtained from the Lower Austria Ethical Commission (GS3-EK-4/908–2024). Participants ($n=14$) were randomized to receive either 15 daily sessions (30 minutes per session; five days per

week for three weeks) of 60-Hz flickering white light (n=8) or sham stimulation, consisting of constant white light (n=6). Side effects were self-reported on a daily basis and a Likert-like questionnaire was administered to investigate the tolerability of the stimulation. Brain activity was tracked using an 8-channel EEG setup during stimulation sessions n. 1, 5, and 15. Data were analyzed with parametric (t-test and ANOVA) or non-parametric (Wilcoxon's rank sum and Kruskal-Wallis) tests, according to normality. Ordinal questionnaire responses were evaluated using the Wilcoxon rank-sum test. Proportions were compared using Fisher's exact test. Participants were young (sham: 25.5 ± 2.59 and active: 28.63 ± 6.37 years of age; $p=0.6$), balanced across sexes (sham: 50%, active: 62.5% female; $p=1$), mostly Caucasian (sham: 66.7%, active: 100%, $p=0.16$). Both constant and 60-Hz flickering light stimulation were well tolerated ('the stimulation was overall tolerable', average score sham: 4.5 ± 0.55 , active: 4.8 ± 0.41 , $p=0.95$). The majority of participants (sham: 83.3%, active: 87.5%, $p=1$) reported side effects, which were minor (such as sleepiness, headache, and dry eyes) and did not differ statistically across groups (total number of side effects: 20 in sham and 18 in active, $p=1$). EEG confirmed that 60-Hz flickering light induced neural entrainment across the occipital, parietal, temporal, and frontal cortex, with high synchrony. The entrainment signal showed a significant reduction by day 19 (last stimulation session) relative to day 1. This decline, accompanied by an emerging desynchronization, is consistent with neural habituation and may reflect homeostatic plasticity mechanisms. We conclude that repeated 60-Hz flickering white light induces robust neural entrainment and large-scale synchrony in the human brain, with evidence of adaptive plastic changes and no major safety concerns (ref. 2). Together with prior evidence that 60-Hz activity modulates emotional processing and cognition, these findings support further examination of this approach as a potential intervention for depressive disorders. Feasibility studies in patients are currently ongoing in the clinic (Lux study, NCT06922812) and at home (Neon study, NCT07111390).

W76. SAFETY AND EFFICACY OF FULL AND HALF-DOSE NEURONAVIGATED ACCELERATED THETA BURST TMS IN TREATMENT-NAÏVE ADOLESCENT DEPRESSION

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Abstract Rates of adolescent depression have risen to crisis levels in recent years, yet first-line treatment options remain limited by modest efficacy, delayed onset, and a considerable side-effect burden. There is a pressing need for novel, safe, and rapid acting interventions. Accelerated fMRI-guided intermittent theta burst stimulation (aiTBS) delivering 10 daily TMS sessions over 5 consecutive days has demonstrated high efficacy, rapid onset, and minimal side effects in adults with treatment-resistant depression leading to FDA clearance in this population. We investigate this aiTBS protocol as a first-line intervention in adolescents with major depression without concurrent or prior pharmacotherapy or psychotherapy. To investigate convenience, tolerability, and dose finding in this novel population, one arm of this pilot trial received a half-dose aiTBS protocol that maintains standard stimulation parameters but reduces the number of daily sessions from 10 to 5.

Methods: All participants receive an fMRI at baseline for individualized precision targeting of the left dorsolateral prefrontal cortex. Primary outcomes include safety, tolerability, and efficacy assessed through systematic side-effect checklists, adverse-event monitoring, and change in the Children's Depression Rating Scale-Revised (CDRS-R) from baseline to one month following treatment. Secondary outcomes include preference, convenience, and overall acceptability of aiTBS as a first-line treatment in this population. Semi-structured interviews with participants and parents as well the Treatment Acceptability Questionnaire are conducted at baseline, immediately post-treatment, and at 1-, 3-, and 6-month follow-up visits. Post-treatment fMRIs measure exploratory changes in functional connectivity with treatment.

Results: To date, 18 participants have been enrolled. 8 have failed screening either due to psychiatric comorbidity or dental hardware which disrupted fMRI targeting. Two participants dropped out prior to treatment, both due to time commitment. 7 participants have completed treatment: 3 full-dose and 4 half-dose. One half-dose participant was unable to tolerate the stimulation intensity consistent with the protocol. Of the 6 participants who received the full or half-dose protocol, 5 met depression remission criteria (≤ 28 CDRS-R raw score) with one only meeting response criteria missing remission by 1 point on the CDRS-R scale. 4 of these participants completed their 3-month follow up visits at which time they maintained depression remission criteria.

Conclusions: Preliminary findings suggest that this trial is feasible and that aiTBS is safe and effective as a first-line treatment for adolescent depression. Preliminary efficacy results suggest no difference between the full-dose and half-dose protocol opening the door to a more convenient and lower cost option for this population. One participant who did not achieve remission at the one-month follow-up received the half-dose protocol, but was unable to tolerate an appropriate treatment intensity.

W77. REAL-WORLD EVIDENCE FROM LEGAL PSILOCYBIN-ASSISTED SERVICES IN OREGON: PSYCHEDELIC PREPAREDNESS AND EXPERIENTIAL PREDICTORS OF MENTAL HEALTH OUTCOMES

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Abstract Background: Psychedelic-assisted therapies are gaining increasing attention as clinical trials report beneficial effects across psychiatric conditions. In parallel, regulatory landscapes are shifting, with facilitated psilocybin sessions now legally available in Oregon. As access expands, there is a growing need to better understand and predict psychedelic experiences to mitigate risk and optimize therapeutic benefits. Accumulating evidence suggests that qualitative features of the acute psychedelic experience are associated with downstream positive and negative mental health outcomes. Psychological “pre-state,” including set, intention, and therapeutic rapport, has emerged as a modifiable determinant of post-session outcomes. The Imperial Psychedelic Predictor Scale (iPPS) is a validated self-report instrument designed to operationalize these constructs and predict features of the acute psychedelic experience. To date, the relationship

between iPPS domains and mental health outcomes in real-world legal psychedelic services has not been examined.

Methods: The current study was a naturalistic, IRB-approved observational study of adults who completed a psilocybin session at licensed service centers in Oregon. Eighty-eight participants completed validated self-reported outcome measures at two timepoints: baseline (pre-session) and 30 days post-session. Outcomes included depressive symptoms (Patient Health Questionnaire-8), anxiety symptoms (Generalized Anxiety Disorder-7), and psychological well-being (World Health Organization - Five Well-being Index). Experiential predictors were measured using the iPPS, including subscales assessing psychological set, intention, and therapeutic rapport. Linear mixed-effects models were fit separately for each outcome, including fixed effects for timepoint and iPPS subscales, and a random intercept for participants. These models were specified to examine process-level associations while adjusting for overall change over time.

Results: Timepoint was a significant predictor across all models, reflecting overall improvements in depression, anxiety, and well-being following a psilocybin session. Beyond these temporal effects, select iPPS domains were independently associated with mental health outcomes. Higher Intention scores (clarity of personal intention for the experience) were associated with lower depressive symptom severity ($b = -0.11$, $p = 0.03$). For anxiety, both Intention and Feeling (positive perceived relationships with others present during the session) were associated with lower symptom severity (Intention: $b = -0.10$, $p = 0.03$; Feeling: $b = -0.21$, $p = 0.04$). No iPPS domains were significantly associated with well-being.

Discussion: Beyond overall symptom improvement over time, clarity of intention and positive therapeutic relationships were independently associated with lower depression and anxiety severity, highlighting these factors as key process-level correlates. Interestingly, positive therapeutic relationships emerged as a significant correlate only in the anxiety model, which may indicate that interpersonal safety and rapport are especially relevant for anxiety-related symptom processes. iPPS domains capturing these constructs may serve as meaningful indicators of psychological context and offer actionable targets for optimizing preparation practices and social context within real-world legal psychedelic care models.

W78. PROTOCOL FOR REAL WORLD SAFETY AND EFFECTIVENESS STUDY OF PSILOCYBIN THERAPY

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Abstract Background: Psilocybin therapy has demonstrated safety and efficacy in controlled clinical trials for a range of mental health conditions, but its real-world application remains largely unexplored. Clinical research has relied on tightly controlled studies with strict inclusion criteria, limiting generalizability. With the legalization of psilocybin services in Oregon and other U.S. states, there is an urgent need to examine its safety and effectiveness in broader, real-world populations, including individuals with comorbidities commonly excluded from most

clinical trials. Therefore, this study aims to evaluate the real-world safety and effectiveness of psilocybin therapy delivered to a diverse population at licensed Oregon service centers and to identify demographic and psychological factors that predict both therapeutic outcomes and adverse events.

Methods: This prospective, longitudinal observational study collects data from individuals receiving psilocybin therapy at licensed service centers in Oregon. Participating centers recruit individuals via email invitation to complete surveys, assessing safety and effectiveness, administered at baseline, 3 days (acute measures only), 1 month (primary endpoint), 3 months, 6 months, and 12 months (long-term follow-up) post-treatment. Exclusion criteria are minimal to reflect real-world clinical diversity. Information is being collected about set and setting, such as number of facilitators, therapeutic rapport and therapeutic modality. All participating individuals complete validated measures of primary mental health outcomes [anxiety (GAD-7), depression (PHQ-9), well-being (WHO-5), psychological flexibility (Psy-Flex), substance use (NIDA-Modified ASSIST and AUDIT-C)], adverse effects (SPSEI), and acute experience measures [mystical experience (MEQ-4), self-compassion (SCS-12), decentering (MPoD-S), emotional breakthrough (EBI), challenging experiences (CEQ-7), and psychological insight (PIQ)]. Participants may also complete additional validated assessments tailored to their presenting concern, in accordance with diagnoses stated in the DSM-5-TR (e.g., individuals with posttraumatic stress disorder complete the PCL-5). Proportions, means, and standard deviations will be presented for questions about effectiveness, safety, and key demographics. For safety data, means, proportions, and MCID changes will be presented. Pre-to-post changes on mental health outcomes will be evaluated using linear mixed models, and generalized linear models (GLM) will test baseline, acute, and psychological predictors of therapeutic response and adverse effects. Only mental health and psychological instruments that demonstrate significant changes from baseline to 1 month will be entered into the GLM.

Discussion: Findings from this study will clarify the real-world safety and effectiveness of psilocybin therapy, characterize the prevalence and nature of adverse outcomes, and identify individual- and treatment-level factors that minimize risk and promote positive and durable therapeutic outcomes. This study will gather critical evidence to inform public policy, minimize potential societal harm, and support the development of evidence-based guidelines for the safe, personalized, and optimized delivery of psilocybin therapy.

W79. REAL-WORLD EXPERIENCE AND IMPACT OF FATIGUE IN NARCOLEPSY AND IDIOPATHIC HYPERSOMNIA FROM THE ASPIRE SURVEY STUDY

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Abstract Purpose: Fatigue, characterized by exhaustion and low energy, is a common and disruptive symptom in narcolepsy and idiopathic hypersomnia (IH) that patients differentiate from sleepiness and that may not be addressed by current treatments. The ASPIRE study presented here examined the impact of fatigue on work productivity and health-related quality of

life (HRQoL) among individuals diagnosed with narcolepsy type 1 (NT1), narcolepsy type 2 (NT2), and IH.

Methodology: Adults in the US who reported a clinical diagnosis of NT1, NT2, or IH participated in an online survey. Participants were recruited through Rare Patient Voice, Hypersomnia Foundation, and Sleep Consortium. Severity of fatigue over the prior week was assessed with the PROMIS-Fatigue Short-Form 6a (PROMIS-Fatigue), for which standardized T-scores range from 33.4-76.8 and higher scores indicate more severe fatigue. Participants were divided into two subgroups: those with mild-to-severe fatigue (T-score ≥ 55) and those with normal fatigue (T-score < 55). Work and activity impairment were assessed with the Work Productivity and Activity Impairment Questionnaire: Specific Health Problem, which examines absenteeism, presenteeism, and activity impairment over the prior week. HRQoL was evaluated using the EQ-5D-5L (score range is 0-1, with higher scores indicating better HRQoL) and the EQ-Visual Analogue Scale (EQ-VAS) (score range is 0-100, with higher scores indicating better HRQoL).

Results: A total of 366 participants (NT1, n=116; NT2, n=127; IH, n=123) were included in the survey. Participants had a mean age of approximately 40 years, more than half (55%) of the participants were employed, and over 80% were female. About 60% of participants received treatment with non-amphetamine wake-promoting agents. Most participants (91%) reported mild-to-severe fatigue with a mean (SD) PROMIS-Fatigue score of 65.74 (7.52). Compared with participants who reported normal fatigue, those with mild-to-severe fatigue had statistically significant increases in work impairment (59% vs 21%; $p < 0.001$) and activity impairment (66% vs 28%; $p < 0.001$). Additionally, those with mild-to-severe fatigue had statistically significant decreases in mean HRQoL scores compared with those with normal fatigue (EQ-5D-5L: 0.61 vs 0.88 [$p < 0.001$]; EQ-VAS: 58 vs 78 [$p < 0.001$]). These findings were consistent when examined by disease subgroup.

Importance: Results of the ASPIRE survey showed that most participants in this general sample with NT1, NT2, and IH reported mild-to-severe fatigue. Presence of mild-to-severe fatigue was associated with negative impacts on work productivity, daily activity, and HRQoL. These findings reveal the burden of fatigue across multiple areas of people's lives and highlight this symptom as an unmet need in the treatment of narcolepsy and IH.

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W80. ACTIVATION OF σ 1R AND 5-HT2A PATHWAYS MODULATES NEUROINFLAMMATION, GLIAL REPAIR PROGRAMS, AND BBB RESPONSES IN DEMYELINATING CNS MODELS

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Abstract Chronic, compartmentalized neuroinflammation limits endogenous repair and contributes to progressive disability in demyelinating disorders such as multiple sclerosis (MS). While sigma-1 receptor (σ 1R) and serotonin 5-HT2A receptor signalling are well characterized in neuropsychiatric pharmacology, their roles in regulating CNS-intrinsic inflammatory and repair mechanisms remain insufficiently defined. The purpose of this study was to determine

whether activation of σ 1R- and 5-HT2A-linked pathways modulates neuroinflammatory signalling and glial repair programs under demyelinating conditions. We employed organotypic cerebellar slice cultures subjected to lysophosphatidylcholine (LPC)-induced demyelination to assess inflammatory signalling, cytokine release, and glial responses. LPC exposure induced robust NF- κ B-associated inflammatory activation accompanied by increased release of TNF α and IL-1 β and loss of myelin-associated proteins. Treatment with N,N-dimethyltryptamine (DMT), a dual σ 1R/5-HT2A agonist, significantly attenuated NF- κ B signalling, reduced pro-inflammatory cytokine release, and preserved expression of the myelin marker CNPase. At the cellular level, DMT promoted oligodendrocyte progenitor cell (OPC) maturation, characterized by suppression of progenitor-associated transcriptional programs and increased expression of myelin-associated genes, including CNPase and MBP. In parallel, DMT enhanced microglial cholesterol phagocytosis, consistent with a shift toward a repair-permissive microglial state. These effects were ligand-specific and were not reproduced by other serotonergic or σ 1R-active compounds, indicating engagement of a distinct receptor-linked signalling axis. Together, these findings establish σ 1R- and 5-HT2A-linked signalling as a CNS-intrinsic regulatory axis that directly couples neuropsychiatric receptor pharmacology to modulation of neuroinflammation and glial plasticity. By demonstrating ligand-specific control of inflammatory and repair-relevant processes in CNS-resident cells, this work advances the field by providing mechanistic insight into how receptor targets traditionally studied in psychiatric contexts can be leveraged to develop CNS-directed, non-immunosuppressive therapeutic strategies for chronic neuroinflammatory and demyelinating disorders.

W81. EXAMINING THE IMPACT OF TRAUMA ON KETAMINE'S EFFICACY IN BIPOLAR I/II DEPRESSION: A SECONDARY ANALYSIS FROM A RANDOMIZED, MIDAZOLAM-CONTROLLED TRIAL

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Abstract Background: Childhood trauma and comorbid post-traumatic stress disorder (PTSD) are highly prevalent in bipolar disorder (BD) and are consistently associated with greater illness severity and poorer response to pharmacological treatments. However, it remains unclear whether childhood trauma or PTSD comorbidity moderate response to ketamine, and whether ketamine may exert therapeutic effects on trauma-related symptoms independent of depressive symptoms.

Methods: Adults with treatment resistant bipolar I/II depression (TRBD; n=63) were randomized to receive four infusions over two weeks of either ketamine (0.5-0.75 mg/kg) or midazolam (0.02-0.03 mg/kg). Depressive symptoms were measured using the Montgomery-Åsberg Depression Rating Scale (MADRS), and PTSD symptoms using the PTSD Checklist for DSM-5 (PCL-5) at baseline, Day 14, and Day 28. Comorbid PTSD was defined as a PCL-5 score ≥ 33 with symptom endorsement consistent with DSM-5 cluster criteria. Childhood trauma was assessed with the Childhood Trauma Questionnaire (CTQ) and operationalized as total trauma severity (CTQ total score), trauma subtype severity (CTQ subscale scores), and maltreatment load (count of trauma subtypes meeting moderate-to-severe thresholds). Linear mixed-effects

models examined whether trauma variables or baseline PTSD status moderated antidepressant response. Additional models assessed PTSD symptom trajectories in participants with comorbid PTSD, adjusting for depressive symptom change, including exploratory analyses by PTSD symptom cluster.

Results: Greater childhood trauma severity ($F(1, 74.05) = 6.01, p = .017$) and maltreatment load ($F(1, 70.85) = 4.41, p = .039$) were significantly associated with higher depressive symptom severity. However, no significant treatment $\times$ time $\times$ trauma interactions emerged for total trauma severity ($F(2, 118.61) = 0.44, p = .644$), maltreatment load ($F(2, 116.24) = 0.06, p = .941$), or any trauma subtype (all $p > .05$), indicating that childhood trauma did not moderate antidepressant response to ketamine versus midazolam. Similarly, PTSD comorbidity did not moderate antidepressant response ($F(2, 152.24) = 0.144, p = .866$), though baseline PTSD status was associated with greater overall MADRS severity ($F(1, 187.97) = 4.98, p = .027$). Among participants with comorbid PTSD ($n = 27$), a significant treatment $\times$ time interaction emerged for total PCL-5 scores ($F(2, 44.59) = 6.19, p = .004$), with ketamine-treated participants showing significantly greater reductions in PTSD symptoms compared to midazolam by Day 28 (mean difference = -13.04 , 95% CI $[-22.87, -3.21]$, $p = .010$). This effect remained significant after adjusting for concurrent changes in MADRS scores ($F(2, 41.93) = 6.52, p = .003$). Cluster-specific analyses showed significant treatment $\times$ time effects for intrusion ($F(2, 38.45) = 4.52, p = .017$), avoidance ($F(2, 41.04) = 10.23, p = < .001$), and negative alterations in cognition/mood ($F(2, 44.36) = 3.36, p = .044$), but not hyperarousal ($F(2, 43.23) = 2.33, p = .110$).

Significance: Compared to midazolam, ketamine demonstrated superior antidepressant efficacy in TRBD patients regardless of childhood trauma history or comorbid PTSD. Importantly, ketamine also led to sustained reductions in PTSD symptoms that were independent of depressive symptom improvement. These findings highlight the therapeutic potential of intravenous ketamine for trauma-exposed individuals with TRBD.

W82. REAL-WORLD PERSISTENCE ON OLANZAPINE/SAMIDORPHAN VERSUS OTHER ORAL SECOND-GENERATION ANTIPSYCHOTICS IN PATIENTS WITH SCHIZOPHRENIA

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Abstract Background: Poor persistence and adherence to oral antipsychotic medications are common in clinical practice and are associated with increased relapse risk. Treatment continuity may indicate that a medication has an acceptable balance of symptom relief and tolerability over

time for a given individual. Prior real-world studies showed that initiating a combination of olanzapine and samidorphan (OLZ/SAM) vs olanzapine in adults with schizophrenia or bipolar I disorder is associated with greater adherence, longer treatment persistence, and fewer disease-related hospitalizations and emergency department visits (proxies for psychiatric relapse). This study evaluated real-world persistence and adherence with OLZ/SAM compared with other oral second-generation antipsychotic (SGA) medications among patients with schizophrenia.

Methods: This retrospective claims analysis used Komodo Healthcare Map data (10/18/2020–12/31/2024). Data from Medicaid-insured adults with schizophrenia and ≥ 1 claim for OLZ/SAM or a comparator SGA (aripiprazole, brexpiprazole, cariprazine, lumateperone, lurasidone, olanzapine, or risperidone) were included. OLZ/SAM claims were prioritized to set the index date. Inverse probability treatment weighting (IPTW) was used to balance cohorts on key demographic/clinical variables. Proportions of patients persisting on the same medication as on the index date for the full study period, durations of persistence (days from index date to discontinuation date [using a ≥ 45 -day gap to define treatment discontinuation] or to end of follow up), and adherence (medication possession ratio [MPR] ≥ 0.80) were compared among the OLZ/SAM and comparator oral SGA cohorts during the 12-month follow-up period. P values ≤ 0.05 were considered statistically significant.

Results: A total of 45,566 patients with schizophrenia were included (OLZ/SAM, $n=1244$; aripiprazole, $n=11,995$; brexpiprazole, $n=421$; cariprazine, $n=1650$; lumateperone, $n=423$; lurasidone, $n=2030$; olanzapine, $n=14,630$; risperidone, $n=13,173$). Comparisons to brexpiprazole and lumateperone were not assessed due to low numbers of patients treated with these medications. In IPTW-adjusted analyses, patients initiating OLZ/SAM vs other oral SGAs were significantly more likely to remain on treatment at 12 months (odds ratio [OR] range, 1.57–2.71; all $P < 0.001$). Mean duration of treatment persistence was significantly longer with OLZ/SAM (201.8 ± 143.6 days) vs all comparators (range, 132.1 ± 129.5 – 174.1 ± 138.8 days; all $P < 0.001$). At least 50% of OLZ/SAM patients remained on treatment for 180 days or longer vs a median duration of 67 to 121 days for comparator oral SGAs. Patients initiating OLZ/SAM vs comparator oral SGAs were also twice as likely to be adherent (MPR ≥ 0.80 OR range, 1.33–2.53; all $P < 0.001$).

Conclusion: OLZ/SAM was associated with a statistically significantly higher proportion of patients persistent on treatment, longer duration of persistence, and greater adherence during 12-month follow-up vs all comparator oral SGAs. More consistent antipsychotic medication use over time may translate into meaningful improvements in outcomes associated with schizophrenia.

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W83. USING ARTIFICIAL INTELLIGENCE/MACHINE LEARNING AND REAL-WORLD DATA TO IDENTIFY PATIENTS WITH SCHIZOPHRENIA FOR WHOM AN ARIPIPRAZOLE MONOHYDRATE LAI IS LIKELY TO BE A FAVORABLE TREATMENT OPTION

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Abstract Background: Schizophrenia (SCZ) is a complex psychiatric condition that disrupts all aspects of life – from cognitive functioning to social relationships to professional attainment. With symptoms appearing typically in adolescence or early adulthood, identifying effective treatments earlier in the patient journey can have profound impact on reducing lifetime and disease burden.¹ Currently, real-world data to support clinicians in making personalized patient treatment decisions is limited. This study aimed to leverage large US electronic health records (EHR) and claims data, and machine learning (ML) methods to identify demographic, clinical, specific treatment choice and timing factors associated with favorable treatment response to aripiprazole monohydrate long-acting injectables (LAIs) in early-stage schizophrenia.

Methods: This prognostic study used real-world 2022-2025 data from a large, integrated EMR and open claims US database in the Atropos Evidence Network™ covering all sites of care including pharmacy.² The ML approach used targeted minimum loss-based super learning ensembles to incorporate drivers of observed treatment selection and outcomes in predicting optimal treatment selection. The model was trained on 70% of the real-world dataset and validated on the remaining 30%. To assess the impact of time to treatment initiation with antipsychotics (APs), each patient's index treatment was defined as the last AP treatment started within 3 years of initial SCZ diagnosis and patients needed ≥1 year follow-up. The primary treatment success metric was lack of inpatient admission (any cause) and AP treatment regimen change (switch or stop). To test robustness, sensitivity analyses were performed (different datasets, study operational definitions, statistical and ML techniques).

Results: Among the 97,215 (validation sample n=28,931) patients starting AP treatment within 3 years of initial SCZ diagnosis and having ≥1 year of follow-up, mean age was 43±16 years, 57% were male, 36% had substance use, 20% used anticholinergics in the year prior to index date. Mean time from SCZ diagnosis to index AP was 1.24±0.98 years. The most common index treatment was an oral atypical AP (43%). Overall, 62% of patients met primary treatment success (no hospitalization, no regimen change at 1 year follow-up). The most important predictor of treatment selection was anticholinergic use in the 3 months prior to index date. The most relevant treatment success predictors were recent patterns of inpatient and emergency room use. The model was able to distinguish between oral therapies and aripiprazole monohydrate LAIs as well as between aripiprazole once monthly [AOM] and aripiprazole 2-month Ready to Use [Ari 2MRTU]. ML-proposed optional treatments suggested aripiprazole monohydrate LAIs should be used more often and earlier after SCZ diagnosis. Based on ML technique and parameters, the

model favored Ari 2MRTU, especially among patients who were recently diagnosed and had any inpatient admission. Predicted treatment success (if patients used ML-proposed optimal treatment for their individual characteristics) was 72% (95%, CI: 71%-74%), which was significantly higher than the overall observed success (62%, $p < 0.001$).

Conclusion: Patients with recent SCZ diagnosis and any inpatient admission are likely to benefit from earlier initiation of AOM or Ari 2MRTU. This ML predictive approach should be refreshed in the future as more AP treatment data becomes available.

W84. ENDOCRINE BIOMARKERS OF SUICIDE RISK IN SCHIZOPHRENIA

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Abstract Background: Suicide is one of the major causes of death in individuals with schizophrenia. Recent research has begun to explore biological biomarkers that may potentially determine which patients with schizophrenia have an increased risk of suicide. This could potentially offer clinical benefit through better risk assessment and, subsequently, tailored treatment options that can reduce mortality. There is substantial evidence that has investigated the association between inflammatory biomarkers and mechanisms involved with suicide in schizophrenia. However, there remains a lack of research investigating endocrine and metabolic biomarkers. Therefore, investigating the endocrine system for this purpose may shed light on both the pathophysiology of schizophrenia and the biological mechanisms that contribute to suicide risk among this population.

Methods: A PubMed search was conducted to find studies assessing endocrine or metabolic biomarkers related to suicidal ideation, suicide attempts, or suicide deaths in people with schizophrenia. From this search, 226 studies were found. The screening of titles yielded 31 studies, and after reviewing the abstracts of these 31 studies, 14 studies were found that were directly relevant to the chosen topic.

Results: The results showed that multiple endocrine systems appear to be dysfunctional in individuals with schizophrenia who exhibit suicidal behaviors. Endocrine Biomarkers included 1) alterations in hypothalamic-pituitary-adrenal (HPA) axis function were detected, with several studies demonstrating elevated baseline and post-dexamethasone cortisol levels in patients with prior or future suicide attempts, although findings regarding dexamethasone non-suppression were mixed, 2) thyroid axis hormone level abnormalities were also observed: suicidal ideation was associated with elevated free thyroxine levels, 3) gonadal axis abnormalities included lower testosterone levels in subgroups who died by violent suicide attempts, 4) reduced parietal cortical pregnenolone levels were reported post-mortem in patients with schizophrenia who had died by suicide. Of note, prolactin and BDNF levels were not associated with suicidality.

Discussion: These findings demonstrate that suicide in schizophrenia appears to be associated with dysfunction of multiple endocrine pathways. While the current research does not establish causality, the findings indicate biologically plausible pathways that require additional investigation and may lead to a re-evaluation of the relationships between endocrine function, psychosis pathophysiology, and suicide risk. Thus, endocrine markers may facilitate the early identification of high risk of suicide in patients with schizophrenia.

W85. CLOZAPINE'S ANTAGONISM IS ROBUST AGAINST KNOWN DRD2 MUTATIONS

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Abstract Schizophrenia is among the top 15 causes of disability worldwide, affecting approximately 3.7 million adults in the United States alone and creating over \$300 billion in economic costs. Despite advancements in treatment, schizophrenia remains challenging to manage, with a recovery rate as low as 13%. Clozapine remains the gold standard pharmacological therapy for treatment-resistant schizophrenia (TRS). While research suggests that up to 40% of patients with TRS respond to clozapine, its use is limited. Given its rare but life-threatening side effects, clozapine is often not used as a first-line agent. Current clinical practice continues to rely heavily on a trial-and-error approach in antipsychotic selection in treating schizophrenia, and the responsiveness varies greatly in individuals. In our study, we combine both in silico and in vitro techniques to examine 14 frequently observed mutations of the human DRD2 receptor and their effects on antipsychotic-DRD2 receptor dynamics. We compared the effects of these genetic variants on clozapine-induced DRD2 antagonism with other frequently used antipsychotics. Using Bioluminescence Resonance Energy Transfer (BRET), we quantitatively measured the functional activation of these DRD2 mutants to dopamine in HEK293T cells. Among the 14 DRD2 SNPs and 10 antipsychotics we screened, 11 out of the 14 SNPs significantly changed promazine's DRD2 antagonism; 9 out of the 14 SNPs significantly changed pimozide's DRD2 antagonism; 6 out of the 14 SNPs significantly changed fluphenazine's DRD2 antagonism; and 4 out of the 14 SNPs significantly changed perphenazine's DRD2 antagonism. Critically, none of the 14 SNPs significantly altered clozapine's DRD2 antagonism. Here we provide the first functional cellular evidence of clozapine's molecular resilience to DRD2 genetic variation, potentially explaining its robust clinical efficacy in treating patients with TRS.

W86. IMPACT OF NEGATIVE SYMPTOMS ON HEALTHCARE RESOURCE UTILIZATION AND COSTS IN SCHIZOPHRENIA: A REAL-WORLD DATA ANALYSIS

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Abstract Introduction: Negative symptoms in schizophrenia are present in approximately 60% of individuals and are associated with adverse patient outcomes. Understanding healthcare resource utilization (HCRU) patterns and economic burden associated with negative symptoms may optimize intervention opportunities and resource allocation. This study examined HCRU and cost differences between adults with and without negative symptoms in schizophrenia using real-world data.

Methods: This retrospective cohort study analyzed electronic health records from NeuroBlu Data (V24R5) linked with a US-based, de-identified, longitudinal medical and pharmacy administrative claims database (1999-2024). Individuals aged ≥ 18 years diagnosed with schizophrenia were included if they had ≥ 1 record of a Mental Status Examination, Brief Negative Symptom Assessment, or Natural Language Processing label indicating negative symptom status linked to their schizophrenia diagnosis. Healthcare utilization and cost outcomes were reported as totals and stratified by setting (inpatient [IP], outpatient [OP], and emergency [ED]). Negative binomial regression models with inverse probability treatment weighting were used to calculate incidence rate ratios (IRRs) for healthcare utilization outcomes, adjusted for demographic and clinical characteristics, psychopharmacological treatments, and insurance type. Cost ratios (CRs) were estimated using gamma regression with zero-inflation models where needed, adjusting for the same covariates.

Results: The linked cohort included 2616 adults (1774 with negative symptoms), 4.4% of the NeuroBlu Data eligible sample. Total HCRU was similar between patients with and without negative symptoms (IRR: 1.05; 95% CI: 0.97-1.14; $P=0.19$), but analyses by setting showed increased utilization of acute services (IRR [IP]: 1.19; 95% CI: 1.03-1.37; $P=0.02$); IRR [ED]: 1.43; 95% CI: 1.24-1.66; $P < 0.001$). Total healthcare cost was higher among patients with negative symptoms than controls (CR: 1.20; 95% CI: 1.05-1.37; $P=0.01$), which was driven by observed cost increase of OP services (CR: 1.16; 95% CI: 1.01-1.32; $P=0.03$). No statistically significant cost differences were observed for acute services (IP/ED), albeit the estimates suggested a trend toward increased IP costs for patients with negative symptoms (CR [IP]: 1.17; 95% CI: 0.99-1.39; $P=0.06$).

Conclusions: In this linked cohort, negative symptoms in schizophrenia were associated with a crisis-driven pattern of healthcare utilization, characterized by significantly higher rates of ED and IP admissions. Although acute visits occurred more often in the negative symptoms cohort, the increased volume did not translate into statistically significant cost increases, suggesting that individual encounters may be less resource intensive. Conversely, the OP visit frequency was similar to those without negative symptoms, yet costs were significantly higher, indicating that patients with negative symptoms require more complex management during routine visits. The higher prevalence of negative symptoms identified in this study compared with prior literature suggests that our cohort captures a broader spectrum of negative symptomatology than reported in other studies.

W87. ONSET, DURATION, AND INCIDENCE OF ADVERSE EVENTS BY DOSE AND TITRATION SCHEDULE OF XANOMELINE AND TROSPIMUM CHLORIDE

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Abstract Introduction: Xanomeline and trospium chloride (KarXT) is approved by the U.S. Food and Drug Administration for the treatment of schizophrenia in adults. KarXT combines the dual M1/M4-preferring muscarinic receptor agonist xanomeline with the peripherally restricted pan muscarinic receptor antagonist trospium chloride to reduce side effects related to xanomeline activation of peripheral muscarinic receptors. The efficacy and safety of KarXT have been demonstrated in the EMERGENT clinical trials and a phase 4 trial with slower titration to evaluate tolerability of administration with and without food. The aim of this post hoc analysis was to compare the onset, duration, and incidence of treatment-emergent adverse events (TEAEs) by KarXT dose (100 mg/20 mg and 125 mg/30 mg twice daily [BID]) and titration schedule with data from these completed trials.

Methods: The phase 4, inpatient, open-label “food effect” trial (NCT06572449) enrolled adults with schizophrenia, Positive and Negative Syndrome Scale (PANSS) total score ≤ 80 , and Clinical Global Impression-Severity (CGI-S) score ≤ 4 . Over weeks 1-4, participants began KarXT treatment at 50 mg/20 mg BID (days 1-7), followed by 100 mg/20 mg (days 8-14), and then increased to a maximum of 125 mg/30 mg (cohort 1) or continued with 100 mg/20 mg (cohort 2) (days 15-28). The phase 2 EMERGENT-1 (NCT03697252) and phase 3 EMERGENT-2 (NCT04659161) and EMERGENT-3 (NCT04738123) inpatient, 5-week, randomized, double-blind, placebo-controlled trials enrolled adults with a confirmed DSM-5 diagnosis of schizophrenia and a recent worsening of psychosis warranting hospitalization, PANSS total score ≥ 80 , and CGI-S score ≥ 4 . BID dosing of KarXT began at 50 mg/20 mg (days 1-2), followed by 100 mg/20 mg (days 3-7), and increased to a maximum of 125 mg/30 mg (days 8-35). Food effect trial analyses of TEAEs by maximum KarXT dose and titration schedule were restricted to weeks 1-4; results from the EMERGENT trials were pooled. Efficacy was measured as a decrease in PANSS total score.

Results: In the food effect trial, TEAEs occurred in 69.9% (KarXT maximum dose: 100 mg/20 mg) and 59.0% (KarXT maximum dose: 125 mg/30 mg) of participants; in pooled EMERGENT, rates were 77.8% and 67.1%, respectively. Peak incidence of procholinergic and anticholinergic TEAEs coincided with transition to the KarXT 100 mg/20 mg dose (food effect: week 2; pooled EMERGENT: days 3-7); incidence of TEAEs plateaued or decreased with transition to the KarXT 125 mg/30 mg dose. Duration of nausea was longer for those maintained on KarXT 100 mg/20 mg in both data sets. PANSS total score decreases were observed with the 100 mg/20 mg and 125 mg/30 mg doses in both study populations.

Conclusions: Overall, the incidence and duration of TEAEs appear to be similar regardless of titration speed to KarXT 125 mg/30 mg BID. However, the data suggest that the duration of certain TEAEs is longer when individuals remain at 100 mg/20 mg BID, potentially due to the higher ratio of X to T of 5:1 vs 4.1:1. In some circumstances, potential improvements in tolerability may be seen with a more rapid titration and/or uptitration to KarXT 125 mg/30 mg BID.

W88. SUVN-L1101142, A MUSCARINIC M4 POSITIVE ALLOSTERIC MODULATOR (M4 PAM) FOR THE TREATMENT OF PSYCHOSIS-RELATED DISORDERS AND CONDITION

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Abstract: The muscarinic M4 receptor subtype shows the highest expression in brain regions such as the hippocampus, striatum, and prefrontal cortex, which are implicated in psychosis. Preclinical and clinical evidence suggests that hyperactive dopamine signaling in the striatum is associated with psychotic symptoms. Activation of the cholinergic system through the muscarinic M4 receptor can robustly modulate striatal dopamine signaling, thereby alleviating psychotic symptoms. Muscarinic M4 receptor positive allosteric modulators (M4 PAMs), which target the allosteric site rather than the orthosteric site of the receptor, have a better safety profile. In this context, we studied the safety and pharmacodynamic properties of an M4 PAM, SUVN-L1101142. The effect of SUVN-L1101142 on the allosteric site of the muscarinic M4 and M2 receptors was characterized using the GloSensor cAMP assay, and on other muscarinic receptor subtypes (M1, M3, and M5) using the CRE-Luc reporter gene assay. The receptor occupancy of SUVN-L1101142 was evaluated in rats. The antipsychotic effects of SUVN-L1101142 were assessed in amphetamine-evoked hyperlocomotion and prepulse inhibition (PPI) deficits, and in a 2,5-dimethoxy-4-iodoamphetamine (DOI)-induced head twitch model in rats. To determine whether the effect observed in the DOI-induced head-twitch test was attributable to M4 receptor activity, the assay was conducted in the presence of an M4 antagonist. The social recognition task was used to evaluate procognitive properties. The likelihood of SUVN-L1101142 eliciting motor side effects was systematically investigated as part of a safety assessment to rule out potential adverse effects on the motor system. A preliminary toxicity study of SUVN-L1101142 was conducted in rats. SUVN-L1101142 was found to be a potent and selective M4 PAM with very high selectivity over other muscarinic receptor subtypes. SUVN-L1101142 attenuated amphetamine-evoked hyperlocomotion and PPI deficits, and DOI-induced head twitch. The efficacy observed with SUVN-L1101142 was attenuated by an M4 receptor antagonist, indicating that the observed efficacy was mediated through M4 receptors. SUVN-L1101142 reversed time delay induced memory deficits in a social recognition task in rats. There was no propensity to induce motor side effects at the tested doses. The observation from the behavioral assays correlated well with the receptor occupancy at the allosteric site of muscarinic M4 receptors. Preliminary toxicity studies in rats did not show any concerns for further development. SUVN-L1101142 has the potential to be a new therapeutic option for the treatment of psychosis-related disorders and condition.

W89. OCCURRENCE OF URINARY RETENTION-RELATED ADVERSE EVENTS WITH XANOMELINE AND TROSPIUM CHLORIDE: RESULTS FROM THE 52-WEEK, OPEN-LABEL EMERGENT-5 TRIAL

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Abstract Introduction: Xanomeline and trospium chloride (KarXT), the first non-dopaminergic therapy for schizophrenia approved in the United States, combines the dual M1/M4-preferring muscarinic receptor agonist xanomeline and the peripherally restricted muscarinic receptor antagonist trospium chloride. The efficacy and safety of KarXT was shown in the 5-week, randomized, double-blind, placebo-controlled EMERGENT-1 (NCT03697252), EMERGENT-2 (NCT04659161), and EMERGENT-3 (NCT04738123) trials and the 52-week, open-label EMERGENT-4 (NCT04659174) and EMERGENT-5 (NCT04820309) trials. Consistent with guidance on the use of trospium (approved alone for overactive bladder), KarXT is contraindicated in individuals with urinary retention. This report reviews the occurrence of urinary retention-related adverse events (AEs) with KarXT in a long-term trial in adults with schizophrenia (EMERGENT-5).

Methods: EMERGENT-5 enrolled adults aged 18-65 years with schizophrenia, no prior KarXT exposure, and stable symptoms appropriate for outpatient care. Eligible participants had received oral antipsychotic therapy within 30 days of screening and discontinued these medications prior to baseline visits. KarXT treatment started at 50 mg/20 mg (xanomeline/trospium) twice daily (BID) and increased to a maximum of 125 mg/30 mg BID based on tolerability. Analyses were conducted in the overall safety population, defined as all participants who received ≥ 1 dose of KarXT; post hoc analysis examined subgroups based on sex and age (< 55 vs ≥ 55 years).

Results: The safety population (N=566) included 375 males and 191 females, with 369 participants < 55 years of age and 197 participants ≥ 55 years of age. A total of 16 (2.8%) and 14 (2.5%) participants experienced ≥ 1 treatment-emergent AE (TEAE) or treatment-related AE (TRAE) of urinary retention, respectively, and 18 (3.2%) and 3 (0.5%) experienced a urinary tract infection (UTI) TEAE or TRAE, respectively. Males and females reported similar incidences of urinary retention TEAEs (2.9% vs 2.6%) and TRAEs (2.4% vs 2.6%). However, in participants aged ≥ 55 years, both urinary retention TEAEs (4.6%) and TRAEs (3.6%) were more frequent compared with those < 55 years (1.9% and 1.9%, respectively). UTI TEAEs were more common in females than males (5.8% vs 1.9%), whereas the incidences of UTI TRAEs were similar for both groups (0.5% vs 0.5%). UTI TEAEs (3.3% vs 3.0%) and TRAEs (0.3% vs 1.0%) were also similar in both the older and younger age groups. Most urinary retention (14/16) and UTI (17/18) TEAEs were mild or moderate in intensity, with median durations of 30 and 15 days, respectively.

Conclusions: Incidences of urinary retention and UTI TEAEs/TRAEs with KarXT were low and generally mild or moderate in intensity in the 52-week EMERGENT-5 trial of adults with schizophrenia. Although subgroup analyses showed slightly greater incidences of urinary retention TEAEs in participants aged ≥ 55 versus < 55 years and of UTI TEAEs in females versus males, incidences of these expected TEAEs remained low regardless of age and gender.

W90. OLANZAPINE AND SAMIDORPHAN IN ADULTS WITH SCHIZOPHRENIA OR BIPOLAR I DISORDER: UPDATED REVIEW OF CLINICAL DATA

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Abstract Background: Combined olanzapine and samidorphan (OLZ/SAM) received US FDA approval in 2021 for the treatment of adults with schizophrenia or bipolar I disorder (BD-I) and was accompanied by a clinical data review summarizing OLZ/SAM's efficacy and safety. The key highlight was that OLZ/SAM provides the established antipsychotic efficacy of olanzapine while mitigating olanzapine-associated weight gain.

Methods: This updated review synthesizes the following clinical studies/analyses conducted over the past 5 years, providing a comprehensive overview of the OLZ/SAM clinical program. Effectiveness, safety, and tolerability of OLZ/SAM were assessed in a 12-week randomized double-blind study conducted in early-in-illness patients, a population at risk of antipsychotic-associated weight gain. A 4-year open-label extension study and subgroup analysis evaluated long-term safety and durability of treatment effect of OLZ/SAM in patients who completed prior studies. An individual patient data meta-analysis compared effects of OLZ/SAM versus olanzapine on weight gain using data from 3 clinical trials. A post hoc analysis explored effects of OLZ/SAM treatment on negative symptoms in patients with an acute exacerbation of schizophrenia. Patient retention rates were also summarized across the OLZ/SAM phase 3 clinical program.

Results: OLZ/SAM treatment was associated with a durable antipsychotic treatment effect, clinically meaningful and durable improvement from baseline in the negative symptoms of schizophrenia, and minimal weight gain and metabolic changes for up to 5 years. Treatment with OLZ/SAM was well tolerated, and substantial retention rates were observed.

Conclusion: These data reinforce OLZ/SAM as a valuable long-term treatment option for patients with schizophrenia or BD-I.

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W91. LONGITUDINAL TRENDS IN ANTIPSYCHOTIC POLYTHERAPY AND ASSOCIATED OUTCOMES IN SCHIZOPHRENIA

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Abstract Introduction: For > 70 years, schizophrenia management has relied on antipsychotic (AP) therapies that directly bind D2 dopamine receptors, largely switching or combining agents to control symptoms. However, safety and efficacy of combining APs are not well understood. This study described the demographic and clinical characteristics of adults with schizophrenia, evaluated AP monotherapy and polytherapy utilization patterns, and investigated the association between polytherapy and adverse events (AEs) and outcomes in real-world clinical practice.

Methods: Adults with schizophrenia initiating AP therapy from 01/01/2018-12/31/2024 were identified using the IQVIA PharMetrics® Plus database. The index date was the first AP claim after 01/01/2018, preceded by a 12-month AP-free baseline period. Monotherapy and polytherapy utilization patterns and associated risks of developing AEs of interest (hypertension, dyslipidemia, obesity, sleep-wake disorder, type 2 diabetes, major adverse cardiovascular events, extrapyramidal symptoms) were evaluated in the follow-up period. Polytherapy was defined as concurrent use of ≥ 2 APs for ≥ 90 days, allowing for a 32-day gap between prescriptions.

Results: 6830 participants met study criteria (63.1% male; mean $\pm$ SD age: 42.8 $\pm$ 16.7 years). After the index date, proportions of participants with ≥ 1 polytherapy episode increased from 8.3% (year 1) to 20.0% (year 5); average $\pm$ SD polytherapy duration increased from 229.1 $\pm$ 107.5 days to 640.1 $\pm$ 570.1 days. Polytherapy most often involved multiple oral second-generation APs (41.7%), oral + long-acting injectable (LAI) second-generation AP combinations (29.6%), and oral first- + second-generation AP combinations (18.8%). The most commonly prescribed monotherapies were oral second-generation APs (76.0%), short-acting injectable first-generation APs (21.5%), and LAI second-generation APs (21.4%). Use of other psychotropic medication also increased from year 1 to year 5 postindex (antidepressants: 45.0% to 63.1%; anxiolytics: 43.6% to 59.1%; mood stabilizers: 21.0% to 29.7%; anticholinergics: 36.3% to 50.1%; and anticonvulsants: 13.3% to 21.9%). Proportions of participants with incident hypertension, dyslipidemia, obesity, sleep-wake disorders, and type 2 diabetes increased during follow-up. Risks of developing these conditions were similar regardless of exposure to monotherapy or polytherapy, except for sleep-wake cycle disorders. Among 793 participants with ≥ 1 polytherapy episode during follow-up, 53.7% had baseline conditions of interest. Of those without, 36.5% had polytherapy before an incident AE. Compared with those receiving monotherapy only, participants with ≥ 1 polytherapy episode had significantly higher all-cause and schizophrenia-related outpatient and total healthcare resource utilization (HCRU) and all-cause and schizophrenia-related outpatient, prescription, and total costs.

Conclusions: Rates of AP polytherapy use increased over time, including combinations of LAI and oral APs as well as multiple oral APs. Adults without underlying conditions of interest developed AP-related AEs during treatment, without significant differences in risk between monotherapy and polytherapy, except for sleep-wake disorders. Polytherapy was associated with higher all-cause and schizophrenia-related HCRU and costs. Increasing incidence and prolonged duration of polytherapy over the illness course underscore the unmet treatment needs of individuals with schizophrenia and the need to re-evaluate treatment approaches as new options emerge.

W92. EFFICACY AND SAFETY OF XANOMELINE AND TROSPIUM CHLORIDE FOR MANIA IN BIPOLAR DISORDER: DESIGN OF THE BALSAM-1 AND BALSAM-2 TRIALS

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Abstract Introduction: Conventional antipsychotic medications are an effective treatment for acute mania related to bipolar-I disorder (BP-I); however, they can be associated with treatment-limiting side effects, including extrapyramidal symptoms, neuroleptic malignant syndrome, hyperprolactinemia, orthostasis, oversedation, seizures, QTc prolongation, and tardive dyskinesia, which may be permanent. Newer second-generation antipsychotics, particularly serotonin-dopamine antagonists, are also effective in reducing mania and mixed features; however, they are associated with significant metabolic events, including weight gain, hyperglycemia, dyslipidemia, and metabolic syndrome. A novel formulation of a dual M1/M4 preferring muscarinic receptor agonist xanomeline in combination with the peripherally restricted pan muscarinic receptor antagonist trospium chloride (KarXT) is approved for the treatment of schizophrenia in adults by the US FDA. KarXT has shown antipsychotic effects and a favorable safety profile in patients with schizophrenia with a lower incidence of weight gain, extrapyramidal symptoms, metabolic syndrome, prolactin elevation, or tardive dyskinesia associated with most other antipsychotic drugs; therefore, KarXT may offer an effective and tolerable treatment option for individuals with acute mania or mania with mixed features related to BP-I.

Methods: Two identical randomized, double-blind, placebo-controlled, phase 3 trials (NCT06951698 and NCT06951711) are assessing the efficacy and safety of KarXT monotherapy with flexible dosing in adults diagnosed according to Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision (DSM-5-TR) with BP-I with acute mania or mania with mixed features. The trials include a maximum 14-day screening period, a 3-week inpatient treatment period, and a safety follow-up visit 2 weeks following end of treatment. Participants who complete the treatment period will have the option to enter a long-term, open-label extension study where all participants receive KarXT. Adults aged 18-65 years are eligible for the study if they have a BP-I diagnosis based on DSM-5-TR criteria, are experiencing an acute episode or relapse of mania or mania with mixed features (≤ 3 weeks), require hospitalization for the acute exacerbation or relapse of mania, and have a Young Mania Rating Scale (YMRS) score ≥ 20 and a Clinical Global Impressions–Bipolar (CGI-BP) score ≥ 4 (moderate) at screening and baseline. The primary endpoint is the change from baseline in YMRS score at week 3, and the key secondary endpoint is the change from baseline in CGI-BP score at week 3. The difference between KarXT and placebo will be estimated using a mixed model for repeated measures. Safety and tolerability will be monitored, including the risk of drug-induced movement disorders and suicide.

Results: Each trial will screen approximately 457 individuals across 60 sites globally and randomize approximately 274 participants 1:1 to receive either KarXT or placebo twice daily.

Conclusions: The objective of these trials is to assess efficacy and safety of KarXT in participants experiencing mania or mania with mixed features associated with BP-I, with the intent of providing an effective and tolerable novel treatment option for these individuals.

W93. REAL-WORLD IMPACT OF OLANZAPINE AND SAMIDORPHAN ON RATES OF RELAPSE AMONG YOUNG ADULTS WITH SCHIZOPHRENIA OR BIPOLAR I DISORDER

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Abstract Background: Combined olanzapine and samidorphan (OLZ/SAM) is approved for the treatment of schizophrenia and bipolar I disorder (BD-I). In real-world studies, OLZ/SAM treatment significantly reduced acute care events, which serve as proxies for relapse, in the 12 months after initiating OLZ/SAM. This claims analysis examined relapse rates (disease-related acute care events) in a subgroup of young adults, a population vulnerable to relapse.

Methods: This claims analysis used data from Komodo Healthcare Map (10/18/2020–12/31/2023). Adults aged 18–34 years with schizophrenia or BD-I, ≥ 1 OLZ/SAM claim, and ≥ 12 months' enrollment in medical/pharmacy benefits before and after the index date were eligible. Disease-related inpatient (IP) admissions and emergency department (ED) visits in the 12-month baseline and follow-up periods were compared; Results are presented as absolute percent changes. All-cause and mental health–related events were evaluated separately. P values ≤ 0.05 were considered statistically significant.

Results: Overall, 564 patients with schizophrenia and 418 with BD-I were included. For patients with schizophrenia initiating OLZ/SAM, proportions of patients with ≥ 1 schizophrenia-related IP admission or ED visit decreased significantly by 12.1% and 6.2% between baseline and follow-up, respectively (both $P < 0.05$). For patients with BD-I initiating OLZ/SAM, proportions of patients with ≥ 1 BD-I–related IP admission or ED visit decreased significantly by 18.7% and 6.7% between baseline and follow-up, respectively (both $P < 0.05$). In both cohorts, reductions in disease-related acute care events were numerically larger than those reported previously for the main study.

Conclusion: For young adults with schizophrenia or BD-I who are in an earlier stage of their illness, initiating OLZ/SAM may be an effective strategy for reducing relapse.

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W94. TRANSLATIONAL EVIDENCE FOR DOPAMINERGIC ALTERATION OF BASAL GANGLIA FUNCTIONAL CONNECTIVITY IN PERSONS WITH SCHIZOPHRENIA

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Abstract: In prior work, a transgenic mouse model of the striatal dopamine dysfunction observed in persons with schizophrenia (PSZ), the D2-receptor-overexpressing mouse (D2-OE), exhibited dopamine-related neuroplasticity in the basal ganglia. These mice show a plastic increase in the density of axonal collaterals from direct pathway D1R-expressing medium spiny neurons of the associative striatum to the globus pallidus externus (GPe; indirect pathway). This phenotype of increased “bridging collaterals” has not yet been demonstrated in PSZ. We aimed to test whether unmedicated PSZ show analogous alterations in connectivity between dorsal caudate (DCa) and GPe using functional magnetic resonance imaging (fMRI) acquired in the resting state (RS-fMRI) and in a self-ordered working memory (WM) task state (TS-fMRI). We predicted that functional connectivity (FC) alterations would be most pronounced during task engagement. Further, we examined whether these alterations are associated with deficits in WM task performance and dopamine function assessed by neuromelanin-sensitive MRI (NM-MRI) and [¹¹C]PHNO positron emission tomography (PET). We conducted a case-control study of unmedicated PSZ and demographically matched healthy controls (HC). 37 unmedicated PSZ and 30 HCs completed RS-fMRI; 29 PSZ and 29 HC also completed TS-fMRI (~30 minutes per paradigm; TR=850 ms; 2 mm voxels). 22 PSZ and 20 HC additionally completed NM-MRI; 7 PSZ and 4 HC also completed PHNO PET with amphetamine challenge. Outcome measures included: 1) group differences in resting-state FC (RS-FC) and task-state FC (TS-FC) between DCa and GPe, 2) NM-MRI contrast ratio in substantia nigra-ventral tegmental area voxels previously shown to be associated with psychotic symptom severity (SN/VTA), and 3) baseline and amphetamine-induced change in PHNO binding potential in DCa. TS-fMRI data were residualized to task-evoked responses and only “task on” TS-fMRI volumes were analyzed. RS-FC and TS-FC between DCa and GPe were calculated as partial correlations within a basal ganglia-thalamo-cortical network, controlling for signal in non-pair nodes (dorsolateral prefrontal cortex, globus pallidus internus, substantia nigra, mediodorsal thalamus). Dunn-Šidák correction was performed for the two primary comparisons (RS-FC and TS-FC). We performed robust multivariable regressions to relate DCa-GPe TS-FC to WM capacity, NM-MRI contrast in SN/VTA, baseline PHNO BPND, and amphetamine-induced PHNO ΔBPND in DCa; models included age, sex assigned at birth, and diagnosis. PSZ exhibited greater DCa-GPe TS-FC than HC (PSZ mean[SD]=0.11[0.10], HC=0.05[0.09]; P=0.0252). DCa-GPe RS-FC did not differ between groups (PSZ median[IQR]=0.08[0.12], HC=0.05[0.16]; P=0.233). Greater DCa-GPe TS-FC was associated with lower WM capacity (β [SE] = -0.31[0.13]; P=0.020) and greater NM-MRI contrast in SN/VTA (β [SE] = 0.40[0.17]; P=0.023). Greater DCa-GPe TS-FC was associated with reduced DCa baseline D2R availability (PHNO BPND; β [SE] = -0.45[0.17]; P=0.039) and increased DCa dopamine release (more negative ΔBPND; β [SE] = -0.82[0.27]; P=0.021). Unmedicated PSZ demonstrate task-dependent DCa-GPe hyperconnectivity that

covaries with WM impairment and markers of striatal dopamine dysfunction. These results provide translational evidence for a dopamine-associated abnormality in associative striato-pallidal circuitry in PSZ, consistent with compensatory “bridging collateral” plasticity observed in the D2-OE mouse, and suggest a potential developmental mechanism for WM deficits in PSZ.

W95. MEMANTINE FOR THE TREATMENT OF PRIMARY NEGATIVE SYMPTOMS IN SCHIZOPHRENIA: A META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

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Abstract Methodological Issue Being Addressed: The large effect size ($d=2.16$) for primary negative symptoms (anhedonia, avolition, alogia, blunted affect, and asociality) obtained after adjusting for confounding factor appears promising with memantine treatment. However, the effect size observed for overall negative symptoms ($d=0.79$) is likely more reliable and consistent with findings from prior meta-analyses. Predominant negative symptoms with minimal psychosis, depression, and extrapyramidal symptoms are suggestive of primary negative symptoms. We criticize deficit versus nondeficit syndrome.

Introduction: There are no approved treatments for negative symptoms in schizophrenia. Memantine is an N-methyl-D-aspartate (NMDA) receptor antagonist. There is a growing body of evidence for memantine as an adjunctive therapy for the negative symptoms of schizophrenia.

Methods: We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and searched for relevant publications in PubMed, Cochrane Library, PsycINFO, Embase, and China Journal Net databases from inception using the following search terms: memantine, schizophrenia, randomized controlled trials (RCTs), RCT, and clinical trial. Searches were limited to English- and Chinese-language articles to date. Standardized mean differences (SMDs) with 95% confidence intervals were calculated using RevMan 5.4 to assess the effect size. Risk of bias was assessed using RoB 2.0.

Results: In total, 13 RCTs were identified (N=681). Memantine was superior to placebo in treating negative symptoms, with an SMD of 0.79 (p=0.0001, N=631, 12 RCTs). Analysis of three studies whose corresponding authors provided original datasets showed an SMD of 2.16 (p = 0.25, N = 97) after adjusting for change in psychosis, depression, and extrapyramidal symptoms, suggesting that memantine is efficacious in treating primary negative symptoms. Additionally, cognitive testing significantly improved, with an SMD of 0.66 (p=0.0001, N=395, eight RCTs). Positive symptoms were not significantly improved (SMD=0.24, p=0.1, N=631, 12 RCTs).

Conclusion: This is the first study, to our knowledge, showing a large effect size for treating primary negative symptoms with memantine. Although statistical significance was not reached because of the small sample size (N=97), the results were as expected because drugs such as memantine that act at NMDA receptors are unlikely to be effective as stand-alone treatments. Future RCTs should evaluate medications modulating NMDA in combination with complementary medications to optimize therapeutic effects for all three domains of schizophrenia psychopathology.

W96. DELIBERATE SELF-HARM IN BOSNIA AND HERZEGOVINA (BIH), WITH SPECIAL REFERENCE TO GENDER, AGE AND ETHNICITY

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Abstract: The aim of the present study is to investigate deliberate self-harm (DSH) in Bosnia and Herzegovina (BiH), with special reference to gender, age and ethnicity. Between 2001 and 2003, known hospital cases of DSH in persons aged 15 or older in the Sarajevo area were monitored using standardised methods. In total, 1428 DSH events were registered, giving an annual mean DSH event rate of 119 per 100 000 (118 for women, 120 for men) and a DSH person rate of 110 (108 for women, 111 for men). The mean person-based DSH rate was 124 for Bosniaks (Muslims), 128 for Croats (Catholics), and 88 for Serbs (Orthodox Christians). Self-poisoning was the most commonly used method in all three ethnic groups (66%), with second-most common method self-harm by a sharp object (17%). A very low proportion used guns or explosives. The rates of DSH in Sarajevo during the study period were comparable to those of many other regions in Europe, though with a quite unique pattern of higher rates among men. We identified fluctuating but significantly not different rates between ethnic groups. The general belief that religious denomination is decisive for level of DSH-rates was not supported by the findings of this study; rather the post-war situation with huge demographic changes was reflected in the results. Disruptions to social integration as a consequence of the war are put forward as possible explanations.

W97. RISK OF SUICIDE ATTEMPT IN NEWLY DIAGNOSED ADHD WITH AND WITHOUT STIMULANT TREATMENT WITHIN THREE MONTHS OF DIAGNOSIS

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Abstract Introduction: ADHD is a common comorbidity of adolescent psychiatric inpatients who present with suicide attempts. Further elucidation of what factors may be related to or protective against suicide attempts would be greatly beneficial in this population. Recently reported research using population level data in Sweden indicates that drug treatment in ADHD improved suicidal behaviors. Multiple other studies agree that stimulant treatment may have a possible protective effect. However, these studies used a multivariate analysis approach and did not consistently account for confounding variables such as use of antidepressants and previous suicide attempts. The purpose of this study is to reexamine previous findings using a US based dataset with a specific focus on the child and adolescent psychiatric population. Further, we aim to use an alternative statistical approach to better clarify the impact of stimulant treatment on suicidality while controlling for confounding variables.

Methods: A retrospective cohort study was conducted using the US collaborative Network dataset of the TriNetX database, aggregating EHR data from 43 health care organizations. Two cohorts were created. Cohort one (232,662 subjects) consisted of Subjects with new encounter diagnosis of ADHD (ICD code F90) between the ages of 10 and 21 who had a first instance of stimulant medication prescription (VA CN800, CN801, CN802, CN809) within 3 months of ADHD encounter diagnosis. Cohort 2 (544,276 subjects) consisted of those with a first encounter diagnosis of ADHD who never had a stimulant prescription, or the prescription was written more than 3 years after diagnosis. Propensity score matching was used to create two balanced cohorts based on characteristics of age at first encounter for diagnosis of ADHD, White race, Black race, Hispanic or Latino ethnicity, Male sex, Prior suicide attempt (ICD T14.91), prior depressive episodes (ICD F32), prior major depression disorder (MDD) recurrent diagnosis (ICD F33), prior bipolar diagnosis (ICD F31), or prior antidepressant prescription (VA CN 600). Balanced cohorts were compared using measure of association analysis with the primary outcome of suicide attempts between 3 months and 3 years post first encounter with ADHD diagnosis. Analysis was performed using the built in analytics tools of TriNetX.

Results: For cohort 1 and 2 respectively, before (after) balancing cohorts using propensity score matching, average age at first encounter diagnosis was 14.7 (14.6) and 14.4 (14.6), percent of subjects with white race was 71.2 (71.2) and 64.3 (71.3), with black race was 12.4 (12.4) and 16.3 (12.4), with Hispanic or Latino ethnicity was 8.4 (8.4) and 10.7 (8.4), with female sex was 40.7 (40.6) and 38.1 (40.5), with a previous suicide attempt was 0.3 (0.3) and 0.3 (0.2), with a previous depressive encounter diagnosis was 9.0 (8.9) and 7.3 (8.8), with previous encounter diagnosis of MDD recurrent was 3.4 (3.3) and 2.3 (3.3), with a previous encounter diagnosis of bipolar disorder was 0.8 (0.8) and 1.5 (0.8), and who were prescribed antidepressants previously was 12.6 (12.6) and 8.5 (12.6). The number of patients with suicide attempts between 3 months and 3 years after first encounter diagnosis with ADHD was 732 and 743 for cohort 1 and 2 respectively. This was an absolute risk of 0.003 in both cases with a risk difference of 0.000, and a z score of -0.287. P value for this z score was 0.774. There does not appear to be a protective effect against suicide attempts of prescribing stimulants within 3 months of initial encounter with ADHD diagnosis.

W98. NOVEL ORAL RAPID-ACTING NEUROACTIVE STEROID FOR TREATMENT OF POSTPARTUM DEPRESSION: A PLACEBO-CONTROLLED PHASE 3 CLINICAL TRIAL OF LPCN 1154A

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Abstract Background: Postpartum depression (PPD), a potentially life-threatening condition, affects 10-20% of new mothers, negatively impacts maternal-infant bonding, maternal mental health, and child development. Treatment options for PPD remain limited, underscoring a clear unmet need for a rapid-acting antidepressant with superior tolerability. LPCN 1154A is an investigational oral neuroactive steroid and positive allosteric modulator of the GABAA receptor being developed as a short-duration (48-hour), at-home treatment designed to provide rapid and sustained antidepressant effects in women with PPD. This Phase 3 trial aimed to evaluate the efficacy, safety, and tolerability of LPCN 1154A in women with PPD.

Methods: This randomized, double-blind, placebo-controlled Phase 3 study (NCT06979544) enrolled women aged 15–45 years with DSM-5–defined major depressive disorder with a peripartum onset and 17-item Hamilton Depression Rating Scale (HAM-D) ≥ 26 . Participants were randomized 1:1 to receive LPCN 1154A or matching placebo for a 48hr at-home treatment period. Antidepressant effects were evaluated with respect to both rapid onset (at 12, 36, and 60 hours) and durability of response (on Days 7 and 30). The primary endpoint was change from baseline in total HAM-D scores at hour 60, with secondary assessments including Montgomery-Åsberg Depression Rating Scale (MADRS) and Patient Global Index of Change to capture broader symptom domains and patient-reported improvement.

Results: At the time of this submission, all participants have completed study procedure, with 90 individuals randomized (mean $\pm$ SD age: 31 $\pm$ 6 yrs; BMI 30 $\pm$ 6 kg/m²) and the dataset remains blinded. The randomized cohort was predominately White (64%), followed by Black/African American (32%), and other racial groups (3%), with 62% identifying as Hispanic or Latino. The mean interval between delivery and Day 1 of treatment was 26 $\pm$ 15 weeks. Baseline HAM-D total score was 28 $\pm$ 3 and was not significantly different by race, ethnicity, parity, delivery method of current pregnancy, nor concomitant antidepressant use. These same participants were classified by MADRS as moderate (20–34; n=32, 36%) or severe (> 34; n=58, 64%), with the severe group showing significantly higher scores on most items (9/10). There have been no reports of drug discontinuations, excessive sedation, loss of consciousness, or serious adverse events (SAEs) related to the study drug.

Conclusions: This presentation will report primary and secondary efficacy outcomes, onset of antidepressant response, durability through Day 30, and detailed safety findings. As a novel, rapid-acting, short-course oral therapy for at-home administration, LPCN 1154A has the potential to address critical unmet needs in PPD and broaden the clinical application of neuroactive steroid modulation in mood disorders. Furthermore, the favorable safety profile of LPCN 1154A supports its potential to deliver a well-tolerated oral treatment option that could meaningfully expand the safety and accessibility of care in women's mental health and related therapeutic areas. This study was supported by Lipocine Inc.

W99. ACUTE TREATMENT OF POSTPARTUM PSYCHOSIS: AN UPDATE FROM THE MASSACHUSETTS GENERAL HOSPITAL POSTPARTUM PSYCHOSIS PROJECT

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Abstract Objective: Postpartum psychosis (PP) is among the most severe perinatal psychiatric illnesses and has significant effects on pregnant women and their families. There are effective, evidence-based treatments, particularly psychopharmacologic treatments. However, it is unclear how evidence-based psychopharmacologic interventions are applied in real-world clinical practice. The present study examined psychiatric interventions received by patients via self-report from the Massachusetts General Hospital Postpartum Psychosis Project (MGHP3), an international cohort of over 450 participants, for both the acute treatment period 3 months post-episode and subsequent treatment across the 2-year postpartum period, including pharmacologic methods, variation by diagnosis, and duration of treatment.

Methods: Data are retrospectively collected from women who experienced PP within 6 months of delivery within the past 10 years from the time of interview. Subjects report data during a one-time structured clinical interview administered by phone, which includes the Mini International Neuropsychiatric Interview for Psychotic Disorders Studies, the MGHP3© Questionnaire, assessment of treatment received, and other relevant history. Descriptive statistics were conducted to report on clinical characteristics and treatment received.

Results: As of February 4, 2025, 453 participants were enrolled in MGHP3. N=346 participants were included in this analysis, after excluding individuals who withdrew, were lost to follow-up, or who had missing treatment responses. Most participants received treatment with psychiatric medications, including the frequent use of atypical antipsychotics (83.4%) and SSRIs (49.2%). Lithium (25.1%), lamotrigine (12.4%), and valproic acid (7.8%) were the most commonly used non-antipsychotic mood stabilizers. Most participants reported taking psychiatric medications for at least 1 year postpartum, and many discontinued psychiatric medications within 2 years after childbirth. Inpatient hospitalization and psychotherapy were also commonly utilized.

Conclusions: Findings highlight variable use of evidence-based care for PP in community settings and a need for closer alignment with the most strongly supported evidence-based treatments. Concerning findings include the variable rates of hospitalization, the underutilization of lithium treatment, the most researched efficacious medication for PP, and the use of valproic acid in this population despite its known risk of teratogenicity and recommendations to avoid in reproductive-aged women. Additional research is needed to assess the prospective treatment of PP, the real-world effectiveness of commonly utilized medications, and associated adherence and tolerability. The understanding of barriers to evidence-based psychopharmacologic therapy is a major priority for the field.

W100. RE104: A NOVEL SEROTONERGIC PSYCHEDELIC 4-OH-DIPT PRODRUG FOR THE TREATMENT OF POSTPARTUM DEPRESSION

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Abstract: We present new results from a Phase 2 trial of RE104, a novel psychedelic 5HT_{2A} agonist prodrug of 4-OH-DIPT, in the first randomized controlled trial of a psychedelic agent for the treatment of postpartum depression (PPD). RE104, a unique, proprietary 4-OH-DIPT prodrug, is a novel psychedelic 5HT_{2A} agonist investigational compound being developed for the treatment of postpartum depression (PPD) and other mental health conditions. Preclinical and clinical characterization confirmed similar pharmacology of RE104 to other well-characterized classical psychedelics such as psilocybin, while demonstrating a significantly shorter and reproducible acute psychedelic experience in the clinic. PPD is a serious disorder occurring in approximately 15% of pregnancies, and is associated with significant distress, dysfunction and disability in affected women as well as adverse effects on infants. Participants (N=84) were randomized to receive a single, subcutaneous dose of 30 mg or 1.5 mg (active control) RE104 for injection at 28 sites across the United States and were subsequently followed for 4 weeks post-treatment. While session monitors were involved in the preparation, dosing session monitoring and follow-up, the study treatment did not include formal psychotherapy. Eligible participants were women aged 18-45, ≤ 15 months post-partum, not breastfeeding, with moderate to severe depression based on an entry HAM-D-17 score of ≥ 24 at screening and baseline. In addition, if applicable, eligible participants could remain on a pre-existing stable regimen of SSRIs or therapy during the study. The primary endpoint was change from baseline at Day 7 in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score. Additional endpoints included changes in the MADRS over the course of the study, rates of response and remission, and changes in maternal function including care and relationship with the infant as assessed by the Barkin Index of Maternal Function (BIMF). Analysis of the primary outcome was via MMRM including treatment, visit and visit-by treatment interaction, and baseline MADRS; an unstructured covariance structure. Analysis of secondary endpoints was performed using descriptive statistics. A single 30 mg dose of RE104 resulted in a statistically and clinically significant reduction from baseline of 23.0 points in the MADRS total score on Day 7, as compared to a reduction of 17.2 points in the active control arm (difference of 5.80; one-sided $p=0.0094$). Clinically meaningful reductions in the MADRS were also observed for RE104 30 mg on the first day following administration and maintained through the Day 28 follow-up. 77.1% of participants treated with RE104 30 mg were responders (with at least 50% improvement from baseline MADRS) to therapy at Day 7 compared to 61.6% of participants on active control. 71.4% of participants on RE104 30 mg achieved remission (with a MADRS score of ≤ 10) at Day 7 compared to 41.0% on active control. Both response and remission improvements were maintained through the Day 28 follow-up period. Maternal well-being and

function, including care of the infant as assessed by the BIMF, also demonstrated substantial improvement. RE104 was observed to be well-tolerated, during the trial with the majority of adverse events being mild to moderate in intensity, resolving spontaneously and consistent with the pharmacology observed with other agents in the class. Consistent with its pharmacokinetics, over 90% of participants on RE104 30mg showed no signs or symptoms posing a risk for discharge at the first measure of discharge readiness, taken 4 hours following treatment. Preliminary results from a contemporaneous lactation study suggest that the total amount of metabolites observed in the breastmilk represents < 0.1% of the 30 mg RE104 administered to the mother representing a safety margin that is an order of magnitude below levels that might be considered of potential concern relative to the infant. These results suggest that breastfeeding following RE104 treatment may be able to resume with limited interruption. In this first sizable randomized controlled trial of a psychedelic agent for the treatment of Postpartum Depression, administration of 30 mg of RE104, was safe and well-tolerated and resulted in rapid, significant and durable improvement.

W101. USE OF LONG-ACTING INJECTABLE ANTIPSYCHOTICS IN FORENSIC PSYCHIATRY: A MULTI-SITE CANADIAN STUDY

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Abstract Background: Long-acting injectable antipsychotics (LAI-As) are widely used in the treatment of psychotic disorders. Their use has been associated with several clinical advantages, including improved medication adherence, lower rates of treatment discontinuation, reduced hospitalizations, decreased relapse rates, lower overall healthcare costs, and reduced mortality. Despite these benefits, prescribing patterns for LAI-As vary considerably across countries, patient populations, and physician practice style. Hence, this study is designed to examine the prescribing patterns of LAI-A in forensic patients, and identify factors associated their use.

Methods: This retrospective multisite study was conducted using data derived from the Ontario Review board Database. he primary outcome variable was treatment with LAI-A, and factors associated with use of LAI-A were identified using logistic regression analysis, performed with STATA-17.

Results: A total of 1,205 participants were included. Majority were male (86.1%) and mean age of the cohort was 42.6 years (SD 13.4). Approximately 51.8% were inpatients with majority (91.6%) legally designated as Not Criminally Responsible (NCR) and 71.0% had documented history of substance use. Psychotic disorders were the most common primary diagnosis (81.6%) while violent offences accounted for the majority of index offences (70.0%). In total, 207 participants (17.2%) were prescribed at least one LAI-A (with a predominance of LAI -Abilify) during the reporting year. LAI-A use did not differ significantly by age or sex but varied across clinical, diagnostic, and legal characteristics. Compared with individuals with other diagnoses, those with psychotic disorders had significantly higher odds of receiving an LAI (adjusted odds ratio [aOR] = 7.81, 95% CI 2.34–25.04, p = 0.001). Similarly, participants diagnosed with mood disorders were substantially more likely to be prescribed an LAI (aOR = 12.19, 95% CI 3.38–43.89, p < 0.001). In contrast, recent sexual violence was independently associated with lower

odds of LAI use. Individuals with documented sexual violence during the reporting year were < half as likely to receive an LAI compared with those without such behaviour (aOR = 0.43, 95% CI 0.21–0.89, $p = 0.023$).

Conclusion: A significant proportion of forensic patients are treated with LAI-A, particularly those with severe psychotic-mood disorders and less likely in individuals with sexual violence. Capacity development and further research are needed to support an effective and safe LAI-A therapy strategy.

W102. SUICIDE RISK OF THIRD-GENERATION ANTIPSYCHOTICS IN PERSONS WITH SCHIZOPHRENIA AND SCHIZOAFFECTIVE DISORDERS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Abstract Background: Clozapine is the only antipsychotic with protective effects against suicide in schizophrenia and schizoaffective disorders (SCZ). However, the high side effect burden and monitoring protocol pose additional barriers to adherence. Third-generation antipsychotics (TGA) are characterized by unique partial agonism of dopamine D2 and D3 receptors and primarily include aripiprazole, oxaripiprazole, brexpiprazole, cariprazine, and lumateperone. TGAs have high tolerability and low rates of discontinuation. Additionally, several TGAs modulate serotonin, dopamine, and N-methyl-d-aspartate neurotransmission that have been implicated in suicide. Given the clear need for a more benign antipsychotic with protective effects against suicide, we aim to investigate the effects of TGAs of suicide in SCZ.

Methods: We searched PubMed, MEDLINE, PsycINFO, Scopus, Cochrane Central Register of Controlled Trials, Europe PMC, and ClinicalTrials.gov databases from inception to December 2023 for TGA studies in SCZ that reported suicide data. Aripiprazole studies were excluded to focus on newer antipsychotics. The primary outcome was suicide deaths and attempts; suicidal ideation was included as a secondary outcome. The revised Cochrane risk of bias tool (RoB 2) was used to assess study quality. Stata SE18 was used to conduct random effects and single proportion meta-analyses for randomized controlled trials (RCT) and single-arm open label extension studies (OLE), respectively. Sensitivity analyses were conducted for RCTs. Subgroup analyses explored the impact of dose, drug type, and comparator arm.

Results: Of 4418 identified articles, 15 RCTs (N = 5700) met inclusion criteria – five brexpiprazole (N = 2260), seven cariprazine (N = 2703), two lumateperone (N = 701), and one oxaripiprazole (N = 36). Five OLEs (N = 2200) were included – three brexpiprazole (N = 1521) and two cariprazine (N = 679). Sample sizes ranged from 36 to 1031, and trial durations ranged from 4 to 72 weeks. The overall incidence of suicide events was low, and 13 studies excluded participants with higher suicide risk. Two RCTs and all OLEs had moderate bias risk; the remaining studies had low bias risk. Compared to placebo control, TGAs neither increased nor decreased the risk of suicide deaths and attempts [RR = 0.65, 95% CI = 0.24–1.72, $p = 0.38$] or suicide deaths, attempts, and ideation [RR = 0.63, 95% CI = 0.34–1.19, $p = 0.15$]. Subgroup and sensitivity analyses did not show significant impacts of TGAs on suicide outcomes. Single

proportion meta-analysis of OLEs showed a significant increase in the incidence of suicide attempts and deaths [pooled incidence = 0.004, 95% CI = 0.000–0.013, $p = 0.048$] and suicide deaths, attempts, and ideation [pooled incidence = 0.024, 95% CI = 0.005–0.054, $p = 0.0013$], but there was marked heterogeneity across OLEs for primary [$I^2 = 71.68\%$; $Q(4) = 12.75$, $p = 0.013$] and secondary [$I^2 = 91.32\%$; $Q(4) = 55.50$, $p < 0.0001$] suicide outcomes.

Discussion: Clozapine remains unique in its protective effect against suicide. There is no current evidence to show that TGAs positively or negatively affect suicide outcomes. The increased incidence of primary and secondary suicide outcomes in OLEs should be interpreted with caution due to high heterogeneity and requires replication in other data. There remains a need for an alternative to clozapine that is equally effective in treating SCZ and preventing suicide while avoiding unwanted side effects. Additionally, alternative ways to include higher risk populations in suicide prevention research should be considered. Future studies into rare suicide outcomes should consider using alternative high-quality study designs, larger sample sizes, and longer-term follow up.

W103. ARIPIPRAZOLE ONCE-MONTHLY FOR PATIENTS LIVING WITH SCHIZOPHRENIA: NUMBER NEEDED TO TREAT, NUMBER NEEDED TO HARM, AND LIKELIHOOD TO BE HELPED OR HARMED

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Abstract Introduction: Choosing an antipsychotic for patients living with schizophrenia requires an understanding of its benefits and risks. This analysis assessed the benefit–risk profile of acute and maintenance treatment with aripiprazole once-monthly 400 mg (AOM 400) in patients living with schizophrenia, using effect size metrics including number needed to treat (NNT), number needed to harm (NNH), and the likelihood of being helped or harmed (LHH).

Methods: Data came from two double-blind studies of patients living with schizophrenia. In Study 291 (NCT01663532), adults experiencing an acute psychotic episode were randomized to AOM 400 or placebo for 12 weeks. In Study 246 (NCT00705783), patients stabilized on oral aripiprazole and then AOM 400 were randomized to continue AOM 400 or switch to placebo for up to 52 weeks. Key efficacy outcomes included $\geq 30\%$ reduction in Positive and Negative Syndrome Scale (PANSS) total score at Week 10 (Study 291) and freedom from relapse at Week 52 (as defined in Study 246). The rate of discontinuations due to treatment-emergent adverse events (TEAEs) was the selected safety/tolerability outcome in both studies. NNT, NNH, and LHH were calculated for these outcomes. In this analysis, NNT and NNH described the number of patients needed to be treated with AOM 400 vs placebo for 1 additional patient to benefit (NNT) or be harmed (NNH). Generally, lower NNT values and higher NNH values indicate a more favorable benefit–risk profile. Negative NNH values, which occur when a safety outcome occurs more often with placebo than AOM 400, were imputed as 1000. LHH is the ratio of NNH to NNT; a LHH > 1 indicates a higher likelihood of benefit than harm.

Results: In Study 291, 60/162 patients (37.0%) in the AOM 400 group and 24/167 patients (14.4%) in the placebo group achieved $\geq 30\%$ reduction in PANSS total score at Week 10, resulting in a NNT of 5 (95% confidence interval [CI]: 4, 8). The rate of discontinuations due to TEAEs was lower with AOM 400 (n=7/167; 4.2%) than placebo (n=13/172; 7.6%), resulting in a NNH of -30 (95% CI: not significant). Using an imputed NNH of 1000, the LHH was 200. In Study 246, 242/269 patients (90.0%) in the AOM 400 group and 81/134 patients (60.4%) in the placebo group were free from relapse at study end, resulting in a NNT of 4 (95% CI: 3, 5). The rate of discontinuations due to TEAEs was lower with AOM 400 (n=19/269; 7.1%) than placebo (n=18/134; 13.4%) resulting in a NNH of -16 (95% CI: not significant). Using an imputed NNH of 1000, the LHH was 250.

Conclusions: Patients living with schizophrenia, experiencing an acute psychotic episode, and receiving AOM 400, were 200 times more likely to achieve treatment benefit over 10 weeks than discontinue due to a TEAE. Additionally, patients living with schizophrenia were 250 times more likely to maintain efficacy over 52 weeks than discontinue treatment due to a TEAE.

W104. MEDETOMIDINE- AN EMERGING ADULTERANT

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Abstract: Drug-related morbidity and mortality in the United States are the highest of any country, a worsening situation further complicated by a dangerous and changing drug supply. Specifically, opioids are a factor in over 7 out of 10 overdose deaths and remain responsible for around 80,000 deaths per year. The landscape of illicit opioids continues to undergo changes. Opioid overdose deaths are described in three waves: wave 1 began in the 1990s with prescription opioids, wave 2 saw a shift to heroin overdose deaths in 2010, and 2013 marked the third wave in which synthetic overdose deaths saw the addition of adulterants to opioids, namely fentanyl. Initially, wave 3 oversaw an increasing content of Xylazine added to fentanyl; however, in recent years fentanyl laced with Medetomidine has been on the rise. Medetomidine is an alpha-2 receptor agonist that is 100-200 times more potent than xylazine, typically used in veterinary medicine. The exposure to medetomidine can cause prolonged sedation, hypotension, bradycardia, and central nervous system depression. An overdose due to a fentanyl-medetomidine combination is more difficult to reverse due to the lack of responsiveness to the antidote naloxone. Also, medetomidine is more likely to cause severe withdrawal symptoms than fentanyl alone and fentanyl laced with xylazine, with patients reporting its use being more likely to present to an emergency department. Common symptoms are tachycardia, severe hypertension, waxing and waning of alertness, tremor, and intractable nausea and vomiting. The treatment of these withdrawal symptoms has been more challenging and prolonged than previous experiences with pure fentanyl. This poster will illustrate the evolution of medetomidine and its pharmacology, as well as discuss typical intoxication and withdrawal symptoms with current treatment approaches. Utilized sources were Pubmed, Ovid, Medline, PsychInfo, EMBASE.

W105. MACHINE LEARNING DETECTION OF AROUSALS FROM AT-HOME SLEEP EEG DEVICE DEMONSTRATES COMPARABLE PERFORMANCE TO EXPERT RATERS IN SLEEP DISORDERS WITH AND WITHOUT ANTIDEPRESSANT USE

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Abstract Introduction: Cortical arousals provide insights into sleep pathologies and sleep quality through relationships to daytime impairment, respiratory event related arousals (RERAs), and hyperarousal patterns in patients with various sleep and psychiatric conditions. Scoring arousals from in-lab polysomnography (PSG) by expert readers is the gold standard, but is burdensome, time-consuming, and subject to significant inter/intra-rater variability. Here, we compare the detection of arousals from PSG to an FDA-cleared, at-home, dry-electrode EEG device that captures cortical arousals and other sleep metrics. We evaluate this system on individuals with sleep disorders with and without concurrent antidepressant use — a meaningful subgroup comparison, as antidepressants are associated with elevated cortical arousability.

Methods: The at-home EEG device and PSG were simultaneously recorded from 50 individuals (ages 25-65, 54% female) overnight, including 12 with sleep disorders taking SSRI antidepressants (SDAD) and 38 not taking antidepressants (SDCTRL). Arousals were scored by five Registered PSG Technologists following AASM guidelines using PSG signals to serve as ground truth for algorithm evaluation. Arousals on the at-home EEG device were detected by a machine-learning algorithm trained on over 15,000 nights. Performance was evaluated by computing the intraclass correlation coefficient (ICC) of the model's Arousal index (ArI; arousals per hour of sleep) to the scorers' ArI, as well as by comparing 30-second epochs with or without arousals to the scorers' majority vote to compute Cohen's Kappa.

Results: The mean ArI ICC between pairs of human scorers was 0.74 (SD=0.092, range: 0.61-0.85). The mean ICC between the at-home EEG device's ArI and individual scorers was 0.78 (SD=0.043, range: 0.72-0.84) overall, 0.83 (SD=0.078, range: 0.69-0.91) for SDAD and 0.77 (SD=0.044, range: 0.70-0.81) for SDCTRL. Comparing the at-home EEG device ArI to the average ArI of all scorers resulted in an ICC of 0.87 (95% CI: 0.80-0.91) overall, 0.91 (95% CI: 0.81-0.97) for SDAD and 0.86 (0.78 - 0.91) for SDCTRL. The at-home EEG device's epoch-level kappa of 0.57 (95% CI: 0.54-0.60) exceeded the pairwise agreement of most individual scorers (0.45 to 0.58, evaluated relative to other scorers' majority vote).

Conclusion: An at-home sleep EEG device with an associated machine learning algorithm can detect arousals with a high epoch-level agreement with expert scorers and provides a reliable estimate of arousal index in multiple populations with disrupted sleep. These findings demonstrate the potential for scalable, objective quantification of sleep fragmentation in real-world settings, enabling more efficient evaluation of therapies and future diagnostic applications.

W106. HIGHER POLYGENIC RISK FOR MITOCHONDRIAL DYSFUNCTION IS ASSOCIATED WITH LOWER CEREBRAL BLOOD FLOW IN YOUTH WITH BIPOLAR DISORDER

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Abstract Introduction: Bipolar disorder (BD) is a polygenic disease characterized by mitochondrial dysfunction and anomalous cerebral blood flow (CBF), which are interconnected. We examined the association of polygenic risk scores for mitochondrial dysfunction (Mito-PRS) with CBF in relation to youth BD.

Methods: 100 participants (17.2±1.6 years old; n=61 BD, n=39 controls) underwent arterial spin labelling magnetic resonance imaging to quantify CBF. Mito-PRS were calculated using adult genome-wide association study summary statistics for BD, extracting variants related to mitochondrial function only. Covariate-adjusted analyses examined the association of Mito-PRS with CBF in global grey matter, and in anterior cingulate cortex and amygdala regions of interest. Sex-stratified analyses and PRS-by-diagnosis interaction effects were also examined. Sensitivity analyses controlled for psychotropic medications, traditional cardiovascular risk factors, mood, and 10 genetic principal components.

Results: Higher Mito-PRS was associated with lower global grey matter CBF in the overall sample ($\beta=-0.29$, $p=0.003$) and within BD ($\beta=-0.36$, $p=0.006$). These findings were significant in females but not males. When controlling for medications and cardiovascular risk factors, most findings remained significant and additional findings emerged. Mito-PRS associations with regions of interest were not significant in primary analyses, but were significant when controlling for cardiovascular risk factors, mood, and 10 principal components.

Conclusion: In a sample of youth with BD, higher polygenic risk for mitochondrial dysfunction was associated with lower global CBF, particularly in females. Controlling for cardiovascular risk factors strengthened study findings. Future studies powered to evaluate cardiovascular risk-related effects, mood-related effects, and putative mediators of the observed findings are warranted.

W107. CHOROID PLEXUS VOLUME AS A BIOMARKER OF KETAMINE-RELATED IMPROVEMENT IN IRRITABILITY IN ADULTS WITH MAJOR DEPRESSIVE DISORDER

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Abstract: Major depressive disorder (MDD) may be associated with abnormalities in choroid plexus volume. A recent report found association of larger choroid plexus volume with greater

improvement with oral antidepressants in individuals with MDD. However, association of choroid plexus volume with changes in rapid-acting antidepressants like ketamine remains poorly understood. This exploratory analyses utilized data from individuals with MDD (n=61) and healthy controls (n=40) from a study (NCT05046184) evaluating neurocircuit mechanisms of irritability where individuals with MDD were randomized to four infusions of ketamine versus midazolam over a two-week period. Freesurfer version 7.1.1 was used to segment choroid plexus (CP) and adjusted for estimated total intracranial volume (eTIV). Association of CP (right and left separately) volume with baseline clinical features and with differential changes in irritability with ketamine versus midazolam based on CP volume were assessed. Mean (SD) of eTIV-normalized right and left CP volumes were 3.1 (1.27) and 3.4 (1.16), respectively. CP volume was not associated with diagnostic status (MDD versus HC), systemic inflammation (creactive protein), and irritability at baseline (all $p > 0.20$). There was a significant CP-volume-by-treatment-by-time interaction for left ($F=2.33$; $df=5, 242$; $p=0.0433$) and right ($F=2.33$; $df=5, 242$; $p=0.0433$) where reductions in irritability with ketamine versus midazolam were greater in those with larger CP volumes as compared to those with smaller CP volumes. We found preliminary evidence for differential improvement in irritability with ketamine versus midazolam based on volume of choroid plexus. Replication and mechanistic studies elucidating the link between CP volume and treatment-related change in irritability are needed.

W108. CHALLENGES AND STRATEGIES FOR TRAINING AND RETAINING THE NEXT GENERATION OF PHYSICIAN SCIENTISTS IN PSYCHIATRY DURING RESIDENCY AND FELLOWSHIP

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Abstract Background: While neuroscience funding and discoveries have grown exponentially in the past decades, the physician-scientist workforce to translate these research findings to the bedside has remained stagnant, with only under 10% of MD/PhD graduates entering psychiatry residency training. This has contributed to an enormous practice gap (i.e., it can take many years before critical findings from research are implemented in psychiatric practice and improve patient outcomes). Residency training is a “critical period” of high attrition for physician scientists, in which protected research time and mentoring (or lack thereof) can “make or break” a research career. Providing support and individualized training and mentorship through structured programs in residency and fellowship is instrumental to train and retain psychiatrists-scientists.

Methods: At the Icahn School of Medicine at Mount Sinai, over the past 17 years we have developed a pipeline of programs to train physicians (MDs and MD/PhDs) in psychiatry research during residency and fellowship. These include the NIMH-funded R25 program “Combined Psychiatry Residency and PhD Training at Mount Sinai” (2013-2024), the R25 program “Training the Next Generation of Psychiatrists-Scientists for Translational Research” (2022-2027), and the T32 program “Training the next generation of clinical neuroscientists” (2020-2025). Our programs aim to train the next generation of Clinician-Scientists equipped to perform translational research in psychiatry. To accelerate their research independence, our

programs are designed to acquire research skills and pilot data during residency for a career development (K) award application to launch productive, independent careers in translational psychiatry research. One key goal is to increase the pool of psychiatrists-scientists who remain involved in research, as there is high attrition after completion of clinical residency training. Our programs provide ample protected research time, individually-tailored training and targeted coursework based on an Individualized Development Plan, outstanding mentoring and networking opportunities, pilot project funding, grant writing seminars and an internal K award review process.

Results: Our programs have been highly successful in achieving the goals. The majority of our trainees have obtained faculty appointments and have remained in academia; > 50% have been retained as faculty at Mount Sinai. The majority of our trainees have obtained external grant funding (9 K awards and multiple R level grants to date), and have published numerous high-quality and high-impact publications. 100% of the graduates from our T32 program have joined the faculty at academic institutions (75%) or industry (25%) immediately after graduation. Trainees who have graduated to date each have an average of 49 publications (range 31-76), with an average of 11 publications each from work conducted during the T32 program.

Conclusions: Structured training programs are needed to train physician-scientists during psychiatry residency and fellowship. These programs can help minimize attrition by providing research protected time and coursework organized based on an Individual Development Plan. This training, coupled with outstanding mentoring, networking opportunities, grant writing seminars and an internal K award review process, will prepare promising clinician scientists and help accelerate the launch of productive, independent careers in translational psychiatry research.

W109. APPLYING SCIENTIFIC AND OPERATIONAL INSIGHTS FROM PRIOR CLINICAL TRIALS TO OPTIMIZE EFFICACY SIGNAL DETECTION IN A PROOF OF CONCEPT TRIAL WITH KYN-5356 IN COGNITIVE IMPAIRMENT ASSOCIATED WITH SCHIZOPHRENIA

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Abstract Background: Despite decades of effort since the MATRICS trial design recommendations and regulatory framework were developed, pharmacological treatment for cognitive impairment associated with schizophrenia (CIAS) remains a completely unmet medical need. Detecting pharmacological efficacy signals in CIAS remains a challenge in clinical development, with numerous trials yielding negative or inconclusive outcomes despite compelling mechanistic hypotheses. KYN-5356 is a novel first-in-class inhibitor of KAT-II (human kynurenine aminotransferase 2) in development for treatment of CIAS. The First-In-Human study in healthy participants delivered consistent evidence of target engagement across biochemical and electrophysiological biomarkers and suggestive evidence of cognitive improvement after a 6-day treatment period.

Methods: Efforts to evaluate scientific and operational factors contributing to failed and negative clinical trial outcomes have identified areas of trial design, population selection, and operational conduct with potential to decrease risk for scientific failure. We describe the integration of

strategies from each of these domains into the design of a Phase 2 Proof-Of-Concept study evaluating the efficacy, safety, PK, and PD effects of KYN-5356 in CIAS.

Results: Study KYN5356-CL-002 is a Phase 2, randomized, double-blind, placebo-controlled 28 day treatment study of 3 dose levels of KYN-5356 and placebo in 150 clinically stable participants with schizophrenia age 18-55. Design elements to reduce measurement variance include using a limited number of highly experienced research sites, selecting a computerized version of the Brief Assessment of Cognition in Schizophrenia (BACS, BAC App) as the primary efficacy endpoint to standardize test administration and reduce participant/site burden, administering the BACS 3 times prior to randomization to wash out practice effects, and consistent BACS assessment timing. The negative impact of treatment non-adherence is addressed by laboratory confirmation of antipsychotic adherence and conducting the study in an inpatient setting, which also serves to minimize variability in participant background environmental factors. The study duration was supported by the rapid-onset mechanism-linked improvement in the BACS Composite T-score and PD assessments in the FIH study. Standard MATRICS entry criteria are augmented by population enrichment via a minimum deficit threshold in BACS score as well as excluding participants with substantial increases or decreases in BACS score prior to randomization. Strategies to reduce operational variance include close oversight/review of cognitive assessment quality with rater feedback and frequent Sponsor-site interaction and collaboration. A subset of approximately 75 participants will participate in a sub-study with electroencephalography (EEG) measurements to assess neuromodulatory effects of KYN-5356 and relationships to baseline characteristics and change in cognition.

Discussion: This is the first study evaluating a selective KAT-II inhibitor in schizophrenia participants with CIAS. This Phase 2 study design has incorporated several design elements derived from analyses of prior CIAS clinical trials to support high-confidence assessment of the efficacy hypothesis in the service developing a treatment to address the long-unmet medical need for treatment of cognitive impairment in schizophrenia.

W110. INITIAL PSYCHOMETRIC PROPERTIES OF THE ANHEDONIA INTERVIEW RATING SCALE CLINICIAN (AIRS) AND SELF-REPORT (AIRS-SR) AMONG POTENTIAL PSYCHIATRY STUDY PARTICIPANTS

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Abstract Introduction: Anhedonia, defined as a significant reduction in pleasure or interest, is a core symptom of Major Depressive Disorder (MDD) and is present across other psychiatric indications, according to the DSM-5-TR and ICD-11. Limitations of commonly used anhedonia measures have been documented (Rizvi et al., 2016). A recently developed measure, the Anhedonia Interview Rating Scale (AIRS; Engler et al., 2025), was designed to address these limitations and align with the FDA's draft guidance on Patient-Focused Drug Development for Clinical Outcome Assessments (FDA, 2022). The present study examined the psychometric properties of the clinician-administered (AIRS) and self-report (AIRS-SR) versions of the AIRS

in a sample of prospective psychiatry trial research participants after initial and secondary rounds of cognitive debriefing and iterative revision of the scales.

Methods: A total of 72 participants with a primary diagnosis of a depressive, anxiety, or stressor-related disorder completed the AIRS and AIRS-SR as part of a broader IRB-approved study examining lived experiences of anhedonia. A subset of participants (n = 40) also completed the Snaith-Hamilton Pleasure Scale (SHAPS). The sample had a mean age of 38.29 years (SD = 12.43), was 65.3% female, and 66.7% self-identified as white. The most common primary diagnoses were MDD (58.3%), Persistent Depressive Disorder (15.3%), and Post-Traumatic Stress Disorder (9.7%).

Results: All participants completed both the AIRS and AIRS-SR, allowing for initial evaluation of internal consistency and convergent validity. Internal consistency was high across scales (Cronbach's α : AIRS Severity = .94, Frequency = .94, Overall = .97; AIRS-SR Severity = .94, Frequency = .94, Overall = .97). Correlations between clinician and self-report versions were strong (Severity $r = .82$; Frequency $r = .86$; Overall $r = .86$). Concurrent validity was supported by significant correlations between AIRS overall scores and the SHAPS (AIRS: $r = .56$, $p < .001$; AIRS-SR: $r = .57$, $p < .001$). Descriptive analyses indicated that anhedonia-related constructs were experienced by most participants to some degree, with adequate variability observed across both clinician and self-report measures.

Conclusions: This study provides the first quantitative evaluation of reliability and concurrent validity for the AIRS and AIRS-SR in a clinical sample. Results indicate strong internal consistency, meaningful variability in responses, and moderate correlations with an established measure of anhedonia. Notably, correlations between clinician and self-report AIRS versions were substantially higher than correlations with the SHAPS, suggesting that the AIRS assesses dimensions of anhedonia not fully captured by existing measures. When considered alongside prior qualitative work (Engler et al., 2025), these findings support the AIRS as a promising tool for assessing clinically meaningful, patient-centered aspects of anhedonia.

W111. A FIRST-IN-HUMAN STUDY TO EVALUATE SAFETY, PHARMACOKINETICS AND PHARMACODYNAMICS OF KYN-5356, A FIRST-IN-CLASS INHIBITOR OF KYNURENINE AMINOTRANSFERASE II (KAT-II)

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Abstract Background: Dysregulation of the kynurenine pathway has been implicated in a number of psychiatric and neurological disorders. In the brain, KAT-II catalyzes the conversion of kynurenine to kynurenic acid (KYNA), a neuroactive metabolite. KYNA acts as an endogenous inhibitor of the nicotinic α -7 and NMDA receptors, both of which are relevant for cognition. In the cerebrospinal fluid (CSF) of people with schizophrenia, KYNA levels are consistently elevated, suggesting a potential mechanism for cognitive impairment associated with schizophrenia (CIAS). Preclinical data show that KYNA directionally modulates cognition with increased KYNA impairing cognition whereas lowering KYNA improves cognition. Thus, reduction of KYNA via targeted inhibition of KAT-II may have beneficial

effects on cognitive function. KYN-5356 is a novel, potent, brain-penetrant, reversible, and selective KAT-II inhibitor that is being developed for CIAS.

Methods: We conducted a first-in-human study of KYN-5356 in adult, healthy subjects (clinicaltrials.gov: NCT06225115) at a single site in the United States. The study was comprised of three parts: Part 1, a single ascending dose study; Part 2, a multiple ascending dose study with 7 days of dosing; and Part 3, a food effect study. The primary objective of Parts 1 and 2, which were randomized, double-blind, and placebo-controlled, was to assess the safety and tolerability of KYN-5356 following single and multiple oral doses. The secondary objective was to evaluate the plasma pharmacokinetics of escalating single and multiple doses of KYN-5356. In Part 2, several pharmacodynamic biomarkers were assessed at baseline and on treatment to determine central target engagement of KYN-5356: CSF was collected to quantitate KYNA levels, electroencephalography (EEG) measurements were obtained to assess neuromodulatory effects, and a computerized version of the Brief Assessment of Cognition in Schizophrenia (BACS, BAC App) was used as a standardized test battery to measure cognitive performance.

Results: For Part 1, a total of 40 male and female participants with a mean age of 32.8 years were randomized to receive a single dose of KYN-5356 or placebo across five single-dose KYN-5356 dosing cohorts. For Part 2, a total of 24 male and female participants with a mean age of 33.2 years were randomized to receive multiple doses of KYN-5356 or placebo across 3 cohorts. For Part 3, a total of eight male and female participants received two single doses of KYN-5356, once after a fasting period, and once after a standardized meal.

Overall, KYN-5356 was safe and well-tolerated. In both plasma and CSF, KYN-5356 displayed excellent pharmacokinetic properties, suggesting adequate exposure in the CNS.

There was clear evidence of target engagement across several central biomarkers: (1) KYN-5356 led to a dose-dependent reduction of KYNA levels in the CSF; (2) KYN-5356 demonstrated statistically significant effects on EEG activity linked to improved function of cognitive pathways; and (3) KYN-5356 showed suggestive evidence of cognitive improvement.

Discussion: To our knowledge, this is the first study that evaluated a selective KAT-II inhibitor in humans. The favorable safety and tolerability profile, the evidence of target engagement across biochemical and electrophysiological biomarkers, as well as the suggestive evidence of cognitive improvement warrant continued clinical development in CIAS. Expansion into additional indications will also be discussed.

W112. DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF PARTICIPANTS RECEIVING COMP360 PSILOCYBIN TREATMENT FOR TREATMENT-RESISTANT DEPRESSION ACROSS TWO PIVOTAL PHASE 3 TRIALS

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Abstract: The ongoing COMP 005 and COMP 006 trials are the largest double-blind, randomized-controlled trials of psilocybin conducted to date, and the first classic psychedelic trials to report Phase 3 data. Here we describe the demographic and clinical characteristics of the

enrolled trial population. Participants aged ≥ 18 years with treatment-resistant depression (TRD, defined as a failure to respond to two, three or four different protocol-defined pharmacological treatments taken at an adequate therapeutic dose for at least 8 weeks) were recruited from outpatient settings. Medical records, validated methods of assessment and centralised medical monitor review were used to ensure eligibility. A Montgomery-Åsberg Depression Rating Scale (MADRS, performed by independent raters) total score ≥ 20 at Screening and Baseline was required to ensure at least moderate depression severity. Prior psychedelic use was capped to ensure the enrolled participants do not reflect more than real world population level usage. Participants taking antidepressant or antipsychotic medications at Screening were required to complete medication washout at least two weeks before Baseline. In COMP 005 participants were randomized 2:1 to receive 25 mg COMP360 or placebo, and in COMP 006 participants were randomized 2:1:1 to 25 mg, 10 mg or 1 mg COMP360 (Compass Pathways' proprietary, synthetic psilocybin formulation). In total 258 (54.3% female; mean age [standard deviation] 45.7 [13.7]) and 581 (51.1% female; mean [SD] age 45.2 [13.4]) were randomized and received study drug in COMP 005 and COMP 006, respectively. Approximately one-third of participants had failed 3 or more pharmacological treatments in the current episode (COMP 005 30.6%; COMP 006 31.8%). Approximately two-thirds (COMP 005 57.8%; COMP 006 62.1%) had a Baseline MADRS score of ≥ 31 indicating severe depressive symptoms. The mean duration of the current depressive episode amongst participants was 36.0 [31.1] and 41.8 [42.5] months, with a mean number of lifetime depressive episodes of 7.5 [9.9] and 6.2 [8.7] denoting the chronic and recurrent nature of TRD and the severity of the population enrolled. Over two-thirds of participants required washout of medications during the screening period (COMP 005 67.4%; COMP 006 76.8%). Prior use of any classic psychedelics, including psilocybin was low in both trials (COMP 005 5.4%; COMP 006 and 6.4%). These data demonstrate that the COMP360 Phase 3 trial populations are broadly in line with other clinical trials of TRD with respect to demographic and clinical characteristics. The trials capture a notably severe cohort, reflected in the high number of lifetime depressive episodes and the chronicity of the current episode. The requirement for at least 8 weeks of antidepressant treatment—exceeding the thresholds typically used in TRD trials—and the confirmation of these failures via medical records further strengthen the rigor and credibility of the severity classification. Notably, many participants had failed other pharmacological and non-pharmacological interventions that were not protocol defined treatment failures, indicating that the number of failures underestimates the actual degree of treatment resistance. Lifetime use of psychedelics was low indicating the representativeness of the trial population. Once completed, these pivotal trials will provide valuable data on durability of effects, and the safety and efficacy of repeat dosing over 52 weeks.

W113. CLOSING THE CARE GAP: EMBEDDING PTSD SCREENING IN PRIMARY CARE WORKFLOWS

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Abstract: Effective treatments for post-traumatic stress disorder (PTSD) exist, yet underdiagnosis and barriers to care persist, driving functional impairment and economic burden. Primary care offers a key setting to improve detection and access, though staffing limitations, time pressure, and competing priorities hinder implementation of screening workflows. We present preliminary findings from integrating the Primary Care PTSD Screen for DSM-5 (PC-PTSD-5) into a primary care clinic and examining provider perspectives on factors that shape sustainable adoption. The PC-PTSD-5 was integrated into the electronic health record (EHR) and routine workflow of a primary care clinic. Screening was triggered for patients with Patient Health Questionnaire-9 (PHQ-9) or Generalized Anxiety Disorder-7 (GAD-7) scores ≥ 10 . A midpoint evaluation used a mixed-methods approach: (1) quantitative monitoring of screening rates, positive-screen yield, diagnostic coding, and referrals; and (2) qualitative analysis using provider surveys and interviews structured by the Consolidated Framework for Implementation Research (CFIR). Large language models were used to accelerate and standardize qualitative coding. Preliminary analyses indicated that screening represented approximately 10% of monthly encounters (140 patients), with 23 patients per month meeting the positive-screen threshold. Among those screened, 22% scored ≥ 3 and 16% scored 4+. To date, 97 new PTSD problem list entries have been added, and 31 referrals have been initiated, with an average wait time of 2.4 months. The conversion rate from positive screen to diagnosis averaged roughly 60%, underscoring a diagnostic gap. CFIR interviews identified several themes, including primary care as a critical access point for discussing PTSD and mental health, limited referral capacity and resource constraints, time pressures, stigma surrounding PTSD and mental health, and opportunities to improve workflow and training. Targeted PC-PTSD-5 screening in primary care reliably identifies patients with probable PTSD, but it does not proportionally increase confirmed diagnoses. These findings highlight the need to pair screening with provider-informed workflow redesign to support adoption and long-term sustainability in primary care practice.

W114. DURABILITY OF EFFICACY AND SAFETY OF COMP360 PSILOCYBIN FOR TREATMENT-RESISTANT DEPRESSION (TRD) ACROSS 26 WEEKS IN A DOUBLE-BLIND, RANDOMIZED, CONTROLLED PHASE 3 STUDY

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Abstract Introduction: COMP360 is a novel, proprietary, synthetic formulation of psilocybin being investigated for treatment-resistant depression (TRD) and post-traumatic stress disorder. COMP 005 is a multi-center, randomized, double-blind, placebo-controlled phase 3 study of the efficacy, safety, and tolerability of COMP360 monotherapy in adults with TRD. Here, we investigate the safety and efficacy of 1 or 2 administrations of 25 mg COMP360 compared to placebo across the 26-week double-blind period of COMP 005.

Methods: Adult participants were enrolled in COMP 005 after meeting eligibility criteria, including presence of TRD as defined as having experienced 2–4 inadequate responses to prior treatments during their current depressive episode. In Part A (6 weeks), participants were randomized in a 2:1 ratio to receive a single administration of either COMP360 25 mg or placebo. The primary efficacy endpoint was change from baseline MADRS total score at Week

6. Part B was a 20-week continuation of COMP 005 in which participants were potentially eligible for a second administration of their originally assigned treatment if they did not achieve remission at Week 6 or, if they did achieve remission and subsequently met relapse criteria during Part B. In the current analysis, descriptive statistics are provided for change from baseline in MADRS total score at Weeks 10, 14, 18, 22 and 26.

Results: 258 participants were randomized and dosed with either COMP360 25 mg (n=171) or placebo (n=87). Least square mean (LSM) change from baseline MADRS total score was significantly greater in participants receiving a single administration of COMP360 than in those receiving placebo at all time points measured during Part A, as early as the day after administration [LSM Difference (95% confidence interval): Day 2: -4.7 (-7.0, -2.3), $p < 0.001$; Week 1: -7.2 (-9.6, -4.8), $p < 0.001$; Week 3: -5.2 (-7.4, -2.9), $p < 0.001$; Week 6: -3.6 (-5.7, -1.5), $p < 0.001$]. During Part B, numerical separation from placebo was maintained across an additional 20 weeks (no statistical analyses performed as prespecified in the Statistical Analysis Plan). 70% of participants in the COMP360 25 mg and 53% of participants in the placebo arm received a second administration during Part B. The most common treatment-emergent adverse events (TEAEs) were headache, nausea, hallucination (visual), and anxiety. Most TEAEs in the 25 mg arm occurred on the days of administration (66%), with the majority of these events (88%) resolving within a day. There were 13 treatment-emergent serious adverse events (SAEs) from 10 participants (3.9%) overall; 8 (4.7%) in the COMP360 25 mg arm and 2 (2.3%) in the placebo arm.

Conclusions: Reductions in MADRS total scores following one or two administrations of COMP360 25 mg were sustained for at least 26 weeks. In Part B, these longer-term changes were numerically > those in the placebo-treated arm.. These data support sustained durability of antidepressant effect of 1 or 2 administrations of COMP360 25 mg.

W115. ELUNETIROM, A FIRST-IN-CLASS, BRAIN-TARGETING, ANTIDEPRESSANT CANDIDATE IN PH2 DEVELOPMENT, TRIGGERS ROBUST BIOENERGETIC AND NEUROPLASTIC IMPROVEMENTS IN PRECLINICAL STUDIES

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Abstract Background: Impaired neuroplasticity, synaptic loss, and dysfunctional mitochondria in the cortical and limbic regions of the brain are hallmarks of many neuropsychiatric disorders. The thyroid hormone, T3, drives neuroplasticity during pre- and postnatal development via upregulation of both brain-derived neurotrophic factor (BDNF) expression and mitochondrial activation. T3 acts on nuclear hormone receptors to directly stimulate neuritogenesis and synaptogenesis and supports the increased energy demands of the growing neurons. While T3 has shown benefit in the adjunctive treatment of major depressive disorder (MDD), it is underutilized primarily due to concern for adverse cardiac effects. We designed the brain-targeting thyroid hormone receptor agonist prodrug, elunetirom, to be CNS targeting and, potentially, act like T3 as an antidepressant but without the undesirable side-effects of T3. In a

phase 1 study of elunetirom, no CNS dissociative or clinically meaningful adverse cardiac effects were observed at any of the dose levels explored.

Methods: The effects of elunetirom and its active metabolite were examined in a series of in vitro and in vivo assays relevant to neuroplasticity and the treatment of major depressive disorder and bipolar depression. Cortical and hippocampal neurons were isolated from Wistar rat embryos. All experimental protocols in animal studies were approved by the appropriate Institutional Animal Care and Use Committee and were conducted in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals. Analysis of variance (ANOVA) was performed on the resulting data; Fisher's test was used for pairwise comparisons, and p value ≤ 0.05 was considered significant.

Results: Elunetirom and its active metabolite demonstrated significant effects on measures of neuroplasticity and mitochondrial health in primary rat neuronal cultures. In a primary culture of cortical neurons, the active metabolite showed significant increases in number of neurons, neurite length, number of roots, and number of neurite extremities. In a primary culture of mature hippocampal neurons, elunetirom also significantly increased markers of mitochondrial biogenesis and synaptogenesis, even in the presence of the neuronal insult amyloid β 1-42. In all experiments, elunetirom's and its active metabolite's effects were comparable to those achieved with the positive control BDNF (50 ng/mL).

Conclusions: Elunetirom is a brain-targeting thyroid hormone receptor agonist prodrug that is in Phase 2 clinical development for MDD and bipolar depression. Elunetirom drives robust neuroplastic effects and improves mitochondrial health in brain neurons. Preclinical and clinical data suggest that elunetirom has the potential to have a rapid and enduring antidepressant effect in humans without cardiac side effects. These potential therapeutic effects are the result of direct actions on the genes that drive restorative bioenergetics and neuroplasticity in brain (e.g., $Ppargc1a \rightarrow PGC-1\alpha$ protein, $Nfe2l2 \rightarrow NRF2$ protein, $Bdnf \rightarrow BDNF$ protein).

W116. LYSERGIDE TARTRATE (LSD; DT120) SAFETY PROFILE FROM PHASE 1 AND PHASE 2 CLINICAL STUDIES

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Abstract: The aim of this analysis is to characterize the safety profile of Lysergide Tartrate (LSD; DT120) at the 100 and 200mcg dose range across studies, emphasizing the timing and nature of adverse events (AEs) to better inform its clinical utility. Lysergide Tartrate (LSD; DT120) is an investigational compound under development for the treatment of generalized anxiety disorder (GAD) and major depressive disorder (MDD), using a single-dose paradigm. Unlike the current standard of care for GAD and MDD, which requires daily medication dosing with resultant persistent adverse event (AE) burden, DT120 is being clinically evaluated as a potential treatment option with improved rapidity of onset, magnitude of efficacy, prolonged durability, and a favorable tolerability profile.

Methods: These safety data were derived from three studies that included 171 adult participants: two Phase 1 open-label, randomized, 2-period, 2-sequence, crossover studies evaluating DT120

100 µg in 27 and 64 participants. A single Phase 2 multicenter, randomized, double-blind, placebo-controlled study evaluating 100 and 200 µg (n=40 per treatment group). Treatment-emergent adverse events (TEAEs), vital signs, and suicidality (Columbia–Suicide Severity Rating Scale) were monitored and reported. TEAEs were coded using MedDRA (v26.0) and categorized as occurring either within 24 hours of dosing or more than 24 hours after dosing. For each AE, severity and relatedness to treatment were determined.

Results: In the Phase 1 studies, > 75% of participants experienced TEAEs. Most TEAEs occurred on dosing day and were consistent with the known acute pharmacodynamic profile of DT120. The most frequently reported TEAEs across the Phase 1 studies were mydriasis, visual hallucinations, euphoric mood, and illusions at similar rates across the cohorts. In the Phase 2b study, TEAEs were reported in 97.5% of participants with DT120 100 µg and 92.5% with DT120 200 µg. The majority of TEAEs occurred on the dosing day and were mild to moderate. The most common adverse events were visual perceptual changes (illusion, pseudo-hallucination and visual hallucination), nausea, headache, euphoric mood, anxiety, mydriasis, and not clinically significant increases in blood pressure. Post-treatment TEAEs occurred in approximately 56% of participants in both groups; the most common were headache, fatigue, low mood, and insomnia. These were comparable to placebo at 38.5%. Related serious adverse events (SAEs), hallucinogen persisting perception disorder, or deaths were not observed. No participants engaged in self-injurious or suicidal behavior, which was assessed using the C-SSRS and AE reporting. There were no reports of suicidal ideation with intent or a plan during the sessions or through the trial. Participants with a history of suicidal ideation showed no increase in severity. Vital sign changes did not reach clinical significance or require intervention.

Conclusions: In the three studies that included 171 eligible participants, a single administration of DT120 100 or 200 µg was characterized by transient sensory-perceptual and physiological effects, largely confined to the dosing day. The majority of TEAEs on dosing day were rated mild to moderate. Across studies, post-treatment TEAEs were uncommon and mild. No suicidality signal was observed. No cumulative or study-wide safety trends emerged. These findings demonstrate a consistent safety profile across studies, supporting further clinical evaluation of DT120.

W117. RATIONAL DEPRESCRIBING: ASCP EXPERT CONSENSUS FOR MOOD DISORDERS

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Abstract Background: Deprescribing in mood disorders remains inconsistently applied despite known risks of polypharmacy, adverse effects, and illness destabilization. The American Society of Clinical Psychopharmacology (ASCP) convened an expert task force to establish consensus-based, clinically actionable criteria for rational deprescribing across major depressive disorder (MDD) and bipolar disorder.

Methods: A 45-member expert panel employed a Delphi methodology to identify high-consensus clinical triggers for deprescribing antidepressants, antipsychotics, lithium, and sedative-hypnotics. Consensus thresholds were predefined, and agreement levels were quantified

across domains, including treatment response, illness course, adverse effects, and diagnostic context.

Results: Consensus supported deprescribing in cases of mechanistic redundancy (100%) and inadequate antidepressant response ($< 25\%$ improvement; 87%). Strong agreement discouraged deprescribing in patients with ≥ 3 lifetime depressive episodes (86%), supporting maintenance treatment. In bipolar disorder, antidepressant tapering was strongly endorsed in the presence of rapid cycling or emergent manic symptoms (95–99%), while prior relapse following discontinuation was a contraindication to deprescribing (77%). Experts favored discontinuing offending antipsychotics rather than adding “antidotes” for adverse effects such as tardive dyskinesia ($> 83\%$) or $\geq 5\%$ weight gain (98%). Time-limited use was recommended for benzodiazepines and Z-drugs (1–3 months; 98%) and low-dose quetiapine for insomnia (3–6 months; 93%). Lithium tapering over ≥ 6 weeks was endorsed to reduce relapse risk (90%).

Conclusions: This consensus framework defines specific, clinically grounded triggers for deprescribing across mood disorders, balancing relapse risk with medication burden. The findings support a shift from indefinite pharmacotherapy toward individualized, mechanism-informed treatment optimization, with clear thresholds for when continuation, tapering, or discontinuation is appropriate.

W118. THE ASSOCIATION BETWEEN KETAMINE AND ESKETAMINE AND UROLOGICAL SYMPTOMS: REPORTS TO THE FOOD AND DRUG ADMINISTRATION ADVERSE EVENT REPORTING SYSTEM (FAERS)

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Abstract Background: Chronic recreational use of ketamine has been associated with urological complications, such as ketamine-induced cystitis (i.e., bladder inflammation, sometimes referred to as “ketamine bladder”). Cystitis results from the toxic effects of ketamine and its metabolites, which cause inflammation, fibrosis and shrinking of the bladder. Symptoms include increased urinary frequency and urgency, dysuria, hematuria and urinary incontinence. It remains unclear the level of risk associated with ketamine/esketamine when prescribed at the dose and frequency used for depression.

Methods: The Food and Drug Administration Adverse Event Reporting System (FAERS) database was searched from inception to March 2026 for reports of urological symptoms. MedDRA terms related to bladder inflammation and lower urinary tract symptoms (LUTS) were utilized. Reporting odds ratios (ROR) were calculated with corresponding 95% confidence intervals (95% CIs). Selective serotonin and serotonin and norepinephrine reuptake inhibitors (SSRI/SNRI) was used as the comparator. Z-statistics were calculated to determine the disproportionality of the RORs. Utilizing bayesian information component (IC) values, the corresponding lower limits of the 95% CI were calculated (IC025).

Results: Compared with SSRI/SNRIs, ketamine showed disproportionate reporting for all specified bladder inflammation outcomes, including cystitis (593 vs. 221 reports; ROR = 21.18, 95% CI [18.13, 24.75]; $z = 38.42$, $p < 0.001$; IC025 = 3.67). Ketamine was also disproportionately associated with LUTS, including micturition urgency (447 vs. 30 reports;

ROR 3.74, 95% CI [2.58, 5.42]; $z = 6.99$, $p = 2.80 \times 10^{-12}$; IC025 = 1.16), bladder pain (120 vs. 6 reports; ROR 2.78, 95% CI [1.23, 6.32]; $z = 2.45$, $p = 1.44 \times 10^{-2}$; IC025 = -0.16), and dysuria (1726 vs. 58 reports; ROR 1.87, 95% CI [1.44, 2.44]; $z = 4.69$, $p = 2.68 \times 10^{-6}$; IC025 = 0.43). With respect to esketamine, disproportionate reports were observed with interstitial cystitis (55 vs 11 reports; ROR = 6.57, 95% CI [3.44, 12.56]; $z = 5.70$; $p < 0.001$; IC025 = 1.21). Nonsignificant associations between esketamine and cystitis, noninfective cystitis, haemorrhagic cystitis and chemical cystitis were observed. Mixed results were observed with respect to whether esketamine is disproportionately associated with LUTS. Esketamine was disproportionately associated with micturition urgency (447 vs 39 reports; ROR 2.87, 95% CI [2.07, 3.98]; $z = 6.31$; $p < 0.001$) and bladder pain (120 vs 11 reports; ROR 3.01, 95% CI [1.62, 5.58]; $z = 3.50$, $p < 0.05$). In contrast, compared to SSRI/SNRIs, esketamine was disproportionately associated with lower odds of dysuria (1726 vs 10 reports; ROR 0.19, 95% CI [0.10, 0.35]; $z = -5.24$, $p < 0.001$; IC025 = -3.38).

Conclusion: Available pharmacovigilance data suggest disproportionate reporting of cystitis-spectrum adverse events and LUTS for ketamine relative to SSRI/SNRI comparators. Esketamine showed no clear cystitis-spectrum signal and mixed LUTS associations. These findings warrant cautious interpretation and further investigation given the limitations of spontaneous reporting and the substantially smaller ketamine and esketamine report base compared with the pooled comparator group. Clinically, these findings may support greater vigilance and routine screening for urinary-related adverse events in patients receiving ketamine.

W119. EFFICACY AND SAFETY OF XANOMELINE/TROSPIUM CHLORIDE DURING TRANSITION FROM ATYPICAL ANTIPSYCHOTICS IN PARTICIPANTS WITH STABLE SCHIZOPHRENIA SYMPTOMS IN EMERGENT-5

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Abstract Introduction: Medication switching is common in schizophrenia; however, clinicians may be concerned about decompensation when switching medications in clinically stable adults. The most frequent reasons for switching antipsychotic (AP) medications may include adverse events (AEs) or a lack of efficacy. Xanomeline and trospium chloride (KarXT), approved by the US Food and Drug Administration for schizophrenia treatment, provides a novel mechanism of action, exerting effects through M1 and M4 muscarinic receptor agonism, which has the potential to reduce the AE burden associated with atypical APs. Previous results from EMERGENT-5 (NCT04820309) have demonstrated that KarXT was safe, with a trend toward symptom improvement over 1 year in clinically stable adults with schizophrenia who switched from a prior AP. This analysis evaluated symptom stability during the 2-week treatment transition period from a previous atypical AP to KarXT and safety following KarXT initiation in participants in the EMERGENT-5 trial.

Methods: EMERGENT-5 was a phase 3, 52-week, multicenter, outpatient, open-label trial in adults with schizophrenia with stable symptoms, no prior KarXT use, a Positive and Negative

Syndrome Scale (PANSS) total score ≤ 80 , and a Clinical Global Impression-Severity (CGI-S) score ≤ 4 . Prior APs were washed out 2 weeks before or 5 half-lives between the screening and baseline visits. Participants initiated KarXT 50 mg/20 mg (xanomeline/trospium) twice daily and uptitrated to a maximum dose of 125 mg/30 mg (xanomeline/trospium) twice daily for 52 weeks. Outcomes assessed in this analysis included the change from screening to baseline in PANSS total, PANSS positive, and PANSS negative scores and the incidence of new-onset treatment emergent AEs (TEAEs) in the 8 weeks following KarXT initiation.

Results: Most participants (91.4%) had ≥ 1 prior AP, most commonly quetiapine (26.3%), risperidone (21.5%), aripiprazole (13.8%), and olanzapine (13.4%). The overall mean (standard deviation [SD]) washout duration was 6.0 (29.2) days. Mean (SD) PANSS total score change from screening to baseline was 0.3 (7.0); this change was similar between groups when stratifying by prior AP (quetiapine: 0.0; risperidone: 0.4; aripiprazole: -0.3; olanzapine: 0.0). The overall mean (SD) PANSS positive score change from screening to baseline was -0.3 (2.6); this change was similar between groups when stratifying by prior AP (quetiapine: -0.3; risperidone: -0.1; aripiprazole: -0.8; olanzapine: -0.2). The overall mean (SD) PANSS negative score change from screening to baseline was 0.3 (3.0); this change was similar between groups when stratifying by prior AP (quetiapine: 0.2; risperidone: 0.1; aripiprazole: 0.3; olanzapine: 0.7). KarXT was generally well tolerated and no new safety or tolerability issues emerged during the transition from prior AP to KarXT. Following KarXT initiation (weeks 1-8), the most common TEAEs were procholinergic and anticholinergic in nature: nausea (18.9%), vomiting (15.4%), and constipation (12.5%). Incidence rates for these new-onset AEs decreased over time.

Conclusions: Switching APs is common among individuals with schizophrenia. PANSS total, PANSS positive, and PANSS negative scores remained stable when transitioning participants from a previous atypical AP to KarXT, regardless of the prior AP used. Incidence rates for new-onset TEAEs declined over time. These data suggest that stable individuals can be safely transitioned from previous APs to KarXT without destabilization of schizophrenia symptoms.

W120. SILENCE IS GOLDEN: SPEECH PRODUCTION DURING PSILOCYBIN ADMINISTRATION SESSIONS FOR THE TREATMENT OF POST-TRAUMATIC STRESS DISORDER

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¹Compass Pathways

Abstract Background: The contribution and nature of participant support in the context of psychedelic trials remains the topic of considerable debate.

Aims: To provide additional detail about the structure and format of the monitoring and support used in Compass Pathfinder Ltd (Compass) trials, focusing on the administration sessions.

Methods: Transcripts from audio recordings collected during a 12-week clinical trial assessing the efficacy of 25 mg COMP360 psilocybin in 22 individuals with posttraumatic stress disorder (PTSD) were examined to quantify speech rates (words per minute, WPM) for both participants

and support providers. Additionally, a thematic analysis of postdosing participant interviews was conducted to provide deeper insight into participants' experiences of monitoring and support during the study.

Results: Comparisons of words per minute (WPM) between support providers and participants clearly differentiated administration sessions from preparation and follow up sessions. During administration, speech from either party was infrequent; on average, silence accounted for 78% of the session time, compared with 25%–30% in non-administration sessions. Thematic analysis of postdosing interviews revealed three overarching themes: (1) support was minimally enacted, yet experientially salient, (2) autonomy was promoted through the introspective psychedelic state and non-directive support, and (3) primary modes of support during altered states of consciousness included reassurance and validation.

Conclusions: The minimal level of verbal interaction and participant reports indicate that the style of monitoring and support used in Compass administration sessions is distinct from approaches commonly employed in traditional psychotherapies, MDMA-assisted therapy trials, and psycholytic treatment models involving psychedelic substances.

W121. A NOVEL INTERACTIVE DIGITAL LEARNING TOOL (DISCOVER TD®) FOR PSYCHIATRY RESIDENT TRAINING ON DIAGNOSIS AND TREATMENT OF DRUG-INDUCED MOVEMENT DISORDERS

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Abstract Background: Misdiagnosis and underdiagnosis are key obstacles to adequate treatment of drug-induced movement disorders (DIMDs) that may lead to incorrect intervention and worsening of symptoms. Training psychiatrists to recognize and differentiate between different types of DIMDs is crucial to guiding treatment. Current gold standards for training in the assessment and management of drug-induced abnormal involuntary movements are lacking. Digital learning tools (DLT) have been shown to be more effective than traditional instructional approaches in medical school, yet DLT approaches are lacking in psychiatry residency training. This study aimed to analyze the use and effectiveness of the interactive digital tool, Discover TD, for improving knowledge about assessment and management of DIMDs in psychiatry residents.

Method: A random nationwide sample of psychiatry residents were invited to complete a pre-intervention quiz, a set of Discover TD educational modules (“cases”), and 2 follow-up quizzes, at 2 weeks and 3 months, respectively. Discover TD is an interactive digital learning tool developed by Neurocrine Biosciences, providing an educational experience using case-based examples of various DIMDs and interactions with virtual avatar patients. Participants are guided through a stepwise process to observe the patient, chat about signs and symptoms, and assess and treat abnormal involuntary movements. Diagnosis accuracy, treatment accuracy, and overall case performance accuracy were scored from 0-100%. Predictors of baseline knowledge and performance were explored using correlations and regression models.

Results: Seventy-six psychiatry residents registered for the study, 67 (88%) completed at least one case, and 42 (55%) completed all 9 cases within 4 weeks. Sixty (80%) reported prior training

in drug-induced abnormal involuntary movements and 59 (79%) reported prior experience administering at least one abnormal involuntary movement scale. The mean pre-quiz, case accuracy, diagnosis accuracy, and treatment accuracy score were 69% (SD=16%), 63% (SD=32%), 55% (SD=33%), and 39% (SD=32%), respectively. No differences in demographics, training factors, or pre-quiz scores were found between case completers (≥ 1 case) and non-completers (< 1 case). Number of cases completed predicted diagnosis ($p < .0001$), treatment ($p < .0001$), and overall case score ($p < .001$), controlling for prior experience, training factors, and pre-quiz score. Correlations between pre-quiz score and performance (case performance, diagnosis accuracy, and treatment accuracy) were nonsignificant.

Conclusions: The results show preliminary evidence that the assessment and treatment accuracy of DIMDs improve with the number of completed Discover TD cases. Future directions include assessing whether case performance gains transfer to improved knowledge about DIMD at 2-weeks and 3-months follow-up. These results advance our knowledge about the utility of DLT in psychiatry residency training.

W122. IMPACT OF A THREE-PART ONLINE EDUCATIONAL WEBINAR SERIES ON PSYCHIATRISTS' KNOWLEDGE, COMPETENCE, AND CONFIDENCE IN DIAGNOSING AND MANAGING TARDIVE DYSKINESIA

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Abstract Background: Tardive dyskinesia (TD) is a persistent condition that requires ongoing monitoring and thoughtful treatment adjustments. This study evaluated the effectiveness of a three-part continuing medical education (CME) webinar series in improving psychiatrists' knowledge, competence, and confidence across the patient journey, from initial diagnosis to long-term management of TD.

Methods: The educational curriculum consisted of three 30-minute distinct online webinars, each webinar had a separate cohort of learners. The modules focused on early identification, evidence-based treatment strategies, and long-term management and monitoring. Effectiveness was assessed with a repeated-pairs pre-/post-assessment study design using 2 to 3 knowledge/competence questions and 1 confidence question, in which each individual served as their own control. A paired samples t-test assessed mean differences in the average number of correct responses from pre- to postassessment, and a McNemar's test assessed significant improvement at the question level. P values $< .05$ were statistically significant. Data were collected between June and December 2025.

Results: Webinar 1 (Diagnosis and Early Identification): Among linked psychiatrists ($n=574$), 34% improved their overall knowledge and competence. Competence in differentiating TD from other drug-induced movement disorders improved from 33% pre- to 47% post-CME, a relative

increase of 42% ($P < .001$). The ability to apply validated tools like the Abnormal Involuntary Movement Scale (AIMS) improved from 49% pre to 62% post-CME, a relative increase of 27% ($P < .001$). Mean confidence in applying these tools rose from 2.47 to 2.83 ($P < .001$). Webinar 2 (Evidence-Based Treatment): Among linked psychiatrists ($n=442$), knowledge regarding the evidence supporting FDA-approved treatments, including vesicular monoamine transporter type 2 (VMAT2) inhibitors improved from 54% pre- to 69% post-CME, a relative increase of 28% ($P < .001$). Mean confidence in utilizing evidence-based treatments increased from 2.35 to 2.7 ($P < .001$). Webinar 3 (Long-Term Management): Among linked psychiatrists ($n=395$), competence related to implementing strategies for long-term monitoring increased from 12% pre- to 22% post-CME, a relative increase of 83% ($P < .001$). Competence related to assessing the ongoing impact of TD on patient quality of life increased from 53% pre to 65% post-CME, a relative increase of 23% ($P < .001$). Mean confidence in implementing long-term monitoring increased from 2.39 to 2.73 ($P < .001$).

Conclusions: Participation in this targeted CME webinar series yielded statistically significant improvements in psychiatrists' knowledge, competence, and confidence across the TD continuum. The data demonstrate measurable educational gains in specific clinical domains, including differentiating movement disorders, applying AIMS, recognizing FDA-approved treatments, and formulating long-term monitoring strategies.

W123. IDENTIFYING AND PREDICTING SYMPTOM TRAJECTORIES IN A BLENDED HYBRID DIGITAL MENTAL HEALTH CLINIC

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Abstract Objective: Blended hybrid digital mental health care is a rapidly expanding treatment model, yet heterogeneity in patient outcomes within these settings remains poorly characterized. We applied latent growth mixture modeling to identify distinct trajectories of depression and anxiety symptoms in a digital psychiatry clinic and examined which digital phenotyping features best discriminate trajectory class membership.

Methods: We analyzed weekly PHQ-9 and GAD-7 scores from 249 patients receiving care in a blended hybrid clinic over an 8-week treatment period. Latent growth mixture models with one to five classes were compared using AIC, BIC, and CAIC to determine the optimal trajectory structure. Following trajectory identification, multinomial logistic regression with 5-fold cross-validation was used to evaluate the ability of changes in digital phenotyping measures to discriminate between trajectory classes. Model performance was assessed using one-vs-all receiver operating characteristic (ROC) analysis with macro-averaged area under the curve (AUC).

Results: For anxiety (GAD-7), three trajectories were identified: Fast Responders (16.1%, $n=40$), Responders (58.2%, $n=145$), and Non-Responders (25.7%, $n=64$). Similarly, three depression (PHQ-9) trajectories emerged: Fast Responders (5.6%, $n=14$), Responders (75.5%, $n=188$), and Non-Responders (18.9%, $n=47$). Multinomial classification models using digital phenotyping features showed the strongest discrimination for Fast Responders (AUC=0.77 for PHQ-9; AUC=0.80 for GAD-7). Performance was moderate for Responders (AUC=0.60 and

0.62, respectively) and poor for Non-Responders (AUC=0.58 and 0.37). Macro-averaged AUCs were 0.65 for depression and 0.60 for anxiety trajectory classification.

Conclusions: Treatment response in blended hybrid care is highly heterogeneous, with approximately one in four patients with anxiety and one in five patients with depression showing minimal improvement despite completing treatment. Digital phenotyping features reliably identified patients experiencing rapid improvement but struggled to distinguish non-responders from the broader treatment population. These findings motivate further exploration of additional digital biomarkers such as app engagement patterns to improve prospective identification of patients at risk for non-response in digital mental health care.

W124. COGNITIVE IMPAIRMENT IN MAJOR DEPRESSIVE DISORDER: A PATIENT-PRIORITIZED TARGET FOR FUNCTIONAL RECOVERY

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Abstract: Background: Cognitive symptoms are less recognized as a core feature of major depressive disorder (MDD) and associated functional impairment. Clinical care and MDD trials often prioritize change in mood symptoms and fail to monitor for improvement in cognitive symptoms. Understanding the patient-perceived burden of cognitive symptoms may inform treatment development and optimization strategies.

Methods: Semi-structured qualitative interviews were conducted with 15 US adults who had clinician-diagnosed MDD (≥ 3 months current or prior antidepressant use) and 5 clinicians treating MDD (2 primary care, 3 psychiatry). Interviews explored symptom experience, functional impact, and treatment priorities. Transcripts were analyzed using established qualitative methods.

Results: Of the 15 adult patients who were interviewed, 13 (86.7%) reported experiencing cognitive symptoms, such as trouble concentrating and thinking. Of the 5 clinicians who were interviewed, 4 (80.0%) reported that patients with MDD typically present with cognitive symptoms. When patients were asked which symptoms were most bothersome, the most common responses were cognitive symptoms and lack of motivation (26.7% [4/15] for each symptom). When asked which symptoms that they most wanted to see improved with new treatment, one-third of patients (33.3% [5/15]) responded with cognitive symptoms. Patients described cognitive symptoms as being persistent and functionally disruptive, contributing to decreased work productivity, difficulty learning new material, impaired task completion, and strained interpersonal communication. While clinicians identified fatigue and depressed mood as primary treatment targets, patients consistently highlighted the need for improvements in cognitive symptoms, such as improved mental clarity and focus.

Conclusions: Cognitive symptoms represent a prevalent and highly prioritized dimension for treatment among patients with MDD. Targeting cognitive improvement is often not prioritized

by clinicians; however, addressing these symptoms is an unmet need that is critical to functional recovery.

W125. EVALUATION OF VEDAI ACROSS CLINICAL PSYCHIATRY: A BLINDED PSYCHIATRIST-RATED STUDY

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Abstract Background: AI tools are increasingly being explored for psychiatric clinical decision support, but standardized evaluation of output quality, safety, and educational value remains limited. VedAI is a psychiatry-focused platform designed to support clinical reasoning across diverse clinical scenarios. We evaluated VedAI's outputs using blinded ratings by psychiatrist through a structured scoring framework.

Methods: VedAI responses were generated for diverse psychiatry-relevant clinical scenarios. Outputs were independently evaluated using a 10-domain rubric assessing diagnostic accuracy, case analysis clarity, chain-of-thought quality, chain-of-reason process, intervention relevance, missed recommendations, educational value, empathy/sensitivity, structured reporting, and citation accuracy. Outputs were independently evaluated using a 10-domain rubric, and individual domain ratings were aggregated into a composite overall performance score (range, 10–50) using pre-specified interpretive thresholds. A secondary assessment used the FAITA-Mental Health framework to assess credibility, user experience, user agency, equity/inclusivity, transparency, and safety/crisis management. Based on internal clinical evaluation metrics and the FAITA framework, the combined use provided a structured approach for assessing psychiatric AI decision-support tools.

Results: A total of 159 evaluations were available for the primary analysis. Mean overall score was 44.72/50 (SD 3.46; 95% CI 44.18–45.26), placing average performance in the upper Strong Quality range. Median overall score was 45 (IQR 43.3–47.25). Overall, 80.5% of outputs were rated Strong or Excellent, 89.9% were Good or better, and 39.6% were Excellent. Highest-performing domains were structured reporting, diagnostic accuracy, citation accuracy, chain-of-thought quality, and intervention relevance. Domains with comparatively greater opportunity for optimization included completeness of recommendations, empathy/sensitivity, and chain-of-reason process. Among 135 FAITA evaluations, mean total score was 20.32/24 (SD 1.41). Strongest FAITA areas were goal clarity, evidence-based content, and bias/fairness, while feedback/support, transparency, and safety/crisis management scored relatively lower. Overall score correlated moderately with FAITA total score ($r=0.56$, $p < 0.001$).

Conclusions: VedAI demonstrated consistently strong performance across diverse psychiatric scenarios, particularly in structure, diagnostic alignment, and educational usefulness. These findings support its potential as a psychiatrist-facing clinical decision support and educational tool. The results supported the feasibility of responsibly deploying specialized AI intelligences in mental health care while maintaining standards for transparency safety, and clinician-centered usability. Further work should strengthen safety-related features and prospectively evaluate performance in real-world workflows.

W126. PHARMACOLOGICAL VALIDATION OF NEUROKIT AS A PORTABLE, SENSITIVE AND REPRODUCIBLE TEST BATTERY IN EARLY CLINICAL CENTRAL NERVOUS SYSTEM (CNS) DRUG DEVELOPMENT

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Abstract Background: NeuroKit has been developed as a portable equivalent to NeuroCart, a well-established and validated test battery that quantifies a wide range of pharmacodynamic (PD) CNS effects in early drug development. NeuroKit incorporates CNS domains previously demonstrated to be informative in early phase clinical trials using NeuroCart: saccadic eye movements (arousal), adaptive tracking (visuomotor coordination, sustained attention), finger tapping (fine motor performance; visuomotor coordination), smooth pursuit (visuomotor coordination), body sway (postural balance), N-back (working memory), VAS Bond and Lader and VAS Bowdle (subjective drug effects). The present study aimed to pharmacologically validate NeuroKit against NeuroCart using three CNS-penetrant compounds with distinct, well-known mechanisms of action, establishing its sensitivity and reproducibility in capturing PD effects in humans compared to NeuroCart in early-phase clinical pharmacology studies.

Methods: In this randomized, double-blind, double-dummy, placebo-controlled, four-way crossover study, 16 healthy male and female participants received single dose of a non-selective GABA-A receptor agonist (lorazepam 2 mg PO), a dopamine reuptake inhibitor and releaser (modafinil 200 mg PO), a NMDA receptor antagonist (S-ketamine IV 0.475 mg/kg for 75 min + 0.275 mg/kg for 75 min) and placebo. NeuroKit and NeuroCart were administered predose, and counterbalanced at five postdose timepoints in each treatment period to account for potential order effects. PD endpoints were analyzed using linear mixed-effects models. Least-squares mean (LSM) and Minimal Detectable Effects (MDE) contrasts were used to estimate treatment-placebo differences for NeuroKit versus NeuroCart and to compare sensitivity to treatment effects between methods. NeuroKit reproducibility was assessed using F-test for inter- and intra-participant variance.

Results: NeuroKit detected treatment effects consistent with NeuroCart in 88% of the endpoint-drug contrasts. Although statistical significance was not observed in the remaining cases, direction and magnitude of treatment effects were consistent across methods. Furthermore, for the most informative endpoints - saccadic peak velocity, adaptive tracking and body sway - significant effects were detected by both NeuroCart and NeuroKit. MDEs were comparable across endpoints, reflecting similar sensitivity between methods. MDEs were lower or equal for NeuroKit than for NeuroCart in 55% of endpoints, including those covering the most relevant CNS domains, while those for NeuroKit were slightly higher than for NeuroCart for psychomotor function. Inter- and intra-participant variance did not differ significantly across all endpoints between both NeuroKit and NeuroCart, reflecting reproducibility.

Conclusions: NeuroKit detected CNS effects consistent with the mechanisms of action of lorazepam, modafinil and S-ketamine, and comparable to the PD profiles previously

demonstrated for these compounds using NeuroCart. Furthermore, NeuroKit demonstrated pharmacological sensitivity and reproducibility when benchmarked against NeuroCart. Together these data support the use of NeuroKit in early-phase clinical studies with CNS-active compounds.

W127. MODELING CONTINUOUS-TIME NETWORK DYNAMICS OF PASSIVE SENSING AND ECOLOGICAL MOMENTARY ASSESSMENT DATA TO CHARACTERIZE TREATMENT RESPONSE IN DIGITAL MENTAL HEALTH CARE

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Abstract: Rapid advances in patient-generated health data platforms have expanded opportunities for digital psychiatric care through passive smartphone sensing and ecological momentary assessment (EMA) data. Yet, prior studies have largely focused on bivariate associations rather than modeling the full multivariate network. Furthermore, the common data missingness issue challenges prevailing discrete-time approaches, which may yield misleading estimates of lagged effects by assuming fixed measurement intervals. To address these gaps, we conducted an exploratory continuous-time structural equation modeling (CT-SEM) analysis. We used data from the Digital Clinic, an 8-week hybrid care model integrating CBT-based telehealth with smartphone-based digital phenotyping. We fit a continuous-time vector autoregressive model to map daily dynamic relationships among passive sensing (hometime, step count, screen time) and active EMA measures (mood symptom severity, functional impairment, and sleep duration). Responder status (end-of-treatment PHQ-9 < 5 or $\geq 50\%$ symptom reduction) was included as a time-invariant moderator of the drift matrix to examine differential network dynamics by treatment outcome. Across 218 participants with mild depression or anxiety symptoms (5,844 observations, responder status moderated 13/36 drift parameters. Most notably, responders displayed markedly faster autoregressive self-regulation of sleep duration ($\Delta AR = -0.85$; responder $AR = -0.79$ vs. non-responder $AR = +0.06$) and functional impairment ($\Delta AR = -0.40$), with near-zero sleep AR in non-responders suggesting sleep duration instability as a potential marker of poor treatment response. Responders additionally showed stronger screen-to-step ($\Delta\beta = +0.82$) and step-to-sleep duration ($\Delta\beta = +0.60$) coupling, a tighter sleep duration–mood symptom severity link ($\Delta\beta = +0.16$), and stronger negative coupling between functional impairment and hometime ($\Delta\beta = -0.40$), suggesting that when responders experience functional difficulty they are less likely to withdraw to the home environment. By contrast, non-responders showed a positive effect of hometime on mood symptom severity ($\beta = +0.30$ vs. $\beta \approx 0.00$ in Responders), consistent with a social isolation–mood deterioration dynamic absent in treatment responders. Responders further showed lower long-run equilibrium levels across five behavioral and symptom dimensions (hometime, screen time, mood symptom severity, functional impairment, and sleep duration), reflecting systematically altered behavioral baselines associated with treatment response.

Thursday, May 28, 2026

Poster Session II with Lunch

T1. KETAMINE TREATMENT FOR NON-MOTOR SYMPTOMS OF PARKINSON'S DISEASE

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Abstract Background: Parkinson's disease (PD) is a neurodegenerative disorder characterized not only by motor impairment but also significant reductions in overall quality of life secondary to the presence of non-motor symptoms such as apathy, anhedonia, anxiety, and pain. Advances in our understanding of PD pathophysiology have increased, revealing promising new targets for interventions aimed at alleviating non-motor symptoms. Emerging evidence suggests that impaired regulation of synaptic plasticity in brain networks outside of primary motor circuits could contribute to these burdensome features of the disease. Ketamine has been shown to enhance synaptic plasticity in brain regions related to motivated behavior and reward sensitivity, as well as well-established antidepressant effects in major depressive disorder. Together, there is strong rationale for investigating ketamine as a treatment for non-motor symptoms in PD.

Methods: In this single-site phase II clinical trial funded by the Michael J Fox Foundation, 51 participants with confirmed PD and depressive symptoms meeting criteria for a current major depressive episode [Montgomery Asberg Depression Rating scale (MADRS) ≥ 15] were randomized to treatment with either IV ketamine 0.5mg/kg/40mins or IV saline placebo delivered over 40mins at an interval of 2 times per week for 3 weeks. The primary outcome measure was change in MADRS score from baseline to end-of-treatment (EOT) [24-72hrs after last dose of study drug]. Other key measures included, MADRS determined response [$\geq 50\%$ reduction in score] and remission [score ≤ 10] at EOT and 1-month after last study drug administration. Additional measures assessing non-motor symptoms, including apathy (Starkstein Apathy Scale, SAS), Anhedonia (Snaith-Hamilton Pleasure Scale, SHAPS), anxiety (State-Trait Anxiety Inventory, STAI), and pain (King's Parkinson's Disease Pain Scale, KPPS) were also collected and analyzed. To evaluate the adequacy of masking, patients and research staff were asked at EOT to guess treatment allocation.

Results: There were no meaningful baseline differences in age, sex distribution, Parkinson's motor symptom severity, depressive symptom severity, or cognitive impairment at baseline. Fifty of the 51 participants randomized (25 placebo, 26 ketamine) received at least one treatment and completed the study. Ketamine was associated with transient increases in systolic and diastolic blood pressure. However, no patients were discontinued from treatment due to cardiovascular events. No evidence of decreased oxygen saturation was observed in the ketamine group compared to the placebo group. One Serious Adverse Event was reported in a participant receiving placebo, consisting of new onset atrial fibrillation and metabolic abnormalities. Most common treatment emergent adverse events in the study were headache (22% ketamine, 31% placebo), nausea (12% ketamine, 12% placebo), dizziness/faintness (8% ketamine, 10% placebo), and early morning awakenings (10% ketamine, 2% placebo). No

Treatment emergent adverse events led to withdrawal. Ketamine was associated with a significantly greater reduction in MADRS score from baseline to the EOT compared to placebo, with a significant group $\times$ time interaction on MADRS ($F=5.26$, $p=0.001$). From baseline to post-treatment, MADRS scores decreased by an average 16-points in the ketamine group, compared with 10-points in the placebo group ($p=0.006$). Additional outcome measures showed the effect was sustained at 1-month follow-up ($p=0.002$) and that response rates were significantly higher with ketamine (73%) compared with in the placebo group (38%) at EOT ($\text{Chi}^2=0.01$); this difference also persisted at the 1-month follow-up (69% vs 29%; $\text{Chi}^2=0.005$). Significant differences were also observed for remission rates at EOT (54% vs 25%; $\text{Chi}^2=0.04$) and at 1-month follow-up (50% vs 17%; $\text{Chi}^2=0.01$). Measures of other associated non-motor symptoms also showed significant and clinically meaningful improvements in apathy (SAS) ($p=0.015$) and anxiety (STAI) ($p=0.005$) at EOT. Both measures showed trends towards sustained benefit at 1-month follow-up (SAS, $p=0.07$; STAI, $p=0.06$). Improvement in anhedonia approached significance at post-treatment ($p=0.055$). Pain, assessed using the KPPS improved over the treatment period in both groups, but appeared to rebound at the 1-month follow-up for participants in the placebo group but not the ketamine treated group, resulting in a 6.3-point difference between groups at that timepoint. 78% of the patients correctly guessed treatment assignment. Of the patients receiving placebo 62% correctly guessed assignment while 92% of those allocated to ketamine correctly guessed treatment assignment. Clinicians correctly guessed assignment for 90% of participants.

Discussion: Overall, this phase II study provides strong preliminary evidence that IV ketamine delivered at 0.5mg/kg/40mins twice a week for three weeks is generally safe and can provide significant and clinically meaningful benefits to patients suffering with a range of non-motor symptoms commonly associated with PD. These treatment effects were evident despite a relatively high level of placebo response. Measures of depression severity, apathy, and anxiety all showed improvement following treatment and the benefits were largely sustained at the 1-month follow up time point. There was additional evidence of beneficial effects on anhedonia and pain at the end of treatment and the one-month follow up respectively. Imperfect treatment allocation masking was suggested by both patient and study team guesses. However, allocation guesses were collected at the end of treatment, and may therefore have been influenced not only by the transient effects of ketamine but also by the longer-term response experienced or observed during the study. Interestingly, despite the likely effect of unblinding, a relatively large placebo response was still observed and adverse events were relatively similar between groups. In sum, the data provide strong preliminary evidence of ketamine's ability to provide benefits to patients suffering from a range of non-motor symptoms associated with PD. Considering the growing prevalence and burden of PD, and the large unmet need for effective treatments of the non-motor symptoms associated with PD, it appears future studies examining Ketamine's potential role in the overall management of PD for some individuals are warranted.

T2. EFFECTS OF ITRACONAZOLE AND CARBAMAZEPINE ON THE PHARMACOKINETICS OF REMLIFANSERIN (ACP-204) IN HEALTHY ADULTS

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Abstract Background: Remlifanserin is a potent serotonin 2A (5-HT_{2A}) receptor inverse agonist/antagonist under investigation for the treatment of Alzheimer's disease psychosis and Lewy body dementia psychosis. In vitro data indicate that oxidative metabolism of remlifanserin is predominantly driven by cytochrome P450 (CYP) 3A4. Separate studies were conducted to elucidate the effects of the strong CYP3A4 inhibitor, itraconazole (ITR), and the strong CYP3A4 inducer, carbamazepine (CAR), on the pharmacokinetics of remlifanserin.

Methods: The pharmacokinetics of a single oral dose of remlifanserin in the absence or presence of multiple oral doses of ITR or CAR were assessed in two phase 1, open-label, fixed-sequence, 3-period drug-drug interaction studies in healthy adults. In the ITR study, treatment periods included: remlifanserin 30 mg alone (Treatment Period 1), multiple doses of ITR 200 mg alone (Treatment Period 2), and remlifanserin 30 mg + ITR 200 mg (Treatment Period 3). In the CAR study, treatment periods included: remlifanserin 90 mg alone (Treatment Period 1), multiple escalating doses of CAR up to 300 mg twice daily alone (Treatment Period 2), and remlifanserin 90 mg + CAR 300 mg twice daily (Treatment Period 3). For both studies, log-transformed pharmacokinetic parameters (maximum measured plasma concentration [C_{max}] and areas under the plasma concentration-time curve from time 0 to infinity [AUC_{0-∞}] and to the last quantifiable time point [AUC_{0-t}]) were analyzed using a mixed-effects model with treatment period as a fixed effect and participant as a random effect. Treatment Period 3 (remlifanserin + ITR or CAR, test group) was compared with Treatment Period 1 (remlifanserin alone, reference group) using geometric least squares mean ratios (%) and corresponding 90% confidence intervals (CIs). Additionally, differences in time to maximum plasma concentration (T_{max}) were analyzed using the exact Wilcoxon rank sum test. Safety endpoints (ie, treatment-emergent adverse events [TEAEs], clinically significant findings on physical examination, vital signs, laboratory tests, and electrocardiogram [ECG] parameters) were assessed across all periods.

Results: A total of 17 participants were included in the pharmacokinetic analysis set for the ITR study, and 16 for the CAR study. Upon coadministration with ITR, the C_{max} of remlifanserin increased to 138% (90% CI: 130% - 147%), and the extent of exposure increased 3-fold compared to remlifanserin administered alone (AUC_{0-∞}: 335% [90% CI: 301% - 374%]; AUC_{0-t}: 312% [90% CI: 275% - 354%]). Upon coadministration with CAR, the C_{max} of remlifanserin was reduced to 48% (90% CI: 43% - 54%), and both AUC_{0-∞} and AUC_{0-t} values were reduced to 33% (90% CI: 29% - 37%), without impact to T_{max} (median difference: 0; p-value: 0.83). No serious TEAEs or clinically meaningful changes in physical examination, vital signs, laboratory tests, or ECG results were reported in either study.

Conclusions: Administration of remlifanserin in the presence of the strong CYP3A4 inhibitor, ITR, markedly increased remlifanserin systemic exposure, whereas coadministration with the strong CYP3A4 inducer, CAR, reduced remlifanserin systemic exposure. Coadministration of remlifanserin with ITR or CAR was safe and generally well-tolerated.

T3. CORRELATION OF PLASMA P-TAU₂₁₇ AND CSF P-TAU₁₈₁ WITH CLINICAL DIAGNOSIS OF ALZHEIMER'S DISEASE: A CROSS-SECTIONAL STUDY OF 1,766 PARTICIPANTS IN THE ALZHEIMER'S DISEASE NEUROIMAGING INITIATIVE

Aishwarya Prasad^{*1}, Anshu Arora¹, Arun Arora¹, Mahima Patil¹, Arifulla Khan¹

Abstract Introduction: Two anti-amyloid monoclonal antibodies received accelerated approval, which increased clinical and public interest in blood biomarkers [1]. On May 16, 2025, the FDA authorized an assay that measures the plasma p-tau217 to β -amyloid1-42 ratio. Despite the rapid expansion of p-tau testing in outpatient labs and growing enthusiasm among clinicians and patients, most studies benchmark p-tau against CSF or PET [2] rather than bedside cognition. Therefore, we evaluated whether plasma p-tau217 and CSF p-tau181 relate to standard cognitive and functional measures that remain central to Alzheimer's disease diagnosis.

Methods: This study is a cross-sectional analysis using data from the Alzheimer's Disease Neuroimaging Initiative (ADNI), a multi-phase, non-randomized, non-treatment study aimed to develop and validate biomarkers. results from ADNI are shared through the University of Southern California (USC) Laboratory of Neuro Imaging (LONI)'s Image and Data Archive (IDA) (<https://ida.loni.usc.edu/login.jsp>). We conducted a cross-sectional, complete-case analysis of baseline data from all ADNI phases, accessed July 7, 2025. Outcomes were MMSE, CDR Global, and ADAS-Cog13. Predictors were plasma p-tau217 and CSF p-tau181, analyzed as continuous variables. Linear regressions were unadjusted given the exploratory aim. To reflect real clinical triage, participants were grouped as cognitively normal or cognitively impaired, where the latter included SMC, EMCI, LMCI, MCI, and AD per ADNI adjudication. For plasma p-tau217 we retained the first visit with a measured value for each participant; a similar baseline selection was applied for CSF p-tau181. No imputation or transformation was performed. Standardized ADNI biomarker and cognitive protocols were used to minimize measurement bias.

Results: Among 4,926 ADNI participants, 116 had baseline plasma p-tau217, 1,650 had baseline CSF p-tau181, and 50 had both. In cognitively normal participants, associations between plasma p-tau217 and ADAS-Cog13 or MMSE were not significant, and CSF p-tau181 likewise showed negligible relations with cognition, with all R^2 values near zero. In cognitively impaired participants, higher plasma p-tau217 related to worse cognition on ADAS-Cog13 ($\beta \approx 0.0025$, $R^2 \approx 0.32$, $p < 0.001$) and to lower MMSE ($\beta \approx -0.0067$, $R^2 \approx 0.25$, $p < 0.001$). CSF p-tau181 showed concordant but weaker associations, including a positive association with ADAS-Cog13 ($\beta \approx 0.49$, $R^2 \approx 0.13$, $p < 0.001$) and a negative association with MMSE ($\beta \approx -0.91$, $R^2 \approx 0.06$, $p < 0.001$). Across biomarkers there were no clinically actionable thresholds that separated cognitively normal from MCI or AD, and distributions overlapped across diagnostic strata.

Conclusions: While plasma p-tau217 and CSF p-tau181 demonstrate high diagnostic accuracy for distinguishing AD from other neurodegenerative disorders, their clinical utility is primarily limited to populations with established cognitive impairment. These biomarkers showed significant correlations with cognitive assessments only in cognitively impaired individuals, not in cognitively normal populations, and lack established threshold values for reliable AD differentiation. The findings suggest that p-tau biomarkers should serve as complementary tools to support treatment decisions and disease monitoring rather than standalone diagnostic markers, with AD diagnosis remaining clinician-led through comprehensive cognitive and functional evaluation.

T4. ASSESSING COMMUNITY PHARMACIST PREPAREDNESS TO IMPLEMENT METHADONE DISPENSING AND OBSERVATION

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Abstract Introduction: Methadone is an evidence-based treatment for opioid use disorder (OUD), however access to methadone for the treatment of OUD in the United States is largely restricted to federally licensed opioid treatment programs (OTPs). Proposed and emerging legislation aim to allow for pharmacy-based methadone dispensing. Community pharmacies are well-positioned to increase patient access to methadone for OUD; however, limited research has evaluated the perceived barriers and facilitators to pharmacy-based methadone dosing and dispensing among pharmacists.

Methods: From April to June 2025, we conducted qualitative semi-structured interviews with a purposive sample of 20 North Carolina community pharmacists who had previously completed a survey on pharmacy-based methadone dosing and dispensing. Pharmacists were purposively sampled based on the rurality of their practice site as well as their attitudes toward pharmacy-based methadone dispensing. Interviews assessed the barriers and facilitators to the implementation of pharmacy-based methadone access through two models: 1) Medication unit model with an OTP; and 2) Modernizing Opioid Treatment Access Act (MOTAA) dispensing of methadone, which would allow pharmacists to dispense methadone like any other controlled substance.

Results: Participants believed pharmacy-based dispensing would increase patients' methadone access and potentially reduce stigma associated with treatment. The biggest concern was the potential for increased misuse and diversion. Most pharmacists preferred the MOTAA model of methadone dispensing over the medication unit model because it could be more easily implemented into the workflow; however, concerns related to wholesaler ordering thresholds emerged. Pharmacists identified a lack of time and a lack of physical space to observe dosing as barriers to the medication unit model. Across both models, pharmacists identified inadequate financial reimbursement, increased communication demands with prescribers, and insufficient training as primary implementation challenges.

Conclusion/ Importance: Community pharmacists view pharmacy-based methadone dispensing as both promising and complex, with feasibility shaped by workflow, space, reimbursement, regulatory, and training considerations. Targeted education on workflow integration and communication with patients and prescribers, alongside policy and payment reforms, will be critical to support pharmacist-led or pharmacist-integrated models of methadone treatment for OUD.

T5. UNDERSTANDING KRATOM'S EFFECTS AND ABUSE POTENTIAL: DESIGN OF THE FIRST FDA-FUNDED HUMAN STUDY

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Abstract: Kratom is a plant used by millions of people in the United States, often to manage pain, improve mood, or ease opioid withdrawal. However, very little clinical research has tested how kratom affects people, whether it is reinforcing or addictive, or how its effects compare to approved opioids . To help fill this major gap, the U.S. Food and Drug Administration funded our team to conduct the first controlled human study designed to measure kratom’s abuse potential. This phase 1 study will be conducted at the Michael E. DeBakey VA Medical Center in Houston, Texas. Healthy adults who have used opioids recreationally but are not dependent on them will be enrolled. Each participant will complete a qualification process to confirm safety and to ensure they can reliably distinguish drug effects from placebo. Participants will then complete six inpatient study sessions and receive kratom at three to four different doses, oxycodone at one or two doses, and placebo in random order. How much participants subjectively “like” the drug using a bipolar 0-100 VAS scale, whether they would want to take it again, and whether they feel “high ” will be measured. These ratings are standard tools used in FDA-required Human Abuse Potential (HAP) studies . Blood samples will be collected to understand how kratom’s active compounds are absorbed and processed, and participant safety will be monitored through vital signs, ECGs, and lab tests. This study will provide the first clear, controlled data on kratom’s subjective effects, safety profile, and potential for abuse—information that is essential for guiding responsible regulation and future research.

T6. MENSTRUAL PHASE-DRIVEN FRONTAL WHITE MATTER MICROSTRUCTURAL DYNAMICS TRACK PROGESTERONE AND CRAVING VARIABILITY IN WOMEN WITH SUBSTANCE USE DISORDERS

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Abstract: Substance use disorders (SUDs) constitute a chronic and relapsing condition characterized by persistent cognitive impairments and craving, accompanied by neurological adaptations often involving the prefrontal cortex. Previous studies highlight critical contributions of white matter adaptations underlying addiction-related functional deficits, employing diffusion magnetic resonance imaging to estimate microstructural features of the brain’s anatomical connections. While dynamic cytoarchitectural and volumetric changes in white matter are known to be mediated by sex steroid hormones, possible relationships between cyclical hormonal fluctuations and white matter pathology in addiction are unknown. Here, we used noninvasive diffusion MRI to analyze white matter microstructure in naturally cycling women with SUDs as a function of menstrual phase, hormones, and drug craving. Twenty women with a diagnosed SUD, 17 cocaine primary (CUD)/3 heroin primary (HUD), were recruited for a study examining menstrual cycle effects on the neurocognitive correlates of addiction. Diffusion-weighted images (DWI) and blood concentrations of estradiol and progesterone were acquired from participants twice, during the late follicular and mid luteal phases of their menstrual cycle. Scans were preprocessed using the MRtrix3 FSL pipeline, and diffusion tensor imaging maps of axial, radial, and mean diffusivities (AD, RD, MD) and fractional anisotropy (FA) were computed with tract-based spatial statistics. Menstrual phase effects were analyzed voxelwise in whole-brain white matter using a within-subject design in FSL Randomise with 5000 permutations per comparison. Due to the small number of HUD participants, DWI from an additional 13 HUD primary women without menstrual data were included to assess SUD-specific effects. Self-reported drug cue-induced craving scores were obtained from participants’ average ratings of 36 picture cues on a 5-

point scale. Voxelwise comparisons identified clusters of significantly increased AD in the luteal vs. follicular phase, located bilaterally in the anterior corona radiata, genu and body of the corpus callosum, and anterior and posterior limbs of the internal capsule (mean effect: paired $t=6.71$, $p < .001$). Tests for FA and other diffusivity metrics were not significant (p 's $> .05$). Across all scans and controlling for phase, AD from the significant voxels was positively correlated with participants' progesterone levels ($r=0.51$, $p=.007$), even when controlling for estradiol (progesterone/estradiol ratio: $r=0.52$, $p=.002$). In CUD subjects, follicular AD correlated negatively with cue-induced craving scores ($r=-0.64$, $p=.008$); similar correlations were not found in the luteal phase or in HUD participants (p 's $> .126$), for whom menstrual phases were mostly unknown. In general, the HUD group exhibited lower AD compared to CUD luteal scans ($t=3.48$, $p=.002$), with no significant difference compared to CUD follicular scans ($t=1.39$, $p=.173$).

Results indicate menstrual cycle-related white matter microstructural dynamics characterized by higher AD in the luteal vs. follicular phase, driven by typical progesterone fluctuations, which negatively tracked cocaine craving in the follicular phase. These findings advance a growing body of evidence for white matter microstructural alterations in the pathology of SUD, highlighting the menstrual cycle as a potential source of sex-specific individual differences in addiction. Further work is needed to better understand effects of sex hormones across SUDs, including dense sampling over the full menstrual cycle, and in postmenopausal and non-naturally cycling populations.

T7. SEMAGLUTIDE FOR THE TREATMENT OF OPIOID USE DISORDER: INTERIM ANALYSIS OF A PILOT RANDOMIZED CONTROLLED TRIAL

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Abstract Background: Medications for opioid use disorder (MOUD, OUD), including buprenorphine and methadone, substantially reduce overdose mortality; however, relapse and treatment discontinuation rates are common, often driven by cue-induced cravings.

Glucagon-like peptide-1 (GLP-1) receptor agonists modulate reward circuitry and reduce cravings in preclinical models and in emerging human studies, suggesting potential utility as adjunctive treatments for OUD. Semaglutide, a weekly injectable GLP-1 agonist, has not been previously studied as an adjunct to MOUD in an outpatient randomized controlled trial.

Methods: This study is a 12-week, double-blind, placebo-controlled, randomized pilot trial enrolling adults with severe OUD stabilized on buprenorphine or methadone. Participants are randomized 1:1 to weekly semaglutide with dose titration per FDA-approved schedules or matching placebo. Repeat study visits are conducted throughout the trial, generating within-subject longitudinal data. Planned outcomes include change in cue-induced opioid craving scores from baseline to study completion using a standard visual-cue reactivity paradigm, clinical efficacy outcomes including relapse to illicit opioid use, neurocognitive measures of reward processing (e.g. attentional bias, delayed discounting, reward-related decision making), and safety and tolerability.

Results: At the time of this interim analysis, seven participants had enrolled, contributing a total of 64 study visits. Participants demonstrate extensive lifetime exposure to multiple substances, including universal lifetime opioid and alcohol use and frequent lifetime stimulant and cannabis use. Longitudinal assessments reveal substantial within-subject variability in cue-induced craving and related motivation measures across visits. Masked safety and tolerability indicate successful dose escalation in most participants, with intermittent delays for some due to gastrointestinal adverse events, consistent with the known safety profile of GLP-1 agonists.

Conclusions: These interim findings demonstrate the feasibility of conducting a randomized, placebo-controlled outpatient trial of semaglutide as an adjunct to MOUD, with successful recruitment, high visit density, and acceptable tolerability. Ongoing analyses will evaluate treatment-related changes in cue-induced craving, reward processing, and clinical outcomes, informing the potential role of GLP-1 receptor agonists in targeting craving-related mechanisms in OUD.

T8. OFFICE-BASED TREATMENT RETENTION AMONG PATIENTS WITH OPIOID USE DISORDER AND RECENT FENTANYL USE: EXTENDED-RELEASE INJECTABLE BUPRENORPHINE VS SUBLINGUAL BUPRENORPHINE

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Abstract: High-potency synthetic opioids, including fentanyl, continue to be the leading cause of drug overdose deaths in the United States. Buprenorphine is an effective, FDA-approved medication for opioid use disorder (OUD), with multiple formulations available. Sublingual buprenorphine (SL-BUP) is widely used but presents challenges for patients, including daily dosing burden, diversion and misuse risk, and stigma, that can contribute to treatment discontinuation, a key driver of opioid-related mortality. Extended-release injectable buprenorphine (XR-BUP) may address these challenges and optimize retention on buprenorphine. Real-world evidence comparing treatment retention between buprenorphine formulations among patients with OUD who use fentanyl is limited.

Methods: A retrospective analysis of electronic medical record data from Ideal Option, a national outpatient network of addiction clinics, included adults with moderate-to-severe OUD, a recent fentanyl-positive urine drug screen (UDS), and no prior XR-BUP use known. Patients were assigned to the Brixadi® (CAM2038) cohort if they received their first dose of CAM2038 during the qualifying period (January 1, 2025–June 30, 2025) and were assigned to the SL-BUP cohort if they received SL-BUP and no XR-BUP medications during the qualifying period. Propensity scores were estimated using all eligible patients based on age, gender, race, tenure with Ideal Option, Medicaid status, UDS availability, polysubstance use, fentanyl UDS positivity, and norbuprenorphine UDS positivity. Eligible patients with a fentanyl-positive UDS at their last visit were then matched 1:3 (CAM2038:SL-BUP). Treatment episodes began at first CAM2038 injection or first appointment with an active SL-BUP prescription and ended at the last day of observation or when a treatment gap within an episode exceeded the day supply of the last prescription received; only the first treatment episode was analyzed. The analysis evaluated the proportion of patients active in treatment with any buprenorphine medication at Day 30, Day 90, and Day 180 from the start of the treatment episode.

Results: Following propensity score matching, 162 patients were included in the CAM2038 cohort (from eligible population of 694) and 486 patients were included in the SL-BUP cohort (from eligible population of 14,852). Treatment retention on buprenorphine was significantly higher in the CAM2038 cohort than in the SL-BUP cohort during the observation period (log-rank test, $P < 0.001$). Treatment retention (95% CI) for CAM2038 vs SL-BUP was: Day 30: 51.85% (43.90%–59.22%) vs 25.51% (21.73%–29.46%); Day 90: 31.48% (24.49%–38.69%) vs 11.73% (9.06%–14.77%); Day 180: 20.37% (14.56%–26.87%) vs 7.20% (5.13%–9.73%).

Conclusions: In this real-world, retrospective analysis of patients with OUD and recent fentanyl use, office-based treatment with CAM2038 was associated with greater retention on buprenorphine compared to SL-BUP over a 6-month period. CAM2038 may offer advantages in sustaining engagement in treatment compared to SL-BUP in patients with OUD who use fentanyl.

T9. REAL-WORLD UTILIZATION TRENDS OF WEEKLY AND MONTHLY INJECTABLE BUPRENORPHINE (CAM2038) IN THE UNITED STATES DURING THE ERA OF HIGH POTENCY SYNTHETIC OPIOIDS

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Abstract Introduction: Brixadi® (CAM2038) is a weekly and monthly injectable buprenorphine medication approved for the treatment of moderate-to-severe opioid use disorder in the United States (US). Specialty pharmacy dispensing data capture real-world CAM2038 utilization at both the patient and population level, providing insight into the distribution of doses and formulations used in clinical practice and patterns of use following treatment initiation.

Methods: This retrospective analysis evaluated US specialty pharmacy data for CAM2038 from September 8, 2023 to October 21, 2025. For weekly and monthly formulations, the percentage of units dispensed for each available dose and the relative utilization of CAM2038 weekly vs monthly was calculated. The proportion of doses and formulations dispensed was assessed cumulatively (to date) and by quarter. Longitudinal, patient-level CAM2038 dose and formulation adjustments were also examined.

Results: Since launch, all doses were utilized for CAM2038 weekly (n=61,087 units dispensed) (8 mg: 15.7%, 16 mg: 18.6%, 24 mg: 36.1%, 32 mg: 29.6%) and CAM2038 monthly (n=173,082 units dispensed) (64 mg: 20.5%, 96 mg: 35.2%, 128 mg: 44.4%). CAM2038 dose utilization gradually shifted throughout the first year post-launch, generally stabilizing by Q2 2024. However, utilization of the monthly formulation increased from 50.1% in Q4 2023 to 79.8% in Q3 2025 of all CAM2038 units dispensed. Of the patients evaluated (N=30,353), 28.0% experienced at least one dose change, with dose increases accounting for 63.3% of adjustments and dose decreases accounting for 36.7%. However, across all CAM2038 units dispensed, 89.5% matched the patient's preceding dose and formulation. Among CAM2038 weekly initiators (n=8370), 51.5% were later dispensed CAM2038 monthly. Of weekly-to-monthly conversions, 5.9% were to a lower equivalent dose, 81.1% to an equivalent dose, and 13.0% to a higher equivalent dose.

Conclusions: These contemporary real-world data demonstrate the clinical need for weekly and monthly CAM2038 formulations in the full range of doses available in the US where high potency synthetic opioids remain prevalent. Dose and/or formulation adjustments following initiation were observed in a notable proportion of patients. These results support current clinical practice guidelines and FDA buprenorphine labeling that promote dosing based on individual patient needs.

T10. THE PHARMACOKINETIC PROPERTIES AND TARGET ENGAGEMENT EFFECTS OF THE NOVEL SEROTONIN TRANSPORTER MODULATOR, SNTX-2643, IN HEALTHY ADULTS

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Abstract: The SENS-01 program used artificial intelligence and nature-derived design insights to identify, SNTX-2643, a novel, potentially rapid-acting modulator of the serotonin transporter (SERT) that is under investigation for the treatment of anxiety disorders. Anxiety disorders are highly prevalent yet often underdiagnosed, inadequately treated, and debilitating conditions that can impair a patient's quality of life and ability to function in all areas. SERT is a genetically and pharmacologically validated target – modulation of which through a unique uncompetitive inhibition mechanism with SNTX-2643, may restore balance to dysregulated neuronal networks implicated in the development of anxiety disorders. The aim of the ongoing Phase 1a study is to determine the pharmacokinetic (PK) profile and pharmacodynamics (PD) of SNTX-2643 in healthy adults. In this ongoing randomized, double-blind, placebo-controlled study, healthy adults receive SNTX-2643 in single ascending dose (SAD cohorts). The study also incorporates additional cohorts to evaluate various aspects of drug activity: 1) A food effect (FE) cohort to investigate the impact of food on rate of absorption and bioavailability and 2) a target engagement (TE) cohort utilizing quantitative electroencephalography (qEEG). The FE cohort is being conducted as an open-label two-period, two-treatment crossover, with a washout period of at least 5 days between dosing periods, in which subjects receive two separate (fasting vs fed) single-dose administrations of SNTX-2643. The objective of the TE Cohort is to evaluate resting qEEG, event-related potentials, and an anxiety inducing aversive video paradigm following a single 3 mg dose of SNTX-2643 versus placebo in a randomized, double-blinded fashion to characterize CNS target engagement. A sufficient number of subjects will be enrolled to allow evaluation of 32 subjects in at least 4 SAD Cohorts (8 subjects per cohort with 6 receiving active and 2 receiving placebo), 14 subjects in the FE cohort all (14 receiving active treatment in both the fasting and fed conditions), and 25 subjects (15 subjects receiving active and 10 receiving placebo) in the TE Cohort. An effort will be made to enroll male and female subjects in each cohort with at least 30% of either sex in each cohort. The following PK parameters will be assessed across all cohorts: maximum plasma concentration (C_{max}), time to maximum plasma concentration (T_{max}), elimination rate constant (λ_z), elimination half-life (T_{1/2}), area under the plasma concentration-time curve to the final sample concentration > the limit of quantification (AUC_{last}), area under the curve from time 0 hours to infinity (AUC_{inf}), oral clearance (CL/F), and volume of distribution in the terminal phase (V_z/F). Safety analyses are included in the study. The study is planned for completion in the first half of 2026 and will be the first evaluation of SNTX-2643 in humans. The study will provide an analysis of

SNTX-2643's PK and PD properties as well as effects potentially relevant to the treatment of anxiety disorders.

T11. EFFICACY AND SAFETY OF ULOTARONT IN ADULTS WITH GENERALIZED ANXIETY DISORDER: RESULTS FROM A PHASE 2/3 RANDOMIZED PLACEBO-CONTROLLED TRIAL

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Abstract Introduction: Generalized anxiety disorder (GAD) is a chronic and persistent psychiatric disorder characterized by pervasive, excessive anxiety and worry often accompanied by signs and symptoms such as tension, restlessness, fatigue, and sleep disturbances. As one of the most prevalent anxiety disorders, GAD exerts a notable impact on functioning, quality of life, and health care utilization. Despite its high prevalence and burden, few novel treatments have emerged in recent years, and existing therapies are limited by an undesirable side-effect burden (eg, sexual dysfunction, weight gain) and often a delayed onset of action, highlighting the need for novel therapies. Ulotaront, a trace amine-associated receptor 1 (TAAR1) agonist with 5-hydroxytryptamine 1A (5-HT_{1A}) activity, is under clinical investigation for GAD and other psychiatric conditions owing to its unique mechanism of action and behavioral signature for anxiolytic, antipsychotic, and antidepressant effects.[1] This study evaluated the efficacy and safety of ulotaront in adults with GAD in a Phase 2/3 randomized placebo-controlled trial.

Methods: This Phase 2/3, randomized, double-blind, parallel-group, placebo-controlled, flexible-dose, multicenter study (NCT05729373) enrolled participants (18–65 years) with a diagnosis of GAD in the USA and Europe, with an exploratory cohort in Japan. At screening and baseline, participants were required to have a Hamilton Anxiety Rating Scale (HAM-A) total score ≥ 20 (including anxious mood and tension scores of ≥ 2), Montgomery–Åsberg Depression Rating Scale (MADRS) total score ≤ 22 , and Clinical Global Impression – Severity (CGI-S) score ≥ 4 . Treatment resistance and unstable medical conditions were exclusionary. Eligible participants were randomly assigned (1:1) to receive flexibly dosed ulotaront (50–75 mg/day) or placebo over 8 weeks. The primary endpoint was change from baseline in HAM-A total score; the secondary endpoint was change from baseline in CGI-S. Additional endpoints included HAM-A response and remission rates, and safety and tolerability.

Results: A total of 451 adults were randomly assigned to ulotaront (n=227) or placebo (n=224). Mean (range) age was 41.1 (18–65) years; most participants were female (70.3%) and were White (74.3%), Black (14.4%), or Asian (4.4%). Ulotaront demonstrated a significant decrease in least-squares mean change from baseline to Week 8 on the HAM-A total score compared with placebo (–12.9 vs –10.9, $P < 0.05$), and separation was observed as early as Week 1. A significantly greater decrease in the change from baseline to Week 8 in the CGI-S was also observed for ulotaront versus placebo ($P < 0.01$). Similarly, a higher HAM-A response rate was observed compared with placebo (54.3% vs 41.7%, $P < 0.01$). Remission rates were also higher in the ulotaront group compared with placebo (22.9% vs 15.1%, nominal $P < 0.05$). Most adverse events (AEs) were mild to moderate. Both serious and severe AEs were infrequent. AEs occurring in the ulotaront group at a frequency of $\geq 5\%$

and > placebo were dizziness, nausea, headache, somnolence, dry mouth, fatigue, vomiting, and constipation. The discontinuation rate due to AEs was low for both the ulotaront (8.4%) and placebo (2.3%) groups.

Conclusion: Ulotaront demonstrated efficacy in improving anxiety symptoms in adults with GAD along with a favorable safety and tolerability profile, supporting its potential as a novel treatment option for GAD.

T12. MAZINDOL IR/SR: A 50-YEAR LEGACY REPOSITIONED AS A FIRST-IN-CLASS OREXIN–MONOAMINE MODULATOR FOR ADHD AND AROUSAL-RELATED DISORDERS

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Abstract: Mazindol, originally introduced in the 1970s, is being repositioned in modern immediate-release (IR) and sustained-release (SR) formulations as a multimodal neuromodulator targeting the intersection of monoaminergic, orexinergic, and opioid signaling systems. Mazindol IR/SR exhibits a unique pharmacological profile combining dopamine and norepinephrine transporter inhibition, serotonergic engagement, partial orexin-2 receptor (OX2R) modulation, and interaction with opioid-related pathways. This integrated mechanism supports a unifying hypothesis: disorders such as adult ADHD, Central Disorders of Hypersomnolence (including narcolepsy), and opioid use disorder (OUD) share a common pathophysiology of alertness instability, reward dysregulation, and impaired motivational control. In a previous randomized, placebo-controlled Phase 2b study in adults with ADHD, mazindol IR/SR demonstrated rapid onset of efficacy (Week 1), robust symptom improvement, and favorable tolerability without stimulant-like dopaminergic release. In narcolepsy and other central hypersomnolence disorders, the POLARIS study demonstrated clinically meaningful reductions in excessive daytime sleepiness and improvements in wake stability. Preclinical models further showed restoration of wakefulness in orexin-deficient paradigms and attenuation of opioid-conditioned place preference and withdrawal behaviors, supporting exploration in fentanyl-related OUD and stimulant–opioid co-use. The therapeutic implications of mazindol IR/SR extend beyond single-indication targeting. Through simultaneous modulation of arousal (orexin), executive function (dopamine/norepinephrine), and reward circuitry (opioid–monoamine interaction), mazindol IR/SR may represent a platform approach for arousal deficit syndromes. This broad-spectrum activity differentiates mazindol IR/SR from classical stimulants and selective OX2R agonists by addressing both wake stabilization and reward regulation within a single pharmacological framework. With a 50-year safety legacy, modern formulation refinement, Phase 2 validation in ADHD, clinical

data in narcolepsy (POLARIS), and translational evidence in opioid-related models, mazindol IR/SR is positioned as a scalable neurotherapeutic candidate across disorders characterized by alertness dysregulation and motivational instability.

T13. COMPREHENSIVE MULTITARGET STRATEGY FOR TYPE 1 DIABETES AND ASSOCIATED NEUROLOGICAL/SLEEP DISORDERS (DANS): INTEGRATING STEM-CELL-DERIVED ISLET REPLACEMENT, IMMUNE MODULATION, AND NEURO-CIRCADIAN THERAPEUTICS

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Abstract: Type 1 diabetes (T1D) manifests as a systemic disorder, with hyperglycemia driving interconnected pathways of neuroinflammation, oxidative stress, β -cell loss, orexin deficits, and circadian disruption. These mechanisms underpin Diabetes-Associated Neurological and Sleep Disorders (DANS), exacerbating metabolic instability alongside neuropathy, cognitive decline, and sleep dysregulation. To address this holistically, NewCelX and its NCEL-101/IsletRx stem-cell-derived islet platform, in strategic collaboration with Eledon Pharmaceuticals, pioneers tegoprubart (anti-CD40L mAb, formerly AT-1501)-mediated immune protection. This enables durable graft survival and potential T1D functional cure, as evidenced by clinical insulin independence without calcineurin inhibitor toxicities, thereby restoring glycemic control to mitigate DANS progression. Synergizing with this regenerative core, Aexon Labs and its multitarget dihydroquinazoline/dihydrobenzoxazine/dihydrobenzothiazine platform (featuring DOXA compounds for orexin restoration, Sig-1R modulation, CTSS/CTSL inhibition, and SGLT2/adiponectin targeting) directly combats DANS through anti-inflammatory, neuroprotective, and metabolic actions—reducing neuroinflammation/oxidative stress, preserving β -cell/neural integrity, enhancing glucose control/insulin sensitivity, and normalizing circadian/energy/cognitive functions. Preclinical data unify these elements: orexin A preconditioning enhances islet graft outcomes (e.g., insulin sensitivity, GLUT-4 expression, β -cell survival) while inhibiting high-glucose-induced NLRP3 inflammasome activation in endothelium via SIRT1-dependent suppression of ROS/NOX4/TxNIP/HMGB1 and IL-1 β /IL-18. Sig-1R/DOXA modulation further amplifies neuroprotection in diabetic complications, complementing tegoprubart's anti-CD40L blockade—which curbs NLRP3-linked inflammation—thus safeguarding grafts and alleviating DANS. This integrated framework—stem-cell regeneration + targeted immunomodulation + neuro-circadian therapeutics—transforms T1D/DANS management, accelerating clinical translation, regulatory progress, and scalable therapies.

T14. INVESTIGATING THE SAFETY, EFFICACY, AND TOLERABILITY OF ADJUNCTIVE CARIPRAZINE TREATMENT TO PSYCHOSTIMULANTS IN ADULTS WITH ADHD: A PRELIMINARY STUDY

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Abstract Background: Many patients with complex and severe ADHD experience sub-optimal benefits with psychostimulant treatment and may require alternative psychotropic medications that target the remaining debilitating symptoms of ADHD. As an atypical antipsychotic acting as a partial Dopamine (DA) agonist at D2 and D3 and Serotonin (5HT) 5HT1A receptors, cariprazine may have the potential to increase DA, Noradrenergic (NA) activity and improve ADHD symptoms. Therefore, this study aimed to examine whether adjunctive treatment of cariprazine would increase the efficacy of standard psychostimulant treatment in patients with ADHD who had an inadequate response to psychostimulants alone.

Methods: Subjects (N=10) included adult psychiatric outpatients (Mage = 42.80, SD = 11.22) previously diagnosed with ADHD, with or without secondary comorbidities. Participants were administered 1.5mg of cariprazine daily for the first week of the study and flexibly titrated up to a maximum of 3mg/day.

Results: Results from paired samples t-tests showed significant improvements in BAARS-IV scores, $t(9) = 2.46$, $p = 0.036$, ASRS scores, $t(9) = 1.88$, $p = 0.046$, CGI-S scores, $t(8) = 3.41$, $p = 0.005$, visuospatial working memory, $t(6) = -2.56$, $p = 0.021$, episodic memory, $t(6) = -3.09$, $p = 0.011$, and response inhibition, $t(6) = -2.53$, $p = 0.022$, between baseline measures and post-treatment.

Discussion: Results from this preliminary study suggest adjunctive treatment of cariprazine may be efficacious in reducing residual ADHD symptoms, lessen clinical severity of global mental illness, and enhance cognitive functioning among individuals with ADHD. Thus, future studies should investigate the mechanisms underlying cariprazine treatment through the normalization of DA activity.

T15. ASRS OUTCOMES ACROSS CORE AND EXPANDED SYMPTOM DOMAINS AFTER 6 WEEKS OF CENTANAFADINE TREATMENT IN ADULTS WITH ADHD: A POOLED POST HOC ANALYSIS OF TWO PHASE 3 TRIALS

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Abstract Background: Attention-deficit/hyperactivity disorder (ADHD) is a chronic and prevalent neurodevelopmental disorder in adults, characterized by core symptoms of inattention, hyperactivity, and impulsivity. Despite treatments that manage core symptoms, significant unmet needs persist for adults with ADHD, particularly with respect to associated features such as emotional dysregulation and executive dysfunction. This pooled post hoc analysis of two phase 3 trials evaluated the effect of centanafadine (CTN)—a norepinephrine, dopamine, serotonin reuptake inhibitor—on patient-reported assessment of the frequency of core symptoms and associated features of ADHD after 6 weeks of treatment in adults aged 18–55 years.

Methods: Data from two identically designed phase 3 trials were pooled. Eligible patients with a primary ADHD diagnosis per DSM-5 were randomized to receive CTN 200 or 400mg/day or placebo. Exploratory endpoints included changes from baseline in the adult ADHD Self-Report Scale (ASRS-18) Total score and Inattention (IA) and Hyperactive/Impulsive (H/I) subscale scores, as well as Executive Function (EF) and

Emotional Dyscontrol (ED) subscale scores from the ASRS Expanded Version at Week 6. The ASRS is a validated, self-administered questionnaire used to screen, assess, and quantify symptom severity using a 5-point Likert scale (0=never to 4=very often). Endpoints were analyzed using a mixed-effects model for repeated measure without adjusting for multiplicity.

Results: A total of 744 adults were included in the efficacy sample (CTN 200mg, n=242; 400mg, n=241; placebo, n=261). At Week 6, adults treated with CTN reported greater improvements in ADHD symptom frequency per ASRS Total score vs placebo (least-squares mean difference 200mg: -4.8, $P < 0.0001$; 400mg: -5.3; $P < 0.0001$). CTN demonstrated similar patient-reported improvements in the ASRS IA (200mg: -2.9, $P < 0.0001$; 400mg: -2.8, $P < 0.0001$) and H/I (200mg: -2.0, $P < 0.0001$; 400mg: -2.6, $P < 0.0001$) subscale scores vs placebo at Week 6. Effect sizes (Cohen's D) were 0.42 and 0.45 for ASRS IA and 0.30 and 0.42 for H/I at the 200mg and 400mg doses, respectively. Consistent with the core symptom domains, improvements were observed in both the EF (200mg: -2.4, $P=0.0007$; 400mg: -2.5, $P < 0.0001$) and the ED (200mg: -0.9, $P=0.0023$; 400mg: -0.9, $P < 0.0006$) subscale scores of the ASRS Expanded Version. For ASRS EF, effect sizes were 0.36 at 200mg and 0.38 at 400mg; for ED, corresponding effect sizes were 0.27 and 0.31, respectively.

Conclusions: CTN was associated with improvements from baseline in the ASRS Total score and subscales assessing both core symptoms and associated features of ADHD, including executive dysfunction and emotional dysregulation, with effects of similar magnitude across domains.

T16. EXECUTIVE FUNCTION SYMPTOM OUTCOMES IN ADULTS WITH ADHD TREATED WITH CENTANAFADINE: A POOLED POST HOC ANALYSIS OF TWO PHASE 3 TRIALS

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Abstract Background: Attention-deficit/hyperactivity disorder (ADHD) in adults frequently includes impairments in executive functions such as organization, planning, time management, and working memory. This pooled post hoc analysis of two phase 3 trials evaluated the effect of centanafadine (CTN)—a norepinephrine, dopamine, serotonin reuptake inhibitor—on patient-reported assessment of executive functioning using the adult ADHD Self-Report Scale (ASRS) Expanded Version after 6 weeks of treatment in adults with ADHD.

Methods: Data from two identically designed phase 3 trials were pooled. Eligible patients (aged 18–55 years) with a primary ADHD diagnosis per DSM-5 were randomized to receive CTN 200 or 400mg/day or placebo. Exploratory endpoints included changes from baseline in the Executive Function (EF) subscale score and individual EF line items from the ASRS Expanded Version at Week 6. The ASRS Expanded Version is a validated, self-administered questionnaire that includes 9 items assessing aspects of executive dysfunction, with responses rated on a 5-point Likert scale (0=never to 4=very often). Endpoints were analyzed using a mixed-effects model for repeated measure without adjusting for multiplicity.

Results: A total of 744 adults were included in the efficacy sample (CTN 200mg, n=242; 400mg, n=241; placebo, n=261). At Week 6, adults treated with CTN reported improvements from baseline in the ASRS EF subscale compared with placebo, reflecting reductions in the frequency of patient-reported executive functioning difficulties (200mg: -2.4, $P < 0.0001$; 400mg: -2.6, $P < 0.0001$). Effect sizes (Cohen's D) for the ASRS EF subscale were 0.36 for CTN 200mg and 0.38 for 400mg, and were comparable in magnitude to those for core symptom subscales assessing Inattention and Hyperactivity/Impulsivity. Consistent with the subscale-level findings, improvements from baseline vs placebo were observed across individual ASRS EF line items at Week 6, including those related to time management, planning and prioritization, task initiation and completion, and working memory-related difficulties.

Conclusions: In this pooled post hoc analysis, CTN was associated with improvements in patient-reported executive functioning in adults with ADHD, as assessed by the ASRS Expanded Version. Improvements were observed across a broad range of executive function items, including time management, planning and prioritization, task initiation and completion, and working memory-related difficulties.

T17. PATHOPHYSIOLOGICAL ANALYSIS OF AUTISM SPECTRUM DISORDER FOCUSING ON PERIPHERAL BLOOD MACROPHAGES

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Abstract: Autism spectrum disorder (ASD) is a complex neurodevelopmental disorder characterized by impaired social interaction, poor communication skills, and restricted or repetitive patterns of behavior and interests. Although its etiology and pathogenesis remain unclear, recent studies suggest that inflammation and immune system abnormalities affect brain development. Microglia, the main immune cells in the brain, are known to influence brain development through the secretion of cytokines, trophic factors, and synaptic phagocytosis. However, it is difficult to directly collect and analyze microglia from living humans. Although the origins of microglia and macrophages differ, microglia are identified as tissue-resident macrophages with similar functions. Therefore, we hypothesized that examining macrophages in ASD could provide new insights into microglial function and ASD pathology. We performed our analysis using macrophages polarized from peripheral blood mononuclear cells by granulocyte-macrophage colony-stimulating factor (GM-CSF) and macrophage colony-stimulating factor (M-CSF). We previously reported that the expression of tumor necrosis factor- α (TNF- α) in differentiated GM-CSF induced macrophages (GM-CSF M Φ) was significantly higher in individuals with ASD than in typically developing (TD) individuals (Yamauchi et al., Autism Research 2021). However, since it remained unclear how this high expression of inflammatory cytokines affects the nervous system, we established a co-culture system using human induced pluripotent stem cell (hiPSC)-derived neurons and macrophages. The results showed that co-culture of GM-CSF M Φ induced dendritic atrophy through the secretion of pro-inflammatory cytokines, interleukin-1 α (IL-1 α) and TNF- α . Macrophages derived from individuals with ASD exerted more severe effects than those derived from TD individuals. Furthermore, we demonstrated that co-administering neutralizing antibodies of TNF- α and IL-1 α rescued the dendritic

atrophy (Takada et al., Molecular Autism 2024). Next, we focused on synaptic phagocytosis capacity. We established an experimental system to evaluate macrophage synaptic phagocytosis by adding synaptosomes purified from hiPSC-derived neurons to polarized macrophages. We revealed that M-CSF MΦ exhibited higher phagocytosis capacity compared to GM-CSF MΦ, whereas ASD-M-CSF MΦ showed a marked impairment in phagocytosis. Additionally, we found a positive correlation between phagocytosis capacity and the expression of CD209, a C-type lectin receptor (Nishi et al., Molecular Psychiatry 2025). These results support the hypothesis of microglial abnormalities in ASD and provide new insights into the pathology of ASD.

T18. PSYCHOTROPIC PRESCRIBING TRENDS WITHIN THE TEXAS JUVENILE JUSTICE DEPARTMENT FROM 2016 TO 2024

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Abstract Background: Psychiatric disorders are highly prevalent among justice-involved youths, with estimates showing up to 75% of these individuals meeting criteria for a mood, anxiety or behavioral disorder. Mental health treatment among justice-involved youth has been shown to reduce recidivism. However, limited data exists regarding psychotropic medication usage within this population. This study aims to investigate trends within the psychotropic medication usage within the Texas Juvenile Justice Department (TJJD).

Methods: This was a retrospective cohort study of all youths detained for any duration in TJJD from 2016 through 2024. Using statewide electronic medical, psychological, and administrative records, we investigated trends in prescribing patterns for major subgroups of psychotropic medications: antidepressants, first-generation antipsychotics, second-generation antipsychotics, mood stabilizers and stimulants. Outcomes were the number of youths prescribed any of these medications. We used linear regression to explore temporal trends in prescribing.

Results: During the study period, the overall population ranged from 1,170 to 2,003 youths. Males (89.1%-91.3%) outnumbered females (8.7%-10.9%). The mean age was 16.1 (SD 1.2, range 10-18). The percentage of youths receiving any antidepressant ranged from 25.7%-65.1%. The percentage of youths receiving a first- or second-generation antipsychotic ranged from 0.1%-0.5% and 19.6%-37.2% respectively. The percentage of youths receiving mood stabilizers ranged from 9.0%-16.0%. The percentage of youths receiving stimulants ranged from 12.1%-17.2%. Linear regression analyses demonstrated significant increases in prescribing rates for antidepressants, second-generation antipsychotics, mood stabilizers, and stimulants ($p < 0.05$). Year explained a substantial proportion of variance for stimulants ($R^2 = 0.78$), antidepressants ($R^2 = 0.73$), and atypical antipsychotics ($R^2 = 0.85$). First-generation antipsychotics showed a nonsignificant downward trend ($p=0.15$).

Discussion: We observed significant increases in the prescribing rates for several classes of psychotropic medications, likely reflecting improved recognition and treatment of psychiatric disorders in this vulnerable population. The negative trend in first generation antipsychotic prescribing, though nonsignificant, may be related to the increased utilization of second-

generation agents with more favorable side effect profiles. Further research is needed to examine if these prescribing trends impact outcomes in justice-involved youth.

T19. SLEEP ARCHITECTURE IN PARTICIPANTS WITH INSOMNIA DISORDER CHARACTERIZED BY PHENOTYPE: OBJECTIVE SHORT SLEEP OR OBJECTIVE NORMAL SLEEP

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Abstract Background: Insomnia can be classified into 2 different phenotypes through objective sleep evaluations (insomnia with objective short-sleep duration [I-SSD]: total sleep time (TST) < 6 hours/night; insomnia with objectively longer, more normal sleep duration (I-NSD): TST ≥ 6 hours/night). I-SSD has the potential for more severe biological consequences. These analyses compared the sleep architecture responses of I-SSD and I-NSD patients to pharmacotherapy using 2 medications with different mechanisms of action, lemborexant (LEM) and zolpidem tartrate extended-release (ZOL).

Methods: Study 304 (E2006-G000-304; NCT02783729) was a 1-month, randomized, double-blind, placebo (PBO)-controlled, active-comparator study in adults (≥55 years) with insomnia disorder. Participants received PBO, LEM 5 mg (LEM5), LEM 10 mg (LEM10), or ZOL 6.25 mg. Least squares mean (LSM) duration of each sleep stage (minutes) was compared across treatment groups on Nights (NT)1/2 and NT29/30 for participants in the I-SSD and I-NSD groups. Treatment-emergent adverse events were recorded.

Results: Of 1006 participants (PBO: 208; ZOL: 263; LEM5: 266; LEM10: 269), 711 (70.7%) were in the I-SSD subgroup, and 295 (29.3%) were in the I-NSD subgroup. Demographic characteristics were mostly balanced. Mean (SD) age was 64.4 (7.0) years for the I-SSD group and 62.8 (6.2) years for the I-NSD group. Males comprised 16.6% of the I-SSD group and 6.4% of the I-NSD group. In I-SSD participants, mean (SD) increases from baseline (BL) in non-rapid eye movement (non-REM) sleep time were significant for LEM5 (55.7 [37.5]; 57.6 [40.5]), LEM10 (59.9 [39.2]; 57.6 [41.6]), and ZOL (59.5 [39.8]; 47.4 [45.9]) versus PBO (19.3 [40.4]; 29.4 [41.0]) on NT1/2 and 29/30, respectively. I-SSD participants treated with LEM had significantly larger differences from BL in non-REM sleep time compared with ZOL at NT29/30. In I-NSD participants, increases from BL in non-REM sleep time were significant for LEM5 (23.2 [22.8]; 25.2 [23.4]), LEM10 (17.3 [20.7]; 16.7 [26.8]), and ZOL (26.1 [34.5]; 15.9 [30.1]) versus PBO (2.7 [25.1]; 3.1 [29.4]) on NT1/2 and 29/30, respectively. The increases from BL in non-REM sleep time were not statistically significant for LEM versus ZOL. In I-SSD participants, mean (SD) increases from BL in REM sleep time were significant at both time points, respectively, for the LEM5 (24.1 [22.0]; 18.1 [22.3]) and LEM10 (34.0 [23.1]; 24.4 [24.8]) subgroups versus the PBO (5.5 [17.4]; 5.5 [21.4]) and ZOL (9.9 [22.3]; 8.7 [22.9]) subgroups. In I-NSD participants, increases from BL in REM sleep time were significant for LEM10 (25.9 [19.9]; 15.7 [20.0]) at NT1/2 and 29/30, respectively, but only at NT29/30 for LEM5 (NT1/2: 8.6 [19.2]; NT29/30: 6.6 [17.8]) versus PBO (NT1/2: 3.8 [16.6]; NT29/30: 1.1 [19.4]). LEM5 and LEM10 led to statistically larger increases in REM sleep time versus ZOL (−4.6 [20.1]; −4.1 [18.9]) at both time points, respectively. LEM was well tolerated in both I-SSD and I-NSD subgroups.

Conclusions: Regardless of whether participants were classified as having insomnia with short sleep duration or normal sleep duration, LEM tended to increase both non-REM and

REM sleep time compared with both ZOL and PBO. The magnitude of change depended on the insomnia phenotype classification, with somewhat larger increases observed in the I SSD subgroup for both drugs. Unlike LEM, ZOL only significantly increased non-REM sleep time versus placebo, likely reflecting its different mechanism of action.

T20. PSILOCYBIN-ASSISTED PSYCHOTHERAPY FOR CLUSTER B PERSONALITY DISORDERS AND COMORBID TREATMENT-RESISTANT DEPRESSION

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Abstract Introduction: Cluster B personality disorders (PDs) are highly comorbid with both major depressive disorder (MDD) and bipolar disorder (BD). An estimated 20% of individuals with MDD and 30% of people with BD (I and II) meet criteria for a concurrent cluster B PD diagnosis. This large subset of individuals with comorbid cluster B PDs and mood disorders (MDD or BD) have a substantially elevated likelihood of suicidal behaviour, which is mediated by the greater length of time spent in a depressive episode compared to those without a PD diagnosis. This suggests that treating depression symptoms in those with concurrent cluster B PD can be critical for reducing lifetime suicide risk. Despite the high rates of comorbidity with depression and association with suicide attempts, individuals with Cluster B PDs and co-occurring depression experience attenuated antidepressant response - in particular, the presence of a comorbid cluster B PD diagnosis is associated with more than double the likelihood of non-response to depression treatments compared to depression alone, inclusive of pharmacological, psychological, and neurostimulation interventions. While psilocybin-assisted psychotherapy (PAP) has shown promise for rapidly reducing depressive symptoms in treatment-resistant depression, no clinical trials to date have reported on PAP in comorbid depression and personality disorders. In fact, individuals with PDs have historically been excluded from most PAP trials.

Method: This study is the first clinical trial to describe a subgroup of ten participants with a comorbid PD and depression (MDD or BD) who underwent PAP within a larger open-label trial and followed for six months. Participants were eligible for up to three doses of psilocybin-assisted psychotherapy during this six-month period. Depression and suicidal ideation (SI) were measured using the Montgomery-Åsberg Depression Rating Scale (MADRS) and MADRS SI item. Quality of life was measured using the WHO-5. Dissociation during and after dosing was measured using the Clinician Administered Dissociative States Scale.

Results: Three participants received one dose, five received two doses, and two participants received three doses of psilocybin accompanied by the psychotherapy protocol (preparatory sessions, monitored dosing sessions, and integration sessions). Mean MADRS scores decreased from 30.4 (SD = 6.1) pre-treatment to 22.5 (SD = 11.7) at day one, 24.9 (SD = 10.9) at week 2, and 22.3 (SD = 11.5) at month 6. SI declined from 3.2 (SD = 1.7) to 1.6 (SD = 2.1) at day one, 2.3 (SD = 2.0) at week 2, and 1.2 (SD = 2.04) at month 6. WHO-5 scores improved from 11.2 (SD = 10.12) pre-treatment to 18.5 (SD = 13.61) at day one, 26.67 (SD = 28.47) at week 2, and 21.71 (SD = 18.45) at month 6. Average dissociation scores decreased post-dosing (peak: M = 13.89, SD = 3.98; post-dosing M = 5.95, SD = 4.85). No serious adverse events were recorded.

Significance: This is the first clinical trial evidence that PAP may reduce depression and SI in comorbid cluster B PDs. However, there was substantial heterogeneity within the sample and outcomes. Further study is merited regarding the inclusion of adults with comorbid personality disorders in clinical trials of psilocybin-assisted psychotherapy.

T21. PHARMACOTHERAPIES FOR CO-OCCURRING STIMULANT USE DISORDER AND ADHD: A NETWORK META-ANALYSIS

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Abstract Importance: Stimulant use disorder (StUD) and attention-deficit/hyperactivity disorder (ADHD) frequently co-occur, complicating treatment decisions and raising concerns regarding stimulant prescribing. Evidence guiding pharmacologic management of individuals with both conditions remains limited.

Objective: To evaluate the efficacy and safety of pharmacotherapies for adults with co-occurring StUD and ADHD using network meta-analysis.

Data Sources: PubMed, Embase, Scopus, Web of Science, and ClinicalTrials.gov were searched through January 28, 2026 for randomized controlled trials (RCTs).

Study Selection: Eligible studies were RCTs enrolling adults with both StUD and ADHD; six trials published between 2002 and 2015 met inclusion criteria.

Data Extraction and Synthesis: Outcomes included stimulant abstinence, negative urine toxicology, ADHD symptom severity, and global clinical improvement. Interventions were methylphenidate, mixed amphetamine salts (MAS), and bupropion. Random-effects network meta-analyses were conducted using standardized mean differences (SMDs) and odds ratios (ORs); treatment ranking was assessed with P-scores.

Results: Higher-dose stimulant regimens demonstrated superior outcomes across multiple domains. MAS showed the greatest benefit for continuous abstinence versus placebo (OR = 8.45; 95% CI, 2.55–27.98; $p = 0.0005$), with the 80-mg dose ranking highest (P-score = 0.87). Pharmacotherapy also increased the odds of negative urine toxicology (OR = 1.65; 95% CI, 1.01–2.71; $p = 0.05$), again favoring higher-dose MAS (P-score = 0.93). ADHD symptoms were significantly reduced overall (SMD = -0.59 ; 95% CI, -0.94 to -0.23 ; $I^2 = 43\%$), with the greatest improvement observed for methylphenidate 180 mg (P-score = 0.91). CGI improvement did not differ significantly from placebo. Lower-dose methylphenidate and bupropion demonstrated smaller or inconsistent effects. Adverse events were generally mild to moderate and comparable to placebo.

Conclusions: In adults with co-occurring StUD and ADHD, stimulant-based pharmacotherapies, particularly higher-dose MAS and methylphenidate, were associated with improved stimulant-use outcomes and ADHD symptom control. These findings support consideration of optimized stimulant dosing with careful monitoring in this population, while highlighting the need for larger, contemporary trials.

T22. EFFECTS OF GLUCAGON-LIKE PEPTIDE 1 RECEPTOR AGONISTS (GLP-1RAS/GLP-1S) INTEGRATION IN PATIENTS UTILIZING ANTIPSYCHOTICS

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Abstract: Psychotropic medications, especially antipsychotics, such as olanzapine and clozapine, have been known to cause the most metabolic adverse effects in psychiatric patients. While lifestyle modifications are highly recommended as a first-line, they are not often followed by most psychiatric patients and so far metformin has been one of the most successful treatments to help reduce the antipsychotic-induced. More recently, glucagon-like peptide-1 receptor agonists (GLP-1/GLP-1RAs) have been on the rise in mitigating metabolic issues in psychiatric and other patient populations. This review utilized a primary literature search across key electronic databases and journals, including PubMed, Embase, and Google Scholar, to identify eligible articles for this review. Key inclusion criteria for this study focused on articles published within 10 years exploring glucagon-like peptide 1 receptor agonist use in patients with concurrent antipsychotic use. Search phrases included “glucagon-like peptide 1 receptor agonist (GLP-1/GLP-1RA) and schizophrenia”, “GLP-1 and antipsychotic use”, and/or “GLP-1 and olanzapine”, which yielded 14 studies that met the inclusion criteria. In 14 reviewed studies, GLP-1s have been shown to decrease weight and BMI in patients experiencing metabolic side effects from antipsychotic use without increasing psychiatric adverse effects. Two preclinical rodent trials found that GLP-1 receptor agonists reduced metabolic disturbances caused by antipsychotics and improved measures such as glucose tolerance and insulin sensitivity. Consistent with these findings, three studies in human populations receiving antipsychotic medications demonstrated significantly greater weight loss in GLP-1 adjunctive therapy groups compared to standard treatment alone. These randomized controlled trials and comparative studies have found that patients were more likely to experience a > 5% weight decrease in weight-loss trials and comparative studies have found that patients were more likely to experience a > 5% weight decrease compared to other methods or placebo groups. Additionally, two studies involving semaglutide demonstrated improvements in metabolic biomarkers beyond weight reduction. These studies reported significant reductions in HbA1c, fasting glucose, and insulin resistance, thereby demonstrating direct metabolic benefits independent of weight-loss effects. Across all reviewed studies, GLP-1 receptor agonists were well tolerated with gastrointestinal side effects being the most commonly reported adverse effect, and no evidence of worsening psychiatric symptoms. GLP-1s have been shown to effectively attenuate metabolic effects associated with antipsychotic use without causing any worsening mental health symptoms in these patients. Further research will be needed to investigate if GLP-1s will have caused any long-term issues in patients who have been on this for years, as well as physical and mental repercussions in the psychopharmacological setting.

T23. PREVALENCE OF PSYCHOTROPIC MEDICATION USE AMONG PATIENTS WITH CHRONIC AND IMMUNE-MEDIATED DISEASES: A REAL-WORLD ANALYSIS USING EPIC COSMOS

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Abstract Background: Psychiatric conditions frequently co-occur with chronic and immune-mediated diseases; however, large-scale real-world data describing psychotropic medication use within these populations are limited. Characterizing psychotropic medication use across medically complex patient groups may help inform future studies of psychiatric comorbidity and prescribing patterns.

Methods: We conducted a retrospective, cross-sectional analysis using Epic Cosmos, a national de-identified electronic health record database, including encounters from October 10, 2022 through October 9, 2025. Adult patients with diagnoses of common variable immunodeficiency (CVID), type 1 diabetes mellitus (T1DM), rheumatoid arthritis, Crohn's disease, ulcerative colitis, multiple sclerosis, systemic lupus erythematosus, and asthma were identified. Psychotropic medication use was defined as prescription of commonly used antidepressants and anxiolytics, including selective serotonin reuptake inhibitors (SSRIs), serotonin–norepinephrine reuptake inhibitors (SNRIs), atypical antidepressants, and benzodiazepines. For each condition, the total disease population and the number of patients prescribed at least one psychotropic medication were quantified. Condition-specific prevalence of psychotropic medication use was calculated.

Results: Psychotropic medication use varied across disease populations. Prevalence ranged from 1.87% among patients with rheumatoid arthritis to 9.83% among patients with ulcerative colitis. Higher prevalence was observed among patients with asthma (7.23%), multiple sclerosis (6.06%), and systemic lupus erythematosus (5.58%). Moderate prevalence was identified in Crohn's disease (3.77%), CVID (3.78%), and T1DM (3.36%). These findings demonstrate measurable psychotropic medication use among patients with chronic and immune-mediated diseases, with notable variation by condition.

Conclusions: Psychotropic medication use is common among patients with chronic and immune-mediated diseases, reflecting frequent co-occurrence of psychiatric treatment within these populations. These descriptive findings are hypothesis-generating and do not imply causality. Future analyses incorporating psychiatric diagnoses, demographic characteristics, and longitudinal data are needed to better characterize patterns of psychiatric comorbidity and psychotropic prescribing in medically complex patients.

T24. PROSPECTIVE REPLICATION OF AN EEG BIOMARKER FOR PREDICTING CHANGES IN ATTENTION IN ALTO-203, AN H3 INVERSE AGONIST

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Abstract Background: Psychiatric disorders are heterogeneous, leading to drugs developed in broad populations showing no or minimal benefit over placebo. Predictive biomarkers may enhance treatment effects by targeting subpopulations for a given drug and reducing trial and error prescribing. ALTO-203 is an H3 inverse agonist that releases dopamine, norepinephrine, acetylcholine, and histamine, suggesting a pro-wakeful, pro-cognitive profile that may be beneficial for Major Depressive Disorder (MDD) and other disorders. A prior Phase 1 trial in healthy volunteers showed acute benefits on subjective positive emotion and alertness, along with improved attention and reduced theta/beta ratio (TBR), a

neurophysiological index of cortical arousal and attentional control. Moreover, subjects with higher TBRs at baseline showed greater changes in attention with ALTO-203 than subjects with lower TBRs, suggesting that ALTO-203 may be better at improving attention in those with higher TBRs ratios. A subsequent study was conducted with a goal of replicating the Phase 1 findings in MDD participants.

Methods: 69 participants with MDD and anhedonia (defined as a Snaith Hamilton Pleasure Scale [SHAPS] > 28) were enrolled in a Phase 2 proof-of-concept (POC) trial of ALTO-203 (NCT06391593). Participants underwent a single-dose period, in which they received two single-doses of ALTO-203 (25µg and 75µg) and placebo in a three-way crossover design with an at least 10-day washout period. The primary outcome was an acute change in positive emotion assessed by the Bond-Lader Visual Analog Scale (BL-VAS). Participants underwent cognitive assessments, electroencephalography (EEG), and sleep and activity monitoring using a wearable device. Following the single-dose period, participants received daily administration of ALTO-203 (25µg or 75µg QD) or placebo over 28 days to evaluate extended safety, tolerability and pharmacokinetics. Our analysis set includes 52 participants that passed blinded prospective central review and completed the single-dose period. Mixed-effects models evaluated the efficacy of ALTO-203 versus placebo; subgroup analyses of subjects with higher TBRs were also tested. Statistical significance was evaluated with two-sided p-values with no correction for multiple comparisons.

Results: There was no significant difference between ALTO-203 and placebo on the BL-VAS as there was a higher than expected placebo response ($p > 0.407$). Compared to placebo, ALTO-203 improved attention (25µg $p < 0.05$; 75µg $p = 0.06$) and decreased TBRs (25µg $p < 0.05$). Improvement in attention with ALTO-203 was greatest among participants with high baseline TBRs (25µg: $p < 0.01$; 75µg: $p < 0.05$ vs. placebo). Increased wakefulness (reduced minutes asleep) supported the wake-promoting effects of ALTO-203 (25µg: $p < 0.05$; 75µg: $p < 0.001$ vs. placebo). ALTO-203 displayed predictable accumulation over multiple doses and was well tolerated, with insomnia as the most frequent adverse event.

Conclusions: These data replicate prior findings that ALTO-203, a novel H3 inverse agonist, improves sustained attention and cortical arousal, and that individuals with higher TBRs are more likely to realize the greatest benefit in sustained attention. These data suggest that ALTO-203 may be best suited for disorders with hypersomnolence or excessive daytime sleepiness, along with deficits in attention. The cross-over design of the study allowed an efficient assessment of ALTO-203 in patients.

T25. BH-200 (NELIVAPTAN), A VASOPRESSIN V1B RECEPTOR ANTAGONIST, IN GENETICALLY DEFINED SUBGROUPS OF MDD: PRECISION TARGETING OF HPA-AXIS DYSREGULATION IN THE OLIVE PHASE 2 PROGRAM

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Abstract: Disturbances of hypothalamic–pituitary–adrenal (HPA) axis function are implicated in a biologically defined subset of patients with major depressive disorder (MDD). Pharmacologic modulation of the stress hormone system, including CRHR1 and vasopressin V1b receptor (V1bR) antagonism, has been explored for decades; however, trials conducted

in unselected MDD populations have not led to regulatory approval. We hypothesized that biological heterogeneity dilutes treatment effects and that stress-axis-driven subgroups can be prospectively identified. In a prior positive Phase 2 trial with the selective V1bR antagonist BH-200 (nelivaptan), a bimodal distribution of response suggested distinct responder populations. Because the dexamethasone–CRH (Dex-CRH) test is not practical for routine use, a genetic classifier (V1b polygenic score; V1bPGS) was developed based on vasopressin signaling biology and Dex-CRH–characterized cohorts. The 14-SNP tool assigns patients to three subgroups (A, B, C), reflecting differential ACTH suppression profiles and putative vasopressin pathway activity. The OLIVE trial was a randomized, double-blind, placebo-controlled Phase 2 trial conducted in eight European countries. A total of 338 patients with MDD were randomized 2:1 to BH-200 250 mg BID or placebo for eight weeks. The prespecified primary endpoint was change from baseline to Week 8 on the 17-item Hamilton Depression Rating Scale (HAM-D-17) in patients classified as Subgroup C. In the modified intention-to-treat population (N=331), BH-200 demonstrated clinically meaningful improvement versus placebo ($\Delta = -2.98$, $p = 0.0003$). Treatment separation emerged early and was sustained through a 4-week follow-up. Response rates ($\geq 50\%$ reduction in HAM-D-17) were 50.0% with BH-200 versus 25.7% with placebo, odds ratio (OR), 2.98 (95% CI, 1.74, 5.10), and remission rates (HAM-D-17 ≤ 7) were 25.8% versus 16.8%, OR 1.62 (95% CI, 0.86, 3.08) respectively. In the prespecified primary analysis population (Subgroup C; n=123), the treatment difference was $\Delta = -1.94$ ($p = 0.153$; Cohen's d 0.28). However, genetic stratification revealed marked heterogeneity of effect. The largest benefit was observed in Subgroup A (n=89), with $\Delta = -4.47$ ($p = 0.005$; Cohen's d 0.55), response rate 58.9% versus 25.9%, OR 4.22 (95% CI, 1.51, 11.83), and remission rate 33.9% versus 11.1%, OR 3.82 (95% CI, 0.98, 14.98), with separation evident from Week 1 onward. Subgroup B (n=119) showed intermediate benefit with $\Delta = -2.85$ ($p = 0.037$, Cohen's d 0.49). These findings suggest biologically informative refinement of the classifier, and support optimization of patient enrichment strategies for subsequent development. BH-200 was generally well tolerated. The most frequent adverse event was headache (8.9%). Elevations of ALT or AST $> 3 \times$ ULN occurred in 5.8% of treated patients. These changes were asymptomatic and reversible during treatment or after discontinuation. No serious adverse events occurred in the active arm, and the hepatic signal appears monitorable within standard safety frameworks. The OLIVE program demonstrates that vasopressin V1b receptor antagonism is a viable antidepressant mechanism, and that integration of a biologically grounded genetic companion diagnostic can enhance signal detection and enrich for larger clinical benefit. This precision psychiatry strategy informs the next phase of clinical development for BH-200.

T26. A PHASE 2 CLINICAL TRIAL EXPLORING EFFICACY AND SAFETY OF THE VASOPRESSIN V1B ANTAGONIST BH-200, A TREATMENT FOR MDD, EVALUATING THE PERFORMANCE OF A GENETIC CLASSIFICATION TOOL TO IDENTIFY A SUBSET OF PATIENTS WITH LARGER IMPROVEMENT

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Abstract Background: A disturbance in the hypothalamus-pituitary-adrenals axis (HPA-axis) function has been implicated in a subset of depressed individuals. BH-200 is a selective V1b receptor antagonist, that previously has shown efficacy in a Phase 2 trial in MDD (N=319). A genetic classification tool was used to identify a subset of MDD patients with a robust response to V1b inhibition.

Methods: Using insights in the biology of vasopressin signaling and results from the Dex-CRH test in depressed individuals, a genetic classification tool was developed. It is based on 14 single-nucleotide polymorphisms (SNPs), and classifies patients into three subgroups, A, B, and C, reflecting different levels of suppression of ACTH release from the pituitary. 338 patients with MDD were randomized (2:1) to treatment with BH-200 (250 mg BID), or placebo for eight weeks, in 8 European countries. The primary efficacy endpoint was change vs. placebo in HAM-D17 total score from baseline to Week 8, in Subgroup C patients.

Results: The estimated mean improvement from baseline to Week 8 in the mITT population (N=331) was larger in the BH-200-treated arm than in the placebo arm ($\Delta = -2.98$, $p = 0.0003$). In all three BH-200 treated subgroups, clinically relevant improvements were observed, but the magnitudes of the mean effects between the BH-200-treated arm and the placebo arm were different; Group A, $n=89$, $\Delta = -4.47$, $p = 0.005$, Cohen's d , 0.55; Group B, $n=119$, $\Delta = -2.85$, $p = 0.037$, Cohen's d , 0.49; and, Group C, $n=123$, $\Delta = -1.94$, $p = 0.153$, Cohen's d , 0.28. In Group A, all comparisons between BH-200 and placebo Week 1 had a $p < 0.05$. The findings were supported by results on the MADRS, and on the CGI-S scale. The improvement from baseline was maintained during the 4-week follow-up period. In the full population, 50.0% of the patients in the BH-200 arm and 25.7% of the patients in the placebo arm were responders ($\geq 50\%$ decrease in baseline HAM-D17 score) at Week 8, Odds Ratio (OR) 3.0. In subgroup A, 58.9% of the patients in the BH-200 arm and 25.9% of the patients in the placebo arm were responders by Week 8, respectively, OR 4.2. In the full population, 25.8% of the patients in the BH-200 arm and 16.8% of the patients in the placebo arm reached remission (HAM-D17 score ≤ 7) at Week 8, OR 1.6. In subgroup A, 33.9% of the patients in the BH-200 arm and 11.1% of the patients in the placebo arm achieved remission by Week 8, respectively, OR 3.8. BH-200 was generally safe and well-tolerated. The most frequent adverse event was headache, in 8.9% of the patients in the BH-200 arm. Three serious adverse events in two patients were reported, all in the placebo arm. In the BH-200 arm, 5.8% of the patients had an elevation of AST or ALT concentrations to > 3 times the upper level of normal. The changes were asymptomatic and all reversed while on treatment or after stopping the treatment.

Conclusion: Specific inhibition of V1b signaling appears to be associated with a clinically relevant improvement of depressive symptoms. In an MDD subpopulation characterized by a prespecified genetic tool, the clinical outcome was substantially better than in the full population. The findings suggest that HPA-axis modulators are a viable, novel class of antidepressants. Though efficacy was observed across the population, use in combination with a genetic selection tool appears to enhance the treatment outcome in a subset of MDD patients, showing the promise of precision psychiatry.

T27. FORVISIRVAT (SP-624), A FIRST-IN-HUMAN SIRT6 ACTIVATOR WITH AN EPIGENETIC MECHANISM OF ACTION, CURRENTLY IN A PHASE 2B-3 STUDY FOR THE TREATMENT OF MAJOR DEPRESSIVE DISORDER

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Abstract: Sirtsei Pharmaceuticals is developing forvisirvat, a first-in-human SIRT6 activator with an epigenetic mechanism of action (MoA), for the treatment of MDD. SIRT6 is a NAD⁺ dependent enzyme. SIRT6-deficient mice have a shortened lifespan and phenotypes associated with age-related impairments, cancer, and metabolic disorders. SIRT6 over-expression in mice protects against metabolic pathologies and increases lifespan. SIRT6 has an epigenetic MoA that includes reduced inflammation, enhanced mitochondrial health, metabolic homeostasis and DNA repair. Each of these may play a role in neurodegeneration, metabolic disorders, and psychiatric disorders such as MDD. Both in vitro and animal studies support forvisirvat's role in MDD. It activates SIRT6 deacetylation of histones preventing transcription of DNA. Forvisirvat reduces lipopolysaccharide (LPS)-induced inflammatory cytokines, silences gene pathways responsible for neuroinflammation including the NFκB pathway. It enhances neuroplasticity as evidenced by long-term potentiation assay in vitro and in vivo and prevents cognitive deficits induced by scopolamine (anticholinergic) or phencyclidine (NMDA antagonist) in the novel object recognition test. Forvisirvat works in multiple depression models including LPS- and ACTH-treated mice, olfactory bulbectomized rats and in a model of treatment-resistant depression (forced swim test in Wistar-Kyoto rats). Four phase 1 trials of single oral doses up to 80mg, and 20 and 40mg for 10 days demonstrated forvisirvat was well tolerated and reached target plasma concentrations in healthy adults, supporting progression of 20 mg daily into a Phase 2 study. A Phase 2 study evaluated the safety and efficacy of forvisirvat 20 mg daily vs placebo for 4 weeks in participants with MDD. No significant difference in the primary endpoint was observed between treatment groups. However, post-hoc analyses found that women treated with forvisirvat experienced consistent significant overall improvement on the primary and secondary efficacy measures whereas men showed no effect on any scale. Safety was comparable to placebo. A Phase 1 quantitative EEG study using brain network analytics (BNA) is ongoing. The first cohort in healthy adults is complete and showed that 20 mg once daily was centrally active and changed BNA profiles relative to placebo after 1 day and 2 weeks of daily treatment. Observed post-dose increases across high-frequency bands support improved cognition, while reduction in delta power support potential antidepressant effects. Evoked response potentials showed improved decision-making speed and context updating and reversing functions, often impaired in MDD. Enrollment of a second cohort of adults with MDD is underway. A phase 2b-3 study is nearing completion. This study is nearly identical in design to the previous Phase 2 study but with a larger n and includes a cognitive test. It seeks to confirm the results from the prior study, with the primary efficacy endpoint in agreement with the FDA pre-specified in females only. Efficacy and tolerability remain challenges to successful MDD treatment. Forvisirvat, a novel SIRT6 activator with effects in preclinical models of depression and cognition, is associated with several mechanisms implicated in MDD. A Phase 2 study suggested efficacy in females, a Phase 2b-3 study is ongoing in an attempt to confirm these findings.

T28. EFFECT OF KETAMINE ON INDIVIDUAL SYMPTOMS OF DEPRESSION IN A RANDOMIZED CONTROLLED TRIAL OF KETAMINE FOR TREATMENT-RESISTANT DEPRESSION

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Abstract: Intravenous ketamine has emerged as an effective rapid acting treatment for treatment resistant depression (TRD). However, the precise mechanism of action of ketamine is not yet understood. Moreover, not all patients respond to ketamine, and it remains unclear who is likely to respond to ketamine. The difficulty in understanding the mechanism of action of ketamine and its clinical effects might be related to the heterogeneity of TRD symptom profiles. An understanding of ketamine's differential effects on depressive symptoms could provide insight into these issues. In this secondary analysis of a randomized controlled trial, 152 individuals with TRD were randomized to receive a single infusion of IV ketamine (n=103) or IV saline (n=49). Clinician-ratings of depressive symptoms were assessed at multiple time points from pre-infusion to 30 days post-infusion using Montgomery–Åsberg Depression Rating Scale (MADRS). We examined the effect sizes of improvements in specific symptoms between ketamine and saline arms in the early post-infusion period (i.e., ≤ 1 day post-infusion), where peak antidepressant effects are observed. Second, we assessed individual symptom improvement related to ketamine in the later treatment period (i.e. post-infusion days 2 – 30), examining individual symptom profiles over time. Also, to study how ketamine affects the relationship between depressive symptoms (the mutual effect of a pair of depressive symptoms on each other), we estimated the depressive symptom networks with Gaussian Graphical Models (GGM) at pre-infusion and 24-hrs-post-infusion. Compared to saline infusion, the greatest effects of ketamine at 24-hr post-infusion were on symptoms of apparent sadness, reported sadness, sleep problems, and numbness ($d_s > 0.2$, $p < 0.05$). For certain symptoms such as lassitude, the greatest improvement in symptoms was found on day 5 ($d_s > 0.5$, $p < 0.05$), and suicidality showed maximal improvement later in treatment on day 21 and day 30 (dday21=0.44, $p < 0.05$). The symptom networks did not reveal an overall network structure change pre- to post-infusion; however, the global strength of the network post infusion increased significantly, suggesting a denser symptom network 24-hrs post infusion. Moreover, the association between apparent sadness and reported sadness increased. Overall, ketamine improved all symptoms, but appeared to improve symptoms of sadness most profoundly, both immediately and in the initial week after treatment. Ketamine also rapidly altered the architecture of symptom networks, appearing to strengthen interrelationships between residual symptoms. Efficacy for ketamine (over saline) in improving suicidal symptoms emerged not rapidly, but only after a greater delay. Our findings suggest potentially divergent efficacy, time course, and mechanisms for different symptoms of depression.

T29. EFFECTS OF SOLRIAMFETOL ON NEUROPSYCHOLOGICAL OUTCOMES IN PATIENTS WITH OBSTRUCTIVE SLEEP APNEA IN THE REAL-WORLD SURVEY STUDY

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Abstract: Patients with excessive daytime sleepiness (EDS) associated with obstructive sleep apnea (OSA) show deficits in cognitive domains including alertness, attention, executive function and decision-making. Solriamfetol (Sunosi®) is a dopamine-norepinephrine reuptake inhibitor with agonistic properties at the trace amine-associated receptor 1 and serotonin 1A receptor approved for treatment of EDS associated with narcolepsy or OSA. Solriamfetol demonstrated improvements in cognitive performance in patients with EDS in OSA in a phase 4 randomized study. Here, we report a post-hoc analysis of

neuropsychological outcomes in patients with EDS in OSA treated with solriamfetol in a real-world setting.

Methods: SURVEY was a retrospective, observational study using data from physicians who prescribed solriamfetol for EDS in OSA. Neuropsychological assessments were performed in a subgroup of patients prior to and 3 months after solriamfetol initiation. Tests included: Test of Attentional Performance (TAP) subtest alertness, the Regensburger Word Fluency Test, the Wechsler Memory Scale subtest visual reproduction, Wechsler Adult Intelligence Scale (WAIS-IV) subtest coding and British Columbia Cognitive Complaints Inventory (BC-CCI). Data were analyzed with repeated measures ANOVA. The relationship between changes in EDS and cognition were assessed via regression.

Results: Before solriamfetol initiation, participants (N=46) showed impaired alertness on the TAP (mean±SD 268.2±21.8 ms with warning signal, 270.2±21.9 ms without), impaired cognitive function on the BC-CCI (8.6±2.2), and reduced psychomotor and visual processing speed on the WAIS-IV coding subtest (7.1±1.5). After 3 months of treatment with solriamfetol, TAP scores improved by a mean of 11.4% (237.7±21.4 ms with warning signal; 239.5±21.3 ms without, $p < 0.01$ for both). BC-CCI scores improved by a mean of 40.8% (5.1±3.1, $p < 0.01$). WAIS-IV coding scores improved by 30.6% (9.3±1.8, $p < 0.01$). Word fluency and memory were not impaired at baseline, or after solriamfetol initiation. Epworth Sleepiness Scale scores improved with solriamfetol treatment by 4.7±2.7 ($p < 0.01$). There was no association between the improvements in cognitive function and change in EDS ($|r|=0.16$, $p=0.3$).

Conclusion: These real-world results show that solriamfetol not only reduces EDS in patients with OSA, but also has the potential to partially reduce OSA-associated cognitive impairment. This effect was not associated with changes in EDS.

T30. METABOLIC PROFILES OF PARTICIPANTS WITH MAJOR DEPRESSIVE DISORDER WITH INSOMNIA SYMPTOMS IN A PHASE 3 TRIAL OF SELTOREXANT VERSUS QUETIAPINE EXTENDED RELEASE AS ADJUNCTIVE THERAPY

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Abstract: Approved adjunctive treatments of major depressive disorder (MDD), like quetiapine XR, belong to the atypical antipsychotic class and have tolerability issues leading to non-adherence. Seltorexant—a novel, selective orexin-2 receptor antagonist—may be a valuable alternative with tolerability advantages. We assessed metabolic profiles of participants with MDD with insomnia symptoms (IS) in a 26-week, double-blind, phase 3, randomized controlled trial (NCT04513912) of seltorexant vs quetiapine XR (QTP-XR) as adjunctive therapy. Participants (aged 18-74 years) had MDD without psychotic features, Insomnia Severity Index total score ≥ 15 , positive IS response on SCID-5-CT scale, and inadequate response to 1-2 antidepressants. Those with controlled type 1 or 2 diabetes for ≥ 2 months prior to screening were eligible. Participants received seltorexant 20 mg or QTP-XR (flexible dosage) in 1:1 ratio adjunctive to SSRI or SNRI. Changes from baseline to week 26 were assessed for total body weight (BW, key secondary endpoint), fasting insulin, fasting

glucose, HbA1C, and Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) score. Low (< 1.9) HOMA-IR implied insulin sensitivity and high (> 2.9) HOMA-IR significant insulin resistance. Body mass index (BMI, kg/m²) categories were: underweight < 18.5 , normal 18.5-25, overweight 25-30, and obese > 30 . Of the 757 randomized participants, 756 received ≥ 1 study drug dose. At baseline, the seltorexant (n=366) and QTP-XR (n=390) groups had mean (SD) HbA1C values of 5.5 (0.6) and 5.4 (0.5), respectively; 104 (28.4%) and 107 (27.4%) had significant insulin resistance; 39 (10.7%) and 27 (6.9%) had controlled diabetes; 29 (7.9%) and 16 (4.1%) were stable on metabolic- and lipid-management regimens; 125 (34.2%) and 132 (33.8%) were underweight/normal; 110 (30.1%) and 129 (33.1%) were overweight; and 131 (35.8%) and 129 (33.1%) were obese. Mean (SD) change in BW (kg) was 0.5 (2.9) for seltorexant (n=268) and 2.1 (3.9) for QTP-XR (n=263) participants who received ≥ 1 dose and had baseline MADRS score ≥ 24 (LS mean difference [95% CI]: -1.7 [-2.2, -1.1], nominal $P < .001$). On average, participants in all BMI categories gained weight (kg); however, mean (SD) increases were numerically lower with seltorexant than QTP-XR: underweight/normal=0.8 (2.7) seltorexant (n=103), 2.5 (3.8) QTP-XR (n=90); overweight=0.8 (2.4) seltorexant (n=79), 2.0 (3.9) QTP-XR (n=91); obese=0.0 (3.6; n=97) seltorexant, 1.9 (4.1; n=93) QTP-XR. In subgroup analyses of participants with diabetes, obesity, or significant insulin resistance at baseline, mean (SD) changes in HOMA-IR numerically decreased with seltorexant (-3.9 [12.1; n=22], -1.8 [8.5; n=84], and -3.6 [9.5; n=70]), respectively vs numerically increased with QTP-XR (4.5 [12.3; n=13], 2.2 [6.5; n=76], and 0.2 [8.6; n=64]). Mean (SD) changes in fasting insulin also numerically decreased with seltorexant (-83.4 [205.4; n=22], -42.1 [193.2; n=86], -86.7 [209.5; n=71], respectively) vs numerically increased with QTP-XR (92.4 [239.5; n=13], 61.8 [196.3; n=77], 22.3 [239.4; n=65]). For glucose or HbA1C, no clinically relevant differences between treatment groups were observed; this is likely attributable to baseline HbA1C being within target range in the majority of participants and optimized glycemic control in those with diabetes. Seltorexant yielded less weight gain than QTP-XR after 26 weeks. In subgroups of metabolically compromised participants, HOMA-IR and insulin changes trended towards improvement with seltorexant but worsening with QTP-XR. Most participants were overweight/obese and had significant insulin resistance at baseline, highlighting the need for safer treatment options in MDD.

T31. DECREASE IN NEGATIVE MOOD AND INCREASE IN POSITIVE MOOD DURING 12 MONTHS OF VAGAL NERVE STIMULATION

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Abstract: In the Diagnostic and Statistical Manual of Mental Disorders, excessive negative mood and anhedonia, defined as loss of interest and pleasure, are considered core depressive symptoms. However, reduced positive mood is not mentioned as a “depressive symptom”

despite it being a stronger predictor of excess mortality in those with depression, when compared with increased negative mood. Further, in their expectations from treatment, patients rank increase in positive mood, hedonic tone, and “meaningfulness of life” as more important than decrease in negative mood (1). Implanted vagus nerve stimulation (VNS) is approved by the US Food and Drug Administration for treatment-resistant depression. Recently, it has been shown that adjunctive VNS treatment in patients with difficult-to-treat depression (DTD) results in clinically meaningful benefits in depressive symptoms, function, and quality of life. Here we present data from RESTORE-LIFE on the impact of 12 months of adjunctive VNS treatment on dimensions of negative and positive mental health. RESTORE-LIFE is a prospective, observational, multi-site, European, post-market naturalistic study intended to assess short-, mid-, and long-term effectiveness and efficiency outcomes among patients with DTD treated with concurrent VNS therapy (2). Participants were aged 18 years or older and had a chronic (> 2 years) or recurrent (≥ 2 prior episodes) major depressive episode that had not sufficiently responded to antidepressant treatments. Analyses were conducted to assess dimensions of negative (depression severity, suicidality, anxiety, negative affect) and positive (life satisfaction and enjoyment, positive affect, hedonic tone, overall functioning, cognitive functioning, meaningfulness of life, and happiness) mental health, correlations between these changes, and the predictors of 12-month outcomes (using regression analyses) on depression scales, suicidality, life satisfaction and enjoyment, and meaningfulness of life. This interim analysis included the first 100 patients who reached 12 months. Statistically significant improvements over 12 months were found on all variables assessing depressed mood, negative affect, suicidality, life satisfaction, positive affect, hedonic tone, cognitive functioning, overall functioning, meaningfulness of life, and happiness. Larger effect sizes (ES) were observed for the clinician-rated Montgomery-Åsberg Depression Rating Scale (ES: -0.77), the patient-rated Quick Inventory of Depressive Symptomatology–Self-Report (ES: -0.54), and suicidality (ES: 0.57) scores. More moderate improvements were observed for the Quality of Life Enjoyment and Satisfaction Questionnaire–Short Form score (ES: 0.38) and the Leuven Affect and Pleasure Scale score (ES for negative affect: -0.38; ES for positive affect, hedonic tone, cognitive functioning, overall functioning, meaningfulness of life, and happiness was between 0.26 and 0.40). At 12 months, only changes from baseline in negative mood predicted negative mood, changes from baseline in negative mood and changes in positive mood predicted suicidality, and only changes from baseline in positive mood predicted positive mood. In conclusion, among patients with DTD in a real-world setting, 12 months of concurrent VNS therapy was associated with a significant decrease in negative mental health and an increase in positive mental health, both of which seem to be independent dimensions.

T32. USE OF A PROSPECTIVE LEAD-IN STUDY TO ENHANCE ELIGIBILITY AND REDUCE SCREEN FAILURE IN MAJOR DEPRESSIVE DISORDER TRIALS

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Abstract Introduction (Aims): High screen failure rates (SFR) remain a persistent challenge in psychiatric clinical trials, increasing costs and slowing study timelines (Fogel, 2018). Recruitment enhancement strategies such as site-sponsored pre-screening programs represent potential means of improving screening efficiency. Our present study evaluated the potential for a multi-site observational lead-in study to reduce the SFR in Major Depressive Disorder (MDD) industry trials.

Methods: SFR was analyzed across 14 MDD clinical trials at 4 trial sites in the Adams Clinical Site Network. The included trials enrolled participants who completed a 6-week, site-sponsored prospective lead-in trial (TRAIT) in which all participants received an FDA-approved antidepressant therapy (ADT). Across trials and sites, the sample consisted of 160 TRAIT participants, and 458 non-TRAIT participants. The relationship between TRAIT participation and SFR was examined using a multilevel mixed-effects logistic regression model. The model allowed trial-level random intercepts and site-level random intercepts nested within trial, and controlled for age, sex, race, travel time, self-reported depressive symptoms (PHQ-9), past/current psychotherapy experience, and ADT history. In addition, study-wide SFR was averaged across trials when the data were available (SFR = 57.19% across 5 trials).

Results: The model indicated that trial-level variability (variance = 1.05; SD = 1.02) exceeded site-level variability (variance = 6.7×10^{-7} ; SD = 0.0008), which was negligible, indicating relative uniformity across the Adams Clinical Site Network. SFR findings revealed that TRAIT participants had 69% lower odds of screen failure in industry-sponsored trials compared with non-TRAIT participants ($\beta = -1.17$, SE = 0.33, $z = -3.53$, $p < 0.001$). The 61.79% SFR observed for non-TRAIT participants was comparable to the available study-wide SFR average, whereas the SFR for TRAIT participants was markedly lower at 45.62%.

Conclusions: Improving screening efficiency is critical for reducing trial costs, accelerating timelines, and ensuring scientific validity (Desai, 2020). The current findings suggest that although trial-level factors such as trial design and inclusion/exclusion criteria are primary drivers of SFR variability, the use of a prospective lead in study can dramatically reduce SFR for MDD clinical trials, especially if implemented uniformly across sites. These results provide support for the practicality of utilizing pre-trial observational studies such as TRAIT to reduce SFR by optimizing recruitment and ensuring screening quality.

T33. METABOLIC BURDEN, INFLAMMATION, AND ESKETAMINE EFFICACY IN TREATMENT-RESISTANT MAJOR DEPRESSIVE EPISODES

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Abstract Background: Esketamine, a rapid-acting glutamatergic agent, has demonstrated clinical promise in treatment-resistant depression (TRD). Recent evidence has linked metabolic and inflammatory markers and response to antidepressant treatment. This study examined change in clinical symptoms and peripheral blood-based biomarkers in individuals with TRD receiving repeated esketamine treatments in a Canadian psychiatric hospital.

Methods: Data was derived from 25 participants with primary diagnosis of major depressive disorder or bipolar disorder receiving twice-weekly intranasal esketamine treatments over four weeks. Depressive symptoms were measured using the Montgomery-Åsberg Depression Rating Scale (MADRS) and Patient Health Questionnaire-9 (PHQ-9). Metabolic syndrome criteria and high-sensitivity C-reactive protein (CRP) were assessed at baseline and after 4 weeks of treatment.

Results: Esketamine treatment was associated with significant decrease in both rater-administered and self-reported depressive symptom severity (MADRS, mean decrease 7.8 points, $p < .001$; PHQ-9, $p < .001$). Pre-treatment, 84% of patients had at least 1 metabolic dysregulation (most commonly elevated blood pressure or increased waist circumference), and 28% had elevated CRP. A higher number of pre-treatment metabolic abnormalities predicted greater decrease in depressive symptoms post-treatment ($p=.037$). Following 4 weeks of treatment, participants had a significant decrease in mean fasting glucose ($p < .001$), and systolic blood pressure ($p=.01$).

Conclusions: In this preliminary analysis, improvement in symptoms of depression was observed over 4 weeks of esketamine treatment. Further, we report evidence of associations between metabolic burden and treatment response to esketamine. These findings support the therapeutic effects of esketamine and emphasize the need for further investigation into its broader clinical and biological impacts.

T34. REAL-WORLD CLINICAL OUTCOMES OF PATIENTS SWITCHING TO TREATMENT WITH DEXTROMETHORPHAN-BUPROPION (45 MG/105 MG)

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Abstract Introduction: Dextromethorphan-bupropion (45 mg/105 mg) (Auvelity®) is an oral, N-methyl-D-aspartate (NMDA) receptor antagonist and sigma-1 agonist approved in the US for the treatment of adults with major depressive disorder (MDD). This study evaluated real-world clinical outcomes after initiation of dextromethorphan-bupropion.

Methods: Adults initiating dextromethorphan-bupropion were identified in US electronic health record (EHR) data collected between August 2022 and March 2025. Outcomes including the Patient Health Questionnaire-9 (PHQ-9), Generalized Anxiety Disorder 2-item (GAD-2), Clinical Global Impressions–Severity (CGI-S), and CGI–Improvement (CGI-I) scales, as well as body weight, were evaluated using pairwise comparisons between index (1st Auvelity prescription) and multiple follow-up timepoints.

Results: Among the 217 patients initiating dextromethorphan-bupropion (58% female; mean age: 43 years), most had comorbid anxiety (88.5%) and/or ADHD (79.3%). Sleep disorders were also common, affecting 45.2% of patients, including insomnia in 37.8% and sleep apnea in 11.1%. Metabolic disorders were reported in 21.2%. Most patients (86.6%) had previously used MDD-related treatments; their last MDD-related treatments before starting dextromethorphan-bupropion were SSRIs (35.0%), NDRI (19.4%), SNRI (18.4%), antipsychotics (14.3%), and esketamine (5.5%). Dextromethorphan-bupropion was initiated as a monotherapy in 71.9% of the patients. At baseline, patients predominantly fell within the moderate-to-severe range of depressive symptoms (26.6%, moderate; 19.7%, moderately severe; 11.7%, severe); the mean PHQ 9 score was 11.48. Improvements in all outcomes were observed starting from Week 1 after dextromethorphan-bupropion initiation and were significant ($P < 0.05$) at Week 2, Week 6, and Month 3, including mean changes in GAD-2 (-0.88, -0.74, and -0.89, respectively). For CGI-I scores, 78.0%, 82.5%, and 83.9% of patients showed improvement at Week 2, Week 6, and Month 3, respectively. Body weight remained stable throughout the evaluation period. Significant reductions in PHQ-9 total score (-2.27, -2.97, -3.27; all $P < 0.05$) and anhedonia, as measured by PHQ-9 Item 1, (-0.33, -0.47, -0.48; all $P < 0.05$) were observed at Week 2, Week 6, and Month 3, respectively.

Conclusions: In this retrospective EHR analysis, adult patients switching to dextromethorphan-bupropion demonstrated rapid and lasting improvements in both patient- and clinician-rated outcomes over 3 months. Most patients had mental-health related comorbidities and attempted various MDD-related treatments; 80% initiated dextromethorphan-bupropion as a monotherapy.

T35. EFFICACY AND SAFETY OF ESMETHADONE (REL-1017) IN PATIENTS WITH MAJOR DEPRESSIVE DISORDER AND INADEQUATE RESPONSE TO STANDARD ANTIDEPRESSANTS: FINDINGS FROM TWO EARLY-TERMINATED PHASE 3 TRIALS

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Abstract Background and Objective: Up to 50% of patients with MDD do not respond to first-line therapy. There is an unmet need for safe, effective, oral rapid acting adjunctive antidepressants. We evaluated the efficacy and safety of esmethadone (REL-1017) in patients with MDD and inadequate response to first-line therapy.

Methods: These were two prematurely terminated near-identical Phase 3 randomized, double-blind, placebo-controlled trials: REL-1017-302 (NCT04855747) and REL-1017-304 (NCT06011577). REL-1017 (75 mg on Day 1 followed by 25 mg daily from Day 2 to Day 28) or matching placebo was administered as adjunctive therapy to adult outpatients with MDD and inadequate response to first line antidepressants. Data were analyzed using mean difference (MD) in Montgomery-Åsberg Depression Rating Scale (MADRS) from baseline to Day 7 and to Day 28, key secondary endpoint and primary endpoint, respectively. The planned sample size was 280 subjects (140 per treatment arm). A planned interim analysis (IA) for sample size re-estimation was conducted by an independent Data Monitoring Committee (DMC) at approximately 75% enrollment.

Results: At IA the DMC recommended early termination for study REL-1017-302 due to low conditional power for meeting the primary endpoint at Day 28. Following the DMC recommendation, both studies were terminated by the former sponsor. Neither trial met the primary endpoint at Day 28. Study REL-1017-302 — ITT population (actual visits) REL-1017 n=119; placebo n=117, changes in MADRS total score from baseline were as follows. Day 7: REL-1017 (n=114) showed a mean (SD) change of -9.7 (8.23) compared with -6.9 (8.58) for placebo (n=110), corresponding to a mean difference of -2.80 (8.41), Cohen's d (ES)=0.33, p=0.0133. Day 14: REL-1017 (n=106) had a mean (SD) change of -11.8 (9.90) versus -10.9 (9.67) for placebo (n=109), with a mean difference of -0.94 (9.79), ES=0.10, p=0.4823. Day 21: REL-1017 (n=110) demonstrated a mean (SD) change of -13.8 (10.41) compared with -12.9 (10.85) for placebo (n=106), yielding a mean difference of -0.86 (10.63), ES=0.08, p=0.5541. Day 28: REL-1017 (n=102) showed a mean (SD) change of -15.2 (10.99) versus -14.5 (10.46) for placebo (n=100), corresponding to a mean difference

of -0.79 (10.73), $ES=0.07$, $p=0.6037$. However, study REL-1017-302 ($N=236$) showed statistically significant rapid antidepressant efficacy at Day 7 (prespecified key secondary endpoint). Day 7 statistical significance was lost at later time points due to improvement in the placebo arm. Within-group improvements in the REL-1017 arm continued across time points. Prespecified MMRM and prespecified per protocol analyses supported Day 7 rapid antidepressant effects. Study REL-1017-304 ($N=27$) showed a similar trend for rapid antidepressant efficacy at Day 7 (MADRS MD REL-1017 vs placebo: -3.8 points) but did not achieve statistical significance due to the small sample size. Exploratory pooled data from both studies ($N=263$) also supported Day 7 antidepressant effects. Consistent with prior trials, totaling over 1000 participants exposed to REL-1017, treatment emergent adverse events were mostly mild or moderate, with no serious adverse events, no meaningful opioid-like effects or dissociative effects, and no signal for metabolic, neurological, cardiovascular, or sexual side effects.

Conclusions: With the limitations of early study termination, Day 7 statistically significant antidepressant effects and favourable safety results, consistent with prior results, support the development of REL-1017 as a rapid-acting, safe and well-tolerated, oral, once daily adjunctive antidepressant.

T36. LUMATEPERONE VERSUS OTHER ADJUNCTIVE ATYPICAL ANTIPSYCHOTICS FOR MAJOR DEPRESSIVE DISORDER: A NETWORK META-ANALYSIS OF COMPARATIVE EFFICACY AND SAFETY

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Abstract Objectives: In 2025, the US FDA approved lumateperone, an atypical antipsychotic, as adjunctive treatment for major depressive disorder (MDD). This network meta-analysis (NMA) compared efficacy and safety of lumateperone with other approved atypical antipsychotics: aripiprazole, brexpiprazole, cariprazine, and quetiapine XR in patients with MDD and inadequate response to antidepressants (ADT).

Methods: Ten short-term, randomized, double-blind, placebo-controlled registration trials formed a star-shaped network of 11 treatment- and dose-specific nodes anchored on placebo+ADT. Trial design, eligibility criteria, and baseline characteristics were similar across trials, yielding broadly comparable populations of adults with MDD and inadequate response to an ADT. Most trials were Phase 3 with a 6-week double-blind period; one trial was Phase 2 with an 8-week double-blind period. Outcomes consistently reported and available for $\geq 9/10$ trials were included. Efficacy outcomes were Montgomery-Åsberg Depression Rating Scale (MADRS) change from baseline, MADRS-based response and remission, and Clinical Global Impression–Severity (CGI-S) change from baseline. Safety outcomes included proportion of patients with $\geq 7\%$ weight increase from baseline, akathisia, and somnolence. Fixed-effect Bayesian NMAs were conducted. Analyses used 3 Markov

Chain Monte Carlo simulations with 30,000 iterations each, including 20,000 burn-in iterations. Normal likelihoods were used for continuous outcomes and binomial likelihoods for binary outcomes with non-informative priors. Treatment effects versus placebo+ADT were estimated; a probability of superiority > 85% (< 15%) indicated that the treatment was favored (unfavored) over placebo+ADT. Network-wide treatment rankings were summarized using surface under the cumulative ranking curve (SUCRA).

Results: All treatment-dose nodes were favored versus placebo+ADT for MADRS change from baseline at Week 6, with similar patterns observed for other efficacy outcomes (response: 10/11, remission: 6/11, CGI-S change: 10/11). SUCRA ranking consistently placed lumateperone first across all efficacy outcomes. Safety profiles varied across treatments. Risk of $\geq 7\%$ weight increase was unfavorable versus placebo+ADT for 6/11 treatment-dose nodes. Lumateperone was the only treatment-dose favored versus placebo+ADT and ranked first for the lowest risk of $\geq 7\%$ weight increase. Risk of akathisia was unfavorable versus placebo+ADT for 9/11 treatment-dose nodes, with lumateperone ranking third best after placebo+ADT. Risk of somnolence was unfavorable versus placebo+ADT for 10/11 treatment-dose nodes, with lumateperone ranking sixth best after placebo+ADT.

Conclusion: Guidelines recommend treatment modification until patients with MDD reach remission, and during their treatment journey patients frequently need to change therapies due to inadequate symptom relief and adverse events. In this NMA, adjunctive lumateperone demonstrated a favorable efficacy profile relative to other approved adjunctive antipsychotics. While safety profiles varied across atypical antipsychotics, lumateperone showed a favorable profile for the weight-related and akathisia endpoints, and less favorable for somnolence risk. Physicians should carefully balance efficacy and safety risks with individual patients when selecting adjunctive atypical antipsychotics for MDD to optimize patient care.

T37. A PHASE IB STUDY EVALUATING SAFETY, PRELIMINARY EFFICACY, AND PUTATIVE BIOMARKERS OF NEUROPLASTICITY FOR THE NOVEL NEUROPLASTOGEN ZALSUPINDOLE (DLX-001) IN MAJOR DEPRESSIVE DISORDER

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Abstract Background: Zalsupindole (DLX-001) is a novel, non-hallucinogenic, non-dissociative neuroplastogen structurally inspired by 5-MeO-DMT in development for major depressive disorder (MDD). This Phase Ib study evaluated the safety, tolerability, pharmacodynamics, and preliminary antidepressant effects of zalsupindole using translational biomarkers of neuroplasticity alongside clinical outcomes.

Methods: In this dose-blinded, single-center, multiple-dose study, adults with recurrent MDD received zalsupindole under one of two dosing paradigms: once-daily dosing for 7 days (Cohort A; n=9) or intermittent dosing on Days 1 and 4 (Cohort B; n=9). Assessments included safety measures, quantitative EEG (qEEG), pharmacokinetics, standardized clinical rating scales, and the Cumulus NeuLogiq® assessment suite. In clinic treatment and assessments occurred through Day 8. Follow-up assessments occurred through Day 36 without additional treatment.

Results: All 18 participants completed the treatment period. Zalsupindole was well tolerated, with no serious adverse events or clinically meaningful changes in vital signs, ECGs, laboratory values, or physical examinations. The most common treatment-related adverse events were transient nausea and headache. As previously demonstrated in a 100+ healthy volunteer trial, no psychotomimetic, hallucinatory, or dissociative effects were observed. Further, the digital cognitive data demonstrated no evidence of acute or persistent cognitive impairment (e.g. due to sedation, dissociation or other effects). Plasma concentrations were consistent with target exposures. Clinically, rapid and sustained antidepressant effects were observed, with meaningful reductions in MADRS scores evident by Day 8 and maintained through Day 36 in both dosing cohorts. Across both cohorts, wake qEEG demonstrated zalsupindole-induced increases in absolute power of slow-wave delta and theta activity, patterns associated with cortical plasticity. Low-burden portable EEG supported replication of the acute theta finding.

Conclusions: Zalsupindole demonstrated a favorable safety and tolerability profile and consistently modulated qEEG biomarkers associated with neuroplasticity, alongside rapid and sustained reductions in depressive symptoms whether dosed daily or intermittently. Importantly, antidepressant effects were observed without evidence of psychotomimetic effects or cognitive compromise (acute or delayed). Together, these findings support the hypothesis that enhanced neuroplasticity may underlie the therapeutic effects of zalsupindole and other plastogens. A Phase II study evaluating daily and intermittent dosing paradigms versus placebo has been cleared to proceed by FDA including at-home administration.

T38. REAL-WORLD EFFECTIVENESS OF INTRAVENOUS KETAMINE ON DEPRESSIVE SYMPTOMS, SUICIDAL IDEATION AND FUNCTIONAL IMPAIRMENT IN ADULTS WITH MOOD DISORDERS

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Abstract Background: Given the strict eligibility criteria typically implemented in clinical trials, questions frequently arise regarding the generalizability of results to real-world clinical practice. We previously reported rapid and robust antidepressant effects of IV ketamine in a real-world effectiveness (RWE) study in patients with treatment-resistant depression (TRD) (n = 205) at an outpatient clinic in Ontario, Canada. Herein, we conducted an updated RWE analysis in a substantially larger participant cohort.

Methods: In this naturalistic study (ClinicalTrials.gov: NCT04209296), adults with a treatment resistant mood disorder (n = 649, Mage = 44) who failed to respond to at least two evidence-based interventions underwent four ketamine infusions over two weeks. Participants received a starting dose of 0.5 mg/kg, with doses increasing to 0.75 mg/kg if they had an inadequate treatment response after the first two infusions. Depressive symptom severity, assessed from baseline to post-infusion 4 on the Quick Inventory for Depression Symptomatology-Self Report-16 (QIDS-SR16), was the primary measure of antidepressant effects. Secondary outcomes included suicidal symptom severity (QIDS-SR16 suicide item) and functional disability (Sheehan Disability Scale (SDS)).

Results: Depressive symptoms (QIDS-SR16) decreased by a mean of 5.02 points (SE = 0.20) following the acute therapeutic course, demonstrating a significant treatment effect ($p < 0.001$, Cohen's $f = 0.68$). Significant reduction in suicidal symptom severity ($p < 0.001$, Cohen's $f = 0.41$) and functional disability ($p < 0.001$, Cohen's $f = 0.34$) was observed. Infusions were generally well tolerated; nausea, increased blood pressure, and transient dissociation were the most common adverse effects observed, with the latter decreasing considerably across successive infusions.

Conclusions: In a large, well-characterized cohort of persons with a treatment resistant mood disorder, IV ketamine was safe, well-tolerated, and associated with clinically meaningful improvements in depression, suicidality, and functional outcomes, supporting its effectiveness in real-world clinical settings.

T39. EVALUATING THE ASSOCIATION BETWEEN ANTIDEPRESSANT EFFICACY AND DISSOCIATION WITH KETAMINE IN TREATMENT-RESISTANT BIPOLAR DEPRESSION (TRBD)

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Abstract Background: Intravenous (IV) ketamine is associated with rapid and robust antidepressant effects at sub-anesthetic doses for treatment-resistant depression (TRD). Ketamine causes variable dissociative effects, creating a wide spectrum of “psychedelic experience” intensity between patients. However, evidence to date investigating whether this mind-altering experience is required for clinical benefits has been mixed and underpowered, leaving this research question largely understudied. There has been minimal research on the role of dissociation with ketamine in bipolar disorder specifically.

Methods: We pooled data from two unpublished clinical trials (both recently completed by our group) including adults with treatment-resistant bipolar depression (TRBD) receiving an acute course of ketamine treatment (four infusions over two weeks). Data was pooled from two multi-site clinical trials; a randomized, midazolam-controlled study (ClinicalTrials.gov: NCT05004896; $n = 33$ in ketamine arm), and a single-arm, open-label study (ClinicalTrials.gov: NCT05339074; $n = 20$ in the ketamine arm), 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 (Day 14) using the Montgomery-Åsberg Depression Rating Scale (MADRS). Assessment of dissociation occurred immediately 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 10.8 points (95% CI: -8.3 to -13.4; $p < 0.001$) from a baseline mean of 30.7 (± 6.5) in the ketamine groups (pooled $n = 53$). The mean CADSS score at the peak of infusion and 20-minutes post-infusion was 18.8 (± 13.7) and 0.8 (± 1.5), respectively. Linear regression analysis showed no significant correlation between peak CADSS scores and change in MADRS ($F(1,51) = 0.024$, $p = 0.88$), with dissociation accounting for only 1.3% of the explained variability in MADRS change.

Conclusion: As one of the first studies to evaluate ketamine's dissociative symptoms in bipolar disorder, with data from the largest randomized clinical trial evaluating ketamine in

this population to date, we found the intensity of dissociative effects did not predict antidepressant response. As our findings suggest that ketamine's clinical benefits may not depend on a meaningful psychedelic experience, these results can provide reassurance to patients who do not experience strong dissociative effects. Moreover, further research can lead to the engineering of novel ketamine-like treatments that minimize psychoactive side effects for improved tolerability.

T40. ADJUNCTIVE LUMATEPERONE 42 MG TREATMENT IN MAJOR DEPRESSIVE DISORDER: EFFICACY ACROSS PATIENT-REPORTED DEPRESSION SYMPTOMS

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Abstract Background: Lumateperone is an atypical antipsychotic indicated for: treatment of schizophrenia in adults; treatment of depressive episodes associated with bipolar I or II disorder (bipolar depression) in adults, as monotherapy and as adjunctive therapy with lithium or valproate; and treatment of major depressive disorder (MDD) in adults as adjunct to antidepressant therapy (ADT). In the Phase 3, randomized, double-blind, placebo-controlled Study 501 trial (NCT04985942), adjunctive lumateperone 42mg met the primary endpoint, significantly improving Montgomery-Asberg Depression Rating Scale (MADRS) Total score vs adjunctive placebo and was generally well tolerated in patients with MDD with inadequate response to ADT. This analysis of Study 501 evaluated the efficacy of adjunctive lumateperone 42mg across patient-reported depression symptoms in patients with MDD, as measured by individual item scores of the Quick Inventory of Depressive Symptomatology-Self Report-16 item (QIDS-SR-16) collected at baseline and week 6/end of treatment (EOT).

Methods: Eligible adults (18-65 years) met DSM-5 criteria for MDD with inadequate response to 1-2 ADT courses and had MADRS Total score ≥ 24 , Clinical Global Impression-Severity scale score ≥ 4 , and QIDS-SR-16 item score ≥ 14 . Patients were randomized 1:1 to 6-week oral lumateperone 42mg or placebo adjunctive to ADT. Change from baseline in QIDS-SR-16 Total score at EOT was measured using an analysis of covariance (ANCOVA) in the intent-to-treat (ITT) population. Post hoc analyses measured changes using an ANCOVA in the ITT population in the 9 symptom domains of the QIDS-SR-16 score: sleep disturbance (highest score of items 1-4), sad mood, appetite/weight (highest score of items 6-9), concentration, self-criticism, suicidal ideation, interest, energy/fatigue, and psychomotor (highest score of items 15-16).

Results: Of 484 patients in the ITT population (lumateperone+ADT, n=241; placebo+ADT, n=243), 93.4% (n=452) completed treatment. Lumateperone+ADT significantly improved QIDS-SR-16 Total score vs placebo+ADT from baseline to EOT (least squares mean difference [LSMD]=-2.4; effect size [ES]=-0.50; $P < .0001$). The QIDS-SR-16 symptom domains with highest baseline scores were sleep disturbance (mean: lumateperone+ADT, 2.7; placebo+ADT, 2.7) and feeling sad (lumateperone+ADT, 2.6; placebo+ADT, 2.6). From baseline to EOT, 8 of 9 QIDS-SR-16 symptom domains significantly improved with lumateperone+ADT vs placebo+ADT: sleep disturbance (LSMD, -0.5; ES, 0.55; $P < .0001$); sad mood (LSMD, -0.4; ES, 0.44; $P < .0001$); appetite/weight change (LSMD, -0.2; ES, 0.22; $P < .05$); concentration (LSMD, -0.2; ES, 0.28; $P < .01$); self-criticism (LSMD, -0.1; ES, 0.17; $P=.065$); suicidal ideation (LSMD, -0.1; ES, 0.19; $P < .05$); interest (LSMD, -0.3;

ES, 0.29; $P < .01$); energy/fatigue (LSMD, -0.2 ; ES, 0.29; $P < .01$); and psychomotor agitation/retardation (LSMD, -0.2 ; ES, 0.30; $P < .01$).

Conclusion: In patients with MDD with inadequate ADT response, lumateperone 42mg adjunctive to ADT significantly improved a broad range of patient-reported depressive symptoms vs placebo, indicating lumateperone as a promising adjunctive therapy to ADT in this setting.

T41. FIRST ONSET AND DURATION OF TREATMENT-EMERGENT ADVERSE EVENTS IN PATIENTS WITH MAJOR DEPRESSIVE DISORDER TREATED WITH ADJUNCTIVE LUMATEPERONE 42 MG: A POOLED ANALYSIS OF 2 RANDOMIZED PLACEBO-CONTROLLED TRIALS

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Abstract Background: Major depressive disorder (MDD) is a common mental illness associated with functional impairment and high rates of comorbidities. Current standard-of-care treatments have adverse effects such as weight gain, sexual dysfunction, and metabolic disturbances that limit tolerability. Lumateperone is an atypical antipsychotic indicated for: treatment of schizophrenia in adults; treatment of depressive episodes associated with bipolar I or II disorder (bipolar depression) in adults, as monotherapy and as adjunctive therapy with lithium or valproate; and treatment of MDD in adults as adjunct to antidepressant therapy (ADT). Two Phase 3, randomized, double-blind, placebo-controlled studies (Study 501 [NCT04985942]; Study 502 [NCT05061706]) established the efficacy and safety of lumateperone 42 mg adjunctive to ADT in patients with MDD with inadequate ADT response. A pooled analysis of these studies assessed the first onset and duration of treatment-emergent adverse events (TEAEs).

Methods: Data were pooled from Study 501 and Study 502, which enrolled males and females (18-65 years) with DSM-5–diagnosed MDD with inadequate response to 1-2 ADTs in the current depressive episode ($< 50\%$ improvement on the Antidepressant Treatment Response Questionnaire). Eligible patients had Montgomery-Asberg Depression Rating Scale Total score ≥ 24 , Clinical Global Impression-Severity Scale score ≥ 4 , and Quick Inventory of Depressive Symptomatology-Self Report-16 item score ≥ 14 . In both studies, patients were randomized 1:1 to 6-week lumateperone 42 mg + ADT or placebo + ADT. First onset and duration of TEAEs were evaluated descriptively.

Results: Of 964 patients treated (lumateperone + ADT, $n=483$; placebo + ADT, $n=481$), 91.4% completed treatment. TEAEs occurred in 68.1% and 45.1% of patients in the lumateperone 42 mg + ADT and placebo + ADT groups, respectively. The most common TEAEs ($\geq 5\%$ in lumateperone + ADT and twice placebo + ADT) were dizziness (lumateperone + ADT, 16.4%; placebo + ADT, 5.0%), dry mouth (12.6%; 3.3%), somnolence (10.1%; 2.1%), nausea (8.5%; 4.0%), fatigue (7.2%; 1.2%), and diarrhea (4.6%; 1.2%). Onset of TEAEs occurred at ≤ 1 week in 45.3% of patients, > 3 to ≤ 4 weeks in 4.1% of patients, and > 5 weeks in 2.1% of patients. At ≤ 1 week, > 3 to ≤ 4 weeks, and > 5 weeks, TEAE onset occurred in 11.8%, 0.7%, and 0.7% of patients for dizziness; 8.3%, 0.7%, and 0.5% for dry mouth; 8.5%, 0.2%, and 0.5% for somnolence; 6.0%, 0.2%, and 0.2% for

nausea; 5.2%, 0.2%, and 0.2% for fatigue; and 2.5%, 0.2%, and 0.2% for diarrhea, respectively. The mean durations of the most common TEAEs for the lumateperone + ADT vs placebo + ADT groups were: dizziness, 9.5 vs 7.7 (median: 5.0 vs 5.0) days; dry mouth, 22.8 vs 17.3 (median: 25.0 vs 17.0) days; somnolence, 14.6 vs 14.9 (median: 9.5 vs 12.0) days; nausea, 7.2 vs 11.0 (median: 5.0 vs 6.0) days; fatigue, 20.7 vs 11.8 (median: 19.0 vs 6.5) days; and diarrhea, 7.3 vs 12.2 (median: 2.5 vs 7.0) days.

Conclusion: In this pooled analysis of 2 studies, majority of the most common TEAEs occurred early in the treatment period and resolved within approximately 1-3 weeks of onset. These data support that lumateperone is generally safe and well tolerated as an adjunctive treatment for patients with MDD with inadequate ADT response.

T42. REMISSION WITH LUMATEPERONE 42 MG ADJUNCTIVE TO ANTIDEPRESSANT THERAPY IN PATIENTS WITH MAJOR DEPRESSIVE DISORDER: ANALYSIS OF SHORT-TERM AND LONG-TERM TRIALS

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Abstract Background: Lumateperone is an atypical antipsychotic indicated for: treatment of schizophrenia in adults; treatment of depressive episodes associated with bipolar I or II disorder (bipolar depression) in adults, as monotherapy and as adjunctive therapy with lithium or valproate; and treatment of major depressive disorder (MDD) in adults as adjunct to antidepressant therapy (ADT). This analysis of 2 Phase 3, randomized, double-blind, placebo-controlled studies (Study 501 [NCT04985942]; Study 502 [NCT05061706]) and open-label extension study (OLE; Study 503 [NCT05061719]) evaluated Montgomery-Asberg Depression Rating Scale (MADRS) Total score remission rates in patients with MDD with inadequate ADT response.

Methods: Studies 501 and 502 enrolled adults with DSM-5 criteria for MDD with inadequate response to 1-2 ADTs in current depressive episode, MADRS Total score ≥ 24 , Clinical Global Impression-Severity score ≥ 4 , and Quick Inventory of Depressive Symptomatology-Self Report-16 item score ≥ 14 . Patients were randomized 1:1 to 6-week placebo+ADT or lumateperone 42mg+ADT. Those completing double-blind treatment could enroll in Study 503 to receive 26-week lumateperone 42mg+ADT. Efficacy was evaluated in overall populations and patient subgroups using logistic regression (pooled 501/502) and descriptive statistics (503). MADRS remission (MADRS Total score ≤ 10), complete remission (MADRS Total score ≤ 5), and sustained remission (MADRS Total score ≤ 10 through end of treatment) were assessed.

Results: The modified intent-to-treat population comprised 950 patients (lumateperone+ADT, n=471; placebo+ADT, n=479) in 501/502; 809 were enrolled in 503. In 501/502, MADRS Total score remission rates at Day 43 were significantly greater with lumateperone+ADT vs placebo+ADT (25.5% vs 13.6%; $P < .0001$), and remission occurred in 529 (65.4%) patients at end of OLE (Study 503). Compared with placebo+ADT, there were significantly greater MADRS remission rates at Day 43 with lumateperone+ADT in patient subgroups in 501/502, higher complete remission rate (10.6% vs 5.6%; $P < .01$), and significantly greater sustained remission rates, from Day 22 (6.2% vs 2.9%; $P < .05$) through to Day 43 (25.5% vs 13.6%; $P < .0001$). In 503, lumateperone+ADT resulted in high MADRS remission rates across patient subgroups. Complete remission was achieved by

44.1% of patients by end of open-label treatment, with sustained remission rates reaching 60.4% by Week 26.

Conclusion: Lumateperone 42mg+ADT demonstrated significantly greater remission rates over placebo+ADT in pooled short-term studies of patients with MDD with inadequate ADT response, with two-thirds achieving remission with 6-month treatment, supporting lumateperone as a promising adjunctive treatment.

T43. PERIPHERAL BIOMARKER RELIABILITY IN MAJOR DEPRESSIVE DISORDER: A META-ANALYSIS OF S100B

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Abstract: S100B is a glial-derived calcium-binding protein that reflects astrocytic activity, neuroinflammatory signaling, and blood–brain barrier regulation. Although extensively investigated as a potential biomarker for major depressive disorder (MDD), findings have been highly inconsistent. This meta-analysis synthesized nineteen studies comparing serum, plasma, or cerebrospinal fluid (CSF) S100B concentrations between individuals with MDD (N = 914) and healthy controls (N = 890). Standardized mean differences (Hedges' g) were pooled using random-effects models with restricted maximum likelihood estimation. The pooled analysis indicated higher S100B levels in MDD (Hedges' g = 0.845, 95% CI 0.388–1.301); however, heterogeneity was extremely high ($I^2 = 90.6\%$), and the 95% prediction interval (–1.226 to 2.916) included zero, indicating substantial variability in study-specific true effects. Subgroup analyses by biospecimen type and univariate meta-regressions examining demographic, clinical, and methodological variables did not identify significant moderators. Evidence of small-study effects was detected. After adjustment for publication bias using trim-and-fill, the pooled effect was attenuated and no longer statistically significant. When publication bias adjustment and the pronounced between-study heterogeneity are considered, the evidence is insufficient to conclude that S100B levels are reliably elevated in MDD. The present findings highlight the methodological and biological complexities inherent in psychiatric biomarker research. These results emphasize the importance of rigorous validation standards for biomarker development in psychiatry, underscoring the need for more sophisticated analytic and integrative methodologies. Such approaches may be essential for advancing more reliable, biologically informed diagnostic and treatment frameworks in psychopharmacology.

T44. EVALUATING THE ABUSE LIABILITY OF KETAMINE IN THE TREATMENT OF MOOD DISORDERS: A SYSTEMATIC REVIEW

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Abstract Background: Ketamine has emerged as a promising rapid-acting treatment for mood disorders and suicidality. Notwithstanding its replicated antidepressant efficacy, ketamine-associated risk for abuse, dependence, and misuse remain of concern.

Methods: We conducted a systematic review of clinical and preclinical studies from database inception to August 2025, including randomized and observational trials, open-label extensions, case reports, and preclinical animal research, assessing ketamine or its enantiomers for outcomes related to abuse potential including craving, drug liking, tolerance, withdrawal, or dependence.

Results: A total of 30 studies (25 clinical and 5 preclinical) met the inclusion criteria. Clinical studies consistently reported minimal evidence of craving, dose escalation, misuse, or illicit use when ketamine or esketamine was administered in controlled, clinically supervised settings. Preclinical findings demonstrated that (S)-ketamine is associated with reward-related behaviours and locomotor sensitization, racemic ketamine shows reinforcing effects at higher doses, whereas (R)-ketamine demonstrates minimal reinforcing effects.

Conclusion: Overall, the body of reviewed literature suggests that ketamine and esketamine carry low abuse liability when delivered in a monitored clinical setting while risk of abuse and misuse were identified largely in case reports and series in which appropriate monitoring was often not conducted. These findings support the safe incorporation of ketamine into treatment protocols for mood disorders while emphasizing the importance of structured administration and ongoing patient monitoring both throughout treatment and follow-up. Further research using longitudinal, prospective designs is warranted to assess potential misuse over extended treatment periods and across diverse patient populations, in order to optimize clinical safety and further inform evidence-based clinical practice guidelines.

T45. PATTERNS OF REAL-WORLD ANTIPSYCHOTIC SWITCHING AFTER INITIATING ADJUNCTIVE CARIPRAZINE OR LUMATEPERONE IN ADULTS WITH MAJOR DEPRESSIVE DISORDER

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Abstract: In major depressive disorder (MDD), patients receiving adjunctive treatment may switch between atypical antipsychotics (AA), a practice associated with worse outcomes (eg, relapse and hospitalization). Understanding real-world AA switching patterns may optimize treatment and improve outcomes. We investigated AA switching patterns among individuals with MDD initiating adjunctive cariprazine or lumateperone.

Methods: The Komodo Research Database Plus was utilized to identify claims data (12/20/2020-7/31/2025) for adults with MDD who initiated adjunctive cariprazine or lumateperone (first dispensing=index) on or after 12/20/2021. Inclusion criteria included ≥ 12 months of continuous insurance enrollment prior to index date (baseline period), ≥ 2 pharmacy claims for the index AA, evidence of concurrent use of an antidepressant, and ≥ 3 months of postindex follow-up. Exclusion criteria included ≥ 1 bipolar disorder or schizophrenia diagnosis during the baseline period or on the index date, ≥ 1 record of a nonindex AA within 14 days preindex, or treatment with a long-acting injectable antipsychotic within 3 months preindex. Baseline demographic and clinical characteristics of AA cohorts were balanced with inverse probability of treatment weighting based on propensity scores. Switching prevalence was assessed at 3, 6, 9, or 12 months postindex, with switch defined as ≥ 2 postindex dispensings of a nonindex AA. A sensitivity analysis was also

performed with switch defined as ≥ 1 postindex dispensing. Odds ratios (OR), their CIs and P values were estimated using logistic regression models comparing switch rates between cohorts.

Results: At all timepoints, AA switching was less frequent among patients who initiated cariprazine (n=24,270) than in those who initiated lumateperone (n=1787). In the weighted cohorts, switch rates among patients who initiated cariprazine and lumateperone were 7.8% and 13.3% at 3 months, 12.9% and 21.5% at 6 months, 16.8% and 27.0% at 9 months, and 19.6% and 29.4% at 12 months, respectively. Patients were 45% less likely to switch at 3 months after initiating cariprazine compared with lumateperone (OR [95% CI]=0.55 [0.48, 0.64], $P < .001$), 46% less likely at 6 months (0.54 [0.47, 0.61], $P < .001$), 46% less likely at 9 months (0.54 [0.48, 0.62], $P < .001$), and 42% less likely at 12 months (0.58 [0.51, 0.67], $P < .001$). A sensitivity analysis where the definition of a switch was relaxed to ≥ 1 postindex dispensing of a nonindex AA showed similar results, with significant ORs at 3, 6, 9, and 12 months. Patients that switched AAs most commonly switched to aripiprazole (cariprazine cohort: 5.0%; lumateperone cohort: 6.0%), brexpiprazole (2.8%; 2.5%), and lurasidone (2.0%; 3.7%). Of all patients initiating lumateperone, 4.4% switched to cariprazine, whereas 1.0% of the patients initiating cariprazine switched to lumateperone.

Conclusions: In patients with MDD, initiating adjunctive cariprazine was associated with a significantly lower likelihood of switching to a different AA compared to adjunctive lumateperone at 3, 6, 9, and 12 months.

T46. COSTS ASSOCIATED WITH ADJUNCTIVE ATYPICAL ANTIPSYCHOTIC-RELATED WEIGHT GAIN AMONG PATIENTS WITH MAJOR DEPRESSIVE DISORDER: AN ECONOMIC MODEL USING NUMBERS NEEDED TO HARM

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Abstract Introduction: The economic burden of major depressive disorder (MDD) is significant and includes costs due to treatment-related adverse events such as weight gain. In this economic modeling study, we quantified real-world direct costs associated with weight gain in patients initiating an atypical antipsychotic (AA) as adjunctive therapy for MDD (aMDD), then applied clinical trial-derived numbers needed to harm (NNHs) for weight gain to compare costs among AAs approved for aMDD.

Methods: Electronic medical records and claims from the Optum Market Clarity Dataset (1/1/2008–6/30/2022) were used to identify adults with a diagnosis of MDD who initiated aripiprazole, brexpiprazole, cariprazine, or quetiapine extended-release (XR) (1st dispensing=index) adjunctive to antidepressant therapy (ADT). Patients were required to have continuous health plan enrollment for ≥ 6 months before and after index, ≥ 2 months of continuous postindex AA use, and evidence of concurrent use of ADT with the index AA. Adjunctive AA-related weight gain was defined as $\geq 7\%$ increase in body weight within 3 months of AA initiation relative to the latest preindex (≤ 3 months) measurement. Follow-up healthcare costs were evaluated from 3 to 6 months postindex and included medical (ie, hospitalizations, emergency department visits, and outpatient visits) and pharmacy costs per patient per month (PPPM). The incremental cost of adjunctive AA-related weight gain was assessed as the mean difference in costs between patients with and without weight gain, with cohorts balanced based on baseline demographic, clinical, and economic characteristics using

inverse probability of treatment weighting. To estimate the comparative costs of treatment-related weight gain per 100 patients treated with each adjunctive AA, previously published NNHs from placebo-controlled trials were applied as measures of weight gain incidence. NNHs were reported with 95% CIs or described as “ns” if the 95% CI included infinity. The perspective was that of the US payer; all costs were converted to 2023 US dollars.

Results: In the real-world analysis, a total of 3534 eligible patients were identified, 350 of whom were considered to have adjunctive AA-related weight gain. Mean (SD) unweighted total medical and pharmacy costs were \$5415 (\$18,458) and \$3995 (\$11,812) PPPM in patients with and without weight gain, respectively. The weighted incremental cost (95% CI) associated with weight gain was \$1414 (\$30, \$2798) PPPM ($P=.045$). Clinical trial-derived NNHs (95% CI) vs placebo for weight gain associated with aMDD were 131 (ns) for cariprazine, 24 (17, 45) for aripiprazole, 38 (21, 177) for quetiapine XR, and 52 (ns) for brexpiprazole. Applying these NNHs to average real-world costs yielded monthly incremental adjunctive AA-related weight gain costs per 100 patients of \$1079 for cariprazine, \$2719 for brexpiprazole, \$3721 for quetiapine XR, and \$5892 for aripiprazole.

Conclusions: Real-world patients treated with AAs for aMDD who experienced weight gain had significantly higher healthcare costs by \$1414 (95% CI: \$30, \$2798) PPPM versus those who did not gain weight. Based on aMDD clinical trial-derived NNHs, the risk of excessive weight gain with cariprazine was lower than with aripiprazole, quetiapine XR, and brexpiprazole; therefore, the estimated cost of adjunctive AA-related weight gain was lower with cariprazine than the other AAs studied.

T47. PRECLINICAL EVALUATION OF ROPANICANT, A NICOTINIC ACETYLCHOLINE $\alpha 4\beta 2$ RECEPTOR ANTAGONIST IN ANIMAL MODELS OF DEPRESSION

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Abstract: Ropanicant is a nicotinic acetylcholine $\alpha 4\beta 2$ receptor antagonist. Based on the literature evidence, it was evaluated in various animal models of depression. To ascertain the antidepressant like property of Ropanicant, a forced swim test was conducted. Ropanicant was evaluated in dominant-submissive studies to ascertain the onset of antidepressant-like properties. To understand the mechanism of action of Ropanicant, various monoamines and brain-derived neurotrophic factor (BDNF) were estimated. As there are reports that an $\alpha 4\beta 2$ receptor antagonist can improve cognition, Ropanicant was assessed in an object recognition task (ORT). Ropanicant reduced the immobility time and increased the duration of swimming in the forced swim test in rats. The doses of Ropanicant, which reduced immobility, had no significant effect on the distance traveled in an open field study. Ropanicant had a rapid onset of action in comparison to reuptake inhibitors in the dominant-submissive assay. Treatment with Ropanicant increased monoamines and BDNF levels in rats, indicating the possible mechanism of action. Unlike tricyclic antidepressants, administration of Ropanicant increased the time spent by rats with the novel object in the ORT. From the ORT, we conclude that Ropanicant has a procognitive like effect. Preliminary toxicity studies showed no safety concerns for further development. Ropanicant has the potential to be a new

therapeutic option with unique properties for the treatment of major depressive disorders. Ropanicant is currently undergoing a phase-2 study (NCT06836063) in the United States to evaluate its safety and efficacy in patients with major depressive disorder.

T48. ROPANICANT (SUVN-911), AN $\alpha 4\beta 2$ NACHR ANTAGONIST: A PHASE 2B, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP STUDY, EVALUATING THE EFFICACY AND SAFETY OF ROPANICANT IN PATIENTS WITH MAJOR DEPRESSIVE DISORDER (MDD)

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Abstract: Ropanicant (SUVN-911) is a potent and selective $\alpha 4\beta 2$ nicotinic acetylcholine receptor (nAChR) antagonist and has demonstrated more than 100 fold selectivity against over 70 receptors which include closely related $\alpha 3\beta 4$ nAChR receptors, GPCRs, ion channels, enzymes, peptides, steroids, second messengers, growth factors, and prostaglandins. Ropanicant showed good oral bioavailability in preclinical species (rats, mice and dogs). Good oral exposures and increased cortical serotonin and norepinephrine levels translated into robust antidepressant like effects in animal models of depression. It showed faster onset of antidepressant activity, procognitive activity, and did not induce sexual dysfunctions in animal models thus, addresses major limitations of the currently used antidepressants. Non-clinical safety of ropanicant has been established in battery of safety pharmacology, general toxicity, embryo-fetal developmental and genotoxicity studies. Ropanicant was well tolerated and safe up to the highest tested dose of 60 mg single dose and 45 mg once daily (qd) for 14 days in healthy subjects. An open-label parallel-group Phase 2a study evaluated the safety and efficacy of Ropanicant in patients with moderate to severe MDD patients across multiple centers in the USA (NCT06126497). A total of 41 patients were randomized to receive Ropanicant either 45 mg qd, 30 mg twice a day (bid), or 45 mg bid in a ratio of 1:1:1, for duration of 14 days. Of the 41 randomized patients, 14 received Ropanicant 45 mg qd, 14 received 30 mg bid, and 13 received 45 mg bid. On Day 14, the Montgomery-Asberg Depression Rating Scale (MADRS) total score had changed significantly from baseline for the 30 mg bid group (-12.7), followed by the 45 mg qd (-10.5), and 45 mg bid (-10.4) groups. Day 14 MADRS total score showed a statistically significant improvement from baseline ($p < 0.0001$) across Ropanicant treatment arms. Ropanicant was found to be safe and well tolerated in patients with moderate to severe MDD across tested doses. The highly statistically significant improvement in the MADRS total score suggested potential treatment benefits of Ropanicant in MDD patients. Currently, a Phase 2b, randomized, double-blind, placebo-controlled, parallel-group, multicenter trial is ongoing (NCT06836063). The study is evaluating the efficacy and safety of Ropanicant 30 and 45 mg bid compared to placebo bid. The primary objective of the study is to evaluate the efficacy of Ropanicant compared to placebo in reducing the depressive symptoms. The secondary objectives are efficacy of ropanicant compared to placebo based on clinician reported outcome, functional impairment, and safety. The primary endpoint is the change from baseline in MADRS total score at Day 43 (Week 6). The study is planned to randomize 195 patients in a 1:1:1 ratio to receive either 30 or 45 mg bid of Ropanicant or placebo bid (65 per

treatment group) for a duration of 6 weeks. Topline data readout is expected in May 2026. Demographics and baseline characteristics of enrolled subjects will be presented at the conference.

T49. CONCURRENT ORAL ANTIDEPRESSANT USE AND CLINICAL OUTCOMES FROM INTRAVENOUS KETAMINE OR INTRANASAL ESKETAMINE IN A REAL-WORLD SAMPLE

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Abstract Background: Intravenous ketamine and intranasal esketamine produce rapid antidepressant effects in patients with treatment-resistant depression (TRD). In routine clinical practice, many patients continue oral antidepressants during ketamine/esketamine treatment; however, it remains unclear whether concurrent antidepressant use, as well as the specific class of antidepressant, influences clinical outcomes.

Objective: To examine the association between concurrent oral antidepressant class and clinical outcomes in a large real-world cohort of patients with TRD initiating treatment with intravenous (IV) ketamine or intranasal (IN) esketamine.

Methods: We conducted a retrospective observational study of patients treated with an acute course (6–8 sessions) of IV ketamine (0.5 mg/kg) or IN esketamine (56 or 84 mg) at the Yale Interventional Psychiatry Service between March 2015 and August 2023. The primary exposure was concurrent oral antidepressant use, divided by class—selective serotonin reuptake inhibitor (SSRI), serotonin–norepinephrine reuptake inhibitor (SNRI), other oral antidepressant, or no antidepressant. Outcomes included mean changes in Montgomery–Åsberg Depression Rating Scale (MADRS) and Quick Inventory of Depressive Symptomatology (QIDS) scores, as well as response ($\geq 50\%$ MADRS reduction) and remission (MADRS ≤ 10). Linear mixed-effects models assessed symptom change over time, and logistic regression models assessed odds of response or remission, adjusting for demographic and clinical covariates and treatment modality (IV ketamine vs. IN esketamine).

Results: The sample included 332 patients (149 IV ketamine; 183 IN esketamine). At treatment initiation, 84 patients were taking an SSRI, 98 an SNRI, 77 another oral antidepressant, and 73 no antidepressant. Depressive symptoms improved significantly over time across all groups (overall adjusted mean change in MADRS -11.7, 95% confidence interval -14.0 to -9.4, $p < 0.01$); however, adjusted changes in MADRS and QIDS scores did not differ significantly by antidepressant class relative to no antidepressant ($p > 0.1$ for all comparisons). Similarly, adjusted odds of response and remission were comparable across antidepressant classes (all $p > 0.1$).

Conclusions: In this real-world cohort, concurrent oral antidepressant use, including antidepressant class, was not associated with differential short-term clinical outcomes following IV ketamine or IN esketamine treatment. These findings suggest that oral antidepressant selection during ketamine/esketamine therapy may be guided by tolerability and prior treatment response rather than expectations of differential efficacy. Prospective, longer-term studies are needed to evaluate potential effects of concurrent antidepressant use on the durability of response to ketamine/esketamine.

T50. PSILOCYBIN TREATMENT FOR CHRONIC NEUROPATHIC PAIN AND DEPRESSION

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Abstract Background: Chronic neuropathic pain and Major Depressive Disorder (MDD) are two debilitating conditions with high rates of treatment resistance. Over 65% of individuals living with neuropathic pain also experience depressive symptoms, yet existing treatments do not adequately address both conditions simultaneously. Recent evidence suggests that psilocybin (the active ingredient in ‘magic mushrooms’), combined with supportive therapy, produces rapid antidepressant effects in adults with MDD. Given that neuropathic pain and depression share several mechanisms, psilocybin presents a promising therapeutic alternative for this comorbidity. However, this has not yet been translated into clinical evidence. Before a large-scale RCT can be conducted, the feasibility of conducting such study needs to be explored, along with its tolerability and therapeutic effects in this population.

Purpose: To address this important gap, this study aims to 1) determine the feasibility and safety of administering psilocybin therapy (25 mg) in adults with comorbid chronic neuropathic pain and MDD, and 2) provide preliminary evidence on whether psilocybin therapy can improve pain and depression symptom severity from baseline to 1-week post-treatment.

Methods: In this phase II open-label trial, 16 adults (aged > 18) with chronic neuropathic pain and DSM-5 MDD will receive one oral dose of psilocybin (25 mg) combined with supportive therapy. Eligible participants must have demonstrated treatment resistance, defined by an inadequate response to conventional therapies per the Canadian guidelines for neuropathic pain and the Antidepressant Treatment History Form. Two trained therapists will provide manualized psychotherapy before, during, and after the psilocybin dosing session. Feasibility outcomes include recruitment, adherence, and retention throughout the 3-month follow-up period. Safety outcomes include the number and severity of adverse events at all time points. Clinical outcomes include pain intensity and interference as determined by Patient Reported Outcomes Measurement Information System (PROMIS) questionnaires, and depressive symptoms as determined by the Montgomery–Åsberg Depression Rating Scale (MADRS). Given the pilot nature of this study, clinical outcomes will be analyzed on an intention-to-treat basis and summarized descriptively. To date, 1 of 16 participants has completed the study intervention.

Results: Enrolment is ongoing, and analyses presented will reflect early-stage data prior to study completion. Findings will focus on feasibility and safety outcomes, including recruitment processes, protocol adherence, and adverse event reporting.

Importance: This is the first registered clinical trial systematically assessing the feasibility, safety, and preliminary efficacy of administering psilocybin treatment to individuals with chronic neuropathic pain and MDD. Results are expected to inform the design of future large-scale trials needed to confirm treatment-related effects. This research could lead to new and innovative treatment pathways for medically complex patients who are often left underserved.

T51. CONVERGENT VALIDITY AND TREATMENT RESPONSIVENESS OF THE PATIENT-RATED DEPRESSION CHECKLIST (PRDC)

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Abstract Background: Major depressive disorder (MDD) is a leading cause of disability globally. The Patient-Rated Depression Checklist (PRDC) was developed to capture depressive symptom frequency and patient-perceived functional impact.

Objective: To evaluate the baseline construct validity, convergent validity, longitudinal convergent responsiveness, and sensitivity to treatment-related impact change as assessed by the PRDC in patients with treatment-resistant depression (TRD).

Methods: Data were obtained from a randomized, placebo-controlled trial of liafensine (1 or 2 mg/day) in adults with moderate-to-severe MDD meeting criteria for TRD. Baseline convergent validity was evaluated using cross-sectional Pearson correlations between PRDC scores and established clinician-rated measures of depressive severity and impression of global illness. Longitudinal convergent responsiveness was assessed using correlations between change from baseline in PRDC scores and corresponding changes in comparator measures. Responsiveness to treatment was further evaluated by estimating effect sizes for PRDC score changes over time and comparing them with those of commonly used clinician-rated instruments.

Results: At baseline, PRDC scores demonstrated moderate cross-sectional correlations with established measures of depressive severity, supporting convergent validity. Longitudinal analyses showed moderate-to-strong correlations between change from baseline in PRDC scores and change in established efficacy measures, indicating convergent responsiveness. PRDC scores also demonstrated sensitivity to both early and sustained treatment effects, with effect sizes comparable to those observed for commonly used clinician-rated instruments.

Conclusions: The PRDC demonstrates moderate convergent validity at baseline, moderate-to-strong longitudinal convergent responsiveness, and robust sensitivity to clinically meaningful change, supporting its use as a patient-centered outcome measure in TRD clinical research and clinical practice

T52. AN INVESTIGATION OF THE PUTATIVE ANTIDEPRESSANT MECHANISMS OF KETAMINE, REELIN, AND MU OPIOID RECEPTOR AGONISTS IN RATS AND IPSC-DERIVED CEREBRAL ORGANOIDs EXPOSED TO CHRONIC STRESS

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Abstract Background: Major depressive disorder (MDD) is a leading cause of global disability, yet current treatment options do not provide symptom relief for many individuals, and delayed treatment onset increases suicide risk. Esketamine, an FDA-approved

antidepressant, rapidly increases long-term potentiation (LTP) and functional synapse density, providing fast symptom relief for treatment-resistant depression (TRD). The opioid system is implicated in the pathogenesis of MDD, and mu opioid receptor (MOR) agonism demonstrates rapid antidepressant potential while inhibition of the opioid receptors attenuates ketamine's antidepressant effects. Translatability, however, is hindered by the significant risk for addiction and dependence. Reelin, an endogenous extracellular matrix glycoprotein, produces rapid antidepressant-like effects that parallel ketamine's timeline and mechanism in a preclinical rodent model of chronic stress. As a collaborative project between the University of Victoria (Canada) and the National Institute of Mental Health (USA), we designed a comprehensive preclinical evaluation of the potential rapid antidepressant effects of low-dose ketamine or reelin in combination with concurrent administration of a low dose of a MOR agonist with a favourable safety profile. We assessed this in both rodents and iPSC-derived cerebral organoids from TRD patients. We aim to develop a safe, tolerable, and effective rapid antidepressant treatment effective for individuals with TRD. The opioids used (olicecidine and a novel opioid compound) are G-protein-biased MOR agonists that provide effective analgesia with improved tolerability. *in vivo*: 32 male rats ($n = 4/\text{group}$) underwent daily injections of corticosterone (CORT; 21 d), followed by reelin (3 μg), olicecidine (2.5, 5, or 10 mg/kg), or a combination of reelin or ketamine (5 mg/kg) with low-dose olicecidine (1 mg/kg). Chronic CORT significantly increased immobility in the forced swim test, which was normalized by treatment with olicecidine (5 mg/kg) and the combination of olicecidine with ketamine, and partially by reelin alone and in combination with olicecidine. The prefrontal cortex (PFC) was microdissected and flash-frozen in liquid nitrogen. Synaptoneurosomes were created from PFC homogenate, and synaptic plasticity-related proteins were quantified using western blot. Protein expression did not differ significantly between treatments; however, trends towards increased levels of p-mTOR, m-TOR, p-AKT, and p-eEF2 (relative abundances to CV group $\sim 1.4 - 1.75$) following treatment with 2.5 mg/kg of olicecidine indicate MOR-dependent subtle synaptic alterations that warrant further investigation with a larger sample size.

in vitro: iPSC-derived cerebral organoids were created using PBMCs collected from patients with TRD or healthy controls. Organoids were treated with vehicle or cortisol for 5 days, followed by treatment with vehicle, reelin (50, 100, or 200 nM), a novel MOR agonist, or a combination of low-dose novel MOR agonist with low-dose reelin (10 nM) or ketamine (0.5 nM). Media IL-6 levels were quantified with ELISA at baseline, 1h post-CORT, 1h post treatment, and 24h post treatment. IL-6 levels significantly increased 24h following treatment with 50 nM of reelin, but not at higher doses. IL-6 was unchanged for all treatments that included the novel MOR agonist compound, suggesting that this compound avoids pro-inflammatory effects at the administered doses.

This preliminary investigation establishes a preclinical rationale for advancing ketamine or reelin in combination with a low-dose MOR agonist as a compelling antidepressant candidate and supports its progression towards clinical evaluation.

T53. A LANGUAGE-DERIVED AFFECTIVE SENTIMENT DIMENSION OF KETAMINE RESPONSE IN DEPRESSION

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Background: Ketamine produces rapid antidepressant effects, yet PHQ-9 total scores obscure heterogeneity in how patients improve. As psychiatry shifts toward dimensional, mechanism-informed models, language offers a direct affective readout that traditional scales may miss. Sentiment analysis can capture these signals, but it is unknown whether sentiment follows reliable treatment trajectories or which patient factors shape its change. Using a large real-world cohort, this study evaluates sentiment as a distinct affective dimension of ketamine response and identifies clinical characteristics that moderate its improvement.

Methods: We analyzed a cohort of 535 adults (mean age 42.9 [SD 14.1]; 55% women) with treatment-resistant depression treated with IV ketamine across a large outpatient network, including major depressive disorder (n=491) and bipolar depression (n=44). Most participants (n=535) completed the standard four-infusions-in-14-days protocol; 234 received off-protocol dosing or discontinued early. PHQ-9 scores were collected at baseline (≤ 30 days pre-treatment), infusion visits #1 and #4, and +3, +9, and +14 days post-treatment. At intake, patients reported comorbidities including anxiety (n=418), OCD (n=72), PTSD (n=172), SUD (n=56), and suicidal ideation (n=289), as well as current psychotropic use such as antidepressants (n=345), antipsychotics (n=71), benzodiazepines (n=159), non-benzodiazepine sedatives (n=78), mood stabilizers (n=88), stimulants (n=114), and other agents (n=68). Free-text responses collected at the same visits as part of the PHQ-9 were tokenized, mapped to AFINN lexicon scores and averaged to produce a single sentiment score. Sentiment trajectories were modeled using a mixed-effects framework as PHQ-derived factors, with log-transformed time as the primary predictor, identical covariates, and random participant intercepts. Fixed effects included age, sex, diagnosis, comorbidities and medication exposure. Secondary analyses examined moderators comorbidity and medication exposure.

Results: Sentiment increased significantly over time ($\beta=0.94$, 95% CI 0.63–1.25, $p < 0.001$). Higher baseline PHQ severity ($\beta=-0.08$, $p=0.001$) and mood stabilizer exposure ($\beta=-0.80$, $p=0.015$) were associated with lower overall sentiment but did not alter its rate of improvement. Two comorbidities moderated trajectories: anxiety predicted a steeper increase (Time $\times$ Anxiety $\beta=0.91$, 95% CI 0.18–1.64), whereas OCD markedly blunted improvement (Time $\times$ OCD $\beta=-1.25$, 95% CI -2.10 to -0.40).

Conclusion: Language-derived sentiment captured an affective dimension of ketamine response not reflected in traditional symptom scores. Although sentiment improved across treatment, its level and trajectory varied by clinical profile, enhanced in patients with anxiety and attenuated in those with OCD. These findings demonstrate that linguistic signals provide complementary insight into emotional change and reveal moderators distinct from PHQ-based domains. Integrating language-derived measures with conventional scales may sharpen mechanistic understanding and support more individualized treatment. Overall, these **Results** underscore the promise of language-based models as scalable tools for phenotyping response and advancing precision strategies in depression.

T54. INTERPRETING PSYCHIATRIC DIGITAL PHENOTYPING DATA WITH LARGE LANGUAGE MODELS: A PRELIMINARY ANALYSIS

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Abstract Background: Digital phenotyping, the passive monitoring of behavioral health via smartphone sensors, offers promising clinical applications but faces implementation challenges in translating complex multimodal data into actionable insights. Digital navigators, healthcare staff who interpret patient data for clinicians, provide a solution, but workforce limitations restrict scalability. Large language models (LLMs) may help address this gap, yet their performance in interpreting psychiatric digital phenotyping data remains unevaluated.

Objective: We sought to provide one of the first systematic evaluations of LLM performance in interpreting simulated psychiatric digital phenotyping data, establishing baseline accuracy metrics for this emerging application.

Methods: We evaluated GPT-4o and GPT-3.5-turbo across 153 test cases covering various clinical scenarios, timeframes, and data quality levels using simulated datasets currently employed in training human digital navigators. Performance was assessed on each model's capacity to identify clinical patterns relative to human digital navigation experts.

Results: GPT-4o demonstrated 52% accuracy (95% CI 46.5%-57.6%) in identifying clinical patterns, significantly outperforming GPT-3.5-turbo (12%, 95% CI 8.4%-15.6%).

Performance varied substantially across clinical scenarios: GPT-4o achieved 100% accuracy for worsening depression and 83% for worsening anxiety, but only 6% for increased home time with improving symptoms. Accuracy declined with decreasing data quality (69% for high-quality data vs. 39% for low-quality data) and shorter observation timeframes (60% for 3-month data vs. 43% for 3-week data). Occasional hallucinations were observed, with models occasionally generating clinically plausible but incorrect interpretations.

Conclusions: GPT-4o's 52% accuracy establishes a meaningful baseline, though performance gaps and hallucinations confirm that human oversight in digital navigation tasks remains essential. These results suggest that current LLMs are less reliable than traditional algorithmic approaches for raw sensor data parsing, yet may still help address workforce scalability challenges when positioned as assistive tools that augment rather than replace human digital navigators. Future research should explore agentic architectures that combine traditional pipelines for structured data processing with LLM capabilities for clinical reasoning and synthesis—potentially capturing the strengths of both approaches to improve psychiatric digital phenotyping workflows.

T55. A SIMULATION-BASED FRAMEWORK FOR CHARACTERIZING RISK IN CLINICALLY-DEPLOYED LARGE LANGUAGE MODELS

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Abstract Background: Large language models (LLMs) are rapidly entering clinical care, yet their probabilistic outputs have produced a variety of grossly unsafe user responses, including failures involving suicidal users. Difficulties in quantifying and mitigating the novel risks posed by LLMs, particularly the uncertainty linking model errors to downstream patient harm, threaten the regulatory evaluation and clinical deployment of LLM-based software as a medical device (LLM-SaMD). Using synthetic interactions between a chatbot and a potentially suicidal user, we demonstrate a simulation-based framework that extends established risk-management principles to LLM-SaMDs, providing a reproducible and generalizable method for estimating and bounding these novel risks.

Methods: Fourteen open-source models ranging from 270M to 70B parameters (Qwen, Gemma, and LLaMA families) were evaluated on three safety-classification tasks central to preventing unsafe therapeutic engagement: suicidal-ideation detection, therapy-request detection, and therapy-like interaction detection. Synthetic datasets were generated by Gemini 2.5 Pro across varied affective states, linguistic structures, and clinical ambiguity, and were manually verified by psychiatrists. Model false-negative rates were integrated with clinically plausible behavioral and prevalence assumptions to estimate P_1 , the likelihood that an LLM-generated hazard progresses to a hazardous situation, and P_2 , the likelihood that a hazardous situation results in patient harm, consistent with ISO 14971 and FDA SaMD risk models.

Results: LLM success at generating and classifying synthetic safety datasets varied by task, with strong performance for neutral and non-therapeutic content but frequent errors in suicidal-ideation and therapy-like interactions, particularly in ambiguous or boundary-case language. Across models, safety performance generally improved with increasing parameter count but included notable outliers. Estimated P_1 values (hazard to hazardous situation) ranged from 1.1×10^{-8} to 1.5×10^{-4} , and P_2 values (hazardous situation to harm) from 4.9×10^{-5} to 4.5×10^{-3} , together spanning up to four orders of magnitude across models and assumptions.

Conclusions: Simulation extends existing device-safety frameworks to help address the novel risks of LLMs. Rather than replacing regulatory judgment, it provides a reproducible method for quantitatively estimating uncertainty, clarifying assumptions, and linking model failures to plausible harms. Our case example demonstrates a generalizable approach that can overcome current regulatory barriers while remaining practical for manufacturers and regulators, supporting transparent oversight that keeps patients safe while avoiding unnecessary barriers to delivering the promise of LLM-SaMDs.

T56. AI-ENABLED PATIENT-DERIVED NEURONAL MODELS FOR MECHANISM-GUIDED ANTIDEPRESSANT SELECTION IN MAJOR DEPRESSIVE DISORDER

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Abstract Background: Major depressive disorder (MDD) is characterized by dysregulated synaptic plasticity, yet antidepressant selection remains largely empirical, contributing to prolonged trial-and-error treatment and poor outcomes. Artificial intelligence offers powerful tools to quantify complex biological phenotypes, but its clinical value depends on grounding algorithms in mechanistic, patient-specific biology. Translational models that link AI-enabled neuronal readouts to real-world treatment response are needed to define when and for whom AI can meaningfully support clinical decision-making in psychiatry.

Methods: Human induced pluripotent stem cells (hiPSCs) were generated from participants in the STAR*D study and differentiated into cortical excitatory neurons. Patients were stratified based on clinical antidepressant response using QIDS criteria ($> 70\%$ improvement vs $< 30\%$). Neurons were treated in vitro with the same antidepressants received clinically. Synaptic plasticity was quantified using AI-enabled high-content imaging, combining automated dendritic spine detection, connectivity analysis, and pattern recognition to generate objective, scalable measures of neuroplasticity across patient-derived neuronal cultures.

Results: Assay sensitivity and biological validity were first confirmed using brain-derived neurotrophic factor (BDNF), which produced a robust, dose-dependent increase in synaptic plasticity across neurons derived from 16 patients ($F = 112.58$, $p < 0.01$). Following validation, antidepressant exposure induced significantly greater synaptic plasticity in neurons derived from clinical responders compared with non-responders. The magnitude and direction of neuronal responses closely mirrored individual STAR*D clinical outcomes and were consistent across antidepressant classes.

Conclusions: AI-enabled analysis of patient-derived neuronal synaptic plasticity provides a mechanistic, functional correlate of antidepressant response, offering a biologically grounded approach to precision psychopharmacology. These findings illustrate how AI can enhance, not replace, clinical judgment by translating complex cellular phenotypes into clinically relevant decision support signals.

T57. SUSTAINED PHARMACODYNAMIC EFFECTS OF EskETAMINE ON CORTICAL EXCITABILITY AND RESTING-STATE BRAIN ACTIVITY: A RANDOMIZED, PLACEBO-CONTROLLED TRIAL

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Abstract Aim: Acute pharmacodynamic effects of esketamine have been well characterized; however, reliable pharmacodynamic measures capturing delayed effects—potentially related to its antidepressant efficacy emerging beyond 24 hours—remain limited. We hypothesized that delayed effects arising after esketamine clearance are mechanistically distinct from acute, peak-concentration-driven psychomimetic and CNS-depressant effects. To address this, we investigated pharmacodynamic biomarkers reflecting acute, delayed, and sustained central nervous system (CNS) effects of esketamine, used as a tool compound for rapid-acting antidepressant activity, using Transcranial Magnetic Stimulation (TMS) and resting-state pharmaco-electroencephalography (pEEG), with the goal of informing biomarker strategies for delayed antidepressant effects in early-phase drug trials.

Methods: In this randomized, double-blind, double-dummy, placebo-controlled, four-way crossover study, 16 healthy participants received a therapeutic intravenous (IV) dose of esketamine (0.40 mg/kg 40-minute IV), oral low-dose of esketamine (0.20 mg/kg), oral high-dose of esketamine (0.45 mg/kg), or placebo. Neurophysiological assessments were conducted from baseline up to 7 days post-dose using TMS combined with electromyography (TMS-EMG) and electroencephalography (TMS-EEG), alongside resting-state pEEG and plasma concentrations of parent drug and metabolites. Outcomes were analyzed using mixed-effects ANCOVA and cluster-based permutation testing.

Results: IV esketamine produced an acute significant reduction in motor-evoked potential amplitude (estimated difference [ED]: $-430.17 \mu V$; 95% CI: -806.74 to -53.61 ; $p = 0.03$), alongside sustained attenuation of long-interval intracortical inhibition (LICI₅₀) persisting beyond drug exposure (ED: $+57.83\%$; 95% CI: 14.24 to 101.43 ; $p = 0.01$). TMS-EEG revealed acute modulation of TMS-evoked potentials across all active treatments, whereas delayed effects were observed only following IV and high-dose oral esketamine. Resting-

state pEEG demonstrated acute reductions in alpha, beta, and delta power during eyes-closed conditions and a sustained increase in delta power during eyes-open conditions following IV and high-dose oral dosing.

Conclusion: TMS- and pEEG-derived measures reveal delayed and sustained pharmacodynamic CNS effects of esketamine persisting up to 7 days post-dose. These findings indicate a temporally dissociable pharmacodynamic profile, distinct from acute, exposure-driven CNS effects, which may be relevant to its delayed antidepressant efficacy.

T58. ALTO-207, A FIXED-DOSE COMBINATION OF PRAMIPEXOLE AND ONDANSETRON, SUGGESTS EFFICACY IN TREATING MAJOR DEPRESSION: FINDINGS FROM A RANDOMIZED, DOUBLE-BLIND PHASE 2A TRIAL

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Abstract Background: Major Depressive Disorder (MDD) is a common, debilitating psychiatric disorder that is a leading cause of global burden. Despite evidence that efficacious treatments exist, the majority of individuals with MDD have an inadequate response to current standard-of-care treatments. Furthermore, approximately 30% fail to respond to multiple antidepressant treatments and are considered to have treatment-resistant depression (TRD). Pramipexole, a dopamine D3-preferring D3/D2 agonist, has demonstrated medium to large treatment effects in MDD and in TRD across multiple studies, yet requires slow titration due to dose-limiting nausea and vomiting. These side effects often lead to discontinuation of treatment or subtherapeutic doses. CTC-501 (now known as ALTO-207) is a fixed-dose combination of pramipexole and ondansetron, a 5-HT₃ antagonist anti-emetic. In a Phase 1 study, ALTO-207 increased maximum tolerated doses and plasma concentrations by at least 2.5-fold using a ~5× faster titration than the pramipexole titration in the approved label, with 60% tolerating the study maximum dose of 6mg. It is unknown, however, whether this combination of compounds would be efficacious in treating depressive symptoms.

Methods: A Phase 2a proof-of-concept randomized trial was conducted in 32 adults with MDD (1:1 randomization) over 8 weeks to assess the safety and efficacy of the combination. Analyses used mixed models for repeated measures (MMRM) on score change from baseline.

Results: Baseline MADRS was 28.5 (SD 5.2). Compared with placebo, CTC-501 resulted in large improvements in MADRS scores (week 8 d=1.10, p=0.025). CGI-S showed a similar pattern (week 8 d=1.00, p=0.04). Effect sizes were ≥0.58 beginning at week 2. CTC-501 reached a mean of 4.1 mg/day of pramipexole within 8 days, which was subsequently well tolerated throughout maintenance with no discontinuation due to adverse events. After an initial titration schedule modification, 77% of CTC-501 subjects reached the study maximum of 5 mg/d pramipexole. Comparison of antidepressant effect sizes across randomized trials of pramipexole and CTC-501 further suggest a dose-response relationship with this Phase 2a study achieving the highest pramipexole dose to date.

Conclusions: CTC-501 (now ALTO-207) is a novel fixed-dose combination of pramipexole and ondansetron that allows for rapid titration to achieve doses of pramipexole that are generally not achieved in practice but are associated with greater efficacy. This combination

demonstrated large effect sizes in reducing both depression severity as well as global illness severity, beginning as early as week 2 of treatment.

T59. EFFECTS OF ALIXOREXTON ON PATIENT-REPORTED DISEASE SEVERITY, COGNITIVE FUNCTIONING, AND FATIGUE IN PATIENTS WITH NARCOLEPSY TYPE 1: RESULTS FROM THE PHASE 2 VIBRANCE-1 STUDY

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Abstract Background: Narcolepsy type 1 (NT1) is traditionally characterized by excessive daytime sleepiness, cataplexy, sleep-related hallucinations, sleep paralysis, and disturbed nighttime sleep. In addition, cognitive impairment and fatigue are often reported by patients, but these symptoms are not adequately treated with current therapies. The effects of alixorexton, an investigational, oral, highly selective orexin 2 receptor agonist, on disease severity, cognition, and fatigue in patients with NT1 were examined in the phase 2 Vibrance-1 study.

Methodology: Vibrance-1 (NCT06358950) was a randomized, placebo-controlled phase 2 study that evaluated the efficacy, including patient-reported outcomes (PROs), and safety of alixorexton in adults with NT1. Patients were randomized 1:1:1:1 to receive double-blinded treatment with placebo or once-daily alixorexton (4, 6, or 8 mg) for 6 weeks, followed by 7 weeks of treatment with alixorexton in an optional open-label extension (OLE) period. PROs evaluated as exploratory outcomes included the Narcolepsy Severity Scale-Clinical Trials (NSS-CT), the British Columbia Cognitive Complaints Inventory-Expanded Version (BC-CCI-E, which includes items assessing both severity and impact of cognitive impairment), the PROMIS-Fatigue Short-form 6a (PROMIS-Fatigue), the Patient Global Impression of Severity (PGI-S) Cognition item, and the PGI-S Fatigue item. Statistical analyses of the PRO endpoints were not adjusted for multiplicity, thus all p-values are nominal.

Results: A total of 92 patients were randomized and treated with placebo (n=23) or alixorexton (4 mg, n=23; 6 mg, n=22; 8 mg, n=24) during the double-blind treatment period; 88 (96%) patients completed OLE treatment. All alixorexton-treated groups showed improvements from baseline in NSS-CT score at Week 6 (4 mg, -9.1; 6 mg, -12.4; 8 mg, -11.0; all p < 0.001 versus placebo), surpassing the 8-point minimum clinically important difference. Improvements on the NSS were sustained at Week 8 and Week 12. Improvements from baseline on the BC-CCI were observed for all alixorexton-treated groups at Week 2, Week 6 (least squares mean [LSM] change from baseline at Week 6: 4 mg, -3.5; 6 mg, -3.7;

8 mg, -4.8; all $p < 0.0001$ versus placebo) and through Week 13. Similarly, most patients treated with alixorexton reported mild or no cognitive impairments at Week 6 on PGI-S Cognition. All alixorexton-treated groups showed improved scores on PROMIS-Fatigue at Week 2; these improvements were sustained through Week 6 (LSM change from baseline at Week 6: 4 mg, -8.7; 6 mg, -12.4; 8 mg, -12.9; all $p < 0.01$ versus placebo) and through Week 13. Scores on PGI-S Fatigue demonstrated a similar trend with most patients treated with alixorexton reporting decreased fatigue severity from baseline at Week 6, and through Week 13.

Importance: Results of the phase 2 Vibrance-1 study showed that patients with NT1 treated with alixorexton achieved nominally significant, clinically meaningful improvements in PRO measures of disease severity, cognitive impairment and fatigue at Week 6. These improvements were sustained through OLE treatment. Funding: Alkermes, Inc.

T60. SAFETY AND EFFICACY RESULTS FROM THE PHASE 2 VIBRANCE-1 STUDY OF THE OREXIN 2 RECEPTOR AGONIST ALIXOREXTON IN PATIENTS WITH NARCOLEPSY TYPE 1

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Abstract Background: Narcolepsy type 1 (NT1), a central disorder of hypersomnolence, is characterized by excessive daytime sleepiness, cataplexy, and orexin deficiency. Alixorexton is a potent, oral, selective orexin 2 receptor agonist being investigated as a treatment for narcolepsy. The randomized, phase 2 Vibrance-1 study (NCT06358950) examined the safety and efficacy of alixorexton in patients with NT1.

Methodology: In Vibrance-1, adults with NT1 were randomized (1:1:1:1) to receive placebo or once-daily alixorexton (4, 6, or 8 mg) for 6 weeks in the double-blind treatment period, which was followed by 7 weeks of alixorexton treatment in an optional open-label extension (OLE) period. The primary endpoint was change from baseline to Week 6 in mean sleep latency (MSL) on the Maintenance of Wakefulness Test (MWT). Key secondary endpoints were change from baseline to Week 6 in Epworth Sleepiness Scale (ESS) score and mean weekly cataplexy rate (WCR) at Week 6. Safety was assessed via treatment-emergent adverse events (TEAEs), which were collected as a secondary endpoint. P values were adjusted for multiplicity.

Results: A total of 92 patients were randomized to placebo (n=23) or alixorexton (4 mg, n=23; 6 mg, n=22; 8 mg, n=24); 88 (96%) patients completed OLE treatment. Least squares

mean [LSM; 95%CI] changes from baseline to Week 6 in MSL versus placebo for the 4, 6, and 8 mg groups were 22.2 (17.2, 27.2), 24.1 (19.0, 29.1), and 26.0 (21.0, 31.0) min, respectively (all $p \leq 0.01$); all alixorexton doses achieved normative levels of wakefulness. At Week 6 mean ESS score was improved for all alixorexton doses (LSM change from baseline versus placebo [95% CI]: 4 mg, -6.4 [-9.6, -3.3]; 6 mg, -8.7 [-11.9, -5.5]; 8 mg, -8.3 [-11.4, -5.2]; $p \leq 0.01$ for all doses). Additionally, all doses of alixorexton reduced WCR at Week 6, with statistically significant improvement observed at the 6 mg dose ($p = 0.01$ versus placebo). Improvements in ESS and WCR were sustained through Week 13. Most TEAEs were mild to moderate in severity and there were no serious TEAEs. Through Week 6, TEAEs reported in $\geq 10\%$ of patients who received alixorexton were pollakiuria, insomnia, salivary hypersecretion, micturition urgency, and blurred vision. In the OLE, these TEAEs occurred primarily in patients who switched from placebo to alixorexton.

Conclusions: Alixorexton achieved clinically meaningful and statistically significant improvements in the MWT and ESS, and resulted in clinically meaningful reductions in WCR at Week 6. Improvements observed in ESS and WCR were sustained through Week 13. Alixorexton was generally well tolerated. Funding: Alkermes, Inc.

T61. THE USE OF MAGNETOENCEPHALOGRAPHY (MEG) IN A FIRST-IN-HUMAN TRIAL TO DEMONSTRATE THE FUNCTIONAL CONSEQUENCES OF TARGET ENGAGEMENT BY DT-101, A NOVEL AMPA RECEPTOR POSITIVE ALLOSTERIC MODULATOR

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Abstract: Development of new drugs for neuropsychiatric disorders is limited by the lack of objective biomarkers that can demonstrate central nervous system engagement and inform early clinical decision-making. In this work, we integrated magnetoencephalography (MEG) into a first-in-human (FiH) clinical trial of DT-101, a novel AMPA receptor (AMPA) positive allosteric modulator (PAM), to assess its utility as a pharmacodynamic biomarker. To our knowledge, this represents the first incorporation of MEG into a FiH trial, and the findings informed dose selection and supported progression to Phase 2 evaluation in major depressive disorder (MDD). MEG provides millisecond temporal resolution and relatively high spatial resolution, and directly measures neural activity, making it well suited to detect pharmacologically induced changes in brain function. MEG was incorporated using two complementary FiH study designs: integration within a Multiple Ascending Dose (MAD) to assess effects after repeated dosing, and a standalone double-blind crossover to enable within-participant comparisons across single doses. Comparable drug-related effects were observed across both designs. Healthy volunteers completed ~1-hour MEG sessions beginning around T_{max}. In the MAD study, three dose cohorts (18:6 DT-101:placebo) were assessed on dosing Day 12 (± 1 day). In the crossover study ($n = 19$), participants received placebo, low-dose, and high-dose DT-101 in randomised treatment periods with washout. MEG paradigms included eyes-open resting state, auditory mismatch negativity (MMN), auditory steady-state response (ASSR), and high-contrast visual gratings to elicit gamma oscillations. Resting-state data were analysed using whole-brain beamforming across eight frequency bands (total range 1–100 Hz), with dose effects assessed using linear mixed-effects models. DT-101 produced dose-related changes across frequency bands, characterised by

reduced activity at lower frequencies, consistent with effects opposite to those previously reported for the AMPAR antagonist perampanel¹. Visual grating stimulation elicited expected occipital gamma responses, with beamforming revealing DT-101 dose-dependent increases in stimulus-induced occipital activity over a broad range of frequencies up to gamma. In the auditory paradigms, DT-101 increased 40-Hz ASSR power without affecting inter-trial coherence, and no drug-related effects were observed with MMN. DT-101 was well tolerated, with cerebrospinal fluid concentrations comparable to plasma levels. Together, these findings demonstrate target-relevant neurophysiological effects and illustrate how MEG can provide informative pharmacodynamic evidence in early-phase psychopharmacology studies. MEG may therefore represent a valuable tool to support dose selection and translational decision-making in psychiatric drug development.

T62. CROSS TRIAL IDENTIFICATION OF A PREDICTIVE ENRICHMENT SUBGROUP FOR ESMETHADONE (REL 1017) IN MAJOR DEPRESSIVE DISORDER USING EXPLAINABLE MACHINE LEARNING

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Abstract Background: High patient heterogeneity and placebo response contribute to frequent late-stage clinical trial failure in major depressive disorder (MDD). Regulatory guidance on enrichment strategies and model-informed drug development (MIDD) emphasizes prospectively identifying patients most likely to benefit from therapy. We evaluated an explainable machine learning-based framework to derive and validate a predictive enrichment strategy for esmethadone (REL-1017) across multiple randomized trials.

Methods: Patient-level data from three independent randomized, double-blind, placebo-controlled trials of esmethadone were analyzed: Phase 2a (analysis set, N=61), Phase 3 RELIANCE I (analysis set, N=205), and Phase 3 RELIANCE III (analysis set, N=208). The program included both adjunctive and monotherapy study designs. Baseline variables included routinely collected demographic, clinical, and symptom-level measures. Subgroup discovery was conducted using an explainable machine learning platform designed for small clinical trial datasets and aligned with MIDD principles. The approach employs unsupervised feature embedding and constrained evolutionary search to identify patient subgroups associated with differential treatment response, while limiting overfitting and preserving interpretability. Subgroup definitions were identified in the Phase 2a trial and locked to assess replicability in Phase 3 trials. Treatment-by-subgroup interactions were assessed using change from baseline in Montgomery–Åsberg Depression Rating Scale (MADRS) total score at study endpoint.

Results: A single Model-Derived Subgroup (MDS) met all replication criteria across trials. The MDS was defined by marked depressive weight loss, a score of 2 (range 0-2) on the Hamilton Depression Rating Scale weight loss item indicating definite weight loss by self-report and baseline body weight that is ≥ 76.3 kg. Within this subgroup, esmethadone demonstrated consistent and clinically large antidepressant effects across all 3 studies, with drug-placebo MADRS differences of 10.4–12.5 points and effect sizes of Cohen's $d = 0.90$ – 1.16 (all nominal $p < 0.05$). This treatment separation exceeded that observed in the full Phase 2a population by 4.7 MADRS points and was 8.2–9.5 points $>$ in the full Phase 3

populations. The prevalence of the MDS differed substantially across trials (38% in Phase 2a versus 12–14% in Phase 3), accounting for attenuation of the treatment signal in unenriched confirmatory studies.

Conclusions: This analysis demonstrates a regulatorily aligned, model-informed enrichment methodology that emphasizes interpretability, cross-trial replication, and prospective feasibility. By grounding subgroup definitions in routinely collected clinical features and validating them across independent trials, this framework addresses key regulatory concerns surrounding post hoc subgroup analyses. Prospective application of this predictive enrichment strategy may improve trial efficiency and therapeutic signal detection for esmethadone and other novel antidepressants, consistent with FDA guidance on enrichment strategies and MIDD.

T63. PREDICTION OF HUMAN PHARMACOKINETIC PROFILES OF GLYPH PLATFORM PRODRUGS USING ANIMAL AND HUMAN DATA VIA A SEMI-MECHANISTIC PHARMACOKINETIC MODEL

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Abstract Background: GlyphAllo™ (SPT-300 or Glyph Allopregnanolone), an oral prodrug of allopregnanolone, is designed to overcome bioavailability limitations of allopregnanolone by shifting absorption toward the lymphatic system, avoiding first-pass hepatic metabolism. GlyphAllo uses the Glyph™ platform, a lymphatic-targeting prodrug technology which reversibly conjugates a drug of interest to a dietary fat molecule using proprietary chemistry, enabling higher oral bioavailability of allopregnanolone. A phase 1 clinical trial (NCT05129865) demonstrated that GlyphAllo dosing in healthy volunteers was generally well tolerated and resulted in therapeutically relevant plasma exposures of allopregnanolone. The objective of this analysis was to develop a semi-mechanistic pharmacokinetic (PK) model to predict human exposures for lymphatic-targeting Glyph prodrugs from preclinical data.

Methods: Allopregnanolone PK profiles were obtained after a single oral dose of GlyphAllo in cynomolgus monkeys and a first-in-human phase 1 study (NCT05129865). A semi-mechanistic PK model was developed with an absorption compartment, five transit compartments to account for the unique absorption kinetics of dietary lipids, and central and peripheral compartments to describe both the monkey and human profiles. Using allometric scaling, clearance (CL), central volume (V1), peripheral volume (V2), and inter-compartmental rate transfer (Q), monkey PK parameters were obtained from a published human intravenous (IV) allopregnanolone population PK model¹. To capture the unique absorption kinetics of lymphatic delivery, optimal absorption (k_a) and transit rate (k_{tr}) PK parameters were fit to the semi-mechanistic PK model using the monkey allopregnanolone concentration-time profiles. These parameters (k_a , k_{tr}) derived from monkey were then combined with human published PK parameters¹ to model the profiles measured in the phase 1 study. All modeling building and graphical analyses were done using NLMIXR2 (Version 3.0.2), RStudio (Version 2024.12.0), and R (Version 4.4.2).

Results: The semi-mechanistic PK model with first order absorption along with five transit compartments and central and peripheral compartments had a better fit of cynomolgus monkey allopregnanolone PK profiles compared to other PK models with fewer or no transit compartments. No misspecification in the structural model was observed. The results showed

that the absorption and transit rate constants from the monkeys translated well to humans and were able to capture the shift in time to maximum concentration (T_{max}) and maximum concentration (C_{max}) of allopregnanolone following oral dosing of GlyphAllo. The goodness-of-fit plots showed a high degree of alignment between predicted and observed data for both monkey and human.

Conclusion: We present a modeling approach to predict human exposures of lymphatic-targeting Glyph prodrugs by first using human PK data of existing drugs and back-transforming them to animal PK data, then subsequently fitting optimal absorption and transit compartment parameters in cynomolgus monkey to capture complex lymphatic absorption kinetics. These absorption parameters from cynomolgus monkeys, along with published human kinetic parameters were then used for modeling human exposures of lymphatic-targeting Glyph prodrugs. Results illustrate the interspecies scaling of GlyphAllo and support the application of this method to predict PK across species for other Glyph molecules in development.

T64. EVALUATING POTENTIAL ABUSE-RELATED ADVERSE EVENTS IN CLINICAL STUDIES OF PSYCHEDELICS AND NOVEL CENTRAL NERVOUS SYSTEM ACTIVE DRUGS TO INFORM LABELING AND SCHEDULING RECOMMENDATIONS: ISSUES, METHODS, AND RECOMMENDATIONS

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Abstract: For CNS-active drugs, conducting an abuse potential assessment (APA) during development is a key component of the overall safety evaluation required by the United States Food and Drug Administration (FDA) and by law per the Controlled Substances Act (CSA) of 1970. The APA is conducted to assist with labeling and scheduling of approved medications, the latter of which serves to protect the public health by controlling the prescribing and use of drugs that may have abuse potential. Assessing the abuse potential of CNS-active drugs requires the evaluation of data from numerous sources, including nonclinical and clinical studies. Per FDA's 2017 Assessment of Abuse Potential of Drugs guidance document, a full APA includes identifying potential abuse-related adverse events (AEs) in all clinical safety and efficacy studies of CNS-active drugs. Psychedelics and novel drugs that produce ambiguous signals in nonclinical and clinical abuse potential studies provide unique challenges to the APA, and thus particular focus on potential abuse-related AE assessment methods is paramount. The objectives of this presentation will be to review the issues involved with assessing potential abuse-related AEs in clinical studies of novel psychoactive compounds and provide recommendations on methods and strategies for collecting abuse-related AE data. Psychedelics and other novel CNS-active drugs may produce profound psychoactive effects that could be associated with the therapeutic response; regardless of their expectedness, these events should be collected and reported as potential abuse-related AEs. Proper abuse-related AE assessment requires a well-planned prospective, systematic methodology, starting with a prespecified list of AE terms that will be closely monitored as events of special interest. Terms related to euphoria, dissociation/psychosis, intoxication, CNS stimulation or depression, and others specific to the drug type or class should be included. Sponsors should review proposed lists of abuse-related AE terms and plans for collecting abuse-related information with FDA's Controlled Substance Staff before implementation to ensure alignment with the Agency. Investigators and staff must be trained

to identify and record information about abuse-related AEs when they occur so that detailed narratives can be written, and all Investigators in multi-site studies should be adequately and similarly trained to avoid variability in AE collection procedures across sites. Comprehensive narratives provide contextual information and help determine if psychoactive effects of the drug (e.g., hallucinations, euphoria, sedation, emotional lability) appear likely to motivate post-treatment recreational use or are instead aversive and unlikely to be sought out. Since no clear objective criteria for such differentiation exist, collecting detailed contextual information and summarizing potential abuse-related AE data in a clear and thorough manner will better inform the Sponsor and FDA and assist in scheduling and labeling decisions. It is imperative that Sponsors, Investigators, sites, and Contract Research Organizations conducting studies with CNS-active compounds work together in implementing a plan for collecting potential abuse-related AE data as these data are vital components of the APA and scheduling proposal submitted by Sponsors in the New Drug Application and provide the data FDA will need in its CSA scheduling recommendation and labeling development. Such data can also inform FDA's potential requirement for post-marketing risk evaluation and mitigation strategies (REMS).

T65. DT-101 – A NOVEL ALPHA-AMINO-3-HYDROXY-5-METHYL-4-ISOXAZOLE RECEPTOR (AMPA) POSITIVE ALLOSTERIC MODULATOR DEMONSTRATES FAVORABLE TOLERABILITY AND FUNCTIONAL BIOMARKERS IN PHASE 1 HEALTHY VOLUNTEER TRIAL

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Abstract Positive allosteric modulators (PAMs) of the α -amino-3-hydroxy-5-methyl-4-isoxazole subtype of ionotropic glutamate receptor (AMPA) enhance glutamatergic signaling and synaptic plasticity, but the clinical development of earlier compounds have been constrained by suboptimal pharmacokinetics and limited therapeutic index (TI). DT-101 is a next-generation, structurally novel, orally bioavailable AMPAR PAM designed to achieve much broader TI through optimized receptor modulation. Importantly, DT-101 has a differentiated pharmacokinetic profile enabling once-a-day pulsatile dosing that is optimal for engaging synaptic plasticity mechanisms. A Phase 1 randomized, double-blind, placebo-controlled trial was conducted with single-ascending dose (SAD) and multiple-ascending dose (MAD) in healthy adult volunteers. The primary objectives were safety and tolerability of DT-101. Secondary and exploratory objectives included the plasma pharmacokinetics (PK) of DT-101 as well as measurements of cerebrospinal fluid (CSF) drug concentration. A separate cohort of healthy volunteers was used to assess the pharmacodynamic responses to single doses of DT-101 using magnetoencephalography (MEG), a method previously shown to be sensitive to modulators of excitatory/inhibitory tone in the brain. DT-101 was considered safe and well tolerated, with no dose-limiting toxicities or clinically meaningful safety findings. DT-101 achieved its predefined target PK profile, demonstrating dose-proportional exposure and favorable half-life supportive of once-daily dosing. DT-101 concentration in CSF was equivalent to unbound plasma concentration, consistent with good exposure into the CNS. MEG analyses demonstrated a clear DT-101-mediated modulation of cortical oscillatory activity and network dynamics consistent with AMPA receptor potentiation, providing direct evidence of functional DT-101 effects in the brain. MEG effects correlated with plasma exposure, enabling data-driven refinement of Phase 2 dose selection. In summary, DT-101 exhibits a favorable safety profile with target-aligned PK,

confirmed CSF exposure, and sensitive MEG-based demonstration of functional glutamatergic modulation. These Phase 1 findings supported advancement of DT-101 into a large, global Phase 2 trial in major depressive disorder (MDD).

T66. USING ARTIFICIAL INTELLIGENCE/MACHINE LEARNING AND REAL-WORLD DATA TO IDENTIFY PATIENTS WITH EARLY STAGE BIPOLAR-I DISORDER FOR WHOM AN ARIPIPRAZOLE MONOHYDRATE LAI IS LIKELY TO BE A FAVORABLE TREATMENT OPTION

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Abstract Background: Bipolar-I disorder (BP-I) is a chronic psychiatric condition marked by significant functional impairment and clinical management challenges, typically requiring sustained maintenance therapy. 1 While evidence exists to support the benefit of early initiation of long-acting injectable antipsychotics (LAIs) compared to oral formulations, real-world data are lacking to guide personalized treatment decisions. 2 This study aimed to leverage large-scale United States (US) electronic health records (EHR) and claims data and apply machine learning (ML) methodologies to identify demographic, clinical, and individual treatment and timing factors associated with most favorable response to aripiprazole monohydrate LAIs (i.e., aripiprazole once monthly [AOM] and aripiprazole 2-month Ready to Use [Ari 2MRTU]) in early-stage BP-I.

Methods: This prognostic study used real-world data from a large, integrated EHR and open claims database in the Atropos Evidence Network™ covering all sites of care and pharmacy fills for patients in the US from 2012-2025.3 The primary ML approach used targeted minimum loss-based super learning ensembles to incorporate drivers of observed treatment selection and likely outcomes in predicting characteristics of BP-I patients for whom aripiprazole monohydrate LAIs are likely to be favorable treatment option. The model was trained on 70% of the real world-dataset and validated on the remaining 30%. To assess the impact of time to antipsychotic (AP) treatment initiation, the index treatment for each patient was defined as the last AP treatment started within 3 years of initial BP-I diagnosis with ≥1 year of follow-up. The primary treatment success measure was absence of both all-cause inpatient admissions and an AP treatment regimen change (switch or stop) during 12-months post-index period. To test robustness, sensitivity analyses were performed (different datasets, study operational definitions, statistical and ML techniques).

Results: Among the 98,972 (validation sample n=29,510) patients starting AP treatment within 3 years of initial BP-I diagnosis and with ≥1 year of follow-up, mean age was 41 ± 15 years, 62% were female, 33% had recent substance use documented, and the mean time from diagnosis to index treatment was 1.06 ± 0.97 years. The most common index treatment was an oral atypical AP (51%). Overall, 66% of patients stayed free of hospitalization and AP regimen change within 1 year of initiating index AP treatment. The most important outcome predictors were recent patterns of inpatient and emergency department utilization. The final

model was able to distinguish between different treatments for BP-I, including between AOM and Ari 2MRTU. The ML policy proposed aripiprazole monohydrate LAIs should be used earlier after diagnosis. Ari 2MRTU demonstrated higher expected benefit over shorter-term LAIs (AOM), but there was still a benefit for both LAIs in this population. Ari 2MRTU had the greatest estimated treatment effect and was preferred for patients within 5 months of initial BP-I diagnosis. The estimated treatment success (if patients had been on the ML policy-proposed optimal treatment) was 74% (95%, CI: 73%-76%). This was significantly better than the overall observed success rate (66%, $p < 0.001$).

Conclusion: Patients with BP-I are likely to benefit from earlier initiation of Ari 2MRTU. This ML predictive approach should be refreshed in the future as more AP treatment data becomes available.

T67. DO NONDSM CRITERIA ENHANCE THE VALIDITY OF THE DSM-5 MIXED FEATURES SPECIFIER IN DEPRESSED PATIENTS?

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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. The DSM-5 definition requires the presence of 3 or more of the 7 symptoms for the majority of the episode. The most controversial aspect of the DSM-5 mixed features criteria are the symptoms included in the definition. To avoid the double counting of symptoms as indicative of both depression and mania, the DSM-5 definition includes only “opposite polarity” symptoms and thus does not include features of depression such as agitation or distractibility. Several authors have been critical of the DSM criteria set for failing to include those symptoms that traditionally have been viewed as central to mixed states (i.e. agitation, irritability, distractibility). We use the acronym AID to refer to these symptoms. In the present report from the Rhode Island methods to Improve Diagnostic Assessment and Services (MIDAS) project we examined the impact on the prevalence and validity of mixed depression of adding the AID symptoms to the DSM-5 criteria set.

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 (DMSI). The DMSI assesses the 7 DSM-5 criteria of the mixed features specifier (elevated mood, inflated self-esteem, increased talkativeness, thought racing, increased energy or goal directed activity, increased activity with potentially painful consequences, decreased need for sleep) as well as the 3 AID symptoms (agitation, irritability, distractibility).

Results: We added the 3 AID symptoms to the 7 DSM-5 criteria and examined the distribution of number of mixed features and the prevalence of mixed features based on different cutoffs. At the DSM-5 cutoff of 3, the prevalence of mixed features increased from 3.9% to 42.7%. Increasing the cutoff to 4 reduced the prevalence of mixed features by more than 15%, and increasing the cutoff to 5 reduced the prevalence by more than another 15%. Even at a cutoff of 5, the prevalence based on the 7 DSM-5 plus 3 AID symptoms was > the prevalence based on the DSM-5 criteria (cutoff of 3 of 7 features) (6.5% vs. 3.9%). Patients who met the mixed features specifier based on the DSM-5 criteria were more likely to be

diagnosed with bipolar disorder. Amongst the patients with major depressive disorder, meeting the DSM-5 mixed features criteria was associated with an increased family history of bipolar disorder. We added the 3 AID symptoms to the 7 DSM-5 criteria and focused on the patients who newly met the mixed features criteria (and did not meet the DSM-5 definition). In these patients, there was no association between the mixed features specifier and a diagnosis of bipolar disorder or a family history of bipolar disorder.

Conclusions: The results of the present study do not support adding the symptoms of agitation, irritability, and distractibility to the DSM-5 definition of the mixed features specifier.

T68. MULTIFOCAL NEGATIVE AFFECT: THE PREVALENCE AND CLINICAL PROFILE OF PSYCHIATRIC OUTPATIENTS WHO ARE DEPRESSED, ANXIOUS AND IRRITABLE

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Abstract Objective: In clinical practice, patients frequently report the concurrent presence of 3 negative affects—anxiety, depression and anger/irritability. We refer to this constellation as multifocal negative affect (MNA). No prior studies have examined the prevalence and correlates of MNA in a large cohort of rigorously evaluated psychiatric outpatients.

Methods: The sample was derived from the 3,800 psychiatric outpatients evaluated with semi-structured diagnostic interviews. We excluded 334 patients who were asymptomatic or minimally symptomatic at the time of their evaluation and 5 patients who were missing data on at least 1 of the 3 symptom ratings. This left a final sample of 3,461 patients. We compared the demographic and clinical characteristics of patients with 1 or 2 negative affects to those with MNA.

Results: Depressed mood, anxiety, and anger/irritability were each present in at least two-thirds of the patients, they were significantly intercorrelated, however < half of the patients met the criteria for MNA. Patients with MNA were more likely to have a history of suicide attempts, to report suicidal ideation during the week preceding the evaluation, to have greater social and occupational impairment and were diagnosed with a greater number of current psychiatric disorders.

Conclusions: The co-occurrence of 3 negative emotional states--depression, anxiety and anger—is associated with an increased likelihood psychosocial morbidity including suicidal behavior and of being diagnosed with multiple psychiatric disorders. The assessment of these affects is not time consuming and may identify patients needing a more thorough diagnostic evaluation than is typically conducted.

T69. THE MCINTYRE AND ROSENBLAT RAPID RESPONSE SCALE (MARRRS): A PSYCHOMETRIC EVALUATION OF PATIENTS WITH TREATMENT-RESISTANT BIPOLAR DEPRESSION

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Abstract Background: A foundational assumption of measurement-based care is that the outcome instruments are validated within relevant populations and are sensitive to patient symptomatology. Extant depression severity scales were initially developed and validated in the context of monoaminergic antidepressants, which assess symptom change over a two-week interval (Rush and Thase, 2018). Initial evidence suggests that the McIntyre and Rosenblat Rapid Response Scale (MARRRS) is sensitive to rapid-acting treatments, particularly intravenous ketamine (McIntyre et al. 2021). The present analysis provides evidence validating the MARRRS for patients with treatment-resistant bipolar I/II depression (TRBD).

Methods: Adults with TRBD were enrolled in a multi-site, randomized, midazolam-controlled clinical trial, receiving four flexibly dosed infusions of ketamine (0.5 - 0.75 mg/kg) or midazolam (0.02 – 0.03 mg/kg) over two weeks. Depressive symptoms were measured using the Montgomery–Åsberg Depression Rating Scale (MADRS), which was administered by trained study personnel at each study visit. Additionally, participants completed the MARRRS at the same visits. The MARRRS is a 14-item self-report questionnaire that evaluates depressive symptoms over a 72-hour period. Each item is scored on a 4-point ordinal scale, with the total score ranging from 0, indicating an absence of symptoms, to 42, indicating a more severe depressed state.

Results: Sixty-eight participants ($Mage = 44.5 \pm 11.6$) were enrolled in the study. There was a significant infusion by group interaction ($F(35, 667.3) = 2.3, p < .001$) on the MARRRS, controlling for the effects of sex and diagnosis. The between group difference at the two-week primary endpoint was -3.8 (95% Confidence Interval (CI): -8.2 to 0.7; $p = 0.09$). The MARRRS had a high internal consistency across all study visits (0.89 to 0.95). There was significant convergent validity between the MADRS and MARRRS across all study visits ($r(1038) = .84, p < .001$). The area under the curve for the MARRRS against the standard MADRS remitter cut-off (i.e., $MADRS \leq 10$) indicated excellent classification accuracy ($AUC = .94, 95\% CI: .91 \text{ to } .96, p < .001$). Evaluation of remission thresholds indicated that a MARRRS cut-off score of 11 provided the best balance between sensitivity (77%) and specificity (94%). Exploratory factor analysis identified a two-factor structure for the MARRRS (dysphoria and psychic anxiety), which accounted for 64.9% of the variance.

Discussion: This analysis represents the first use of the MARRRS to assess depressive symptomatology within a randomized controlled trial and suggests that the self-report measure is valid for patients with TRBD receiving intravenous ketamine. The MARRRS was validated against a clinician-rated measure of depressive severity (i.e., the MADRS) and demonstrated strong sensitivity to depressive symptoms, excellent classification accuracy, and high inter-item reliability. To enhance clinical utility, a cut-off score of 11 on the MARRRS was identified as reliably distinguishing remitters from non-remitters. Overall, these findings support the use of the MARRRS as a pragmatic tool for monitoring rapid antidepressant response.

T70. CHANGES IN SLEEP PATTERNS WITH PSILOCYBIN-ASSISTED PSYCHOTHERAPY: AN EXPLORATORY ANALYSIS OF A RANDOMIZED CLINICAL TRIAL FOR TREATMENT-RESISTANT DEPRESSION

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Abstract Introduction: Sleep disturbances are highly prevalent in depression, with insomnia being the most commonly reported sleep issue. Beyond being a core feature of depressive disorders, sleep disturbances are also associated with poorer treatment outcomes and functional impairment, highlighting the importance of evaluating sleep-related outcomes in novel therapeutics. Psilocybin-assisted psychotherapy (PAP) has demonstrated promising antidepressant effects in treatment-resistant depression (TRD). However, psilocybin has been thought to disrupt sleep, raising concerns about its impact on a core symptom of depression and its overall tolerability profile. The objective of this analysis was to determine changes in sleep following PAP in a sample of individuals with TRD.

Methods: We conducted a randomized, waitlist-controlled clinical trial (NCT05029466) evaluating PAP in 30 participants with TRD, including those with major depressive disorder (MDD, n=26) and bipolar II disorder (BDII). All participants received a single 25 mg dose of psilocybin with preparatory and integration psychotherapy. The primary outcome of the trial was antidepressant efficacy. In this secondary analysis, sleep was assessed using sleep-related items from the Quick Inventory of Depressive Symptomatology (QIDS) and Montgomery-Åsberg Depression Rating Scale (MADRS) throughout the 6 month trial period. Sleep-related items captured various domains of sleep, including sleep onset, quality and early morning awakening, allowing for evaluation of both insomnia-related symptoms and overall sleep quality. As an exploratory analysis, we report our results descriptively and do not formally test for statistical significance, given the small sample size and multiple outcomes.

Results: 30 participants received PAP for TRD. As previously reported, psilocybin was well tolerated, with no serious adverse events and robust, rapid antidepressant effects. Sleep, as measured by QIDS and MADRS items, did not worsen post-treatment. Instead, preliminary data suggest a trend toward improved sleep quality, with reductions in the QIDS sleep onset and insomnia item scores of 0.43 point (on a 3 point scale) between baseline (2.53 ± 0.78) and primary endpoint (2.11 ± 0.83), and by 0.7 between baseline and secondary endpoint (1.8 ± 1.00). The MADRS sleep item data further corroborates this trend, with a decrease of 0.52 points on a 6 point scale between baseline (1.87 ± 1.59) and primary endpoint (1.34 ± 1.56).

Conclusion: This secondary analysis provides preliminary evidence that psilocybin does not exacerbate sleep disturbances in individuals with TRD or BDII and may offer benefits. Notably, observed improvements occurred despite concerns that serotonergic psychedelics, such as psilocybin, may impair sleep, indicating small but potentially favourable sleep outcomes in the context of this clinical trial. Given the contrast with existing literature, further research is warranted to evaluate the effects of PAP on sleep using objective and comprehensive sleep measures in future clinical trials.

T71. PSILOCYBIN FOR ANHEDONIA: A SYSTEMATIC REVIEW OF CLINICAL AND PRECLINICAL EVIDENCE

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Abstract Background: Anhedonia is a debilitating core feature of major depressive disorder (MDD) and bipolar depression (BD) and is associated with significant burden on both functioning and quality of life. Psilocybin has recently emerged as a novel antidepressant treatment in MDD, yet its effects on anhedonia specifically have yet to be systematically reviewed. This review evaluates available clinical and pre-clinical research, exploring whether psilocybin influences anhedonia outcomes in animal models and individuals with depression.

Methods: A systematic search was conducted of PubMed and Ovid databases from inception to June 10th 2025, using search terms related to psilocybin, anhedonia/reward-related processes, and MDD/BD. Studies were screened independently by two reviewers. Risk of bias was also conducted independently by the same two reviewers.

Results: The systematic search initially identified 428 records. After removing duplicates, 345 records were screened, resulted in the inclusion of eleven studies, including five clinical studies and six animal studies. Across clinical studies, reductions in anhedonia were consistently observed following psilocybin-assisted psychotherapy wherein two randomized clinical trials reported greater improvements in anhedonia relative to control or comparator groups. Changes in anhedonia were primarily assessed using the Snaith-Hamilton Pleasure Scale (SHAPS), with one study utilizing a validated MADRS anhedonia factor. Three included studies additionally incorporated neuroimaging measures, examining associations between changes in anhedonia and emotional expression. Results from animal studies demonstrated improved reward sensitivity and motivation after psilocybin exposure.

Conclusion: Initial pre-clinical and clinical studies suggest that psilocybin may be beneficial for anhedonia. Despite encouraging early findings, interpretation is limited by heterogeneity in dosing strategies, small samples sizes, and variability in the manner of which anhedonia was measured, with most clinical studies assessing only consummatory pleasure. While current evidence suggests psilocybin may meaningfully ameliorate anhedonia, further controlled research evaluating anhedonia as a primary outcome, using comprehensive and standardized measures, is needed.

T72. DON'T LET AI MAKE YOU MOODY: ASSESSING RACIAL BIAS IN LARGE LANGUAGE MODELS' CLINICAL DECISION-MAKING IN MOOD DISORDERS

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Abstract Background: Racial disparities in the diagnosis and treatment of mood disorders, particularly bipolar disorder, have been widely reported in psychiatric practice. Black patients are more likely to receive antipsychotic-focused or restrictive treatment approaches and less likely to receive guideline-concordant mood-stabilizing therapies compared with White patients, even when their clinical presentations are similar. Racial minority groups, including

Hispanic and Asian patients, have also been shown to experience delayed diagnosis, differential prescribing patterns, and barriers to equitable psychiatric care. As artificial intelligence (AI), in the form of large language models (LLMs), is increasingly explored for clinical decision support and psychiatric education, concerns have emerged that these systems may echo existing treatment inequities. Although prior studies have identified racial bias in AI-generated psychiatric recommendations across multiple diagnoses, less is known about how LLMs differ in treatment recommendations for mood disorders when patient race is varied.

Objective: This study aims to examine whether general and medical-focused LLMs generate different treatment recommendations for identical mood disorder presentations when patient race is explicitly stated, implicitly suggested, and omitted.

Methods: Standardized clinical cases representing mood disorders (bipolar I disorder, bipolar II disorder, and major depressive disorder) will be developed. For each mood disorder category, cases will be systematically varied by race (White non-Hispanic, African American, Hispanic, Asian) and by one of three framing conditions: neutral condition with no reference to race, implicit condition using a name empirically associated with a racial group, and explicit condition stating the patient's race. A formulary, including cost, will also be provided to each of four LLMs (general-purpose LLMs ChatGPT and Grok, and medical-focused LLMs OpenEvidence and DoxGPT). Hyper-specific prompts will delineate these demographic attributes, diagnosis, and the same formulary, and request a succinct response with medications of choice along with risk of recurrent mood episodes (low-, medium-, and high-risk). Outputs will be analyzed to determine treatment variations in terms of medication(s), cost of medication(s), and risk of recurrent mood episodes compared to race per LLM.

Outcomes: This study aims to identify race-associated differences in LLM-generated treatment recommendations for mood disorders. Findings will inform the responsible use of AI in psychiatric care by clarifying how treatment recommendations vary across race and model type.

T73. EVALUATING THE POTENTIAL RISK OF KETAMINE-INDUCED HEPATOTOXICITY IN THE TREATMENT OF MOOD AND ANXIETY DISORDERS: A SYSTEMATIC REVIEW

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Abstract: Ketamine is a dissociative anesthetic with potential for treating mood, anxiety, and related disorders; however, concerns have emerged regarding hepatotoxicity in the context of chronic treatment. Systematic searches of PubMed, Scopus, and Ovid databases were conducted from inception to August 2025. Eligible studies included randomized controlled trials (RCTs), observational studies, and case reports/series reporting liver function outcomes following therapeutic ketamine administration for mood, anxiety, or related psychiatric disorders. Of 635 screened records, 13 met inclusion criteria: five RCTs, three observational studies, and five case reports/series, encompassing 1,017 patients receiving ketamine primarily for MDD/TRD and BD/TRBD. Across RCTs (n = 888), 75 hepatic adverse events were reported, predominantly mild and transient aminotransferase elevations, with no cases meeting Hy's Law criteria. Observational studies identified occasional aspartate

aminotransferase (AST) and alanine aminotransferase (ALT) elevations and rare instances of impaired liver function. Case reports described more severe presentations, which improved with dose reduction or discontinuation. Evidence suggests that ketamine at dosing regimens typically used for depression may cause liver enzyme elevations, but impaired liver function and serious hepatotoxicity appears rare. However, considering real-world data of severe drug-induced liver injury (DILI), routine liver monitoring remains justified throughout ketamine treatment.

T74. COGNITIVE OUTCOMES FOLLOWING SERIAL KETAMINE INFUSIONS IN TREATMENT-RESISTANT BIPOLAR I/II DEPRESSION: RESULTS FROM A RANDOMIZED, MIDAZOLAM-CONTROLLED TRIAL

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Abstract Background: Bipolar disorder is associated with significant cognitive impairment, particularly in memory, attention, processing speed, and executive functioning, which contributes to poor functional outcomes and reduced quality of life. Ketamine has been hypothesized to exert procognitive effects via neuroplastic mechanisms in addition to its antidepressant properties; however, evidence remains limited. Moreover, high doses and frequent use of ketamine have been associated with neurotoxicity. Critically, the cognitive effects of ketamine have not been systematically evaluated in bipolar depression, leaving its efficacy and safety in this population unclear.

Methods: Adults with treatment resistant bipolar I/II depression (TRBD; n=68) were randomized to receive four infusions over two weeks of either ketamine (0.5-0.75 mg/kg) or midazolam (0.02-0.03 mg/kg). Participants completed a comprehensive cognitive battery at baseline, Day 14, and Day 28, including the Digit Symbol Substitution Test (DSST), Trail Making Test Parts A and B (TMT-A/B), and California Verbal Learning Test–Second Edition (CVLT). Baseline impairment was defined as performance > 1.0 SD below age-adjusted normative means. Cognitive outcomes were analyzed using paired samples t-tests within treatment arms, baseline-adjusted ANCOVAs at Day 14 and Day 28, and linear mixed-effects models (LMMs). Subjective cognitive symptoms were assessed using the Montgomery-Åsberg Depression Rating Scale (MADRS) item 6.

Results: At baseline, substantial cognitive impairment was observed across executive function/processing speed (TMT-B, n = 37; TMT-A, n = 29; DSST, n = 15) and verbal learning and memory (CVLT list B, n = 29; trials 1–5 total, n = 28; trial 1, n = 23; long-delay free recall, n = 16; short-delay free recall, n = 14). Within-group analyses showed significant improvement in the ketamine group on the DSST, TMT-A, and MADRS item 6 at Day 14 and Day 28, and on CVLT trial 1, trials 1–5 total, short- and long-delay free recall at Day 28 (all p < .020; Cohen's d = .069–1.34). Only the TMT-B did not show improvement at either timepoint. In the midazolam group, significant improvements were observed on the DSST, TMT-A, and TMT-B at Day 14 and Day 28, and on MADRS item 6 and multiple CVLT indices (trial 1, trials 1–5 total, list B, short- and long-delay free recall) at Day 28 (all p < .028; d = .27–1.15). Between-group ANCOVAs revealed no significant differences in cognitive outcomes at Day 14 or Day 28, except for higher CVLT list B scores with midazolam at Day 28 (mean difference = 1.04; F(1, 53) = 4.55, p = .038, η^2 = .079) and lower MADRS item 6 scores with ketamine at Day 14 (mean difference = -.951; F(1, 58) =

10.16, $p = .002$, $\eta^2 = .149$). Consistent with this finding, the only significant group-by-time interaction in the LMMs was MADRS item 6 ($F(1, 128.78) = 3.28$, $p = .041$).

Significance: Despite high rates of baseline cognitive impairment, ketamine did not produce superior cognitive improvement relative to midazolam across objective cognitive domains. Cognitive changes over time were largely similar between groups, suggesting nonspecific or practice-related effects. Importantly, the absence of adverse cognitive effects across a broad neuropsychological battery supports the short-term cognitive safety and tolerability of repeated intravenous ketamine administration in TRBD.

T75. A PILOT STUDY OF SODIUM-GLUCOSE COTRANSPORTER-2 (SGLT2) INHIBITOR EMPAGLIFLOZIN IN MAJOR DEPRESSIVE DISORDER

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Abstract Background: Sodium-glucose cotransporter-2 (SGLT2) inhibitors are unique among antidiabetic medications for the ketogenic properties. In population-based studies, they have associated with the lowest risk of incident depression of any antidiabetic medications, reduced dementia risk, and reduced risk of suicidal behaviors. Evidence from imaging, transcriptomic, genetic and cerebrospinal fluid studies points to mitochondrial impairments as associated with mood disorders, and SGLT2 inhibitors have demonstrated energetic-enhancing effects in preclinical studies. Given these data and encouraging reports of the antidepressant properties of ketogenic diets, this pilot study sought to test the feasibility, safety, and efficacy, in a preliminary way, of SGLT2 inhibitor empagliflozin in major depressive disorder.

Methods: Nine (of a planned twelve) participants with MDD confirmed by DSM-V criteria have completed a six-week, single-arm, open-label study of empagliflozin. Participants are administered 10mg of empagliflozin for two weeks and then 25mg of empagliflozin for four weeks for a total of six weeks on the medication. 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 -hydroxybutyrate (BHB) levels. Here, we report the comparisons between baseline and after six weeks of treatment.

Results: Among the first nine patients, mean BMI was 30.8 kg/m² (SD 7.8), age was 33.5 years (SD 12.0), hsCRP 5.2 mg/L (SD 7.3), and HbA1c 5.2% (SD 0.35). There were six females and three males. MADRS total scores were found to be significantly lower than baseline starting from week 4 of treatment (median change = -9.5, $V = 1$, p -value = 0.02071) and continuing through week 6 (median change = -13, $V = 0$, $p = 0.007813$). The effect sizes for the changes in MADRS total scores from baseline at weeks 4 ($r=0.843$, Cohen's $d = 3.134$) and 6 ($r=0.891$, Cohen's $d = 3.925$) were large. BHB levels trended towards increase with a baseline mean of 0.14mM and endpoint mean of 0.36mM, but the change was not significantly different from baseline at week 2 (median change = 0.05, $V = 22$, p -value = 0.2049) or week 6 (median change = 0.1, $V = 29$, p -value = 0.1484) of treatment. Spearman correlation between change in BHB and MADRS was non-significant at 6 weeks ($\rho 0.71$, $p=0.06$). There was no subject dropout, however, one participant was only partially adherent.

Conclusion: In this small pilot study of individuals with MDD on empagliflozin, the medication was well tolerated, in line with studies in diabetes, heart failure, and chronic kidney disease. Empagliflozin treatment was associated with decreased depression severity scores and a trend towards increased peripheral fasting ketones. We did not observe a significant association between change in ketones and change in depression scores. Further studies of SGLT2 inhibitors in psychiatric disorders may complement studies of other ketogenic treatments.

T76. EFFICACY OF CARIPRAZINE FOR ANHEDONIA SYMPTOMS: A POOLED ANALYSIS OF PATIENTS WITH MAJOR DEPRESSIVE DISORDER AND BIPOLAR I DEPRESSION

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Abstract Introduction: Anhedonia is a core feature of major depressive disorder (MDD) and bipolar I (BP-I) depression and is associated with suicidality and comorbidities. Cariprazine (CAR), a dopamine D3-preferring D3/D2 and serotonin 5-HT1A receptor partial agonist, is approved for the treatment of manic/mixed and depressive episodes of BP-I and for the treatment of MDD as an adjunctive therapy to antidepressants. This pooled analysis evaluates the anti-anhedonic effects of CAR in MDD and BP-I depression.

Methods: Data were collected from pivotal clinical trials evaluating CAR for the adjunctive treatment of MDD (NCT03738215 and NCT01469377) and the treatment of BP-I depression (NCT02670551, NCT01396447, and NCT02670538). The trials were 6-8 weeks in duration, with CAR doses of 1-4.5 mg/d in MDD and 1.5-3 mg/d in BP-I. The pooled analysis compared the change from baseline to week 6 or week 8 (NCT01469377 only) between CAR and placebo in Montgomery-Åsberg Depression Rating Scale (MADRS) anhedonia factor score (items: 1 [apparent sadness], 2 [reported sadness], 6 [concentration difficulties], 7 [lassitude], and 8 [inability to feel]). Extracted data included least-squares (LS) mean changes, standard errors, and the least-squares mean differences (LSMDs) with 95% CIs derived from mixed models for repeated measures. A multilevel random-effects model accounted for multiple treatment arms sharing the same placebo group and within-study clustering. Dose and study duration were examined as exploratory moderators and heterogeneity was assessed using Cochran's Q test and variance component estimates.

Results: CAR significantly reduced MADRS anhedonia factor scores compared to placebo in all 5 included studies. In MDD, the change from baseline to week 6/8 was significantly greater for CAR vs placebo for both doses evaluated in NCT03738215 (1.5 mg/d, LSMD [95% CI]: -1.54 [-2.56, -0.52]; 3 mg/d, -1.09 [-2.11, -0.07]) and the 2-4.5 mg/d dose group in NCT01469377 (1-2 mg/d, -0.81 [-1.79, 0.17]; 2-4.5 mg/d, -1.28 [-2.27, -0.29]). In BP-I depression, the change from baseline to week 6 was significantly greater for CAR vs placebo for both doses in NCT02670551 (1.5 mg/d, -2.05 [-3.15, -0.95]; 3 mg/d, -2.46 [-3.56, -1.36]) and NCT01396447 (1.5 mg/d, -2.22 [-3.40, -1.04]; 3 mg/d, -1.27 [-2.47, -0.07]) and for CAR 1.5 mg/d in NCT02670538 (1.5 mg/d, -1.14 [-2.21, -0.07]; 3 mg/d, -0.92 [-2.01, 0.17]). The multilevel random-effects model yielded a pooled LSMD in MADRS anhedonia factor score for CAR vs placebo of -1.46 (95% CI: -1.91, -1.00, $P < .001$). Exploratory moderator analyses showed no effect of dose or study duration on the magnitude of the treatment effect

($P=.63$). There was no significant heterogeneity in the primary model ($Q[9]=9.52$, $P=.39$) and between-study variance was modest ($\sigma^2=0.12$), while the within-study (arm-level) variance was negligible, indicating most variability reflected differences between studies rather than dose arms.

Conclusions: Cariprazine demonstrated a transdiagnostic effect on symptoms of anhedonia both as adjunctive treatment in MDD and monotherapy in BP-I depression, suggesting cariprazine may be an effective treatment for symptoms of anhedonia regardless of indication.

T77. DIFFERENTIAL EFFECTS OF TRANSCRANIAL PHOTOBIOMODULATION ON FUNCTIONAL NETWORK REORGANIZATION ACROSS CLINICAL POPULATIONS

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Abstract: Transcranial photobiomodulation (t-PBM) is a noninvasive neuromodulation method that enhances cerebral mitochondrial function with emerging evidence as a network modulator in healthy adults [1]. However, its influence on the temporal organization of intrinsic brain states remains unclear. Static connectivity analyses overlook rapid shifts in network configuration that may underlie cognitive and mood states as well as therapeutic response. To address this, we applied Co-Activation Pattern (CAP) [2] analysis to dissect the spatiotemporal stability of brain networks in two distinct clinical populations: Alzheimer's disease (AD) and Major Depressive Disorder (MDD). Our framework isolated disease-specific signatures (Analysis 1), session-related effects of t-PBM (Analysis 2), diagnosis-specific modulation (Analysis 3), and dose-related effects within AD (Analysis 4). Data were drawn from two clinical trials: an AD study with a single t-PBM session (medium-dose continuous wave vs. high-dose pulsed wave) and an MDD study (medium- vs. high-dose). Detailed cohort characteristics, participant demographics, study design, including fMRI parameters, are described elsewhere [Iosifescu et al., 2017 Healthcare; Iosifescu et al., 2023 Photonics). Each participant completed pre-, during-, and post-stimulation fMRI scans. During the stimulation condition, participants received t-PBM at either medium- (CW, irradiance ~300 mW/cm²) or high-dose (PW, peak irradiance 900 mW/cm², average irradiance 300 mW/cm²) while in the MRI scanner. The analyzed sample included the following groups: AD high dose ($n = 14$), AD medium dose ($n = 28$), MDD high dose ($n = 11$), and MDD medium dose ($n = 17$). Preprocessing included fMRIPrep and XCP-D, with band-pass filtering (0.01–0.1 Hz) and 4S1056Parcels parcellation. CAPs were identified via temporal clustering; occurrence, incidence, and dwell time were quantified. Our analytic strategy was designed to systematically isolate disease signatures from intervention effects:

Analysis 1: Baseline CAP differences were tested with Welch's t-tests. MDD showed higher CAP5 dwell time ($t(58.84)=2.39$, $p=0.030$) and occurrence ($t(53.91)=2.50$, $p=0.030$). No other CAPs survived FDR; CAP3 and CAP4 differences were nominal only.

Analysis 2: Within-group mixed-effects models showed session effects only in MDD medium dose. CAP1 dwell time ($F(2,35.5)=7.79$, $p=0.0047$) decreased pre to during ($p=0.018$) and increased during to post ($p=0.0013$); CAP1 incidence ($F(2,37.0)=4.99$,

$p=0.018$) decreased post vs pre ($p=0.013$) and vs during ($p=0.045$). CAP3 incidence also differed ($F(2,36.0)=5.24$, $p=0.030$) via a during→post reduction ($p=0.009$). No AD effects.

Analysis 3: Between-group effects appeared only in medium dose. CAP2 dwell ($F(1,44.9)=8.07$, $p=0.010$) and occurrence ($F(1,44.1)=9.38$, $p_{\text{FDR}}=0.010$); CAP3 incidence ($F(1,44.7)=6.39$, $p=0.023$) and occurrence ($F(1,44.0)=6.82$, $p=0.023$); CAP4 incidence ($F(1,45.0)=7.28$, $p=0.029$); CAP5 dwell ($F(1,42.9)=12.3$, $p=0.003$) and occurrence ($F(1,43.6)=10.3$, $p=0.004$).

Analysis 4: No FDR-significant AD dose effects. CAP2 occurrence showed a nominal difference ($t(32.03)=2.35$, $p=0.025$; $\text{FDR}=0.075$). Other metrics nonsignificant.

MDD showed baseline default-mode CAP instability with greater dwell and occurrence than AD. Only MDD under medium dose showed session-related CAP modulation, mainly in attention and visual networks. Medium-dose stimulation also amplified diagnostic differences across multiple CAPs, whereas high dose and all AD conditions showed minimal effects. Overall, MDD exhibited greater context-sensitive network flexibility, with medium dose most effective for revealing disease-specific dynamics.

T78. COMPARISON OF THE EFFICACY OF NEUROMODULATION THERAPIES IN SCHIZOPHRENIA: A SYSTEMATIC REVIEW AND NETWORK META-ANALYSIS

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Abstract Background: Schizophrenia is a chronic and disabling psychiatric disorder affecting approximately 1% of the global population. Although antipsychotic medications are the primary treatment for schizophrenia, many patients experience persistent symptoms or side effects resulting in non-adherence. Neuromodulation therapies including electroconvulsive therapy (ECT), repetitive transcranial magnetic stimulation (rTMS), transcranial direct current stimulation (tDCS), theta-burst stimulation (TBS), transcranial random noise stimulation (tRNS), transcutaneous vagus nerve stimulation (tVNS), magnetic seizure therapy (MST), and deep brain stimulation (DBS) have emerged as potential adjunctive or alternative interventions, however, their relative efficacy remains unclear.

Objective: To compare the efficacy of neuromodulation therapies for schizophrenia using a systematic review and network meta-analysis.

Methods: This systematic review and network meta-analysis follows PRISMA-NMA guidelines and is registered in PROSPERO (CRD420251237506). PubMed, MEDLINE, Embase, APA PsycINFO, Web of Science, and CINAHL were searched from inception through November 9, 2025. Eligible studies include English-language randomized controlled trials evaluating neuromodulation therapies as monotherapy or adjunctive treatment in individuals with schizophrenia spectrum disorders. The primary outcome is change in overall symptom severity measured using validated psychiatric rating scales. Secondary outcomes include changes in positive symptoms, negative symptoms, and cognitive functioning. Risk

of bias will be assessed using the Cochrane RoB 2 tool, and certainty of evidence will be evaluated using the CINeMA framework. A frequentist random-effects network meta-analysis will be conducted using the netmeta package in R.

Results: The initial search yielded 3,839 unique articles after removal of duplicates. Title and abstract screening, full-text review, and data extraction are currently in progress. Final comparative efficacy estimates and treatment rankings will be presented at the 2026 ASCP Annual Meeting.

Conclusions: This study will provide the first comprehensive comparative synthesis of neuromodulation therapies for schizophrenia, informing clinical decision-making and future research.

T79. HARMONIZING ADVERSE EVENT CRITERIA TO IMPROVE CNS-RELATED SAFETY AND ABUSE SIGNAL DETECTION IN CLINICAL TRIALS

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Abstract: Accurate adverse event (AE) collection is central to evaluating the safety, abuse, and dependence potential of CNS-active drugs, including psychedelics, and to informing labeling and scheduling decisions. Yet current regulatory and operational frameworks create a number of challenges to capturing the full spectrum of CNS-related events. A recurring problem, highlighted by the FDA including by its 2024 advisory committee review of MDMA-assisted therapy (U.S. Food and Drug Administration, 2024), is the systematic under-capture of positive or pleasurable effects (eg, elevated mood, prosocial behavior, empathogenic responses) that are treated solely as therapeutic outcomes rather than AEs relevant to abuse liability and risk management. This issue is compounded by the ICH E6(R3), (International Council for Harmonisation, 2025) and FDA definition of an AE as “any unfavorable medical occurrence in a trial participant administered the investigational product,” which can implicitly discourage documentation of experiences perceived as beneficial but directly relevant to scheduling and risk communication. Additional complexity arises when highly subjective descriptions (eg, “feeling connected,” “more open,” “expanded”) are coded into broad MedDRA preferred terms such as “mood altered,” “dysphoria,” or “feeling abnormal” that away strip nuance, obscure mechanistically important patterns, and limit cross-study comparability. These challenges are further amplified in psychotherapy-augmented and psychedelic paradigms, where expectancy effects and functional unblinding influence both participant reporting and investigator interpretation of AEs. To harmonize AE criteria in CNS-active drug trials, we propose: (1) adoption of working definitions that explicitly encompass both positive and negative experiences across somatic, affective, cognitive, and perceptual domains; (2) key dimensions for characterizing CNS-related events (eg, valence, intensity, time course, phenomenology, context, and abuse relevance); (3) a draft taxonomy structure intended to support more consistent mapping from verbatim language to MedDRA terms; (4) a practical guidance for training study personnel to recognize and code positive-effect and mixed-valence experiences without inflating therapeutic endpoints; as well as (5) a practical guidance for training study participants to report experiences they perceive as therapeutic along with those they perceive as undesirable. Together, these harmonized criteria are intended to support the acquisition of more complete

and consistent AE datasets, improve CNS-related safety and abuse signal detection, and better align CNS-active drug programs with evolving regulatory expectations and public health needs.

T80. REAL-WORLD EXPERIENCE AND IMPACT OF COGNITIVE IMPAIRMENT IN NARCOLEPSY AND IDIOPATHIC HYPERSOMNIA FROM THE ASPIRE SURVEY STUDY

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Abstract Purpose: People living with narcolepsy and idiopathic hypersomnia (IH) often report cognitive impairment as a disruptive symptom that is not managed by current treatments. This survey study examined whether cognitive impairment was associated with work productivity and health-related quality of life (HRQoL) among people diagnosed with narcolepsy type 1 (NT1), narcolepsy type 2 (NT2), and IH.

Methodology: The ASPIRE study was an online survey study conducted in the US among adults who self-reported a clinical diagnosis of NT1, NT2, or IH. Participants were recruited through Rare Patient Voice, Hypersomnia Foundation, and the Sleep Consortium. Cognitive impairment was assessed using the British Columbia Cognitive Complaints Inventory-Expanded Version (BC-CCI-E). This tool evaluates cognitive impairment using 6 items, which assess concentration, memory, word finding, expressing thoughts, slow thinking, and problem-solving (score ranges from 0-18, with higher scores representing greater impairment). Participants were divided into two subgroups, those with mild-to-severe cognitive impairment (scored > 4) and those with no/minimal impairment (scored ≤4). The impact of cognitive impairment on daily life was assessed by 3 additional items of the BC-CCI-E. The Work Productivity and Activity Impairment Questionnaire: Specific Health Problem, assessed work impairment (absenteeism and presenteeism) and activity impairment over the previous week. Participants' HRQoL was assessed using EQ-5D-5L (score ranges from 0-1) and EQ-Visual Analogue Scale (EQ-VAS) (score ranges from 0-100), with higher scores representing better HRQoL for both scales.

Results: Three hundred and sixty-six participants (NT1: n=116; NT2, n=127; IH, n=123) were included. Participants had a mean age of approximately 40 years, more than 80% were female, and 55% were employed. About 60% of participants received treatment with non-amphetamine wake-promoting agents. Mean (SD) BC-CCI-E score was 9.2 (4.2), and 89% of participants reported mild-to-severe cognitive impairment. In the majority of participants, cognitive impairment interfered with work (95%), routine activities (94%), and relationships (81%). Mild-to-severe cognitive impairment was also associated with statistically significant increases in work impairment (58% versus 25%; $p < 0.001$) and activity impairment (65% versus 41%; $p < 0.001$) compared with no/minimal impairment. Additionally, mild-to-moderate cognitive impairment was associated with statistically significant reductions in HRQoL scores compared with no/minimal impairment (EQ-5D-5L: 0.61 versus 0.85 [$p < 0.001$]; EQ-VAS scores: 58 versus 74 [$p < 0.001$]). Observations from the survey were consistent across participants when examined by NT1, NT2, and IH disease subgroups.

Importance: In individuals living with NT1, NT2, and IH, cognitive impairment is a prevalent and burdensome symptom that negatively impacts work productivity, daily functioning, relationships, and overall HRQoL. The results of the ASPIRE survey call attention to an important unmet need to address cognitive impairment in these populations. Funding: Alkermes Inc.

T81. A HEAD-TO-HEAD ASSESSMENT OF VMAT2 TARGET OCCUPANCY OF ONCE-DAILY VALBENAZINE COMPARED TO DEUTETRABENAZINE EXTENDED RELEASE

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Abstract Background: Vesicular monoamine transporter 2 (VMAT2) inhibition is a known therapeutic mechanism for the treatment of tardive dyskinesia (TD) and chorea associated with Huntington's disease (HD). A relationship between VMAT2 target occupancy (TO) levels and clinical efficacy was predicted in previous analyses of positron emission tomography (PET) data in non-human primates after administration of $[+]-\alpha$ -dihydrotetrabenazine ($[+]-\alpha$ -HTBZ), which is the primary active metabolite of valbenazine (VBZ). However, VMAT2 TO levels associated with administration of FDA-approved VMAT2 inhibitors were yet to be assessed in humans. Therefore, we conducted the first study in healthy male volunteers to measure VMAT2 TO levels after single doses of once-daily VBZ and deutetrabenazine extended release (DTBZ XR, an XR formulation of a previously developed VMAT2 inhibitor without published clinical safety and efficacy data).

Methods: The study included a cohort of 8 participants who had arterial input function for absolute quantification of PET data with analyzable pharmacokinetic (PK) data and who underwent a two-period crossover treatment design: VBZ (40 or 80 mg), followed by ≥ 7 -day washout and then DTBZ XR (24 or 48 mg), or vice-versa (i.e., DTBZ XR, followed by washout and VBZ). $[18F]AV-133$ PET scans were conducted at the reported time of maximum plasma concentration (T_{max}) for the active HTBZ metabolites for each compound: 4-8 hours post-dose for VBZ metabolite ($[+]-\alpha$ -HTBZ); 3-5 hours post-dose for DTBZ XR total metabolites (total of $[+/-]-\alpha$ -deuHTBZ and $[+/-]-\beta$ -deuHTBZ). Outcomes included the following: VMAT2 TO, derived from volume of distribution (VT) in predefined brain regions of interest and modified Lassen plot analysis; relationship between plasma concentration of VBZ / DTBZ XR metabolites and VMAT2 TO (i.e., exposure-occupancy); predicted VMAT2 TO at steady-state; and plasma concentrations of VBZ / DTBZ XR metabolites for 24 hours after VBZ and DTBZ XR dose.

Results: VMAT2 TO levels were higher after single doses of VBZ (40 and 80 mg) than single doses of DTBZ XR (24 and 48 mg). The least-squares (LS) mean VMAT2 TO was 76.5% for VBZ and 38.3% for DTBZ XR, with a LS mean difference of 38.2% ($P=0.0002$). Population PK modeling was used to predict maximal steady-state HTBZ metabolite concentrations (C_{max}) following daily VMAT2 inhibitor dosing. Estimated VMAT2 TO based on steady-state C_{max} was higher with VBZ (82% for 40 mg, 92% for 80 mg) than with DTBZ XR (52% for 24 mg, 68% for 48 mg). 24-hour plasma concentrations of HTBZ metabolites showed less variability with VBZ than with DTBZ XR.

Conclusions: Substantially greater VMAT2 occupancy was found after single doses of VBZ than after single doses of DTBZ XR, as indicated by PET scans and higher predicted steady-state TO. In addition, less variability in plasma metabolite concentrations indicated a more predictable exposure with a once-daily drug (VBZ) than with a once-daily formulation (DTBZ XR).

T82. OPIOID USE IN PATIENTS WITH FIBROMYALGIA: A RETROSPECTIVE CLAIMS ANALYSIS

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Abstract Background: Fibromyalgia (FM) is a chronic pain disorder that presents significant diagnostic and therapeutic challenges, compounded by the presence of multiple comorbidities. Despite approved therapies for FM, opioids continue to be widely prescribed in patients with FM for pain management. This study (1) quantified the use of opioids and benzodiazepines in patients diagnosed with FM via a retrospective claims database analysis and (2) characterized patients by age, insurance coverage, and polypharmacy.

Methods: This is a retrospective database analysis conducted using closed claims from the Symphony database (04/2021 – 04/2024). The patient cohort was defined as adult (aged ≥ 18 years) patients with FM identified via the presence of FM ICD-10-CM code anytime during the study period. Opioid use captures patients with ≥ 1 pharmacy claim for any opioid drugs during the study period. The results presented comprise the third year (2023-2024; Y3 cohort).

Results: A total of 261,776 patients were included in the Y3 cohort. The mean (SD) age of the cohort was 52.3 (13.02) years. The majority of patients (92.1%) were female, and 49.6% patients were white non-Hispanic. Among these patients with FM, 48.3% (n=126,391) were covered under Commercial or Medicare Advantage insurance. Of these 126,391 patients, 40.2% of patients were prescribed opioids, with most claims for tramadol (13.7%), followed by oxycodone (13.1%). The average medical possession ratio (MPR) was 0.39. Opioid use observed among patients across all payer types (Commercial, Medicaid, and Medicare) in the age groups 61-65 (n=35,471), 66-70 (n=15,403), 71-75 (n=9,533), and > 75 (n=10,123), was 43.1%, 39.2%, 38.5% and 34.4%, respectively. By comparison, opioid use was lower in the 18-25 age group (12.5%; n=5,982). Concomitant opioid and benzodiazepine use, a polypharmacy choice that often elicits harmful side effects and contradicts guidelines, was observed in 19.1% of patients covered under Medicare Advantage or Commercial insurance. In age groups 61-65, 66-70, 71-75, and > 75 , concomitant opioid and benzodiazepine use was 20.9%, 17.9%, 16.4% and 15.6%, respectively. Use was even higher among geriatric women with sleep issues (n=68,319) at 22.7%.

Conclusions: This study quantifies opioid use in patients with FM. Furthermore, it provides valuable insight into the increased risk that geriatric patients with FM are exposed to due to concomitant opioid and benzodiazepine use. The persistent, prevalent use of opioids, despite not being indicated for FM, highlights the need for safer, more effective non-opioid analgesics for FM. Funding: This study and support for this abstract were funded by Tonix Medicines, Inc. (Chatham, NJ)

T83. COMPLICATIONS OF AN ABRUPT SWITCH FROM A FULL ANTAGONIST TO A PARTIAL D2 AGONIST

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Abstract: Abrupt switching between antipsychotic medications remains a common yet high-risk practice among mental health providers. While partial agonists at dopamine type 2 (D2) receptors such as aripiprazole offer valuable options, particularly in a long-acting injectable (LAI) form to support adherence, they require careful transition protocols to avoid dopaminergic instability. When switching from a full D2 receptor antagonist to a partial agonist, dopaminergic instability may occur due to differences in binding affinity and adaptive D2 receptor upregulation. These dynamics can precipitate rebound psychosis, withdrawal symptoms, and clinical deterioration if proper overlap protocols are not followed. This presentation highlights a clinically significant case demonstrating the consequences of an abrupt switch from a full D2 antagonist to a partial agonist LAI, and to advance safer switching practices through improved understanding of receptor pharmacodynamics.

Case presentation: We describe a 27-year-old Hispanic female with bipolar I disorder, previously stable on oral risperidone 2 mg twice daily. Her risperidone was abruptly discontinued, and she was transitioned directly to aripiprazole 400 mg intramuscular LAI without oral supplementation. Within several days, she experienced worsening command auditory hallucinations and suicidal ideation, prompting emergency hospitalization. Toxicology screening was negative. She also reported brief transient vision loss that resolved spontaneously. Medical and neurological work-up were unremarkable. She was restarted on oral risperidone with clinical stabilization prior to transfer to outpatient transfer.

Discussion: LAI antipsychotics reduce relapse risk and improve medication adherence, but their safe use requires an appreciation of pharmacokinetics and receptor interactions. In this patient, the history of long-term exposure to a full D2 antagonist likely led to compensatory upregulation and increased sensitivity of dopamine receptors. When risperidone was abruptly discontinued, these now sensitized receptors were suddenly exposed to endogenous dopamine, resulting in the abrupt worsening of command auditory hallucinations and suicidal ideation. An additional challenge in this transition arises from the difference in receptor-binding affinity. Aripiprazole binds to D2 receptors with almost a tenfold higher affinity than risperidone, and when introduced, it can competitively displace the residual risperidone that was present on the receptor sites. In this particular case report, because aripiprazole LAI requires time to reach therapeutic concentrations, its early displacement of risperidone was likely minimal, making the abrupt cessation of risperidone the primary driver of the patient's withdrawal and rebound symptoms. The exhibited discontinuation syndrome may have been preventable with oral supplementation—had the transition involved any agent other than a partial agonist, as oral aripiprazole would have accelerated displacement even further. This case therefore illustrates how abrupt switching from a full D2 antagonist to a partial agonist can increase risk of dopaminergic dysregulation and instability.

Conclusion: Understanding receptor dynamics and implementing appropriate cross-titration strategies are essential when switching from full D2 antagonists to partial agonists, particularly with LAI initiation. This case illustrates a preventable cause of clinical deterioration and reinforces the need for evidence-based protocols that account for receptor pharmacology, pharmacokinetics, and adherence history to ensure safe antipsychotic transitions in practice.

T84. IMPACT-2: A PHASE 2 RANDOMIZED, DOSE-RESPONSE TRIAL OF TSND-201 (METHYLONE) FOR THE TREATMENT OF PTSD

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Abstract Background: TSND-201 (methylone) is currently in clinical development for the treatment of post-traumatic stress disorder (PTSD). Non-hallucinogenic compounds with rapid and sustained therapeutic benefits may be clinically useful and more accessible to patients compared to classical psychedelics. TSND-201 is a highly selective, rapid-acting neuroplastogen that releases serotonin, norepinephrine, and dopamine to increase neuroplasticity. TSND-201 is non-hallucinogenic in humans and animal models, consistent with its lack of direct activity at serotonin (5-HT)_{2A} receptors. TSND-201 shows consistently rapid, robust, and durable benefit in animal models of PTSD, depression, and anxiety. Previously presented results from another phase 2 randomized, placebo-controlled clinical trial in participants with PTSD (IMPACT-1) demonstrated rapid, robust, and long-lasting efficacy using a split dose (150 mg + 100 mg administered 90 min later) once weekly for four weeks. Based on these findings, TSND-201 was granted Breakthrough Therapy Designation by the FDA. Here, we share results that support the dose-response relationship of TSND-201 in participants with PTSD.

Methods: The IMPACT-2 study was a 12-week, multi-center, randomized clinical trial evaluating the safety, efficacy, and dose-response of 3 dose levels of TSND-201 in participants with PTSD. Eligible participants were adults with moderate-to-severe PTSD. Participants were randomized 1:1:1 to receive blinded doses of either 50 mg (N=17), 100 mg (N=15), or 150 mg (N=15) of TSND-201 given once per week for 4 weeks. Following the 4-week treatment period, participants were followed for an additional 8 weeks to evaluate the durability of the therapeutic effect. PTSD symptom improvement was evaluated on the CAPS-5 and PCL-5. Safety was assessed by monitoring adverse events, vital signs, and C-SSRS.

Results: On the CAPS-5, treatment with 50, 100, or 150 mg TSND-201 resulted in a mean change from baseline to Week 12 of -26.7, -26.5, and -32.9 points, respectively. Rates of response and remission demonstrated clear dose proportionality. Response ($\geq 50\%$ improvement on the CAPS-5) and remission (≤ 11 points total score on the CAPS-5) rates for the 50, 100, 150 mg doses were 64.3%, 76.9%, and 78.6%, and 42.9%, 46.2%, or 71.4%, respectively, demonstrating a clear dose response. Results from the unblinding questionnaire revealed that most participants guessed that they received the low dose, regardless of actual treatment received: 41.5%, 40.0%, and 40.0% in the 50, 100, and 150 mg groups, respectively. Only 1 participant (6.7%) in the high dose group correctly guessed they received the high dose compared with 2 patients (13.3%) in the 100 mg group and 3 patients (17.8%) in the 50 mg group. TSND-201 was well-tolerated with an adverse event profile consistent with prior studies.

Conclusion: TSND-201 demonstrated rapid, robust, and durable effects on PTSD symptoms and clear dose-proportional activity with favorable tolerability. Overall, the study supports further clinical development of TSND-201 as a treatment for PTSD.

T85. SYMPTOMS OF POST-TRAUMATIC STRESS DISORDER IN INDIVIDUALS WITH MODERATE-TO-SEVERE METHAMPHETAMINE USE DISORDER AND CHANGES WITH TIRZEPATIDE TREATMENT

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Abstract Background: Post-traumatic stress disorder (PTSD) is prevalent among individuals with methamphetamine use disorder (MtUD) and contributes substantially to psychiatric morbidity and functional impairment. While tirzepatide was being investigated as a potential treatment for methamphetamine use in this study, its impact on co-occurring PTSD symptoms remains unexamined. This research assessed longitudinal changes in PTSD symptoms among participants with baseline provisional PTSD who received tirzepatide.

Methods: Data were obtained from the TRIUMPH (Tirzepatide for Individuals with Comorbid Obesity and Methamphetamine Use Disorder) study, a clinical trial evaluating the efficacy of tirzepatide in adults with moderate or severe MUD (NCT06745128). Provisional PTSD was determined using the PTSD Checklist for DSM-5 (PCL-5) symptom cluster criteria. PTSD symptoms were evaluated longitudinally with the PCL-5, utilizing baseline scores as the reference point in linear mixed-effects models. Baseline demographic and clinical characteristics, including Generalized Anxiety Disorder 7-item (GAD-7), 16-item Quick Inventory of Depressive Symptomatology Self-Report version (QIDS-SR), and irritability domain of Concise Associated Symptom Tracking (CAST-IRR), were summarized for participants who met provisional PTSD criteria. Individuals with moderate-to-severe MtUD who participated in an open-label trial of 32-week-long treatment with tirzepatide for a weight-related indication were included. Self-report symptoms of depression were assessed with the 16-item Quick Inventory of Depressive Symptomatology Self-Report version (QIDS-SR) at baseline (i.e., prior to first injection) and weekly thereafter during the 32-week treatment period and 4-week follow-up period. Repeated-measures mixed-model analyses were used to assess changes in PCL-5 domains.

Results: Twelve participants (out of 35 enrolled) met provisional PTSD criteria at baseline, comprising a subgroup with clinical severity characterized by near-daily methamphetamine use, heightened craving, and considerable psychiatric comorbidity. The mean baseline PCL-5 score was 56.1, and the standard deviation (SD) was 14.72, indicative of severe PTSD symptom burden. Participants also exhibited elevated levels of anxiety (mean GAD-7 = 15.3; SD = 6.11), depression (mean QIDS-SR = 11.0; SD = 4.20), irritability (mean CAST-IRR = 20.4; SD = 3.65), and functional impairment as compared to those who did not meet the provisional PTSD criteria. Longitudinal analyses demonstrated significant reductions in PTSD symptoms relative to baseline (visit 1) at follow-up visits, with the greatest reduction observed at week-36 (estimate = -20.59, standard error = 7.54; $p = .008$). Other follow-up visits showed consistent, but nonsignificant, decreases in PCL-5 scores.

Conclusions: In adults with methamphetamine use disorder meeting provisional PTSD criteria, tirzepatide administration was associated with clinically meaningful reductions in PTSD symptom severity over time. These findings underscore the importance of evaluating comorbid psychiatric symptoms in substance use intervention trials and further investigation in larger studies.

T86. A SYSTEMATIC LITERATURE REVIEW ON ANTI-PSYCHOTIC UTILIZATION IN MINORITY POPULATIONS AND KEY CLINICAL CONSIDERATIONS

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Abstract Introduction: Recent research has highlighted disparities in minority subgroups in the diagnoses of psychotic disorders. Some studies have attributed these disparities to social determinants of health (SDOH). Further research shows disparities in the antipsychotics utilized to treat these psychotic disorders. However, less research has been done to determine if race and ethnicity may shape the pharmacological response and treatment outcomes.

Aim: Our main objective is to explore antipsychotic use amongst ethnic minorities and determine whether certain clinical considerations should be had when prescribing this class of medication within these populations.

Methods: A literature search was conducted on PubMed with a focus on peer-reviewed articles published within the last 5 years exploring antipsychotic utilization in minority populations. The search string included 'Antipsychotic' (and) 'Black'/'Hispanic'/'East-Asian'/'South Asians'/'Native Hawaiians'/'Pacific Islander'/'Native American' patients. 282 articles screened. After excluding case reports, literature reviews, meta-analyses, and editorials, the search yielded 38 articles included in our review.

Results: Anti-psychotic use and response differed amongst different minority populations. Clozapine was well-studied, and several studies highlighted the underutilization of clozapine as a treatment option for Hispanic, Black, and Native American patients with psychotic disorders. Results show that Black and Native American patients have an increased prevalence of benign ethnic neutropenia (BEN) (4.6% and 10.1%, respectively), which may lead to an overestimation of the risk of severe neutropenia and hesitation for use. In contrast, East-Asian patients showed an increase in adverse reactions to standard clozapine titration, were slower metabolizers, and found benefit at lower doses, resulting in a decrease in tolerability to clozapine if standard treatment guidelines were followed in this population. Risperidone was also well-studied amongst minority populations. Black patients had better adherence and lower positive symptoms on a long-acting injectable (LAI) risperidone than oral risperidone, but no significant improvement was noted in their Hispanic counterparts. Additionally, CYP2D6*17 alleles commonly found in individuals of Sub-Saharan African ancestry can increase the metabolism of risperidone and decrease its efficacy. When looking at Chinese patients, specific NRG1 gene polymorphisms determined cognitive improvement with risperidone use, whereas positive psychotic symptoms improved regardless of the genotype. In Korean patients, risperidone had an 80% increased relative risk of drug-induced Parkinsonism, when compared to aripiprazole, but no clinically significant increase in risk for dystonia or akathisia. East Asian patients were also found to be slower metabolizers for SGAs such as lurasidone, brexpiprazole, and quetiapine, possibly needing lower doses, but had favorable tolerability to aripiprazole. Black patients were less likely to have trialed with a second-generation anti-psychotic (SGA) before LAI initiation when compared to other groups. Amongst LAIs, Paliperidone LAI was frequently found to be well-tolerated across all minorities.

Conclusion: Minority populations show distinct clinical considerations in antipsychotic dosing, tolerability, and adverse effects. Factoring in the racial and ethnic differences will allow us to maximize on treatment options that are already available and improve treatment outcomes and adherence. Further research comparing antipsychotic metabolism and response in minority populations is still needed.

T87. DT120 (LYSERGIDE, LSD): ASSESSING THE POTENTIAL RISK OF CARDIAC VALVULOPATHY AFTER CHRONIC DOSING IN RATS

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Abstract Background: DT120 (lysergide D-tartrate, LSD, MM120) is under development as a potential treatment for generalized anxiety disorder and major depressive disorder. DT120 may elicit profound changes through interaction with 5-HT_{2A}, 2B, and 2C receptors, among others. Activation of 5-HT_{2B} receptors is linked to changes causing the valvular heart disease. We studied the effect of administration of DT120 in several chronic studies in rats.

Methods: (Study 1) Male (M) and female (F) rats were dosed with 0, 0.5, 2 and 6 mg/kg daily (QD) or 6 mg/kg weekly (QW) for 13 weeks. (Study 2) M and F rats dosed QW with 0, 0.5, 2 and 6 mg/kg of DT120 for 26 weeks with a 4-week recovery. Toxicity (clinical observations, body weights (BW), food consumption (FC), clinical, anatomic pathology and toxicokinetics) were assessed in both studies. At necropsy the heart was assessed macroscopically both externally and internally, having opened all four heart chambers, before fixation. The samples that included the atria and aorta were bisected to include the left atrio-ventricular valve and the aortic valve in the same plane. Hematoxylin and eosin-stained sections were examined microscopically and graded using a 5-point grading system from minimal to severe.

Results: (Study 1) Exposure of DT120, measured by maximum observed concentration (C_{max}) and area under the concentration time curve (AUC₀₋₂₄), generally increased and was dose proportional in F and < dose proportional in M, with C_{max} achieving 108 ng/ml in M and 249 ng/ml in F 6 mg/kg QW group on day 85. QD dosing resulted in some accumulation, while QW did not. DT120-related changes in the BW were in animals in 6 mg/kg QD, but not in the QW group. Lower FC was in M in 6 mg/kg QD group. No DT120-related heart weight differences or macro- or microscopic findings were noted for animals administered 6 mg/kg/occasion QW, and no DT120 related findings were noted in the valves of animals administered 0.5, 2, or 6 mg/kg/occasion QD or QW. (Study 2) Following DT120 administration, LSD was measured in the plasma on Day 1, 29, 92, 155 (Group 4 females only) and 176. Sex differences in LSD C_{max} and AUC₀₋₂₄ values were generally > 2-fold, with higher exposure observed in F, compared with M. Exposure generally increased with the increase in dose with C_{max} achieving 345 ng/mL in M and 112 ng/mL in F on Day 176 at 6 mg/kg. BW and FC were slightly changed in M and F in 6 mg/kg groups with full recovery. No DT120-related macro- or microscopic finding in the myocardium or the heart valves were recorded.

Conclusions: Following chronic QD and QW administration of DT120, no DT120-related heart weight or heart weight ratio differences, macroscopic or clear microscopic observations in the myocardium, aortic and mitral valves were noted. Together with the toxicokinetic results, these data provide no evidence of ventricular or valvular remodeling associated with prolonged administration of DT120 in rats.

T88. REAL-WORLD TREATMENT PATTERNS IN MANIC/MIXED BIPOLAR I DISORDER: A US RETROSPECTIVE COHORT STUDY

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Abstract Introduction: Bipolar I disorder (BP-I) is a chronic psychiatric condition characterized by alternating manic and depressive symptoms, often with mixed features. The management of BP-I is complex due to symptom heterogeneity and the need for long-term pharmacotherapy. Real-world evidence on treatment patterns for manic/mixed episodes remains limited. This study described demographic and clinical characteristics and treatment patterns among US patients with manic symptoms/mixed features of BP-I.

Methods: This retrospective cohort study using IQVIA Pharmetrics claims data was conducted from January 2019 to July 2025. Adults aged 18 to 65 years with ≥ 1 inpatient or ≥ 2 outpatient claims with ICD-10 diagnoses of manic/mixed BP-I during July 2019 to July 2025 were included. Baseline was 6 months before index diagnosis; follow-up continued until death, disenrollment, or study end. Descriptive statistics summarized demographics and treatment patterns, including monotherapy and combination therapy.

Results: Among 22,026 patients (mean age: 39.5 years; 62% female), 36% received medication at baseline and 64% during follow-up. The most prescribed medications were lamotrigine (30%; mean duration: 406 days), quetiapine (29%; 334 days), aripiprazole (27%; 254 days), valproate (14%; 303 days), and lithium (10%; 353 days). Twenty percent of patients received combination therapy, most commonly lamotrigine + antipsychotic (11%), valproate + antipsychotic (5%), and lithium + antipsychotic (4%). Patterns were heterogeneous, reflecting clinical complexity.

Conclusions: Findings highlight the variability in BP-I management and underscore the need for individualized strategies. Future research should examine drivers of treatment selection and outcomes in routine care.

T89. ML-007C-MA, A NOVEL INVESTIGATIONAL M1/M4 MUSCARINIC AGONIST IN PHASE 2 DEVELOPMENT FOR THE TREATMENT OF SCHIZOPHRENIA AND ALZHEIMER'S DISEASE PSYCHOSIS

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Abstract: Muscarinic agonists have emerged as a new class of therapeutic agents for the treatment of psychosis with a mechanism distinct from typical and atypical antipsychotics. M1 and M4 receptor subtypes show the highest expression in brain regions implicated in psychosis, negative symptoms, and cognition, and thus have therapeutic potential across several neuropsychiatric disorders including schizophrenia and Alzheimer's disease psychosis. ML-007C-MA is an investigational fixed-dose combination of a novel M1/M4 muscarinic agonist, ML-007 and fesoterodine fumarate, a peripherally-acting muscarinic

antagonist. Fesoterodine is ideally suited for the combination due to its low brain penetration, predictable pharmacokinetics, and favorable physicochemical properties that enabled precision matching of the exposure profiles. By synchronizing the pharmacokinetic exposures of agonist and antagonist components in the periphery, ML-007C-MA was designed to mitigate cholinergic side effects while maintaining strong activation of M1 and M4 receptors in the brain to drive efficacy. In preclinical evaluations, ML-007 was determined to be a potent brain-penetrant agonist at both M1 and M4 receptors with high oral bioavailability, low protein binding, and low peripheral tissue accumulation. ML-007 also showed robust activity across mouse models of psychosis and cognitive impairment. Four Phase 1 clinical trials were then conducted, with a total of 270 healthy participants and more than 1,500 doses of ML-007 administered alone, co-administered, or co-formulated with fesoterodine. These trials evaluated a broad range of doses and dose ratios to identify an optimal range of agonist-to-antagonist ratios to minimize peripheral cholinergic side effects. This ratio was then co-formulated into a fixed dose product, ML-007C-MA that was found to be generally well tolerated with minimal titration at doses selected for Phase 2 studies. Most treatment-emergent adverse events were mild and transient in nature, with no severe or serious adverse events observed. Pharmacokinetic parameters were similar between adult and elderly study participants and confirmed that dosing in the Phase 2 trials did not require administration in a fasted state. ML-007C-MA has the potential to be a well-tolerated treatment option that is currently being evaluated in two Phase 2 clinical trials: the ZEPHYR trial for schizophrenia and the VISTA trial for Alzheimer's disease psychosis.

T90. EFFICACY OF XANOMELINE AND TROSPIUM CHLORIDE ACROSS SYMPTOM DOMAINS IN ADULTS WITH SCHIZOPHRENIA: RESULTS FROM THE 52-WEEK, OPEN-LABEL EMERGENT-5 CLINICAL TRIAL

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Abstract Introduction: Xanomeline and trospium chloride (KarXT), combining the dual M1/M4-preferring muscarinic receptor agonist xanomeline with the peripherally restricted muscarinic receptor antagonist trospium chloride, is approved for treatment of schizophrenia in adults in the US. KarXT demonstrated significant improvement in Positive and Negative Syndrome Scale (PANSS) total score versus placebo in the pivotal phase 3, 5-week, double-blind, placebo-controlled, randomized EMERGENT-2 (NCT04659161) and EMERGENT-3 (NCT04738123) clinical trials. Continued long-term improvement in PANSS total score was also observed with KarXT treatment in the 52-week, open-label extension EMERGENT-4 trial (NCT04659174) in participants who completed the treatment period of EMERGENT-2 and EMERGENT-3. In this post hoc analysis, long-term efficacy of KarXT is assessed across schizophrenia symptoms in the phase 3, multicenter, 52-week, open-label, outpatient EMERGENT-5 (NCT04820309) trial using PANSS Marder 5-factor analysis.

Methods: EMERGENT-5 enrolled adults with confirmed schizophrenia who had stable symptoms with antipsychotic (AP) use and no prior exposure to KarXT. Participants were aged 18-65 years with a primary DSM-5 diagnosis of schizophrenia, PANSS total score ≤ 80 , and Clinical Global Impression-Severity (CGI-S) score ≤ 4 . Participants had received oral AP therapy within 30 days of screening and discontinued these medications prior to their baseline

visit. After initial assessments, participants were initiated with twice-daily (BID) oral doses of KarXT 50 mg/20 mg and titrated to a maximum dose of KarXT 125 mg/30 mg BID for the remainder of the 52-week treatment period. Change from baseline (CfB) in PANSS total score was examined in the modified intention-to-treat population (mITT; participants with ≥ 1 dose of trial medication and ≥ 1 baseline and postbaseline PANSS assessment). Post hoc analysis evaluated CfB in PANSS Marder 5-factor scores. Adverse events (AEs) were assessed in the safety population (participants with ≥ 1 dose of trial medication).

Results: The safety and mITT populations consisted of 566 and 558 participants treated with KarXT, respectively. The mean $\pm$ standard error baseline PANSS score in the mITT population was 66.0 $\pm$ 0.44, reflecting a mildly ill population. Long-term treatment with KarXT resulted in improvements in PANSS total score (CfB at week 52, -5.5 $\pm$ 0.66). Additionally, score reductions from baseline to week 52 were observed in each of the PANSS Marder factors. The largest improvement was in the PANSS Marder positive factor, with a -2.1 $\pm$ 0.23-point CfB resulting in a mean score of 18.2 $\pm$ 0.28 at 52 weeks. Similarly, score reductions from baseline to week 52 in PANSS Marder negative (15.6 $\pm$ 0.29; CFB, -1.1 $\pm$ 0.27), uncontrolled hostility (6.3 $\pm$ 0.15; CFB, -0.3 $\pm$ 0.17), disorganized thought (14.0 $\pm$ 0.22; CFB, -0.8 $\pm$ 0.20), and depression/anxiety (6.1 $\pm$ 0.16; CFB, -1.2 $\pm$ 0.18) factors indicate broad and sustained efficacy with KarXT over the 52-week trial period. No new safety signals were observed; additionally, KarXT was not associated with motor symptoms, somnolence, weight gain, or other AEs often reported with D2 receptor-acting AP treatments.

Conclusions: In the long-term, open-label, outpatient EMERGENT-5 trial, KarXT demonstrated consistent efficacy across symptoms among adults with schizophrenia who transitioned from other AP treatments. KarXT was generally well tolerated and no new safety signals were observed.

T91. THE METABOLIC-COGNITIVE PATHWAY IN SCHIZOPHRENIA: EXAMINING FASTING GLUCOSE, LIPIDS, AND BLOOD PRESSURE AS PREDICTORS OF COGNITIVE IMPAIRMENT AND DEMENTIA RISK

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Abstract Background: Schizophrenia is increasingly recognized as a systemic disorder characterized by pervasive metabolic, vascular, and bioenergetic abnormalities. Cognitive impairment is a core and often treatment-refractory feature of schizophrenia and a major determinant of functional outcome. Individuals with schizophrenia also display high rates of metabolic syndrome, type 2 diabetes, dyslipidemia, and hypertension, and have an increased risk of dementia. While peripheral metabolic abnormalities are well documented, their association with cognitive impairment in schizophrenia are not as well understood.

Objective: To examine associations between metabolic markers (glucose metabolism, lipids, blood pressure, and anthropometric measures) and cognitive performance across domains in individuals with schizophrenia compared with healthy controls.

Methods: This study examines comprehensive metabolic profiles in 120 participants (60 with schizophrenia, 60 healthy controls) aged 18-45. Metabolic assessments include fasting blood glucose, fasting insulin, complete lipid panel (total cholesterol, LDL, HDL, triglycerides), and blood pressure measurements. Cognitive function is evaluated using the MATRICS

Consensus Cognitive Battery (MCCB) to assess working memory, attention, verbal learning, and visual learning. Anthropometric measures (BMI, waist circumference) are also collected. Multiple linear regression analyses will examine the associations between metabolic parameters and cognitive outcomes, while controlling for age, sex, education, antipsychotic medication (as measured by chlorpromazine equivalents), and smoking status.

Expected Results: We hypothesize that higher insulin resistance (fasting insulin/HOMA-IR), more atherogenic lipid profiles (higher triglycerides/lower HDL), elevated blood pressure, and higher adiposity will be associated with poorer cognition, with stronger effects in participants with schizophrenia versus the control group. Preliminary analyses indicate significant inverse correlations between fasting glucose levels and insulin resistance and MCCB total scores. Full statistical analyses in progress.

Expected Conclusion and significance: Metabolic dysregulation is a potentially modifiable risk factor for cognitive impairment in schizophrenia. Targeting metabolic and vascular abnormalities may represent a critical strategy for preserving cognition and reducing dementia risk in this population.

T92. INPATIENT INITIATION OF THE LONG-ACTING INJECTABLE ANTIPSYCHOTIC ARIPIPRAZOLE LAUROXIL FOR THE TREATMENT OF ACUTE EXACERBATIONS OF SCHIZOPHRENIA

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Abstract Background: Treatment of schizophrenia exacerbations requires balancing acute symptom control with the longer-term goal of optimizing continued outpatient treatment. Long-acting injectable (LAI) formulations can address both goals when clinicians have an understanding of, and confidence in, LAI safety and efficacy. This report focuses on clinical outcomes for aripiprazole lauroxil (AL) initiated during hospitalization for acute schizophrenia.

Methods: This post-hoc analysis assessed the 2-week inpatient period of the 25-week ALPINE study, which evaluated AL (active control: paliperidone palmitate) for treatment of acutely exacerbated schizophrenia. Patients enrolled as inpatients and randomized to AL 1064mg every-2-months, started after a 1-day initiation regimen (AL NanoCrystal Dispersion plus one 30mg oral aripiprazole dose), were included. Efficacy was assessed using the Positive and Negative Syndrome Scale (PANSS). Early treatment response was defined as $\geq 20\%$ reduction in PANSS total score from baseline (predose) to discharge. Safety was assessed based on adverse events (AEs).

Results: Ninety-nine patients were randomized to AL; 90 (90.9%) patients completed the 2-week treatment period. Mean (SD) baseline PANSS total score was 94.1 (9.0). At day 15, least-squares mean (SE) change from baseline in PANSS total score was -15.4 (1.3) for AL-treated patients; 55.2% met early treatment response criteria. Common AEs ($\geq 5\%$) were injection site pain (15.2%), akathisia (9.1%), and headache (5.1%).

Conclusion: Initiation of AL can be completed with a 1-day regimen in hospitalized patients, providing symptom reduction with confidence of having drug on board to support the transition to outpatient care. Funding Statement: This study was funded by Alkermes, Inc.

Medical writing and editorial support were provided by Peloton Advantage, LLC, an OPEN Health company, and funded by Alkermes, Inc.

T93. SAFETY AND EFFICACY OF ARIPIPRAZOLE LAUROXIL IN AN OUTPATIENT SETTING AFTER INITIATION DURING HOSPITALIZATION FOR AN ACUTE EXACERBATION OF SCHIZOPHRENIA

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Abstract Background: The period following discharge from an acute schizophrenia hospitalization carries a high risk of relapse, rehospitalization, suicide, and medication nonadherence. Treatment strategies must prioritize sustained symptom control beyond discharge. Aripiprazole lauroxil (AL) is a long-acting injectable antipsychotic that can be initiated during acute care, ensuring adequate coverage after discharge to bridge inpatient stabilization with outpatient maintenance.

Methods: This post-hoc analysis focused on the outpatient period of a 25-week phase 3b study evaluating the use of AL (with paliperidone palmitate as active control) started during a short hospitalization for acute schizophrenia. Adult patients who were enrolled as inpatients, randomized to AL (1064mg every-2-months), discharged after 2–3 weeks, and followed as outpatients (≤ 23 weeks) were included. Efficacy was evaluated using Positive and Negative Syndrome Scale (PANSS) scores, and safety was monitored based on adverse events (AEs), both from day of hospital discharge through the end of study.

Results: Of 99 patients randomized to AL, 84 (84.8%) remained in the study postdischarge; 56 (66.7%) completed outpatient treatment. After acute inpatient symptom improvement, mean (SD) PANSS total score was 77.3 (14.2) at discharge; additional least-squares mean (SE) change was -5.3 (1.3) at 23 weeks postdischarge. The most common AE ($\geq 5\%$) was weight increase (10.7%). Six patients (7.1%) discontinued because of AEs.

Conclusion: After inpatient initiation of AL every-2-months, schizophrenia symptom severity remained stable during outpatient care. AL's safety and tolerability profile supports its use for maintenance treatment following transition from inpatient care. Funding Statement: Sponsored by Alkermes, Inc. Writing and editorial support were provided by Peloton Advantage, LLC, an OPEN Health company, and funded by Alkermes, Inc.

T94. LB-102 FOR ACUTE SCHIZOPHRENIA IN ADULTS: RESULTS FROM THE PHASE 2 NOVA1 CLINICAL TRIAL, FOCUSED ON PANSS TOTAL SCORE RESPONDER AND CGI-S REMITTER RATES

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Abstract Background: LB-102 (N-methylated amisulpride) is a novel benzamide antipsychotic currently under development for the treatment of patients with acute schizophrenia as well as other neuropsychiatric diseases. Primary analysis of the large-scale, phase 2 NOVA1 study in adults with acute schizophrenia (NCT06179108) highlighted that LB-102 had a clinically significant treatment effect on the Positive and Negative Syndrome Scale (PANSS) total score and Clinical Global Impression of Severity (CGI-S) score after 4 weeks of treatment. This analysis explores response rates to LB-102 on the PANSS total score and CGI-S at the end of Week 4.

Methods: NOVA1 was a randomized, double-blind, placebo-controlled trial in eligible adults (18–55 yr) diagnosed with schizophrenia. Participants were randomized (3:3:3:1) to oral once-daily placebo (PBO), LB-102 50mg, LB-102 75mg, or LB-102 100mg (exploratory). The primary analysis was change from baseline to Week 4 in PANSS total score, with effect sizes and responder/remitter rates calculated based on observed cases. Post hoc analyses were conducted to determine PANSS total score response rates of $\geq 20\%$, $\geq 30\%$, and $\geq 40\%$ at Week 4, with PANSS item scores rescaled (0–6; total score range: 0–180) to adjust for the mathematical floor effect. CGI-S remission was defined, a priori, as a participant with a CGI-S rating of 3 (mildly ill), 2 (borderline mentally ill), or 1 (normal, not at all ill) at Week 4.

Results: 359 participants were randomized (PBO, n=108; 50mg, n=107; 75mg, n=108; 100mg, n=36), with 261 (73%) completing the 6-week trial. LB-102 met the primary endpoint, with mean changes from baseline to Week 4 in PANSS total score being -9.3 (PBO, n=93), -14.3 (50mg, p=0.0009 vs PBO; effect size=0.61, n=91), -14.0 (75mg, p=0.0022; effect size=0.41, n=84), and -16.1 (100mg, nominal p=0.0017; effect size=0.83, n=23). Post hoc (floor-adjusted) analysis of PANSS total scores demonstrated a higher proportion of responders for all LB-102 doses compared to PBO for the $\geq 20\%$ (50mg, 57.1%, p=0.03; 75mg, 53.6%, p=0.02; 100mg, 78.3%, p=0.001 vs PBO, 38.7%) and $\geq 30\%$ (50mg, 31.9%, p=0.03; 75mg, 31.0%, p=0.01; 100mg, 39.1%, p=0.02 vs PBO, 16.1%) PANSS total score responders, as well as $\geq 40\%$ PANSS total score responders for LB-102 50mg (20.9%, p=0.01) and 75mg (16.7%, p=0.02) compared to PBO (6.5%). All LB-102 doses demonstrated significantly greater improvements from baseline to Week 4 in CGI S score compared to PBO (50mg, least squares mean difference, -0.33 [standard error, 0.10], p < 0.001; 75mg, -0.28 [0.10], p=0.005; 100mg, -0.45 [0.15], p=0.003). LB-102 50mg (23.4%, p=0.001) and 75mg (17.6%, p=0.02) demonstrated significantly greater CGI-S remitter rates at the end of Week 4 compared to placebo (7.4%). Treatment-emergent adverse events (TEAEs) were reported in 56% (PBO), 69% (50mg), 57% (75mg), and 75% (100mg) of participants. Ten participants reported TEAEs leading to withdrawal (PBO, n=2; 50mg, n=2; 75mg, n=3; 100mg, n=3) and 5 reported serious TEAEs (PBO, n=2 [including 1 death]; each LB-102 arm, n=1).

Discussion: This phase 2 clinical trial provided robust evidence demonstrating the efficacy and safety of LB-102 for adults with acute schizophrenia, with greater PANSS total score responder and CGI-S remitter rates at the end of Week 4 compared to placebo.

T95. ROLE OF GLP-1 RECEPTOR AGONISTS IN MANAGING ANTIPSYCHOTIC-RELATED METABOLIC DYSFUNCTION AND WEIGHT GAIN

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Abstract Background: Patients receiving antipsychotic medications for severe and persistent psychiatric illness frequently experience significant metabolic side effects, including weight gain, insulin resistance, and type 2 diabetes. Glucagon-like peptide 1 (GLP-1) receptor agonists have shown promising results in addressing antipsychotic-induced weight gain (AIWG) and improving metabolic outcomes. This literature review evaluated the effects of GLP-1 receptor agonists on weight loss and metabolic changes in patients with AIWG.

Methods: A systematic literature search was conducted on PubMed using the following keywords: (“Glucagon-Like Peptide 1 Receptor Agonists”) AND (“Antipsychotic Agents”) AND (“Obesity”), with filters applied for the past 20 years to include clinical trials (randomized and open) and meta-analyses. The search yielded 10 relevant studies. Data from all included studies were reviewed to address changes in body weight, and metabolic changes among patients with AIWG treated with GLP-1 receptor agonists.

Results: Of the 10 studies identified, two clinical trials evaluated semaglutide (HISTORI and COaST). The HISTORI trial included patients with schizophrenia on second-generation antipsychotics and obesity. The trial demonstrated that semaglutide reduced body weight by 9.21 kg (95% CI, -11.68 to -6.75) and significantly decreased HbA1c levels ($P < .001$) compared to placebo. The COaST trial enrolled patients receiving clozapine with $< 5\%$ baseline weight change; the semaglutide group achieved a statistically significant weight reduction of 13.88% ($P < .0001$). The HISTORI trial also showed improvement in quality of life by 3.75 points on the SF-36v2 (95% CI, 1.52–5.98; $P = 0.001$). Data on earlier GLP-1 receptor agonists, including exenatide and liraglutide, demonstrated mixed results. Exenatide trials showed either no significant weight change or weight loss comparable to placebo ($P = 0.98$). Liraglutide studies demonstrated improvements in glucose tolerance ($P < 0.001$), reductions in body weight (-5.3 kg; 95% CI), systolic blood pressure (-4.9 mm Hg; 95% CI), and visceral fat (-250.19 g; 95% CI). Only one study evaluated weight change one year after liraglutide discontinuation, showing a return to baseline weight. The most commonly reported adverse effects were gastrointestinal, including nausea, vomiting, and diarrhea.

Conclusion: GLP-1 receptor agonists, particularly newer agents such as semaglutide, are a promising and effective option for managing AIWG and metabolic dysfunction in patients requiring long-term antipsychotic therapy. These agents may play an important role in comprehensive care by decreasing the metabolic side effects of antipsychotics. However, larger randomized trials with longer follow-up are needed to better define long-term safety, durability of weight loss, and maintenance strategies after GLP-1 receptor agonists discontinuation.

T96. REAL-WORLD USE OF XANOMELINE AND TROSPIUM CHLORIDE IN SCHIZOPHRENIA: PATIENT CHARACTERISTICS, TREATMENT PATTERNS, AND OUTCOMES

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Abstract Introduction: Schizophrenia imposes a substantial burden on patients and health systems in the United States. For decades, pharmacologic treatment of schizophrenia has relied on D2 dopamine receptor antagonists, which can have substantial side effects, such as cardiometabolic conditions and extrapyramidal or other movement disorders. KarXT (xanomeline and trospium chloride) was approved by the US Food and Drug Administration

in September 2024 for the treatment of schizophrenia and represents a new treatment option that exerts effects through M1 and M4 muscarinic receptor circuits rather than D2 dopamine receptors. This study aims to describe real-world clinical characteristics, treatment patterns, and outcomes of adults initiating KarXT treatment for schizophrenia.

Methods: This retrospective observational study analyzed administrative claims from the Komodo Research Database (January 1, 2016-April 30, 2025), a large, nationally representative database with approximately 300 million patient journeys and healthcare encounters from more than 150 payers across Medicaid, commercial, and Medicare insurers. Adults with schizophrenia who initiated KarXT between September 2024 and March 2025 were included. Demographics and clinical characteristics were assessed over the 12 months prior to KarXT initiation (baseline). Adherence (proportion of days covered [PDC]) and persistence (time to discontinuation with a 45-day allowable gap) were evaluated post KarXT initiation (follow-up). Rates of antipsychotic (AP) and other psychotropic medication use were compared before and after KarXT initiation.

Results: A total of 1443 adults with schizophrenia who initiated KarXT were included (mean age=42.2 years); most were insured by Medicare and Medicaid. Prior to KarXT initiation, the study cohort had high utilization of APs (99%) and other psychotropic medications, including antidepressants (74%), anticholinergics (56%), anxiolytics (51%), and mood stabilizers (48%). The prevalence of cardiometabolic conditions, mental health-related comorbidities, and other AP-associated disorders was also high ($\leq 49\%$). During the follow-up, adherence and persistence to KarXT were relatively high, with 72% having a PDC $\geq 80\%$ and approximately 81% persisting on KarXT through month 4. AP use decreased after KarXT initiation (rate ratio [RR]=0.74 for orals, $P < 0.001$; 0.78 for long-acting injectables, $P < 0.001$), as did use of mood stabilizers (RR=0.87, $P < 0.001$) and anticholinergics (RR=0.84, $P < 0.001$). A decreasing trend was observed for antidepressant use (RR=0.96, $P=0.053$).

Conclusions: Adults with schizophrenia who initiated KarXT in the first 6 months of availability exhibited high treatment and comorbidity burdens. During the brief follow-up, adherence and persistence to KarXT were relatively high. Following KarXT initiation, use of APs, mood stabilizers, and anticholinergics reduced significantly, suggesting a potential shift toward a simplified treatment regimen for managing schizophrenia.

T97. REAL-WORLD COMPARISON OF OLANZAPINE/SAMIDORPHAN VS OLANZAPINE: AN ASSESSMENT OF TREATMENT PATTERNS AND ACUTE CARE EVENTS AMONG PATIENTS WITH SCHIZOPHRENIA OR BIPOLAR I DISORDER

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Abstract Background: Combined olanzapine and samidorphan (OLZ/SAM) provides the antipsychotic efficacy of olanzapine while mitigating olanzapine-associated weight gain. In a 4-year open-label study, OLZ/SAM maintained symptom control, with small changes in body weight and minimal changes in lipid/glycemic parameters. The objective of this real-world

claims analysis was to compare treatment patterns and acute care events in patients with schizophrenia or bipolar I disorder (BD-I) initiating OLZ/SAM vs olanzapine.

Methods: This claims analysis used Komodo Healthcare Map data (10/18/2020–12/31/2023). Medicaid-insured adults with schizophrenia or BD-I with ≥ 1 OLZ/SAM or olanzapine claim were eligible; OLZ/SAM claims were prioritized over olanzapine claims to set the index date. Patients were propensity score matched 1:1 on baseline demographic/clinical variables between the OLZ/SAM and olanzapine cohorts. Treatment patterns (adherence, persistence, discontinuation), acute care events including inpatient (IP) admissions and emergency department (ED) visits (all cause, mental health related, or disease related [often used as a proxy for relapse]), and numbers of days hospitalized per patient were compared between cohorts during the 12-month follow-up period. P values ≤ 0.05 were considered statistically significant.

Results: After matching, 1614 patients with schizophrenia (OLZ/SAM, n=807; olanzapine, n=807) and 1008 with BD-I (OLZ/SAM, n=504; olanzapine, n=504) were included across both treatment cohorts. In both cohorts, OLZ/SAM was associated with significantly higher adherence, longer persistence, and lower discontinuation rates vs olanzapine (all $P < 0.001$). OLZ/SAM was associated with significantly lower likelihood of ≥ 1 all-cause, mental health-related, or disease-related IP admission (odds ratio [OR] range, schizophrenia: 0.52–0.59, all $P < 0.001$; BD-I: 0.52–0.58, all $P < 0.001$) or ED visit (OR range, schizophrenia: 0.47–0.54, all $P < 0.001$; BD-I: 0.62–0.74, all $P < 0.05$). Across all-cause, mental health-related, and disease-related events, mean numbers of days hospitalized per patient were significantly lower (range, schizophrenia: –4.7 to –5.7 days, all $P < 0.01$; BD-I: –3.2 to –4.5 days, all $P < 0.001$) for OLZ/SAM vs olanzapine.

Conclusion: OLZ/SAM treatment offers meaningful real-world effectiveness benefits over olanzapine, as observed by favorable treatment patterns and significantly lower likelihood of acute care events in this analysis of claims data. Significantly lower likelihood of disease-related acute care events suggests a lower likelihood of relapse with OLZ/SAM treatment vs olanzapine. Funding Statement: This study was funded by Alkermes, Inc. Medical writing and editorial support were provided by Peloton Advantage, LLC, an OPEN Health company, and funded by Alkermes, Inc.

T98. REAL-WORLD OUTCOMES AND PSYCHOLOGICAL PREDICTORS IN AN 8-WEEK HYBRID DIGITAL CLINIC FOR DEPRESSION AND ANXIETY

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Abstract: Hybrid digital care models combining clinician support with mobile health technology may improve access and outcomes for depression, yet real-world data on mechanisms of change remain limited. This study evaluated symptom outcomes and psychological process variables in an eight-week Digital Clinic integrating clinician sessions, Digital Navigator support, and the mindLAMP smartphone application. The objectives were twofold: to describe real-world clinical outcomes associated with this hybrid model using PHQ-9 and GAD-7 scores, and to examine psychological factors, specifically self-efficacy and emotional self-awareness, as predictors of symptom improvement. Participants were 50 adults receiving hybrid care for mild to moderate depression and/or anxiety (analytic sample representing 78.1% of the enrolled cohort). Depressive and anxiety symptoms were assessed weekly using the PHQ-9 and GAD-7, respectively. Psychological processes assessed at intake and completion included self-efficacy (PROMIS) and emotional self-awareness (ESQ).

Paired t-tests evaluated change over time; correlations and regression analyses examined associations between process changes and symptom improvement. Participants demonstrated significant and clinically meaningful reductions in depressive symptoms ($d = 0.64$) and anxiety symptoms ($d = 0.71$) over the eight-week treatment period. Correlational analyses indicated that symptom change was associated with improvements in psychological resources. For depressive symptoms, greater PHQ-9 reduction was associated with larger improvements in self-efficacy ($\rho = -.47$, $p < .001$) and emotional self-awareness ($\rho = -.27$, $p = .029$). Similarly, GAD-7 change was negatively correlated with self-efficacy change ($\rho = -.55$, $p < .001$) and modestly correlated with emotional self-awareness change ($\rho = -.20$, $p = .050$). These findings support the effectiveness of hybrid digital care in producing clinically meaningful symptom improvements, supporting its integration within psychopharmacology care pathways. Importantly, self-efficacy showed the most consistent association with symptom reduction across outcomes, emerging as a potential key mechanism of change. This advances the field by identifying a modifiable target for intervention optimization. Routine measurement of psychological process variables within digital care platforms may support personalization by helping clinicians monitor mechanisms of change and tailor interventions accordingly. These results provide actionable evidence for scaling hybrid models while maintaining focus on therapeutic processes that drive improvement.

T99. RESTING-STATE EEG SIGNATURES OF SUICIDAL IDEATION SEVERITY AND INTENSITY IN TREATMENT-RESISTANT DEPRESSION: PRELIMINARY BASELINE DATA FROM TWO ONGOING CLINICAL TRIALS

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Abstract Background: Suicidal ideation (SI) is prevalent among persons with treatment-resistant depression (TRD) and is associated with increased all-cause mortality risk. Identifying scalable neurophysiologic correlates of SI is important for improving risk characterization and for identifying treatments that normalize suicide-relevant circuitry. Resting-state electroencephalography (EEG) spectral power is a scalable index of circuit dynamics that may differentiate graded SI burden.

Methods: Baseline EEG recordings from two ongoing phase II TRD trials were analyzed, integrated intravenous racemic ketamine plus internet-based cognitive behavioral therapy (KET-CBT, NCT06480500; $n = 30$) and psilocybin-assisted psychotherapy dose comparison (PSI-1V2, NCT06341426; $n = 29$). Analyses were conducted within each trial and in a pooled baseline dataset. Resting eyes-open (EO) EEG was prespecified as the primary condition to standardize wakeful vigilance, and eyes-closed (EC) EEG was analyzed as a sensitivity condition to evaluate state dependence. Morlet time-frequency decomposition yielded log10 band power in delta, theta, alpha, beta, and gamma bands, summarized across whole-scalp and a priori regions of interest. SI burden was indexed using the Columbia-Suicide Severity Rating Scale (C-SSRS) SI severity score modeled as an ordinal predictor. EO-only and EC-only models tested monotonic severity-power trends using robust standard errors, adjusting for age, sex, depressive symptom burden, number of comorbid diagnoses, and total exposure to stimulants, benzodiazepines, serotonergic psychedelics, and

glutamatergic agents. Paired EO+EC models tested severity-by-eye-state interactions with participant-clustered standard errors. Within each severity level, C-SSRS intensity (1-25) was modeled with severity-by-intensity effects and eye-state dependence. False discovery rate (FDR) q-values are reported.

Results: In the pooled dataset, eleven participants reported no SI and among those with nonzero severity, C-SSRS severity spanned 1-5 (mean $\pm$ standard deviation; 1.83 ± 1.02) and intensity spanned 7-18 (13.10 ± 2.77). SI severity is positively associated with EO alpha power across global and regional summaries (whole-brain: $\beta = 0.169$, $p < 0.001$, $q = 0.002$; frontal: $\beta = 0.134$, $p = 0.02$, $q = 0.008$; central: $\beta = 0.163$, $p < 0.001$, $q = 0.004$; posterior: $\beta = 0.196$, $p < 0.001$, $q = 0.003$), as well as EO posterior beta power ($\beta = 0.108$, $p < 0.001$, $q < 0.001$). Severity effects differed by eye-state, with significant severity-by-eye-state interactions most prominent in whole-brain and frontal theta and posterior beta. Trial-stratified analyses were directionally compatible with pooled estimates, including an EO posterior beta association in KET-CBT ($p = 0.002$, $q < 0.05$) and an EO posterior delta association in PSI-1V2 ($p = 0.001$, $q < 0.05$). Within-severity analyses identified a robust intensity effect in KET-CBT at severity level 2, where higher intensity predicted lower EC posterior beta power ($p < 0.001$, $q > 0.55$).

Conclusion: In TRD, baseline SI burden is associated with graded differences in resting EEG spectral power, most consistently in EO alpha and beta features, with robust eye-state-dependent modulation in theta and beta bands. Severity and within-severity intensity exhibited partially distinct EEG associations, supporting longitudinal evaluation of whether treatment-related changes in EO spectral signatures track SI improvement and enhance SI stratification beyond symptom ratings.

T100. ATTITUDES TOWARD ARTIFICIAL INTELLIGENCE CLINICAL DECISION SUPPORT IN PSYCHIATRY TRAINING: CURRENT EVIDENCE AND FUTURE DIRECTIONS

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Abstract Background: Artificial intelligence (AI) is increasingly integrated into healthcare, with psychiatry adopting predictive modeling, suicide risk assessment, and documentation support. AI Clinical Decision Support (CDS) tools hold promise for improving diagnostic accuracy, personalizing treatment, and streamlining workflows. Yet ethical concerns, autonomy, and limited training temper enthusiasm. The primary objective of this review is to examine evidence on clinician attitudes and identify gaps in psychiatry training.

Methods: A literature review was conducted across PubMed, PsycINFO, and Scopus using keywords including artificial intelligence, psychiatry, clinical decision support, attitudes, residents, education, and mental health professionals. Studies were included if they examined AI perceptions, attitudes, training, or adoption among psychiatrists, trainees, or mental health professionals. No date or language limits were applied. The search yielded 210 records; after duplicate removal, 40 full texts were reviewed, and 9 met inclusion criteria.

Results: Across regions, clinicians showed cautious optimism toward AI through various applications. Surveys in Nigeria and Saudi Arabia evaluated CDS for diagnosis and treatment planning in hospital psychiatry, recognizing its potential but limited familiarity. Concerns

included empathy, confidentiality, and data security. A mixed-methods study found nearly half of clinicians lacked AI training, yet many valued predictive algorithms for suicide risk, symptom monitoring, and relapse detection, especially outpatient. Broader physician surveys reinforced ambivalence: clinicians doubted AI could replace relational aspects but endorsed its use for documentation, efficiency, and diagnostic support. Educational studies highlighted the potential of adaptive AI learning platforms in psychiatry and psychology training. Systems-level analyses emphasized big data analytics for hospital efficiency and forecasting, while noting barriers with infrastructure, workforce, and readiness.

Conclusions: This review synthesizes evidence, underscoring both optimism and skepticism toward AI in psychiatry. While professionals recognize AI's potential for diagnosis, prediction, and education, adoption remains constrained by training gaps and ethical concerns. No studies examined psychiatry residents' perspectives, leaving a gap in understanding how trainees view AI in relation to trust, autonomy, and curricular integration. Another gap is cultural context: most studies did not assess how regional and cultural differences influence attitudes, trust, or ethical concerns. Training AI models on linguistically and ethnically cognizant datasets is essential to reduce bias and improve cultural relevance across populations. By identifying these limitations, this review clarifies the evidence base and highlights directions for future research, including trainee-focused investigations and culturally informed approaches to AI in psychiatric education.

T101. THE NATIONAL PREGNANCY REGISTRY FOR PSYCHIATRIC MEDICATIONS: RISK OF MAJOR MALFORMATIONS FOLLOWING FETAL EXPOSURE TO SECOND GENERATION ANTIPSYCHOTICS

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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, 2025, 3940 women were enrolled in the NPRPM, including 1375 in the exposure group and 2456 in the comparison group. Medical records were obtained for 75% of participants. A total of 3014 participants (1049 exposed to an SGA in the first trimester, 1965 unexposed to an SGA during pregnancy) completed the postpartum interview and were eligible for analysis. Of 1080 infants in the exposure group, 28 confirmed major malformations were identified. In the control group of 1997 infants, 32 malformations were identified. The absolute risk of major malformations was 2.59% in the exposure group and 1.60% in the comparison group. No specific patterns of major malformations were observed in either group.

Conclusion: According to CDC national data, the prevalence of major malformations is approximately 3% among all live births in the United States. In this analysis, the absolute risk of neonatal major malformations was similar at 2.59% in the exposed group, while it was lower at 1.60% 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. Ongoing data collection through the Registry is critical in defining the risk estimate more precisely and reducing uncertainty.

T102. PREGNANCY OUTCOMES AFTER FIRST-TRIMESTER EXPOSURE TO VORTIOXETINE: PROSPECTIVE OUTCOMES FROM THE MGH NATIONAL PREGNANCY REGISTRY FOR PSYCHIATRIC MEDICATIONS

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Abstract Purpose: Vortioxetine is an antidepressant used to treat major depressive disorder (MDD), a disorder that is common among women of reproductive age. To date, the reproductive safety of vortioxetine in humans has been limited. We sought to provide preliminary systematic data from the Massachusetts General Hospital National Pregnancy Registry for Psychiatric Medications (NPRPM) on the risk of major malformations after exposure to vortioxetine in the first trimester of pregnancy.

Methods: The NPRPM is a longitudinal ongoing study in which pregnant women with psychiatric disorders are enrolled to prospectively assess for major congenital malformations after in utero exposure to psychotropics. Data regarding women who took vortioxetine during the first trimester were extracted from the NPRPM database. Data for this analysis were assessed as a rigorously ascertained case series to determine the incidence of major malformations. The primary outcome of major malformations following first trimester exposure was obtained by maternal postpartum interview and medical record review.

Results: As of November 14, 2025, n=54 women who reported taking vortioxetine during the first trimester had evaluable data. Among this sample, there were no major malformations.

Conclusions: These preliminary data represent the only rigorous and prospectively ascertained pregnancy outcomes after first trimester vortioxetine exposure. No major malformations were observed. While these data are reassuring, the relatively small sample size limits conclusions on the safety of vortioxetine in pregnancy.

T103. RISK OF MAJOR MALFORMATIONS FOLLOWING FIRST TRIMESTER EXPOSURE TO CARIPRAZINE: PRELIMINARY DATA FROM THE MGH NATIONAL PREGNANCY REGISTRY FOR PSYCHIATRIC MEDICATIONS

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Abstract Objective: Systematically collected pregnancy safety data for cariprazine have been lacking, despite growing use of this medication across psychiatric indications. The goal of this analysis was to determine the risk of major malformations among infants of mothers with psychiatric illness who used cariprazine during the first trimester of pregnancy compared to unexposed controls.

Methods: The National Pregnancy Registry for Psychiatric Medications (NPRPM) is a prospective pharmacovigilance program in which pregnant women with psychiatric diagnoses are enrolled during pregnancy and followed through the postpartum period. Labor and delivery and pediatric medical records are reviewed for evidence of major malformations followed by final adjudication by a dysmorphologist blinded to medication exposure. Infants with first-trimester exposure to cariprazine were compared to controls not exposed to second-generation antipsychotic medications.

Results: As of September 9, 2025, N=4125 have enrolled in the study. Of those enrolled, 58 cariprazine-exposed infants and 2098 infants in the comparison group were eligible for inclusion in analyses. There were no major malformations in the cariprazine-exposed group (absolute risk 0.00%; 95% confidence interval, 0.00–6.16%) compared to 32 infants with major malformations in the control group (1.53%; 1.05-2.15%).

Conclusions: This prospective cohort shows that 0/58 infants in the group exposed to cariprazine in the first trimester had major malformations compared to 32/2098 who were not exposed. Although these data are preliminary and cannot rule out modest teratogenic effects, they are nonetheless important to provide to health care providers and the public, as cariprazine use has been rising among women of reproductive age.

T104. ARTIFICIAL INTELLIGENCE–ASSISTED PARTICIPANT RECRUITMENT FOR PSYCHIATRIC CLINICAL TRIALS: A COMPARATIVE EVALUATION OF LEAD QUALITY AND ENGAGEMENT

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Abstract Background: Efficient participant recruitment remains a persistent challenge in psychiatric clinical trials. Conventional recruitment vendors frequently distribute shared pools of leads to multiple clinical sites with limited customization of screening criteria, potentially reducing the efficiency of identifying eligible participants. Artificial intelligence assisted recruitment strategies coupled with state-of-the-art media buying powers may improve participant identification by integrating targeted digital advertising with automated prescreening and engagement assessment.

Methods: Over a 16-week observational evaluation, CalNeuro Research Group assessed recruitment outcomes associated with an AI-driven recruitment vendor, Trial For Good. Trial For Good utilizes proprietary strategies to advertise psychiatric clinical research opportunities and direct prospective participants to an AI-guided prescreening interface. Participants provided self-reported clinical and demographic information, which was analyzed using AI-based algorithms designed to assess engagement patterns and estimate participant intent and anticipated reliability in site communication. Recruitment metrics, including engagement and lead quality, were compared with those obtained through centrally managed vendor campaigns previously utilized by the site.

Results: AI-assisted recruitment was associated with increased lead volume and higher participant engagement relative to traditional vendor campaigns. Leads generated through the AI-guided prescreening process demonstrated greater responsiveness and communication with the clinical site. Additionally, the AI-based model reduced the proportion of unqualified participants referred for site-level screening, thereby decreasing the prescreening burden on site staff and allowing greater allocation of resources to enroll participant visits and ongoing study procedures. Three metrics were used to quantify the success of Trial For Good: leads generated, screening visits, and randomizations. Over a 16-week period from November 3, 2025, to March 1, 2026, Trial For Good generated 353 leads, compared with an average of 68 leads from common vendors such as Radius365- Flex and Splash Clinical. From these Trial For Good leads, 123 subjects came onsite for a screening visit, whereas an average of 50 subjects from Radius365-Flex and Splash Clinical leads attended onsite screening during the same period. Trial For Good resulted in 6 randomizations, compared with an average of 2 randomizations from the other vendors. Additionally, 4 other subjects from Trial For Good met all screening eligibility criteria but were unable to randomize due to external circumstances.

Conclusions: AI-assisted recruitment and automated prescreening may enhance the efficiency of participant identification in psychiatric clinical trials. By evaluating engagement signals and participant-reported clinical information prior to site referral, AI systems may improve lead quality and reduce screening burden for high-enrolling research sites. Further evaluation is warranted to determine the impact of AI-driven recruitment strategies on enrollment timelines and study completion rates.

T105. ACTIVE AND PASSIVE DIGITAL PHENOTYPING TO MEASURE OUTCOMES IN A 12-MONTH STUDY OF XANOMELINE/ TROSPIUM CHLORIDE IN SCHIZOPHRENIA: LONGITUDINAL PREDICTION OF TOTAL CHANGES WITH EARLY LEVELS OF PHYSICAL ACTIVITY

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Abstract: Active and passive digital phenotyping hold substantial promise for refining measurement of treatment outcomes in clinical trials. These indices include actigraphy, global positioning, facial and vocal expression, as well as device-based ecological momentary assessment (EMA) surveys. In a large-scale (n=350) treatment study, we previously found that actigraphy-based step counts increased and the severity of indicators of avolition indexed with EMA decreased, with substantial intercorrelations. Previous observational digital phenotyping studies had shown that higher step counts longitudinally predicted better cognitive performance. Further, those studies also indicated that greater within-participant baseline variance in EMA-measured productive activities longitudinally predicted better functional outcome. Following the strategies of those earlier observational studies, step-count data collected early in a 12-month open label study of xanomeline/trospium chloride were evaluated for utility to predict overall EMA-measured treatment changes, with early variability in EMA survey responses as examined as additional predictors. Participants were 312 male and female outpatients with schizophrenia answering EMA surveys 3 times per day, 7 days per week, one week per month. On EMA survey days, participants wore an actigraph. EMAs queried location, social context, and activities. EMA-measured activities targeted behavioral indicators of avolition and were separated into recumbent, seated, standing, and moving. Participants answered 33,657 EMA surveys and provided 7957 participant-days of actigraphy. There were treatment-related reductions over 12 months in being home and alone, as well as decreases in sedentary activities and increases in standing and moving, (all $X^2 > 29.73$, $p < .002$). Steps increased in the same time period, ($X^2 = 33.10$, $p < .001$). Increased step counts correlated with decreased sedentary activities and increases in standing and moving over the treatment period, (all $X^2 > 40.59$, $p < .001$). HLM analyses indicated that step counts in the first 2 months predicted overall changes in all 4 EMA activity variables, (all $X^2 > 6.49$, $p < .01$), above and beyond the effects of time in treatment. Early within-participant variance in activity variables did not predict longitudinal changes, but within-participant variance decreased for all EMA variables (all $X^2 > 51.57$, all $p < .001$) and reductions in variance were concurrently correlated with decreased severity of sedentary activities and increased standing and moving over the entire treatment period (All $X^2 > 228.48$, $p < .001$). Indices of physical activity measured early in a 12-month treatment study with passive digital strategies predicted study-long treatment response, suggesting that physical activity is a factor worth considering in future studies. Behavioral indices of avolition, indexed by their level of physical demands, decreased both in severity and in within-subject variance, suggesting improvements across both severity and variability indices. These two factors can index both the magnitude and momentary consistency of treatment response. Concurrent measurement of both level and variance of different treatment outcomes would not be possible without momentary digital phenotyping. The convergence of easily collected passive digital data and active EMA survey data allow for broader assessment of treatment related improvements in everyday activities and functioning than

legacy clinical assessment strategies and may predict be able to measure long-term outcomes of developing treatment strategies.

T106. EXOSOMES AND A NOVEL MITOCHONDRIAL MECHANISM OF EPIGENETIC REGULATION OF BRAIN PLASTICITY IN TREATMENT RESISTANT DEPRESSION

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Abstract: Treatment resistant depression (TRD) is a leading cause of disability worldwide; there is a dearth of new mechanistic models for the development of better therapeutic strategies. Our group provided the first evidence that boosting mitochondrial metabolism of acetyl-L-carnitine (LAC) leads to a rapid and long-lasting antidepressant response in multiple rodent models by activating epigenetic processes of histone acetylation. Our translational work showed decreased levels of this pivotal mitochondrial metabolite LAC in clinical phenotypes of depression linked to childhood trauma and insulin resistance. Unlike the role of systemic mitochondrial metabolism, molecular mechanisms of brain mitochondrial metabolism and the related epigenetic pathways in TRD remain to be determined. Here, we isolated neuronal exosomes from plasma of healthy control subjects and subjects with TRD in the context of transcranial magnetic brain stimulation (TMS). Subsequently, we characterized key molecular markers of mitochondrial metabolism and the related pathways. Ongoing analyses showed a link between a key mitochondrial marker assayed in neuronal exosomes and a treatment resistant course of illness (n=93, p < 0.05). These findings were specific to neuronal exosomes as no association was found in total (not neuronally-enriched) exosomes (p=0.7). These phenotypes are also characterized by corresponding changes in the levels of key epigenetic markers important for histone acetylation. Ongoing experiments are aimed at determining the role of this pathway in the responses to TMS. In all, these findings suggest that mitochondrial metabolism has important effects on epigenetic processes in patients with TRD and point to a novel model of mitochondrial-related epigenetic regulation as a mechanistic target for the rapid regulation of plasticity.

T107. PERSPECTIVES OF NURSE PRACTITIONERS AND PHYSICIAN ASSOCIATES ON PRESENTING LONG-ACTING INJECTABLES TO ADULTS WITH SCHIZOPHRENIA: A DELPHI PANEL STUDY

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Abstract Purpose: Healthcare providers (HCPs), including nurse practitioners (NPs) and physician associates (PAs), commonly prescribe oral antipsychotics (APs) to treat adults with schizophrenia, but daily administration requirements can present adherence challenges and limit clinical effectiveness. While long-acting injectable (LAI) APs have demonstrated improved AP adherence and clinical outcomes (e.g., reduced hospitalizations and relapses) compared with oral APs, they remain infrequently prescribed due to stigma, patient concerns and misconceptions about LAIs, and reimbursement constraints, along with limited HCP/patient awareness.

Objective: This study aims to achieve consensus on strategies for HCPs to discuss and offer LAIs to adults with schizophrenia, promote acceptance among eligible patients, and accelerate utilization of LAIs earlier in the treatment journey. This study addresses a critical knowledge gap by focusing on NP and PA perspectives, whose central roles in schizophrenia treatment and management have been underrepresented in prior research.

Methodology: A 3-round double-blinded modified Delphi panel was convened, composed of NPs and PAs specializing in the treatment of adults with schizophrenia and use of LAIs in the United States. Round 1 was composed of individual 90-minute opinion-based interviews informed by literature review and expert NP, PA, psychiatrist, and patient perspectives. Insights were used to develop preliminary consensus statements for Round 2, which was a 30-minute online survey. Panelists rated their level of agreement on a 5-point Likert scale and provided feedback on the proposed statements. Round 3, in progress at the time of this submission, is a 30-minute online survey where panelists will re-rate modified statements based on Round 2 feedback. Percent agreement was defined as the proportion of panelists who responded “strongly agree” or “agree” to a given statement. Consensus was defined a priori as $\geq 50\%$ agreement (50-79%: moderate consensus, $\geq 80\%$: strong consensus, 100%: unanimous).

Results: 12 panelists participated in Rounds 1 and 2 (92% NPs, 83% female, 50% non-White). Panelists had experience in inpatient and outpatient settings, providing both in-person and telepsychiatry services, with varied tenure treating adults with schizophrenia (median: 10 years, range: 2-18 years). All 29 statements in Round 2 achieved consensus (26 strong, 7 unanimous, 3 moderate). Key HCP-related barriers to successful LAI offers included limited infrastructure for on-site LAI administration and lack of familiarity with LAIs. Perceived patient-related barriers to timely LAI initiation were concerns and misconceptions about injectable medications, insurance coverage restrictions, and transportation challenges. To address patient-related barriers, there was strong alignment on offering LAIs proactively and often in the schizophrenia treatment journey, centering conversations on patient experience, personal goals, autonomy, and both peer-to-peer and HCP-patient knowledge sharing. Panelists agreed that training on-site staff, investing in LAI inventory, and fostering external partnerships can help to overcome both patient- and HCP-related barriers, in addition to providing education on clinical and logistical aspects of LAI prescribing to HCPs.

Conclusions: These interim results highlight strong alignment among NPs and PAs specializing in the care of adults with schizophrenia on best practices for engaging in patient-centered discussions surrounding LAIs. These insights reflect actionable strategies for overcoming barriers to early LAI prescribing that can be leveraged by HCPs with all levels of experience with LAIs.

T108. A NOVEL, BRAIN PENETRANT KAT-II INHIBITOR, KYN-5356, REDUCES BRAIN KYNURENIC ACID LEVELS AND ENHANCES GLUTAMATERGIC AND CHOLINERGIC TRANSMISSION

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Abstract Background: Dysregulation of the kynurenine pathway of tryptophan degradation has been implicated in a number of psychiatric and neurological disorders. In the brain, the enzyme kynurenine aminotransferase II (KAT-II) is critical for the conversion of L-kynurenine (L-KYN) to kynurenic acid (KYNA). KYNA, in turn, is an endogenous inhibitor of nicotinic alpha-7 and NMDA receptors, both of which are critical for cognition. Elevated KYNA levels have been consistently reported in the brain and cerebrospinal fluid (CSF) of individuals with schizophrenia and may impair cognitive function in the disease. Preclinical data show that KYNA bi-directionally modulates cognition, with increased KYNA impairing and reduced KYNA improving cognition. Thus, targeted inhibition of KAT-II may have beneficial effects on cognitive function in humans. KYN-5356 is a novel, potent, brain-penetrant, reversible, and selective KAT-II inhibitor in development for Cognitive Impairment Associated with Schizophrenia (CIAS). Here, we present preclinical proof of concept data evaluating the effect of KYN-5356 on KYNA levels and on neurotransmitter systems relevant for cognition.

Methods: Studies were conducted in cynomolgus monkeys and marmosets. The effect of systemic administration of KYN-5356 on KYNA levels was assessed following exogenous administration of L-KYN. Acetylcholine levels were measured in the hippocampus by in vivo microdialysis. The ability of KYN-5356 to enhance cholinergic transmission was also evaluated by electroencephalography (EEG) using the scopolamine reversal model.

Results: KYN-5356 showed adequate bioavailability, brain penetration and a favorable temporal pharmacokinetic profile. As expected, L-KYN administration significantly increased brain and CSF KYNA. KYN-5356 dose-dependently reduced the KYNA/L-KYN ratio in hippocampus and prefrontal cortex, by as much as 50% at the highest dose tested. In separate experiments, a microdialysis probe was inserted in the hippocampus of cynomolgus monkeys. Local infusion of KYN-5356 produced a robust and steady increase in extracellular acetylcholine levels. To assess impact on functional networks, animals were implanted with EEG electrodes. KYN-5356 strongly increased cognitively relevant alpha and beta band activity. Consistent with preclinical and clinical studies, scopolamine, a potent muscarinic blocker, produced a significant increase in delta and theta activity, and KYN-5356 significantly attenuated its effect. Specifically, the effect of scopolamine on delta activity was reduced by more than 50%, while the effect on theta band was nearly completely blocked. This shows that KYN-5356 robustly enhances cholinergic transmission, suggesting that the effect of the drug is not limited to disinhibition of alpha-7 nicotinic receptors.

Discussion: KYN-5356 is a potent, brain-penetrant small molecule suitable for clinical development. KYN-5356 effectively and dose-dependently reduced KYNA levels in the brain. We elucidated a multimodal mechanism of action for KYN-5356 with neurochemical and electrophysiological effects indicative of enhanced cholinergic and glutamatergic transmission. Thus, KYN-5356 is a highly suitable candidate for the treatment of cognitive dysfunction in a range of psychiatric and neurological disorders. A first in human clinical

study with KYN-5356 was recently completed, and the compound is currently being evaluated in a proof of concept study in CIAS.

T109. RACIAL DIFFERENCES IN ANTIDEPRESSANT INITIATION AND OUTCOMES AFTER A ONE-TIME PSYCHIATRIC CONSULTATION: A MIXED-METHODS STUDY

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Abstract Background: Many patients with major depressive disorder (MDD) access psychiatric care through a one-time psychiatric consultation and are referred back to their primary care provider (PCP) for treatment. Racial disparities in antidepressant outcomes are well documented, but it is unclear whether inequities emerge within this transition.

Methods: Adults diagnosed with MDD at a large urban academic mental health hospital were followed for three months after a one-time psychiatric consultation. The primary outcome was implementation of at least one recommended antidepressant initiation or change. Secondary outcome was symptom improvement. Pre-specified moderators included gender, income, discrimination in medical settings, beliefs about depression care, and adherence. Logistic and linear regression analyses were conducted. Categorical principal component analysis (CATPCA) was conducted to identify unsupervised clustering of variables (loadings $\geq |0.4|$ considered meaningful; Cronbach $\alpha > 0.7$ indicating acceptable internal consistency). Qualitative analysis of interview transcripts was conducted using constructivist grounded theory and mapped onto the Capability, Opportunity, Motivation–Behavior (COM-B) framework.

Results: Fifty-six participants (28 BIPOC; 28 Caucasian) completed questionnaires and chart review. Of the 56, 24 completed semi-structured interviews. Overall, 75% implemented at least one recommended antidepressant initiation or change; 93% of these changes occurred within one month. This did not differ by race ($\chi^2=1.0$, $p=0.31$). Mean PHQ-9 decreased by 2.8 ± 6.6 points ($N=51$), which also did not differ by race ($F_{1,49}=0.6$, $p=0.43$). Moderation analyses were negative. CATPCA identified four dimensions, of which 2 were associated with race: first dimension clustered Caucasian identity with higher socioeconomic status, older age, and perceiving depression as impactful; second dimension clustered Caucasian identity with following treatment recommendations, adherence, interest in medication, positive consultation experience, and more comprehensive documentation. The primary outcome did not cluster with race. Qualitative analysis identified capability barriers (limited mental health literacy), opportunity barriers (rushed encounters, misalignment with providers), and motivation barriers (perceived harm, stigma, doubts about effectiveness) in both groups. Racialized participants more frequently described systemic misalignment and internalized stigma, while Caucasian participants more frequently described financial barriers.

Conclusions: Although no racial differences were observed in early antidepressant uptake or treatment outcomes, unsupervised machine learning analysis and qualitative findings reveal structural and experiential inequities.

T110. EFFICACY AND SAFETY OF COMP360 PSILOCYBIN FOR TREATMENT-RESISTANT DEPRESSION (TRD) IN TWO PHASE 3 DOUBLE-BLIND RANDOMIZED CONTROLLED STUDIES

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Abstract: COMP360 is a novel, proprietary, synthetic formulation of psilocybin being investigated for treatment-resistant depression (TRD) and post-traumatic stress disorder. COMP 005 and COMP 006 are multi-center, randomized, double-blind, controlled phase 3 studies investigating the efficacy, safety, and tolerability of COMP360 monotherapy in adults with TRD. We investigated the efficacy and safety of COMP360 in the first six weeks (primary endpoint) following either one (COMP 005) or two (COMP 006) administrations.

Methods: Adult participants were enrolled after meeting study eligibility, including presence of TRD as defined as having experienced 2–4 inadequate responses to prior treatments during their current depressive episode. Participants in COMP 005 were randomized in a 2:1 ratio to receive a single administration of either COMP360 25 mg or placebo. Participants in COMP 006 were randomized in a 2:1:1 ratio to receive two doses (3 weeks apart) of COMP360 25 mg, 10 mg, or 1 mg. The primary endpoint for both studies was change in MADRS total score from baseline to Week 6.

Results: For COMP 005, 258 participants were dosed with either COMP360 25 mg (n=171) or placebo (n=87). The primary endpoint was achieved: the least square mean (LSM) change from baseline MADRS total score at week 6 was significantly greater in participants receiving a single administration of COMP360 25 mg than in those receiving placebo ($p < 0.001$) with an LSM difference (LSMD) of -3.6 [95% confidence interval (CI): -5.7, -1.5]. All time points measured reached statistical significance from the day after dosing (Day 2) onwards. For COMP 006, 581 participants were dosed to either COMP360 25 mg (n=296), 10 mg (n=142), or 1 mg (n=143). The primary endpoint was achieved: the LSM change from baseline MADRS total score at week 6 was significantly greater in participants receiving two doses of COMP360 25 mg than those receiving 1 mg ($p < 0.001$) with an LSMD of -3.8 (CI: -5.8, -1.8). The COMP360 10 mg group showed a smaller difference than 25 mg when compared to the 1 mg group (LSMD of -2.5, CI: -4.9, -0.2; $p=0.016$). All time points measured reached statistical significance from the day after dosing (Day 2) onwards for both the COMP360 25 mg and 10 mg groups compared to the 1 mg. The adverse event (AE) profile for COMP 005 and COMP 006 is consistent with the known profile of COMP360 psilocybin, where most treatment-emergent AEs (TEAEs) occurred on the day of administration (65.6% and 68.3%, respectively) and resolved within 1 day (88% and 84.3%, respectively). The most common TEAEs included headache, nausea, hallucination (visual), and anxiety. In the 25 mg arm, there were 5 treatment-emergent serious AEs (SAEs) from 4 participants (2.3% overall) in COMP 005, and 6 treatment-emergent SAEs from 6 participants (2% overall) in COMP 006. The Data and Safety Monitoring Board noted that there is no evidence, to date, of a clinically meaningful imbalance between treatment arms in suicidality in either study.

Discussion: COMP360 25 mg rapidly and meaningfully reduces depressive symptoms in adults with TRD across both single- and two-dose paradigms, with a possible added benefit seen after a second dose in COMP 006. Across COMP 005 and COMP 006 to date,

COMP360 is demonstrating a generally well-tolerated and safe profile, with most of the TEAEs occurring on the day of drug administration and the majority resolving within one day. Notably, the absence of a meaningful suicidality imbalance among groups, to date, are clinically reassuring in this high-risk population.

T111. ESKETAMINE NASAL SPRAY FOR RELAPSE PREVENTION IN PATIENTS WITH TREATMENT-RESISTANT DEPRESSION: A POST HOC ANALYSIS OF PREDICTORS OF RELAPSE IN PLACEBO-TREATED PATIENTS IN SUSTAIN-1

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Abstract Background: SUSTAIN-1 (NCT02493868) was a phase 3, double-blind, multicenter, randomized withdrawal study evaluating the efficacy of continuing esketamine nasal spray plus an oral antidepressant (ESK+OAD) versus placebo nasal spray plus an OAD (PBO+OAD) in delaying relapse among adults with treatment-resistant depression (TRD). In this post hoc analysis, we evaluated the potential predictors of relapse among patients randomly assigned to the PBO+OAD arm of SUSTAIN-1, focusing on baseline demographics and disease-related characteristics that may increase vulnerability to relapse following discontinuation of ESK.

Methods: This analysis included patients who completed induction and optimization with ESK+OAD, achieved stable remission, and were subsequently randomly assigned to discontinue ESK and receive PBO+OAD, rather than continue ESK+OAD treatment, during the maintenance phase. Relapse was defined per criteria in the SUSTAIN-1 protocol (Montgomery-Åsberg Depression Rating Scale total score ≥ 22 for 2 consecutive assessments and/or hospitalization for worsening depression or any other clinically relevant event). We used an exploratory approach, evaluating 45 candidate predictors (baseline demographic characteristics and psychiatric history) chosen from the literature and authors' clinical judgment. Initial screening used univariate Cox proportional hazards models; variables with nominal significance ($p < 0.3$) were advanced (no multiplicity adjustment). To identify independent predictors given the heterogeneity of TRD, those candidate predictors were entered into a stepwise multivariable Cox proportional hazards model, with candidates entered sequentially and removed if they became nonsignificant; the final model retained predictors with $p < 0.05$. Hazard ratios and 95% confidence intervals are reported.

Results: Patients in stable remission who discontinued ESK and received PBO+OAD experienced a higher risk of relapse compared with those who continued ESK+OAD treatment (ESK+OAD vs PBO+OAD, HR 0.49, 95% CI: 0.29, 0.84). Of 176 patients in stable remission, 45.3% of patients in the PBO+OAD arm experienced relapse ($n = 39/86$) compared with 26.7% of patients in the ESK+OAD arm ($n = 24/90$). In the PBO+OAD arm, risk of relapse was associated with number of prior unsuccessful antidepressant treatments (2 vs ≥ 3 ; HR 0.45; 95% CI: 0.22, 0.93; $P = 0.030$), Columbia-Suicide Severity Rating Scale score at screening (lifetime history of suicidal behavior vs no event; HR 4.38; 95% CI: 1.14, 16.83; $P = 0.032$), and baseline Clinical Global Impression-Severity (CGI-S) scale category (markedly ill vs mildly and moderately ill; HR 16.62; 95% CI 2.09, 131.89; $P = 0.008$; only 1 patient experienced relapse in the CGI-S mildly and moderately ill category).

Conclusions: This post hoc analysis identifies potential baseline clinical factors that could be associated with higher risk of relapse following discontinuation of ESK among patients with

TRD. These results support continued ESK treatment or more vigilant monitoring strategies for patients who have ≥ 3 prior antidepressant treatments, have a lifetime history of suicidal behavior, or are categorized as CGI-S “markedly ill,” as they have a higher risk of relapse.

T112. VALIDATION OF THE NEUROKIT PLATFORM FOR CENTRAL NERVOUS SYSTEM PHARMACODYNAMIC ASSESSMENT IN HEALTHY VOLUNTEERS

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Abstract Background: Quantifying pharmacodynamic (PD) effects of central nervous system (CNS) active compounds in early-phase clinical development requires sensitive and reproducible neurophysiological and neuropsychological assessments. The NeuroCart test battery has demonstrated the ability to quantify CNS drug effects across multiple functional domains but relies on specialized infrastructure that limits broader deployment. NeuroKit is a portable adaptation of NeuroCart designed to maintain sensitivity to CNS pharmacologic effects while enabling scalability across clinical research settings. This study is the second part in a two-part validation study that evaluates the reliability and external validity of NeuroKit when implemented at an independent US research site and compared against established data from the first in-house validation study. With the first study concluding validity against the NeuroCart, this second study aims to demonstrate reproducibility in an off-site setting.

Methods: This ongoing study is a randomized, double-blind, placebo-controlled, three-period crossover validation trial conducted in healthy adults aged 18 to 45 years at Clinical Pharmacology of Miami (CPMI). Sixteen participants receive single oral doses of lorazepam 2mg, modafinil 200mg, and placebo across three treatment periods, separated by 7-10 day washouts. NeuroKit assessments are performed at baseline and multiple post-dose timepoints aligned in time with those performed during the first part of the validation study at the Centre for Human Drug Research. The tests measure CNS PD effects across several domains, including saccadic eye movements (arousal), adaptive tracking (visuomotor coordination, sustained attention), finger tapping (fine motor performance; visuomotor coordination), smooth pursuit (visuomotor coordination), body sway (postural balance), N-back (working memory), VAS Bond and Lader and VAS Bowdle (subjective effects). CPMI data will be compared with reference results from the CHDR study using mixed-effects modeling to assess between-site reliability and equivalence of PD outcomes. All parameters will be log-transformed before analysis, to express the differences between the sites as ratios and estimate the 90% confidence interval (CI) around the ratio. The analysis will commence with the full model including the treatment, time, treatment by time, site (CPMI/CHDR), treatment by site, site by time and treatment by site by time as fixed factors, and participant, participant by treatment, and participant by time as random factors and the average baseline measurement per treatment period as covariate.

Results: Primary outcomes include NeuroKit-derived PD measures sensitive to sedation and stimulation, including saccadic reaction time, saccadic peak velocity, smooth pursuit performance, adaptive tracking accuracy, working memory performance, body sway, and psychomotor function. Analyses will evaluate effect sizes for drug-induced changes and assess whether PD responses observed at CPMI replicate previously characterized CNS effects of lorazepam and modafinil observed at CHDR.

Conclusions: This study aims to establish the reproducibility and external validity of the NeuroKit platform outside its development site. Demonstrating equivalence between CPMI and CHDR datasets would support the use of NeuroKit as a scalable tool for PD profiling of CNS-active compounds in early-phase clinical trials. Successful validation would enable broader availability of standardized CNS biomarker assessments, increase their application in clinical trials with patients and strengthen the translational assessment of novel therapeutics.

T113. CONNECTEDNESS AS A MECHANISM OF CHANGE IN PSILOCYBIN-ASSISTED COGNITIVE BEHAVIORAL THERAPY

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Abstract Background: Psilocybin-assisted therapy has shown robust antidepressant effects among individuals with major depressive disorder (MDD); however, mechanisms of the treatment remain unclear. While depression has been conceptualized as a disorder of disconnection, psilocybin is thought to facilitate connectedness. This analysis of an open-label trial of psilocybin-assisted cognitive behavioral therapy (PA-CBT) examined changes in connectedness over the treatment and its associations with depressive symptoms and psychosocial functioning.

Methods: Adults with MDD were enrolled in PA-CBT, which included twelve psychotherapy sessions and two psilocybin sessions (10 mg, 25 mg) over 4 months and were followed for 3 months post-treatment. Connectedness was measured using the Watts Connectedness Scale, depressive symptoms with the Hamilton Depression Rating Scale, and psychosocial functioning with the Global Assessment of Functioning. Linear mixed-effects regression models examined changes over time in connectedness and its associations with depressive symptoms and psychosocial functioning. Connectedness was also examined as a mediator in the relationship between psychedelic effects (mystical experiences and psychological insights) and depressive symptoms.

Results: Among fifteen participants, connectedness increased significantly from baseline to post-treatment (Hedges' $g = 0.62$), though these changes were not sustained at follow-up. Higher connectedness over the treatment period was associated with improved depressive symptoms and psychosocial functioning across the seven-month study ($p < 0.001$). Increased connectedness from baseline to post-treatment predicted improved depressive and functioning outcomes at follow-up, controlling for baseline scores. There was preliminary evidence of connectedness as a mediator between psychedelic effects and depressive symptom improvement.

Conclusion: This study provides further quantitative evidence that connectedness may be a mechanism by which psilocybin treatment benefits individuals with MDD. Future larger randomized controlled trials, including our ongoing trial comparing PA-CBT to standard psilocybin-assisted therapy, are needed to clarify whether connectedness functions as a treatment-specific mechanism and to develop interventions that sustain connectedness over time.

T114. NEXT-GENERATION PHARMACOTHERAPIES FOR MOOD AND ANXIETY DISORDERS: A COMPREHENSIVE REVIEW OF PHASE II/III DRUG DEVELOPMENT ACROSS DIVERSE MECHANISMS

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Abstract: Despite the high global burden of mood and anxiety disorders, there remains a substantial unmet need for effective, mechanistically distinct treatments, as approximately 30% of patients fail to respond to standard antidepressants. Over the past 15 years, drug development has shifted away from traditional monoaminergic approaches toward glutamatergic, neuroplastic, ion channel, and other novel mechanisms. This presentation provides a structured synthesis of Phase II/III industry-sponsored clinical trials active within the past three years targeting mood and anxiety disorders, drawing on data from press releases, published abstracts, MEDLINE, and entries from the U.S. ClinicalTrials.gov registry. We categorize investigational agents into four mechanistic domains—glutamatergic/GABA modulators, ion channel modulators, psychedelic and psychedelic-like compounds, and other novel targets—and summarize key efficacy signals, durability outcomes, safety considerations, and trial design features. Several late-stage compounds demonstrate promising efficacy for treatment-resistant depressive and anxiety disorders. For example, in a Phase II trial, osavampator, an AMPA receptor positive allosteric modulator (PAM), demonstrated a -7.5 Montgomery-Åsberg Depression Rating Scale (MADRS) reduction at day 56 ($p = 0.0016$) for the 1mg dose compared to placebo in patients with Major Depressive Disorder (MDD). In the psychedelic space, COMP360 (psilocybin) demonstrated a placebo-adjusted MADRS reduction of 3.6 points at week 6 in a Phase III trial ($p < 0.001$), with confirmatory findings from a second Phase III study showing a 3.8-point placebo-adjusted improvement following two 25 mg doses. MM120 (LSD) demonstrated significant reductions in Hamilton Anxiety Rating Scale (HAM-A) scores at week 4 (-5.0 to -6.0 points across higher doses), supporting its potential as a rapid-acting treatment for generalized anxiety disorder (GAD). Additionally, the novel compound fasedienol met its primary endpoint in a Phase III trial, demonstrating significant reductions in public speaking anxiety (-5.8 Subjective Units of Distress Scale [SUDS], $p = 0.015$). Across mechanisms, emerging findings suggest rapid-onset antidepressant effects, potential improvements in treatment-resistant populations, and growing interest in short-duration or event-driven pharmacologic paradigms. Nonetheless, persistent challenges remain, including approaching therapeutics where functional unblinding may occur, how to consider a novel conceptualization of occupancy-driven v. event-driven pharmacology, and the role of supporting psychotherapy. Taken together, this presentation clarifies emerging patterns across mechanisms while outlining the key methodological and translational challenges that will determine whether these novel therapies can be implemented at scale.

T115. OPEN-LABEL, RANDOMIZED STUDY TO ASSESS SAFETY AND EFFICACY OF SLOW AND ACCELERATED SWITCHING TO XANOMELINE/TROSPIMUM FROM STANDARD OF CARE ATYPICAL ANTIPSYCHOTICS IN PARTICIPANTS WITH SCHIZOPHRENIA

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Abstract: Antipsychotic (AP) medications may cause significant side effects resulting in treatment discontinuation and relapse. Xanomeline/trospium chloride (KarXT), a dual M1/M4 muscarinic receptor agonist combined with a peripheral pan muscarinic receptor antagonist, does not block D2 dopamine receptors, potentially lowering the risk of cardiometabolic and extrapyramidal adverse events (AEs). Medication switching is common among those with schizophrenia, and healthcare providers may benefit from clinical data on how to switch patients from APs to KarXT.

Methods: This 8-week, multicenter, randomized, open-label, outpatient trial assessed the efficacy and safety of a switch from atypical APs to KarXT monotherapy in adults aged 18-65 years with schizophrenia based on DSM-5 criteria. Participants were randomized 1:1 to 2 treatment groups: slower transition from AP to KarXT over 4 weeks (25% reduction in AP dose/week) or faster transition from AP to KarXT over 2 weeks (50% reduction in AP dose/week). Participants in both treatment groups followed the same KarXT titration schedule and were initiated at KarXT 50 mg/20 mg (xanomeline/trospium) twice daily for 7 days then titrated to 100 mg/20 mg twice daily for 7 days. If tolerated, participants could then titrate to a maximum dose of 125 mg/30 mg on day 15. The primary endpoint was all-cause discontinuation of KarXT. Secondary endpoints included change from baseline to week 8 in Positive and Negative Syndrome Scale (PANSS), Clinical Global Impressions-Severity (CGI-S), and Personal and Social Performance (PSP) scores. Secondary safety endpoints were KarXT AE-related discontinuation and AE incidence. Results from the trial were based on descriptive analyses and stratified by prior AP (-pine APs [pAPs, olanzapine/quetiapine] or non-pine APs [npAPs, aripiprazole/lurasidone/risperidone]) at the time of switching.

Results: A total of 53 participants (52 with AP data) were enrolled in the slower transition group (pAPs: n=35; npAPs: n=17) and 52 in the faster transition group (pAPs: n=31; npAPs: n=21). Approximately 86% of participants completed 8 weeks of treatment, with discontinuation rates of 15.1% (pAPs: 11.4%; npAPs: 17.6%) and 13.5% (pAPs: 12.9%; npAPs: 14.3%) in the slower and faster transition groups, respectively. No participant discontinued due to lack of efficacy. Mean changes in PANSS total scores from baseline to week 8 were -4.2 in the slower transition group (pAPs: -3.7; npAPs: -5.8) and -3.1 in the faster transition group (pAPs: -2.8; npAPs: -3.4). Mean change in CGI-S scores was -0.2 in both the slower (pAPs: -0.2; npAPs: -0.3) and faster (pAPs: -0.1; npAPs: -0.3) transition groups. From baseline to week 8, mean PSP scores increased by 1.1 (pAPs: 1.3; npAPs: 1.0) and 0.7 (pAPs: 0.0; npAPs: 2.0) in the slower and faster transition groups, respectively. Forty-nine percent of participants (pAPs: 50.0%; npAPs: 47.4%) had ≥ 1 treatment-emergent AE (TEAE); none were serious. TEAE rates were consistent with pooled analyses from EMERGENT-1-3. In the slower and faster transition groups, 1.9% and 3.8%, respectively, discontinued treatment early due to TEAEs.

Conclusions: Overall, both slower (4 week) and faster (2 week) transitions from atypical APs to KarXT were generally safe and effective among participants with schizophrenia, suggesting that either transition method may be considered. These results may aid clinical decision-making, providing evidence-based guidance on how to switch to KarXT from oral atypical APs.

T116. FROM NIGHTMARES TO DEPRESSION: AGE-STRATIFIED NEUROPSYCHIATRIC EFFECTS OF MONTELUKAST

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Abstract: Purpose: To evaluate whether neuropsychiatric adverse drug reactions (ADRs) associated with montelukast demonstrate age-stratified symptom patterns and to examine developmental neurobiological mechanisms that may explain differential vulnerability across pediatric populations.

Content: Montelukast, a cysteinyl leukotriene receptor antagonist widely prescribed for asthma and allergic rhinitis, has been associated with neuropsychiatric ADRs including sleep disturbances, agitation, anxiety, depression, and rare psychotic reactions. In 2020, the U.S. Food and Drug Administration issued a boxed warning highlighting serious mental health risks. Pharmacovigilance analyses suggest that these ADRs follow a developmentally patterned presentation. Infants and younger children most frequently exhibit sleep disturbances such as nightmares, night terrors, and insomnia, whereas adolescents more commonly present with internalizing psychiatric symptoms including depression, anxiety, and suicidal ideation. Developmental neurobiology may help explain this pattern. In early childhood, increased blood–brain barrier permeability and immature serotonergic circadian regulatory systems may increase susceptibility to sleep disruption when leukotriene signaling is altered. During adolescence, maturation of corticolimbic circuits involved in emotional regulation—including serotonergic, dopaminergic, and glutamatergic systems—may increase vulnerability to affective symptoms when neuroinflammatory signaling pathways are disrupted.

Methods: A systematic search of PubMed, PMC, and pharmacovigilance databases was conducted for studies examining montelukast-associated neuropsychiatric events across pediatric and adult populations. Twelve key studies published between 2015 and 2025 were identified and synthesized.

Results: Across pharmacovigilance datasets and observational studies, neuropsychiatric ADR reporting was consistently higher in pediatric montelukast users than in adults. Younger children were disproportionately represented in reports of nightmares, night terrors, and insomnia, often emerging within days of treatment initiation. A multicenter pediatric cohort study reported increases in neuropsychiatric symptom reporting from 14.8% at baseline to 34.3% after one month of treatment. A large population-based case-crossover study involving over 160,000 pediatric patients found a 28–38% increased risk of neuropsychiatric events following montelukast exposure. Adolescents more frequently demonstrated internalizing psychiatric symptoms including depression and anxiety. Although some large registry-based studies have reported no significant association between montelukast and neuropsychiatric outcomes, the developmental distribution of symptom types remains relatively consistent across multiple pharmacovigilance datasets.

Importance: Recognition of developmentally patterned neuropsychiatric ADRs has important implications for clinical practice. Sleep disturbances in younger children may represent early warning signs of medication-related central nervous system effects, while mood or behavioral changes may be more prominent in adolescents. Understanding these age-specific vulnerability patterns may improve patient counseling, monitoring, and risk-benefit decision-making when prescribing montelukast in pediatric populations. These

findings also highlight the need for prospective age-stratified pharmacoepidemiologic studies to better define neuropsychiatric risk associated with leukotriene receptor antagonists.

T117. IMPROVEMENT OF PREDOMINANT NEGATIVE SYMPTOMS IN PATIENTS WITH SCHIZOPHRENIA ON PALIPERIDONE PALMITATE 6-MONTH LONG-ACTING INJECTABLE: POST-HOC ANALYSIS OVER 3 YEARS

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Abstract Background: Schizophrenia is an often debilitating disorder with persistent negative symptoms, cognitive impairments and functional deficits, which are key contributors to long-term disability. Negative symptoms often persist long-term, and their remission is critical for functional recovery. Paliperidone palmitate 6-month formulation (PP6M) has demonstrated efficacy in preventing relapse in patients with schizophrenia. This post-hoc analysis of phase 3 studies assessed the effect of PP6M over 1–3 years in patients with predominant negative symptoms (PNS).

Methods: Adults previously stabilized on PP1M or PP3M in a 12-month (M) phase 3 noninferiority double-blind (DB) study (NCT03345342), who completed the DB phase without relapse, and continued on PP6M in a 24M single-arm, open-label extension (OLE; NCT04072575) study, were analyzed. Improvements in the Positive and Negative Syndrome Scale for Negative Subscale Score (PANSS-NSS) and Negative Symptoms Factor Score (PANSS-NSFS), secondary negative symptoms (SNS; Disorganized Thoughts, Uncontrolled Hostility-Excitement, and Anxiety-Depression), Personal and Social Performance (PSP), and PANSS total score over 36M were assessed in a subset of pts with PNS from DB and OLE phases. PNS was defined as a clinically meaningful elevation of negative-symptom severity (≥ 2 items in the moderate or greater range [≥ 4]) and a global negative symptom burden exceeding a predefined threshold (sum score > 20), while positive and depressive symptoms remained low/ $<$ moderate [< 4].

Results: Of 701 patients from the DB phase, 87 had PNS (mean[SD] age: 41.6 (11.93) years; 71.3% male) of which 80 completed the DB phase; 31 patients continued PP6M in the OLE.

At baseline (BL), the mean (SE) PANSS NSS was 20.8 (0.26; n=86). Scores improved to 18.4 (0.43; n=80) at 12M, a mean (SE) change from baseline (CFB) was -2.3 (0.36; 95% CI: $-3.03, -1.60$; $p < 0.001$), and further improved to 16.3 (0.84; n=23) at 36M (mean [SE] CFB: -3.9 [0.91; 95% CI: $-5.75 -1.98$]; $p < 0.001$). Median (range) CFB in PANSS NSS were -2.0 ($-10, 6$) at 12M and -5.0 ($-11, 7$) at 36M. At BL, the mean (SE) PANSS NSFS was 19.7 (0.25; n=86). Scores improved to 16.7 (0.40; n=80) at 12M, with a mean (SE) CFB of -3.0 (0.37; 95% CI: $-3.70, -2.23$; $p < 0.001$) and were maintained through 36M at 15.1 (0.83; n=23). Median (range) CFB in PANSS NSFS were -2.0 ($-11, 6$) at 12M and -5.0 ($-12, 7$) at 36M. Mean (SE) CFB to 36M (n=22) in SNS were minimal for Disorganized Thoughts (-2.9 [0.56; 95% CI: $-4.08, -1.74$; $p < 0.001$], from BL of 15.2 [0.34]); for Uncontrolled Hostility-Excitement (0.0 [0.34; 95% CI: $-0.66, 0.75$; $p=0.894$], from BL of 4.7 [0.10]); and for Anxiety-Depression (-0.9 [0.50; 95% CI: $-1.96, 0.14$; $p=0.086$], from BL of 5.4 [0.19]). The mean (SE) BL PANSS total score was 58.5 (0.68). Mean (SE) CFB at 12M: -5.0 (0.76), 95% CI ($-6.54, -3.51$) $p < 0.001$, improved to -9.5 (1.76), 95% CI ($-13.21,$

–5.88), $p < 0.001$ at 36M; median (range) CFB 12M: –4.0 (–22, 13), 36M: –12.5 (–21, 6). The mean (SE) BL PSP total score was 59.0 (1.18). Mean (SE) CFB to 12M was 4.9 (0.84; 95% CI: 3.18, 6.52; $p < 0.001$), increasing to 10.5 (2.09; 95% CI: 6.21, 14.87; $p < 0.001$) at 36M. Median (range) CFB in PSP were 4.0 (–9, 27) at 12M and 10.5 (–5, 33) at 36M.

Conclusion: In patients with PNS, significant reductions were observed in PANSS NSS and PANSS NSFS, with improvements maintained through long term follow up of 1–3 years. Corresponding significant improvements in PSP scores demonstrated meaningful enhancement in personal and social functioning. Together, these findings support that the PP6M treatment was associated with consistent and clinically meaningful improvements in negative symptoms and functioning over 3 years in patients with schizophrenia displaying PNS.

T118. EFFICACY OF SUBLINGUAL DEXMEDETOMIDINE IN THE HOME SETTING FOR REDUCTION IN AGITATION ACROSS BASELINE SEVERITY OF SYMPTOMS IN PATIENTS WITH SCHIZOPHRENIA OR BIPOLAR DISORDER

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Abstract Background: BXCL501 is a sublingual film formulation of dexmedetomidine, a selective alpha-2 adrenergic receptor agonist, which has been approved for treatment of episodes of agitation in patients with schizophrenia or bipolar disorders under the supervision of a healthcare provider. In the home setting, where most episodes of agitation occur and no healthcare provider is present, there are no FDA-approved therapies for this indication. In order to address this patient need, a Phase 3 safety trial of the lower of the two approved doses of BXCL501 (120mcg) was initiated following consultations with the FDA. The primary objective of the trial was to investigate whether patients could safely self-administer BXCL501 in the absence of a healthcare provider. In addition, patient-reported efficacy data were collected as an exploratory objective.

Methods: A randomized, double-blind, placebo-controlled, Phase 3, 12-week trial (SERENITY At-home, NCT05658510) in adult patients with episodes of agitation associated with a primary diagnosis of bipolar disorders or schizophrenia in the community (at home) setting. The primary objective of the trial was safety and tolerability. Efficacy was also evaluated as an exploratory objective. The main exploratory efficacy measure was a modified clinical global impression – severity (mCGI-S). mCGI-S was scored by patients themselves and by caregivers/informants, if present, on a scale of 0 (no agitation) to 3 (severe agitation). This report describes the efficacy analyses based on pre-dose levels of symptom severity.

Results: Primary data analyses indicated that BXCL501 was safe and tolerable when administered in unsupervised setting. Efficacy data were available for all 208 patients whose agitation episodes were treated with BXCL501 or placebo. In these patients, over 2437 episodes, a greater reduction in symptoms was seen with BXCL501 compared with placebo ($P < 0.05$). In the severe symptoms subset, the mean reduction was 2.4 in the BXCL501 group and 1.6 with placebo. The differences were smaller in the moderate and mild subsets, but they both trended in the same direction (1.3 vs 1.2 and 0.6 vs 0.4, respectively). The reductions remained consistent throughout the 3-month study, with no indication of attenuation of benefit with repeat administration. In addition, a greater proportion of patients

experienced full resolution of symptoms with BXCL501 compared with placebo across the episodes regardless of severity at baseline ($P < 0.0005$).

Conclusions: In this pivotal safety study, as-needed doses of sublingual dexmedetomidine 120 mcg were safe, well tolerated, and reduced the severity of agitation in subjects with schizophrenia or bipolar disorder over a 12-week treatment period when administered on an as-needed basis. Over repeat dosing, the reduction in symptoms remained consistent throughout the duration of the trial. Greater reductions in symptoms were observed with BXCL501 than with placebo regardless of pre-dose severity, but the largest differences were observed among patients who experiences severe symptoms for the measured episode.

T119. LONG-TERM METABOLIC AND CARDIOVASCULAR SAFETY AND TOLERABILITY WITH XANOMELINE AND TROSPIMUM CHLORIDE: POOLED RESULTS FROM EMERGENT-4 AND EMERGENT-5

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Abstract: Currently approved treatments for schizophrenia are associated with a variety of cardiometabolic risks. Xanomeline and trospium chloride (KarXT) is a novel agent that combines the dual M1/M4-preferring muscarinic receptor agonist xanomeline and the peripherally restricted pan muscarinic receptor antagonist trospium chloride. KarXT is approved in the US for the treatment of schizophrenia in adults. The efficacy and safety of KarXT in schizophrenia were demonstrated in the 5-week, randomized, double-blind, placebo-controlled EMERGENT-1 (NCT03697252), EMERGENT-2 (NCT04659161), and EMERGENT-3 (NCT04738123) trials. KarXT was not generally associated with clinically meaningful weight gain or adverse metabolic side effects compared with placebo in the acute trials; increases in blood pressure (systolic/diastolic) and heart rate were small and transient. Here, long-term metabolic and cardiovascular safety and tolerability are characterized in data pooled from two 52-week, open-label, phase 3 trials.

Methods: EMERGENT-4 (NCT04659174) and EMERGENT-5 (NCT04820309) enrolled adults aged 18-65 years with schizophrenia. Participants had either rolled over from the short-term trials (EMERGENT-4) or had stable symptoms appropriate for outpatient care (EMERGENT-5). Eligible participants received KarXT orally starting at 50 mg/20 mg (xanomeline/trospium) twice daily (BID) and increasing to a maximum of 125 mg/30 mg BID as tolerated. Data from EMERGENT-4 and EMERGENT-5 were pooled; analyses were conducted in the safety population, defined as all participants who received ≥ 1 dose of KarXT.

Results: A total of 718 adults comprised the pooled safety population. At baseline, participants had a mean body mass index of 29.5 kg/m² and hemoglobin A1c (HbA1c) of 5.8%, indicating some baseline cardiometabolic risk. Cholesterol and triglyceride levels remained stable after 52 weeks (mean $\pm$ standard deviation [SD] change, cholesterol: -0.07 ± 0.79 mmol/L; triglycerides: -0.07 ± 0.83 mmol/L). Fewer participants had cholesterol or triglycerides above the upper limit of normal at their last assessment compared with baseline. HbA1c remained stable over the course of treatment. Prolactin decreased by 3.1 ± 15.0 μ g/L from baseline to week 52. KarXT was associated with small increases in supine systolic (mean $\pm$ SD change from baseline to week 52: 1.7 ± 13.4 mmHg) and diastolic blood pressure (BP; mean $\pm$ SD change from baseline to week 52: 1.3 ± 8.4 mmHg); peak changes in systolic and diastolic BP occurred at day 8. KarXT was also associated with a small

increase in heart rate (HR; mean $\pm$ SD change from baseline to week 52: 2.3 ± 12.5 beats/min) that was not clinically significant; peak change was observed at day 14. Peak changes in BP and HR partially attenuated with continued treatment.

Conclusions: KarXT exhibits a long-term favorable cardiometabolic profile; all metabolic parameters either improved or remained stable over 52 weeks of treatment. KarXT was associated with a low risk for cardiovascular TEAEs with small, generally transient increases in BP and HR.

T120. SCHIZOPHRENIA-RELATED HOSPITALIZATION HISTORY BEFORE LONG-ACTING INJECTABLE ANTIPSYCHOTIC INITIATION AND ITS ASSOCIATION WITH SUBSEQUENT ADHERENCE AND HOSPITALIZATIONS AMONG DUAL-ELIGIBLES: THE CRITICAL PERIOD STUDY

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Abstract Background: Real-world evidence has demonstrated that long-acting injectable antipsychotic (LAI) use is associated with improved medication adherence and a reduced risk of schizophrenia (SCZ)-related hospitalizations. It is theorized that the timing of first LAI use may play a critical role in influencing patient outcomes. The CRITICAL PERIOD study examined the SCZ-related hospitalization history prior to initiating an LAI and its association with antipsychotic (AP) adherence and healthcare resource use in dual-eligible Medicare beneficiaries with SCZ in the United States.

Method: Using 2006-2021 national Medicare and Medicaid claims we identified dual-eligible beneficiaries with a diagnosis of SCZ who initiated an LAI between 7/1/2009 and 12/31/2021 (first observed LAI fill date = index date). Patients were required to have continuous Medicaid or Medicare fee-for service Part D coverage from their first observed SCZ diagnosis date until the index date (pre-index period), and 12-months continuous post-index coverage. Patients were stratified by the number of SCZ-related hospitalizations in the pre-index period (0, 1, 2-5, or ≥ 6 hospitalizations). Outcomes included adherence to any LAI and all-cause, mental health related, and SCZ-related hospitalizations during the 12-month post-index period. Logistic regressions were used to assess how the number of SCZ-related hospitalizations during the pre-index period was associated with outcomes, while controlling for demographic and clinical characteristics. Sensitivity analyses were conducted among patients ≤ 35 years and ≤ 25 years on index date.

Result: The final sample consisted of 9,472 patients initiating an LAI; patients had a median age of 29 years and were primarily male (70%) and non-White (59%). Over half (54%) of patients had 0 SCZ-related hospitalizations in the pre-index period; the remaining patients had 1 (21%), 2 to 5 (20%), and ≥ 6 (4%) SCZ-related hospitalizations, respectively. The median time from first observed SCZ diagnosis to first observed LAI initiation was 9 months (5 for 0, 12 for 1, 24 for 2 to 5, and 45 for ≥ 6 SCZ-related hospitalizations). In descriptive analyses, an increasing number of SCZ-related hospitalizations in the pre-index period was associated with lower rates of adherence to any LAI (41% to 23%) and higher rates of any all-cause (26% to 72%), mental health related (22% to 71%), and SCZ-related hospitalization

(18% to 66%) during the 12-month post-index period. Logistic regressions confirmed these results: for instance, compared to patients with 0 SCZ-related hospitalizations, those with 2 to 5 SCZ-related hospitalizations in the pre-index period had lower odds of adherence to any LAI (OR: 0.81, p LESS THAN 0.01) and higher odds of any all-cause (OR: 1.91, p LESS THAN 0.01), mental health related (OR: 2.10, p LESS THAN 0.01), and SCZ-related hospitalization (OR: 2.36, p LESS THAN 0.01) in the post-index period. Sensitivity analyses among patients ≤ 35 years and ≤ 25 years on index date showed similar findings.

Discussion: This study found that dual-eligible Medicare beneficiaries who had one or more SCZ-related hospitalizations before starting an LAI had lower odds of maintaining adherence and higher risk of subsequent hospitalizations. These findings underscore the importance of timely LAI initiation, as waiting until patients experience one or more SCZ-related hospitalizations may miss a critical window when earlier use could improve adherence, stabilize symptoms, and reduce healthcare utilization.

T121. OUTCOMES IN DEPRESSION SYMPTOMATOLOGY WITH HIGH AND LOW LEVELS OF SUICIDAL IDEATION

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Abstract: Psychedelic therapy demonstrates promising antidepressant effects in patients with difficult-to-treat depression. However, patients that experience suicidal ideation (SI) are frequently excluded from clinical trials due to safety concerns. Excluding patients with high SI limits the generalizability of findings and access to potentially effective treatments. We examined whether the presence of high SI predicts treatment response to psilocybin therapy, as well as whether the change in SI from pre- to post-treatment predicted depressive outcomes.

Methods: 45 patients across three difficult-to-treat depression studies by Aaronson et. al, received a single 25mg dose of COMP360 alongside therapeutic support. The Montgomery-Åsberg Depression Rating Scale (MADRS) was used to assess depressive symptom severity at baseline and 12 weeks post-treatment. The Columbia-Suicide Severity Rating Scale (C-SSRS) was used to assess SI at baseline and immediately following treatment. Subjects were divided into two groups based on screening scores: high SI (C-SSRS > 2) and low SI (≤ 2 C-SSRS). Paired one tailed t-tests were conducted to assess mean MADRS differences at baseline and Week 12. An analysis of covariance (ANCOVA) was conducted to examine whether MADRS Week 12 scores differed between SI groups after controlling for the severity of depression at baseline. An exploratory linear regression was conducted to assess whether the change in C-SSRS scores predicted MADRS outcomes at Week 12 across all patients.

Results: Patients in both groups experienced reductions in depressive symptoms ($t(19) = 10.16$, $p < .001$; $t(24) = 10.67$, $p < .001$) regardless of group assignment ($t(38) = 1.51$, $p > .069$). Controlling for baseline depression severity, no significant difference was found between high and low SI groups ($F(1, 42) = 2.12$, $p = .153$). The change in C-SSRS scores from baseline to immediately after treatment did not significantly predict depression outcomes at Week 12 ($F(1, 42) = 0.01$, $p = .907$).

Conclusions: Patients across three studies with varying degrees of SI experienced improvement to depression. These results exemplify that patients that experience high SI

receive comparable benefit from psilocybin therapy as those with low SI. In addition, the change in SI from pre- to post-treatment did not predict long-term depressive outcomes. Despite historical exclusion, depressed patients with higher levels of SI may be a target for psilocybin treatment. Future research should examine the safety and efficacy of psychedelic therapy in populations with higher suicidal ideation.

T122. REAL-WORLD SAFETY AND EFFECTIVENESS OF LURASIDONE IN CHINESE CHILDREN AND ADOLESCENTS WITH SCHIZOPHRENIA: A POST-HOC ANALYSIS OF A POST-MARKETING SURVEILLANCE STUDY

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Abstract Background: Compared to adults, dosing in children and adolescents with schizophrenia should be more individualized due to potential age-related differences in drug metabolism. This analysis aimed to investigate the real-world use of lurasidone in Chinese pediatric patients with schizophrenia, using data from a post-marketing surveillance (PMS).

Methods: Patients receiving lurasidone monotherapy were included in this post-hoc analysis, using data from a 12-week, prospective, observational, single arm, open-label, multi-center PMS conducted in patients with schizophrenia receiving lurasidone in China. Patients were stratified into pediatric (< 18 years) and adult (≥18 years) groups. Pediatric patients were also stratified based on whether their final titration dose exceeded 40 mg/d to assess differences in safety. Adverse events (AEs) were collected to evaluate the safety profile. Brief Psychiatric Rating Scale (BPRS) and International Classification of Diseases 11th Revision (ICD-11) Symptom Rating Scale were used to evaluate effectiveness.

Results: One hundred and forty pediatric patients (51 male/89 female) were included, accounting for 9.5% of the total 1481 patients receiving lurasidone monotherapy. 96.4% patients (135/140) completed the surveillance. The average age was 15.4 (range: 10-17) years old. The initial dose of lurasidone was slightly lower for pediatric patients than for adults (mean±SD: 35.7±10.94 mg/day vs. 39.4±10.70 mg/day, $p < 0.001$). The proportion of pediatric patients starting lurasidone at 20, 40, 60, and 80 mg was 25.7%, 72.1%, 0.0%, and 2.1%, respectively, while the corresponding figures for adults were 11.7%, 83.9%, 0.2%, and 4.2%. Pediatric patients underwent rapid titration, with the first dose adjustment occurring approximately 1 week (7.1±8.87 d) after initiating lurasidone, increasing to 58.4±19.65 mg/d. In contrast, adults had their first dose escalation after 10.3±13.07 days, adjusting to 60.1±20.95 mg/d. The mean daily doses for pediatric patients and adults were 65.1±17.95 and 61.7±21.53 mg/d, respectively ($p = 0.044$). Six AEs (4 cases of weight gain and 2 cases of drowsiness) occurred in 6 pediatric patients (4.3%, 6/140) during the surveillance. All AEs were mild. In comparison, 61 AEs occurred in 54 adult patients (4.1%, 54/1332), with weight gain (1.8%), prolactin elevation (0.8%), akathisia (0.4%), and nausea (0.3%) being the most frequent. The mean weight gain at week 12 from baseline was 0.1±2.21 kg in pediatric patients and 0.2±2.07 kg in adults. Lurasidone also led to a greater reduction in the BPRS anxiety/depression subscore in pediatric patients compared to adults (4.6±3.47 vs 3.5±3.33, $p < 0.001$), from 10.8±4.15 at baseline to 6.4±2.85 at week 12. Similar trends were seen in ICD-11 ratings, with greater reductions in depressive mood ($p = 0.052$), cognitive ($p = 0.013$), and positive symptoms ($p = 0.001$) in pediatric patients compared with adults.

Conclusion: Lurasidone use in Chinese pediatric patients featured a lower initial dose but faster titration to a slightly higher mean daily dose compared to adults. Lurasidone 40-80

mg/d was well-tolerated, with low AE rates, and demonstrated significant efficacy, particularly for anxiety/depression symptoms. It has excellent metabolic advantages, which are of vital importance for children and adolescents in the growth and development stage. Lurasidone appears to be a promising treatment option for Chinese children and adolescents with schizophrenia.

T123. REAL-WORLD EVIDENCE OF CLINICAL TREATMENT RESPONSE FOLLOWING INTRAVENOUS RACEMIC KETAMINE VERSUS INTRANASAL ESKETAMINE IN ADULTS WITH MAJOR DEPRESSIVE DISORDER

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Abstract Background: Ketamine is a powerful and rapid-acting antidepressant, though intravenous (IV) racemic ketamine is not currently FDA-approved for any psychiatric condition. In contrast, the S-enantiomer of ketamine, esketamine, was approved by the FDA in 2019 as an adjunctive therapy for treatment-resistant depression. While pharmacologically related, it is not clear if there are significant clinical differences in treatment response or remission between IV ketamine and intranasal esketamine. Here we present real-world comparisons between these two treatment modalities.

Methods: We analyzed de-identified electronic health record data from a U.S. healthcare technology platform serving over 800 community psychiatric clinics to conduct a retrospective comparative effectiveness analysis of IV ketamine and intranasal esketamine. Patients with a clinical diagnosis of Major Depressive Disorder (MDD) who received IV racemic ketamine or intranasal esketamine were identified (those exposed to both were excluded). Cohorts were coarse-matched on age, gender, median income of the zip code of patient address, and baseline Patient Health Questionnaire-9 (PHQ-9) score.

Results: The PHQ-9 was used as a measure of depression severity. Logistic regression with robust standard errors estimated odds of remission (defined as $\text{PHQ-9} \leq 4$) and response ($\geq 50\%$ PHQ-9 reduction from baseline) within 90 days. Data were analyzed on a total matched sample of $N=3,510$ patients, with a mean age of 43.3 (SD=13.9). Most (61%) were women, and a majority of the sample identified as White (64%). The median household income (based on patient zip code) was \$99,560. The mean baseline PHQ-9 was 17.9 (SD=5.2). Ketamine-treated patients achieved significantly higher remission rates than esketamine-treated patients (34.4% vs. 25.9%; odds ratio: 1.50, 95% CI: 1.30–1.73, $p < 0.001$; Number needed to treat = 12). Response rates also favored ketamine (63.1% vs. 58.3%; odds ratio: 1.22, 95% CI: 1.07–1.40, $p = 0.004$; Number needed to treat = 21).

Conclusions: In this large, longitudinal real-world cohort of adults with MDD, both treatments were associated with symptom improvement. However, IV racemic ketamine demonstrated higher remission and response rates compared with intranasal esketamine over 90 days, indicating that the route of administration and pharmacologic composition may meaningfully influence clinical outcomes. The main weakness of this analysis is that treatment assignments were not randomized, hence unmeasured confounding variables may contribute to differences in outcomes. These findings support further prospective investigation comparing the two treatment modalities.

T124. MULTICLASS ENVIRONMENTAL TOXICANTS FOUND IN CEREBROSPINAL FLUID (CSF) AND PLASMA SAMPLES FROM PREGNANT WOMEN: POTENTIAL ASSOCIATIONS WITH POSTPARTUM DEPRESSIVE SYMPTOMS

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Abstract Background: Humans are exposed to a wide range of potentially neurotoxic environmental chemicals. However, assessing their overall impact on the central nervous system (CNS) remains challenging due to the difficulty in quantifying multi-class chemicals at low concentrations and the lack of direct access to the CNS. Our study leverages a unique collection of paired plasma and cerebrospinal fluid (CSF) samples from pregnant women in an urban pregnancy cohort. We aimed to comprehensively profile environmental toxicant exposures in CSF and plasma, and explore their potential associations with postpartum depression symptoms.

Methods: We curated a list of 143 environmental chemicals from 16 distinct classes with potential toxicity to the central nervous system (CNS) via a thorough literature review. We developed and validated an automated, low-volume, high-sensitivity targeted multiclass assay. The limits of detection (LOD) ranged from 0.001-1.0 ng/mL using only 0.2 mL of plasma or CSF. We quantified and characterized the distribution of these 143 potential neurotoxic chemicals in 25 paired CSF-plasma samples, collected from pregnant women prior to delivery. We assessed postpartum depression symptom severity at 6 weeks postpartum using the 10-item self-report Edinburgh Postnatal Depression Scale (EPDS), which is a widely used, validated measure considered the gold-standard for screening for postpartum depression. We first conducted univariate descriptive statistics (e.g., percentiles, median, means, range, etc.) for all analytes in plasma and CSF and other study variables of study participants. We then focused subsequent analyses on those analytes detected ($>$ LOD) in at least 50% of samples in each biofluid. We conducted exploratory analyses of prospective associations between chemicals levels in CSF and plasma in pregnancy with EPDS scores at 6 weeks postpartum. Due to the small sample size, we only explored the mixture effect of these chemicals using Weighted Quantile Sum (WQS) regression adjusting for maternal age and race.

Results: We found wide detection of environmental chemicals not only in plasma but also in CSF, with 16 and 18 toxicants detected in all CSF and plasma samples, respectively. 11 analytes were found in both body fluids in all individuals. Additionally, 51 analytes in CSF and 57 analytes in plasma were detected in $>$ 50% of samples, including 31 commonly detected in both matrices. 17 analytes, mainly phthalates and pesticides, showed higher concentrations in CSF than in plasma. Weighted Quantile Sum (WQS) regression suggested a potential prospective association between the exposure mixture and EPDS scores at 6 weeks postpartum. In CSF, 33 of 50 beta estimates were positive (mean=1.9, SE=7.5, 95% CI: [-12.7, 16.5]), whereas in plasma only 15 of 50 beta estimates were positive (mean=-0.64, SE=8.5, CI: [-2.4, 4.0]). Although these estimates were not statistically significant, as expected given the small sample size, these pattern suggests that associations between environmental exposures and EPDS may differ by biological matrix, with stronger signals observed in CSF.

Conclusion: Our exploratory “exposome-scale” study is among the first to report a prevalent detection of numerous multi-class environmental chemicals with potential neurotoxicity in CSF, suggesting their ability to cross the blood-CSF barrier. Their collective presence in CNS may play a role in maternal postpartum mental health and warrants further investigation.

T125. CONTINUOUS MULTIMODAL PASSIVE MONITORING OF DEPRESSIVE SYMPTOMS VIA SMARTPHONE: CLINICAL VALIDATION OF A NOVEL DIGITAL HEALTH TECHNOLOGY

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Abstract Background: Standard episodic assessments of depressive symptoms place a high burden on patients and fail to capture critical inter-visit symptom dynamics. Passive, smartphone-based digital health technologies (DHTs) offer a continuous, objective, and low-burden alternative for tracking disease trajectories. This presentation highlights the clinical innovation and validation of EMOCARE, a novel passive multimodal DHT designed to continuously and automatically monitor depressive symptom severity in real-world settings.

Methodology: The EMOCARE system operates on a patient’s smartphone to acquire multimodal behavioral data during routine use without requiring active patient input. The technology passively extracts novel mood biomarkers from opportunistic facial snapshots and short audio snippets, while also capturing actigraphy/motion signals and digital behavior patterns, such as screen unlock and session metrics. These behavioral and physiological proxies are transformed into a quantitative depressive symptom severity score (0–100 scale), which is updated daily through the server-side aggregation of encrypted data. To evaluate the clinical validity and real-world feasibility of this multimodal approach, an interim pooled analysis was conducted across 3 prospective observational studies involving adults with Major Depressive Disorder or Bipolar Disorder. The continuously generated EMOCARE scores were compared against established clinician-rated anchors (e.g., MADRS, HAM-D17) and self-reported scales (e.g., PHQ-9, GAD-7).

Results: In the pooled dataset, continuous passive monitoring demonstrated strong feasibility and robust clinical alignment. The algorithmically derived scores exhibited moderate-to-strong concurrent associations with reference symptom scales (Spearman’s rho ranging from 0.613 to 0.833). Within-person longitudinal concordance was notably strong against the clinician-rated MADRS (repeated-measures correlation $r = 0.895$, $p = .016$). Furthermore, the continuous passive scores accurately tracked dynamic symptom trajectories over time, demonstrating strong sensitivity to change when compared to consecutive-visit changes on the PHQ-9 ($\rho = 0.834$, $p < .001$). Data density criteria (requiring ≥ 7 valid days in a 14-day window) confirmed measurement integrity, though adherence requirements remain a consideration for broader real-world scaling.

Conclusion: These findings provide strong preliminary evidence that continuous, passive multimodal smartphone monitoring can generate interpretable severity estimates that align closely with gold-standard episodic scales. By seamlessly capturing objective behavioral, vocal, and facial markers of depression, this technology addresses a critical unmet need for longitudinal, low-burden patient tracking. This scalable approach offers significant clinical value for the early detection of relapse, objective assessment of treatment response, and the extension of high-fidelity patient monitoring.

T126. COMPARABLE SYMPTOM IMPROVEMENT WITH ELECTROCONVULSIVE THERAPY AND ESKETAMINE IN TRANSGENDER AND GENDER NON-CONFORMING ADULTS WITH TREATMENT-RESISTANT DEPRESSION

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Abstract Background: Transgender and gender non-conforming adults have higher prevalence and severity of depressive disorders than cisgender adults, with increased rates of anxiety, PTSD, substance use, and suicidality. Emerging data suggest greater severity and suicidality among those seeking care for treatment-resistant depression (TRD).

Electroconvulsive therapy (ECT) and esketamine are effective for TRD: ECT remains the gold standard with 60–80% response and 50–60% remission rates, while esketamine provides rapid antidepressant effects and is FDA-approved for TRD and depressive symptoms with acute suicidal ideation/behavior. No prior studies have examined or compared outcomes in gender non-conforming or transgender adults.

Methods: Adults with TRD who self-identified as gender non-conforming or transgender were included in a retrospective chart review using data from a large academic center. Two cohorts were analyzed: (1) 9 patients receiving esketamine (5 gender non-conforming, 3 transgender male, 1 transgender female); (2) 9 receiving ECT (4 gender non-conforming, 3 transgender male, 2 transgender female). Montgomery–Åsberg Depression Rating Scale (MADRS) and Quick Inventory of Depressive Symptomatology (QIDS) scores were measured at baseline and after 8 sessions. Paired-sample t-tests assessed changes.

Results: In the esketamine group, MADRS improved from 37.44 (SD=10.31) to 25.00 (SD=14.92), $t(8)=-3.29$, $p=.005$. QIDS improved from 21.00 (SD=3.39) to 12.78 (SD=7.74), $t(8)=-3.74$, $p=.002$. In the ECT group, MADRS improved from 37.89 (SD=7.81) to 25.56 (SD=13.32), $t(8)=-3.39$, $p=.005$. QIDS improved from 20.67 (SD=4.21) to 13.56 (SD=7.49), $t(8)=-3.03$, $p=.008$.

Conclusion: In this preliminary analysis of transgender and gender non-conforming adults with TRD, both esketamine and ECT were associated with significant comparable reductions in depressive symptom severity after eight treatments. Rather than indicating a single preferred modality, these findings suggest that multiple evidence-based treatment pathways may yield meaningful clinical improvement for gender diverse patients. Extending beyond traditional efficacy framing, the results support flexible, individualized TRD treatment approaches in populations historically underrepresented in clinical research. Larger prospective studies are needed to confirm these observations and further characterize treatment response across gender identities.