2023 ASCP ANNUAL MEETING

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ASCP
American Society of Clinical Psychopharmacology

THE CHANGING LANDSCAPE OF CLINICAL PSYCHIATRY: NOVEL THERAPEUTICS, METHODS AND ASSESSMENTS

MAY 30 - JUNE 2, 2023

Tuesday, May 30, 2023

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

Panel Sessions

*^COVID-19, PAXLOVID AND CLOZAPINE - EDUCATION AND DISSEMINATION OF KNOWLEDGE AND THE NEED FOR CLINICAL VIGILANCE

Roy Chengappa, University of Pittsburgh Medical Center

Overall Abstract: Respiratory and urinary tract (and other) infections can elevate normal clozapine levels to toxicity. Several case-reports have appeared in the literature to suggest that COVID-19 infection in patients has led to clozapine toxicity, and that this clinical emergency can occur rapidly. There is evidence that the SARS-CoV-2 infection inhibits hepatic cytochrome enzymes considerably, especially the CYP1A2, 3A, and 2C19 isoenzymes. These enzymes represent the major and minor metabolic pathways for clozapine and the inhibition these enzymes can potentially elevate clozapine to toxic levels. Clozapine toxicity can lead to severe morbidity and even mortality.

Secondly, the nirmatrelvir-ritonavir protease inhibitor combination (aka: Paxlovid) has received emergency use authorization by the US FDA for use in mild to moderate COVID-19 disease to prevent progression to severe disease/hospitalization. Ritonavir in the combination drug is a potent CYP3A4 inhibitor and is used to "boost" nirmatrelvir's levels and action against viral replication. If clozapine treated patients are considered as candidates for nirmatrelvir/ritonavir therapy when they experience mild to moderate COVID-19, it is possible that the metabolism of clozapine could be significantly impaired to raise clozapine to dangerous levels. Dissemination of this knowledge to the prescriber and wider health care community as well as to clozapine treated patients and caregivers is vital to retain patients on this important medication.

Clozapine is the only FDA approved medication for treatment resistant Schizophrenia and is severely underutilized in the USA. Monitoring patients who have been initiated or stabilized on clozapine to obtain the full benefit of this medication is crucial. This panel will review the impact of COVID-19 on hepatic cytochromes especially as it relates to clozapine metabolism as well as the potential for severe drug-drug interactions if clozapine treated patients are being considered for treatment with nirmatrelvir/ritonavir when they develop mild to moderate COVID-19. We will review our efforts to disseminate the knowledge on the potential for clozapine associated toxicity to patients and caregivers in a large clozapine clinic (nearly 200 patients) and also our efforts to disseminate the knowledge nationally in the USA to the prescriber community.

Learning Objectives:

1. Review the knowledge on the impact of COVID-19 and of Nirmatrelvir/Ritonavir combination on the metabolism of clozapine and the potential for clozapine toxicity.
2. Review the efforts to disseminate this knowledge of the potential for clozapine toxicity due to COVID-19 and the potential use of nirmatrelvir/ritonavir in clozapine treated patients in a large clozapine clinic and nationally in the USA.

PAXLOVID AND CLOZAPINE – PHARMACOKINETIC AND PHARMACODYNAMIC CONSIDERATIONS

Jonathan Leung, Mayo Clinic, Rochester, MN

Individual Abstract: There has been increasing awareness of the potential influence from infection, including COVID-19, on the cytochrome P 450 (CYP) system and drug metabolism. Specifically, inflammatory processes decrease CYP450 activity due to the influence from various cytokines. This can lead to clozapine toxicity. Knowledge of how clozapine is metabolized and how COVID-19 and its treatments impact clozapine serum concentrations is important for all clinicians.

Clozapine is metabolized primarily by cytochrome P 450 (CYP) 1A2 as well as 3A4, 2C19, and 2D6. This knowledge can help clinicians determine important drug interactions. Following diagnosis of mild to moderate COVID-19 infection, ritonavir-boosted nirmatrelvir may be prescribed. Ritonavir is a potent CYP3A4 inhibitor and per the ritonavir-boosted nirmatrelvir package insert, clozapine is contraindicated due to the theoretical risks of toxicity. Unfortunately, no formal pharmacokinetic studies have been completed to support this guidance. Of note, formulations of ritonavir for treatment of HIV-1 infection, based on prescribing information, are not contraindicated with clozapine. Additionally, ritonavir is a mild inducer of both CYP1A2 and 2C19 making this interaction complex and unpredictable. Because of these issues, many recommendations to manage clozapine in the setting of ritonavir-boosted nirmatrelvir can be found from various sources. Clinicians must also consider the impact that infection itself has on clozapine metabolism, which is also variable.

Before starting ritonavir-boosted nirmatrelvir, a baseline serum clozapine concentration should be obtained for comparison, if needed at a future time. However, close clinical monitoring and mindful follow-up is likely the most important "tool" when considering any clozapine dose adjustment. Empiric dose reductions in the absence of clinical toxicity is generally not recommended both in the setting of COVID-19 infection itself or initiation of ritonavir-boosted nirmatrelvir. But depending on the clinical scenario any dose reduction should prompt close follow-up for retitration, should psychiatric symptoms or cholinergic rebound development. If signs of mild-moderate toxicity do develop with ritonavir-boosted nirmatrelvir, it is advisable to 1) promptly recheck the clozapine serum concentration and 2) lower clozapine dosing by 25% to 50%. Ritonavir-boosted nirmatrelvir is only a five-day course and following treatment, and clozapine can be retitrated to the prior treatment dose (assuming no toxicity, no fever, and overall, the patient is improving from infection from COVID-19).

Learning Objectives:

1. Describe the metabolic pathway of clozapine and relevant interactions.
2. Describe the management of clozapine following the initiation of nirmatrelvir/ritonavir tablets.

Literature References:

1. Siskind D, Honer WG, Clark S, et al. Consensus statement on the use of clozapine during the COVID-19 pandemic. J Psychiatry Neurosci. 2020;45(3):222-223.

2. Leung JG, de Leon J, Frye MA, et al. The Modernization of Clozapine: A Recapitulation of the Past in the United States and the View Forward. J Clin Psychopharmacol. 2022;10.1097/JCP.0000000000001606. doi:10.1097/JCP.0000000000001606

COVID AND THE CLOZAPINE CLINIC: EDUCATING PATIENTS AND FAMILIES ABOUT COVID-19 INDUCED CLOZAPINE TOXICITY AND PAXLOVID

Jessica Gannon, University of Pittsburgh School of Medicine

Individual Abstract: Background: COVID-19 has presented unique challenges in treating individuals with clozapine, though maintenance of this medication, for most patients, is essential. Clozapine patients are at increased risk of COVID-19 infection compared to individuals taking other antipsychotics. While the extant literature has reassuringly suggested that patients taking clozapine are not at increased risk for severe COVID-19 infection complications, including clozapine toxicity, have been reported. Furthermore, while novel treatments for COVID-19 have emerged, the use of one commonly prescribed agent, Nirmatrelvir/Ritonavir, can elevate clozapine levels, further increasing the risk of clozapine toxicity with COVID-19. In our presentation, we will review a Quality Improvement Council approved effort to educate healthcare professionals and patients on COVID-19 related clozapine toxicity and on the drug-drug interaction between Nirmatrelvir/Ritonavir and clozapine, which can also lead to clozapine toxicity.

Methods: At an academic medical center in a large healthcare system, we identified two educational pathways to promote patient safety related to decreasing the risks of COVID-19 related clozapine toxicity, including avoiding co-prescribing Nirmatrelvir/Ritonavir and Clozapine. First, we focused on educating those treating clozapine patients. Physicians and advanced practice professionals (APPs) who prescribe clozapine were targeted for rapid education through targeted email communications via our system's Pharmacy and Therapeutics Committee. Next, we created two on-line videos approved for continuing education credits. These include practical information specific to physicians and APPs, nurses, and pharmacists and are accessible both within and outside of our healthcare system. Finally, we worked with our hospital information technology (IT) team and electronic health record (EHR) vendor to ensure that co-prescription of clozapine and Nirmatrelvir/Ritonavir triggered a major interaction warning.

Our second educational pathway focused on patient and family education. Starting with our academic clozapine clinic (173 patients), and with endorsement of faculty and staff, members of our multidisciplinary team reached out by phone to each patient to review risks of clozapine toxicity with COVID-19 and serious interactions between Nirmatrelvir/Ritonavir and clozapine. Standard documentation was developed and incorporated into reportable autotexts in both our EHRs. Reports of autotext use were generated to monitor progress and cross checked with pharmacy generated reports. Patients who were unreachable by phone were sent letters.

Results: At the time of this submission, 126 individuals had watched the educational videos. 208 unique patients had been successfully educated. 85% of the original cohort was reached by phone. The remainder of clinic patients were mailed letters, which included common questions and answers collected from the phone calls. Other patients educated included those prescribed clozapine outside of the clozapine clinic, ex by our Assertive Community Treatment Teams.

Conclusion: Timely practice change has been critical during COVID-19, both to ensure evidence-based prescribing and patient safety. This is especially true for high-risk patients, including those prescribed clozapine. Flexible quality improvement projects focused on

education of both healthcare professionals and patients can help promote adoption of rapidly evolving best practices.

Learning Objectives:

1. Debate the benefits of utilizing Quality Improvement processes to rapidly implement needed changes in prescribing practices.
2. Review the importance of multidisciplinary as well as patient and family education in supporting best practices in safe maintenance of clozapine prescribing during the COVID-19 pandemic.

Literature References:

1. Govind R, Fonseca de Freitas D, Pritchard M, et al. Clozapine treatment and risk of COVID-19 infection: retrospective cohort study. Br J Psychiatry. 2021 Jul;219(1):368-374.
2. Siskind D, Honer WG, Clark S, et al. Consensus statement on the use of clozapine during the COVID-19 pandemic. J Psychiatry Neurosci. 2020 Apr 3;45(4):200061.

LEVERAGING SMI ADVISER'S COMMUNITY AND INFRASTRUCTURE TO RAPIDLY DISSEMINATE CRITICAL INFORMATION ON COVID-19, PAXLOVID, AND CLOZAPINE

Robert Cotes, Emory University School of Medicine, Dept. of Psychiatry and Bevhaioral Sciences

Individual Abstract: SMI Adviser, also known as the Clinical Support System for Serious Mental Illness, is a 5-year initiative funded by the Substance Abuse and Mental Health Services Administration and administered by the American Psychiatric Association. The mission of SMI Adviser is to advance the use of person-centered care and to connect clinicians caring for those with SMI to resources supporting evidence-based treatment decisions. SMI Adviser has a broad multidisciplinary audience with all offerings available for free via a website and app. Currently, SMI Adviser has over 53,000 subscribers and over 1.67 million website impressions. SMI Adviser supports a Clozapine Center of Excellence (CCOE). The CCOE develops content on clozapine through accredited webinars, 12-week virtual learning collaboratives, monthly 45-minute forums, consultation to clinicians or organizations, an email listserv, and clinical tips and resources. The CCOE community develops tips on clozapine based on what is most timely from their clinical or research experience, tips are peer-reviewed, edited, and published on the website.

After Paxlovid was given an initial emergency use authorization by the FDA in December 2021, there was an urgent need to disseminate information to clinicians, given the concern for a pharmacokinetic interaction with clozapine. Two such tips were developed by CCOE members. The first, Recommendations for Managing Patients on Pimozide, Lurasidone, or Clozapine During a Treatment with a 5-Day Course of Paxlovid, was written by Joan Striebel, MD and published to the website on 1/13/22, less than a month after Paxlovid became available. As of 11/9/22, the tip has had 337 views. A second tip incorporating new findings from the literature called Vigilance and Monitoring for Clozapine Toxicity During COVID-19 Infection and Recommendations for Management, was published 8/9/22, and was co-authored by Roy Chengappa, MD, and Jane Thomas, BSN, RNBC. The tip provided practical guidance to clinicians on the impact of Paxlovid on antipsychotic metabolism and discussed the impact of mild to moderate COVID-19 infection on antipsychotic plasma levels. Since 11/9/22, the tip has had 515 views on SMI Adviser. After publication on the website, both tips were shared

on the Clozapine and LAI Centers of Excellence Exchange listserv, which has 528 members as of 11/9/22.

The COVID-19 pandemic has forced clinicians to rapidly adapt and make clinically consequential decisions despite various unknowns and a developing evidence base. The potential interaction between Paxlovid and clozapine is an example of how SMI Adviser has used its various platforms to help synthesize evidence and disseminate information to a wide-reaching group of practitioners.

Learning Objectives:

1. Describe the mission of SMI Adviser and the Clozapine Center of Excellence.
2. Describe the process by which up-to-date, peer-reviewed information can be disseminated through SMI Adviser.

Literature References:

1. Siskind D, Honer WG, Clark S, et al. Consensus statement on the use of clozapine during the COVID-19 pandemic. J Psychiatry Neurosci. 2020;45(3):222-223.
2. Lenoir C, Terrier J, Gloor Y, et al. 2021. Impact of SARS-CoV-2 Infection (COVID-19) on Cytochromes P450 Activity Assessed by the Geneva Cocktail. Clin Pharmacol There. 110 (5), 1358-1367. doi:10.1002/cpt.2412

*^3 INNOVATIONS IN PSYCHOPHARMACOLOGY EDUCATION: DIGITAL PSYCHIATRY COURSES, PATIENTS AS TEACHERS, AND NOVEL KETAMINE JOURNAL CLUB

Sagar Parikh, University of Michigan, Ann Arbor

Overall Abstract: With rapid advances in psychopharmacology, there are great challenges in providing comprehensive Education to practitioners that is both scientifically accurate and clinically applicable. Research in Education has shown a major gap between translating new neuroscience and psychopharmacology advances into everyday practice, suggesting the need for novel formats for Education that incorporate a variety of educational techniques and involve a variety of learning strategies that reflect different learning needs. This panel discussion will allow description and reflection on 3 different models of Education. The 1st model will explore special learning needs around the Introduction: duction of ketamine as a major new psychiatric medication, led by Oxford psychiatrist and doctoral fellow Dr. Sara Costi. A novel Journal club started at Oxford University aims to connect international researchers with clinicians using the most recently published studies on ketamine and related compounds. The format consists of two parts; a brief, live recorded online presentation delivered by an author/speaker, with a chaired Q and A session, followed by an unrecorded informal continuation for audiences to engage in instant reciprocal feedback using cameras. One year follow up questionnaires and faculty reflection provide key insights into this educational innovation. A 2nd pedagogic strategy involves inviting patients to serve as educators with lived experience, presented by ASCP President Dr. Les Citrome. Understanding the lived experience, appreciating the need for collaborative decision making, and identifying patient perspectives on desired treatment goals provides another lens for clinicians to consider how they wish to select and deliver treatment. This model also requires a new way for psychiatrists to serve on an Education panel with individuals with lived experience and today's presentation will particularly focus on the benefits and challenges of teaching psychopharmacology with individuals with lived experience. A 3rd presentation by Dr. Sagar Parikh will address the development of numerous web sites and mental health apps that may be used either alone or in tandem with standard

psychiatric care. Since these digital psychiatry applications are not regulated by any government agency, there are unique challenges in identifying and selecting the right digital psychiatry tools to disseminate. Furthermore, there is little guidance on how to integrate these novel approaches in everyday clinical practice. In this 3rd presentation, several different models including along the longitudinal courses, rounds, and also workshops--identical to 1 previously held at the ASCP annual conference--will be described and examined with the benefit of outcome questionnaires. Together, all 3 presentations will provide different approaches to providing psychopharmacology Education as well as providing specific knowledge about how to Introduction: duce novel treatments such as ketamine or digital psychiatry tools into practice.

Learning Objectives:

1. Identify two novel ways to teach psychopharmacology.
2. Explore how to integrate people with lived experience as co-teachers of psychopharmacology.

EVALUATING NOVEL CME APPROACHES TO TEACH CLINICIANS HOW TO USE MENTAL HEALTH APPS AND WEBSITES

Sagar Parikh, University of Michigan, Ann Arbor

Individual Abstract: Introduction: duction: Mental health apps and websites are widely promoted. Unlike medications, no regulatory body or academic authority routinely oversees or evaluates all E-mental health tool (e-mht) health claims. Despite widespread use by both patients and clinicians, few formal continuing medical education (CME) events or articles exist to guide individuals how to select appropriate digital tools. In response, we created three types of education events (course, workshop, webinar) with differing formats to teach clinicians how to evaluate apps and websites. Here we provide educational outcomes.

Methods: A needs survey identified learning styles, knowledge and skills desired, preferred event formats, and preferences about e-mht, including currently used tools. We established 3 learning objectives (1) learn how to evaluate mental health apps (2) identify best apps and websites for mood and anxiety disorders and (3) demonstrate and practice these e-mht. We evaluated three products: a 3-session online course; a 1-session webinar for clinicians; and a conference workshop. The online course had an initial 2-hour interactive class, followed by monthly 1-hour sessions that both taught new material and reviewed participant experiences. Teaching formats included lectures, case-based examples, peer learning, and tool demonstrations. Two single-session webinars were done, as well as one online workshop at a national conference. Two instructors, a psychiatrist and a psychiatry resident, co-taught all events, using identical slides adjusted for length of training event. Using Dixon's evaluation framework, questionnaires measured satisfaction, knowledge, attitudes, and tool uptake in practice. From these questionnaires, we report findings on course satisfaction (scored 1-5 with 5 being excellent), confidence after training in selecting an app (scored high, medium, or low), and respondent's intention to use app in their practice (scored unlikely, maybe, or likely). Workshop evaluations were different.

Results: Course attendance was 97, with 47 evaluations (48%), while 29/52 (55%) webinar attendees completed evaluations. At the workshop, 51/98 (52%) submitted evaluations. Overall satisfaction was "highly or very" 89% for courses and 90% for webinars. Speakers were rated "highly or very" at 94% for courses and 90% for webinars. In confidence in selecting

an app, “high” ratings were 40% in courses and 43% in webinars. Intention to use newly learned e-mht in practice “likely” 79% in courses and 76% in webinars. In workshop, 51% strongly agreed relevance to practice, and 60% indicated an intention to implement a change in practice, with most citing new use of specific e-mht.

Conclusion: These educational events were very popular, demonstrated high satisfaction, knowledge/confidence gain, and high intention to use e-mht in practice. Facilitating digital transformation of the health care system will need more clinician training. Our CME events offer promising pilot data for more future CME programs, ideally supplemented by evaluation of impact on patients.

Learning Objectives:

1. Describe three different approaches to teaching clinicians about e-mental health tools.
2. Contrast formats and outcomes between the 3 different educational approaches, presenting evaluation data and providing guidance for designing future education events on digital psychiatry.

Literature References:

1. Torous J, Bucci S, Bell IH, et al. The growing field of digital psychiatry: current evidence and the future of apps, social media, chatbots, and virtual reality. World Psychiatry. 2021;20(3):318-335. doi:10.1002/wps.20883
2. Torous, J., Camacho, E., and Myrick, K. (2021). Equitable and Informed Digital Mental Health: Skills, Evaluation, and Integration of Apps into Care. TMS Proceedings 2021. https://doi.org/10.1037/tms0000058

THE OTHER EXPERT IN THE ROOM: PERSONS WITH LIVED EXPERIENCE

Leslie Citrome, New York Medical College

Individual Abstract: Professional education regarding disorders and their treatments has commonly been done without direct patient and caregiver input as to content. It is currently unusual to include persons with lived experience in delivering scientific presentations. This is unfortunate, because first-person narratives are very helpful in bringing a human face to complex diseases and help better frame the different treatment options being considered. To be described are ways of identifying the ideal candidate that can team up to complement a medical professional's presentation, and thus incorporate topics that otherwise never get meaningfully discussed. Examples will be shown using pre-recorded outtakes of actual presentations conducted using this teaching technique.

Learning Objectives:

1. Describe the importance of having persons with lived experience participate in the medical education process.
2. Describe ways of incorporating persons with lived experience in professional medical education.

Literature References:

1. Agrawal S, Kalocsai C, Capponi P, Kidd S, Ringsted C, Wiljer D, Soklaridis S. "It was great to break down the walls between patient and provider": liminality in a co-produced advisory course for psychiatry residents. Adv Health Sci Educ Theory Pract. 2021 May;26(2):385-403. doi: 10.1007/s10459-020-09991-w. Epub 2020 Sep 12. PMID: 32920699.

2. Ferguson G, Abi-Jaoude A, Johnson A, Saikaly R, Woldemichael B, Maharaj A, Soklaridis S, Nirula L, Hasan M, Wiljer D. Collaborating with Families: Exploring Family Member and Health Care Provider Perspectives on Engaging Families Within Medical Education. Acad Psychiatry. 2018 Jun;42(3):329-337. doi: 10.1007/s40596-017-0878-y. Epub 2018 Feb 12. PMID: 29435945.

THE KETAMINE INTERNATIONAL JOURNAL CLUB: A NOVEL JOURNAL CLUB FORMAT ON THE USE OF KETAMINE AND RELATED COMPOUNDS FOR PSYCHIATRIC DISORDERS

Sara Costi, University of Oxford

Individual Abstract: The Ketamine and related compounds International Journal Club (KIJC) represents a novel format of online journal club aiming at connecting international clinicians and researchers with the authors of the most recent publications on the use of ketamine and related compounds for the treatment of psychiatric disorders. The KIJC was conceptualized and run by academic clinicians at the University of Oxford and psychiatric trainees, independent of industry funding, and targeted an audience of clinicians, clinical and pre-clinical scientists, industry, and policymakers. A main aim of the KIJC was fostering bidirectional knowledge exchange, with immediate feedback from clinicians complementing the insights of speakers. The speakers were selected among the authors of the most recent peer-reviewed publications retrieved from PubMed on the use of ketamine for the treatment of psychiatric disorders. The presentations incorporated were a balance of randomized control trials, pre-clinical studies, experimental medicine, human mechanistic trials, and case series. The KIJC meetings were held as webinars using the video conferencing software Zoom, on the second and fourth Tuesday of most months. Meetings were held at the same reference time worldwide (5:30 pm GMT), with invitations emailed in a newsletter to all recipients on a mailing list a few days prior. The novel format of online presentation at KIJC was a structured two-part meeting. Part one was a live recorded presentation delivered by the speaker for approximately 20 minutes, followed by a 15-minute chaired Question and Answer (Q and A) session submitted by the live audience (attendees) and moderated by two visible panelists. The live recordings and exempted access to the presented publications for personal study, were made available for indefinite viewing on the KIJC website. Part two was an optional and unrecorded continuation where the audience was promoted from attendees to panelists. This allowed the audience to use their cameras and microphones and engage in a further 25-minute informal discussion between all the meeting participants. Following the first year, speakers and attendees of KIJC completed an online survey to evaluate the acceptability of the journal club's format, its ability to inform clinical and research practice, and its networking potential between speakers and audience. Two separate anonymized feedback surveys were conducted simultaneously using the webtool SurveyMonkey. Speakers were given 14 statements, and audience members 12 statements, to which they could either agree, disagree, or neither agree nor disagree with, and select their main career role. Amongst speakers, the evaluated domains reached 82% acceptability, 65% influenceability, and 77.7% networkability. Amongst the audience, the evaluated domains reached 85.6% acceptability, 81% influenceability, and 100% networkability. Overall, the novel format presented was acceptable, informed clinical practice, and promoted networking among its intended participants. There is an ongoing need for further evaluation of the current format used and for developing novel methods of delivering evidence-based virtual medical education.

Learning Objectives:

1. Consider a different way of delivering remote medical education to establish a learning environment that is interactive and engaging for attendees and speakers.

2. Evaluate the effectiveness of a novel journal club format via a 3-domain classification system (acceptability, clinical practice influenceability, and networkability)

Literature References:

1. Cervero RM, Gaines JK. The Impact of CME on Physician Performance and Patient Health Outcomes: An Updated Synthesis of Systematic Reviews. J Contin Educ Health Prof. 2015; 35:131–138
2. Mark I, Sonbol M, Abbasian. Running a journal club in 2020: reflections and challenges. BJPsych Bull. 2021; 45:339–342
3. Dedeilia A, Sotiropoulos MG, Hanrahan JG, et al. Medical and Surgical Education Challenges and Innovations in the COVID-19 Era: A Systematic Review. In Vivo. 2020; 34:1603–1611
4. Sarabipour S Virtual conferences raise standards for accessibility and interactions. eLife 2020; 9: e62668
5. Parikh SV, Bostwick JR, Taubman DS. Videoconferencing Technology to Facilitate a Pilot Training Course in Advanced Psychopharmacology for Psychiatrists. Acad Psychiatry. 2019; 43:411–416
6. Ryznar E, Wright SM, Roy D. The Current State of Journal Clubs in Psychiatry Residency Programs: Results from a National Survey of Program Directors. Acad Psychiatry. 2022; 1–6

+*HOW TO MAKE PROGRESS IN SUICIDE PREVENTION: DESIGNING AND CONDUCTING CLINICAL TRIALS AMONG HIGH RISK PATIENTS

Samuel Wilkinson, Yale School of Medicine

Overall Abstract: Suicide is among the top 10 causes of mortality worldwide, with 45,979 suicide deaths occurring in the United States in 2020. Unfortunately, despite renewed public efforts to confront this problem, suicide rates have increased markedly in the last 15 years. The total number of suicides deaths has increased by >60% from 1999 to 2019. Suicide-related visits to the emergency department have increased 42% in the last 20 years. For certain groups (e.g., adolescents, young adults, and minority youth), suicide risk has risen dramatically in the last decade. Recently, the Director of the National Institute of Mental Health has called for a renewed effort to combat this public health problem and reduce the rate of suicide.

For many decades, the vast majority of clinical trials conducted among patients with mental illness have excluded patients at risk of suicide. Reasons for this include regulatory challenges, a desire to avoid liability, and discomfort working directly with high-risk patients. Recognizing the great evidence gap that exists from decades of neglect of this issue, there has been increased interest recently in designing and conducting trials that enroll patients with significant suicidal ideation. These include trials involving ketamine or esketamine, lithium, as well as novel approaches to psychotherapeutic interventions. The current panel brings together perspectives from academia and industry experts.

The panel will discuss issues regarding the design and conduct of clinical trials that target and enroll patients with significant suicidal ideation. Subtopics to be discussed include crafting appropriate inclusion and exclusion criteria, the medical setting from which patients are enrolled, the selection of a proper comparator arm, selection of primary and secondary

outcomes, and management of regulatory oversight. In these discussions, insights will be drawn from ongoing and recently completed trials that specifically recruit patients considered at high risk of suicide. These trials include the FDA-registered ASPIRE trials of esketamine (Dr. Carla Canuso), a recently completed trial of lithium for suicidal behaviors in mood disorders among veterans (Dr. Michael Ostacher), the ongoing ENDURE trial of esketamine and cognitive behavioral therapy (Dr. Samuel Wilkinson), and an ongoing trial of intravenous ketamine and cognitive training intervention (Dr. Rebecca Price). The discussant will be Dr. Larry Alphs, one of the architects of the INTERSEPT trial that led to clozapine's FDA indication for reducing risk of recurrent suicidal behavior in patients with schizophrenia/schizoaffective disorder.

Learning Objectives:

1. To understand the current regulatory framework for designing and conducting clinical trials that enroll high-risk patients.
2. To discuss the key design aspects of such trials and the ways in which the field needs to change to facilitate more trials in this population.

TESTING THE REAL-WORLD EFFECTIVENESS OF A SYNERGISTIC, NEUROPLASTICITY-BASED INTERVENTION FOR RAPID AND DURABLE SUICIDE RISK REDUCTION

Rebecca Price, University of Pittsburgh

Individual Abstract: Rapidly-acting pharmacological agents, such as subanesthetic ketamine, offer the promise of a new opportunity to address suicidal crises with the urgency they require, but this promise remains unfulfilled to date. Over a decade ago, we first reported that intravenous (IV) ketamine showed large, rapid effects on suicidal ideation and implicit suicidal cognition (i.e., implicit associations between "self" and "escape") among depressed patients and suggested that such rapid effects might have real-world clinical utility in the face of a suicidal crisis. Yet, in spite of substantial interest in ketamine from the research, clinician, and patient communities alike, fundamental questions about ketamine's actual clinical utility and effectiveness in real-world clinical settings remain virtually untested. In controlled research settings, ketamine rapidly reduces suicidal thoughts as early as 2-24 hours after a single infusion, both in depressed patients and in transdiagnostic patients selected for high suicide risk. Yet, a significant barrier to clinical adoption of this treatment approach is the lack of evidence for durability of these effects, raising concerns about illusory recovery and subsequent rebound of suicide risk, and Introduction: ducing significant barriers to patient access and uptake in real-world clinical settings. Efforts to extend ketamine's rapid effects non-pharmacologically remain in early stages.

In an ongoing randomized controlled trial (RCT; target n=200), we are testing the real-world effectiveness of a recently developed synergistic treatment approach, involving a single infusion of IV ketamine followed by a very brief, fully automated, digital cognitive training intervention ("Automated Self-Association Training"; ASAT), using a deployment-focused study design. We recruit a highly heterogeneous sample of recent suicide attempters on a tertiary-care Consultation-Liaison (CL) psychiatry service and deliver all study interventions as an adjunct to treatment-as-usual (which involves medical stabilization, followed by psychiatric inpatient hospitalization and subsequent outpatient referral). Participants are randomized to four groups (in a 2 x 2 design): ketamine followed by 4 days of the digital ASAT

intervention; ketamine followed by a sham variant of ASAT (i.e., a computer task not targeting suicide-relevant cognition); or one of two no-infusion arms: ASAT-alone; or sham-ASAT alone. Patients are followed longitudinally for 1 year, enabling a test of both rapid and enduring effects of this novel intervention combination on depression symptoms and suicidal thoughts and behaviors during a high-risk period for recurrent suicidality. In a pilot feasibility and safety trial we conducted among 16 transdiagnostic patients, recruited using identical methods and offered a single, open-label ketamine infusion, we observed rapid, statistically significant decreases across multiple measures of depression and suicidal symptoms (p's < 0.001) with large to very large effect sizes (Cohen's d's: 1.7–8.8) observed at acute timepoints (24 h; 5 days). In addition, these rapid gains were uniformly maintained out to 6 months post-infusion, with no evidence that new safety concerns or iatrogenic effects emerged. If our ongoing RCT upholds and extends these preliminary findings, it could suggest ketamine, paired with our novel digital therapy, might be readily integrated into the settings where high-risk patients already receive healthcare, with the potential to become an important and novel tool in the treatment of acute suicidal crises.

Learning Objectives:

1. Describe the strengths and limitations of previous findings regarding ketamine's impact on suicidality.
2. Describe the rationale and preliminary findings on Automated Self-Association Training (ASAT)

Literature References:

1. Price RB, Spotts C, Panny B, Griffo A, Degutis M, Cruz N, Bell E, Do-Nguyen K, Wallace ML, Mathew SJ, Howland RH. A novel, brief, fully automated intervention to extend the antidepressant effect of a single ketamine infusion: A randomized clinical trial. Am J Psychiatry. In press.
2. Shivanekar SP, Gopalan P, Pizon AF, Spotts C, Cruz NA, Lightfoot M, Rohac RM, Baumeister A, Griffo A, Panny B, Kucherer S, Israel A, Rengasamy M, Price RB. A pilot study of ketamine infusion after suicide attempt: new frontiers in treating acute suicidality in a real-world medical setting. Int J Environ Res Public Health. 2022; 19:13792.

A SUICIDE PREVENTION TRIAL OF LITHIUM AT THE VA: CONDUCTING TRIALS IN PEOPLE AT HIGH RISK OF SUICIDE

Michael Ostacher, Stanford University School of Medicine

Individual Abstract: Lithium is recommended in many guidelines for the prevention of suicide. A major limitation of meta-analyses of trials examining suicide outcomes related to lithium use (in bipolar disorder, especially, but in also in major depressive disorder) is that most of those trials excluded participants who were actually at risk of suicide, by design, limiting the generalizability of the results suggesting that lithium (compared to placebo or other drugs) prevents death by suicide and all-cause mortality. The VA designed and initiated a trial that attempted to address this issue by enriching the design to be focused on people who were at highest risk of self-directed violence or suicide: those who recently made an attempt or who were hospitalized to prevent one. Because the sample required to directly answer the question about deaths from suicide or all-cause mortality is so large, a proxy measure was proposed, examining suicide attempts, self-directed violence, and aborted attempts.

The trial was ultimately stopped for futility after 519 veterans (mean [SD] age, 42.8 [12.4] years; 437 [84.2%] male) were randomized: 255 to lithium and 264 to placebo. No overall difference in repeated suicide-related events between treatments was found (hazard ratio, 1.10; 95% CI, 0.77-1.55). A total of 127 participants (24.5%) had suicide-related outcomes: 65 in the lithium group and 62 in the placebo group. One death attributed to suicide occurred in the lithium group and one in the placebo group.

Results of this study and its design will be presented during this symposium, with specific attention to the design of the study, how the follow up of participants was structured given their being at high risk of suicide, and the impact of those study design decisions on the measurement of outcomes.

Lithium remains recommended for the prevention of suicide in bipolar disorder but also in major depressive disorder. The basis of those recommendations will be discussed. The gaps in data and the impact of study methodology on outcomes will need to be addressed in order to have data that clinicians and patients can act upon in practice.

Learning Objectives:

1. At the end of the session the participant will understand what the impact of study design on suicide outcomes are in this VA trial of lithium vs placebo for suicide prevention.
2. At the end of the session the participant will understand how sample size affects the ability to estimate effects in trials of lithium for suicide prevention.

Literature References:

1. Katz IR, Rogers MP, Lew R, Thwin SS, Doros G, Ahearn E, Ostacher MJ, DeLisi LE, Smith EG, Ringer RJ, Ferguson R, Hoffman B, Kaufman JS, Paik JM, Conrad CH, Holmberg EF, Boney TY, Huang GD, Liang MH; Li+ plus Investigators. Lithium Treatment in the Prevention of Repeat Suicide-Related Outcomes in Veterans With Major Depression or Bipolar Disorder: A Randomized Clinical Trial. JAMA Psychiatry. 2022 Jan 1;79(1):24-32. doi: 10.1001/jamapsychiatry.2021.3170. PMID: 34787653; PMCID: PMC8600458.
2. Harrington KM, Liang MH, Hannagan K, Thwin SS, Ferguson RE, Morgenstern N, Flores E, Katz IR. Design and conduct of a provider survey to determine a clinically persuasive effect size in planning VA Cooperative Study #590 (Li+). Contemp Clin Trials Commun. 2016 Aug 31;4:149-154. doi: 10.1016/j.conctc.2016.08.004. PMID: 29736478; PMCID: PMC5935897.

DESIGNING AND IMPLEMENTING STUDIES IN PATIENTS WITH MDD AT IMMINENT RISK FOR SUICIDE: INSIGHTS FROM A DRUG DEVELOPMENT PROGRAM

Carla Canuso, Janssen Research and Development

Individual Abstract: Esketamine nasal spray is indicated for the treatment of depressive symptoms in adults with major depressive disorder with acute suicidal ideation and behavior (MDSI). Regulatory approval of this indication was based on two Phase 3 studies (ASPIRE I and II) and a Phase 2 study (PERSEVERE). The medication is also being studied in a Phase 2 study of adolescents with MDSI (DIRECTION). Taken together, the Janssen team has studied over 650 patients at imminent risk for suicide from across the globe. In doing so, the team has gained insight and experience in managing the key considerations and challenges in designing and implementing a drug development program for this patient population. These topics

include subject selection, efficacy outcomes and scale validation, signal-detection, safety management and monitoring, comparators, regional differences, regulatory requirements, and ethical considerations. Further, the non-specific treatment effects that hospitalization and lengthy assessments may have on measures of suicidality will be addressed. Finally, with the anticipation of new data from the DIRECTION study becoming available, unique insights relative to the study of suicidal adolescents will also be discussed.

Learning Objectives:

1. Attendees will gain insight into study design and implementation methods that allow for safe and ethical participation of these vulnerable patient populations in clinical trials.
2. Attendees will learn about unique methodological challenges that may arise in the measurement of suicidality in acute treatment trials.

Literature References:

1. Canuso, CM, Singh, J., Fedgchin, M., Alphs, L., Lane, R., Lim, P. Pinter, C., Hough, D., Sanacora, G., Manji, H., Drevets, W. Efficacy and Safety of Intranasal Esketamine for the Rapid Reduction of Symptoms of Depression and Suicidality in Patients at Imminent Risk for Suicide: Results of a Double-Blind, Randomized, Placebo-Controlled Study. Am J Psychiatry, 2018; 00:1-11; doi: 10: 1176/appi.ajp.2018.17060720?
2. Canuso, CM, Ionescu DF, Li X, Qiu X, Lane R, Turkoz I, Nash AI, Lopena TJ, Fu DJ: Esketamine Nasal Spray for the Rapid Reduction of Depressive Symptoms in Major Depressive Disorder with Acute Suicidal Ideation or Behavior J Clin Psychopharmacol. 2021 Sep-Oct 01;41(5):516-524. doi: 10.1097/JCP.0000000000001465

+*HOW TO MAKE PROGRESS IN SUICIDE PREVENTION: DESIGNING AND CONDUCTING CLINICAL TRIALS AMONG HIGH RISK PATIENTS

Samuel Wilkinson, Yale School of Medicine

Individual Abstract: Suicide is among the top 10 causes of mortality worldwide, with 45,979 suicide deaths occurring in the United States in 2020. Unfortunately, despite renewed public efforts to confront this problem, suicide rates have increased markedly in the last 15 years. The total number of suicides deaths has increased by >60% from 1999 to 2019. Suicide-related visits to the emergency department have increased 42% in the last 20 years. For certain groups (e.g., adolescents, young adults, and minority youth), suicide risk has risen dramatically in the last decade. Recently, the Director of the National Institute of Mental Health has called for a renewed effort to combat this public health problem and reduce the rate of suicide.

For many decades, the vast majority of clinical trials conducted among patients with mental illness have excluded patients at risk of suicide. Reasons for this include regulatory challenges, a desire to avoid liability, and discomfort working directly with high-risk patients. Recognizing the great evidence gap that exists from decades of neglect of this issue, there has been increased interest recently in designing and conducting trials that enroll patients with significant suicidal ideation. These include trials involving ketamine or esketamine, lithium, as well as novel approaches to psychotherapeutic interventions. The current panel brings together perspectives from academia and industry experts.

Dr. Wilkinson will discuss his ongoing experience conducting trials that specifically enroll patients at risk for suicide. He currently serves as overall PI of the CBT-ENDURE study (Cognitive Behavioral Therapy Following Esketamine for Major Depression and Suicidal

Ideation for Relapse Prevention). The CBT-ENDURE study is a multisite study (Yale, Emory, University of Alabama-Birmingham) that recruits both inpatients and outpatients with suicidal ideation who are treated with esketamine and randomly assigned to CBT or treatment as usual. Dr. Wilkinson will discuss study methods, selection of outcomes, regulatory challenges, and study progress.

Learning Objectives:

1. To understand challenges to conducting studies enrolling high-risk patients
2. To discuss possible solutions to managing these challenges

Literature References:

1. The Effect of a Single Dose of Intravenous Ketamine on Suicidal Ideation: A Systematic Review and Individual Participant Data Meta-Analysis. Wilkinson ST, Ballard ED, Bloch MH, Mathew SJ, Murrough JW, Feder A, Sos P, Wang G, Zarate CA Jr, Sanacora G. Am J Psychiatry. 2018 Feb 1;175(2):150-158.
2. Cognitive Behavioral Therapy to Sustain the Antidepressant Effects of Ketamine in Treatment-Resistant Depression: A Randomized Clinical Trial. Wilkinson ST, Rhee TG, Joormann J, Webler R, Ortiz Lopez M, Kitay B, Fasula M, Elder C, Fenton L, Sanacora G. Psychother Psychosom. 2021;90(5):318-327.

*DRUG DISCOVERY AND PRECISION MEDICINE APPROACHES TO REDUCE CLINICAL BURDEN OF SUBSTANCE USE DISORDERS

Madhukar Trivedi, UT Southwestern Medical Center

Overall Abstract: Overdose deaths due to substances, such as methamphetamine and fentanly, have sharply increased over the past 5 years in the United States. This has been accompanied by increase in the prevalence of substance use disorders. For example, there has been over 10-fold increase in the prevalence of methamphetamine use disorder (MUD) in black Americans from 2015 to 2018. The public health burden of substance use disorders has been compounded by the lack of effective therapeutic interventions, and by the additive burden of these disorders overall health of individuals. Therefore, our proposed symposium will bring together a panel of early- and mid-career investigators and senior researchers who will present cutting-edge preclinical and clinical research on novel approaches to treatment of these disorders. The first presentation will focus on a serotonergic aversive mechanism that underlies individually variable protection against drug seeking behaviors. Specifically, dephosphorylation of serotonin 2C receptor increases vulnerability to cocaine seeking behaviors and restoration of this receptor function by blockade of Phosphatase and Tensin Homolog deleted on Chromosome 10 (PTEN) increases behavioral avoidance to cocaine. Therefore, phosphorylation mechanisms of serotonin 2C receptor may represent novel therapeutic targets for cocaine use disorder. The second presentation will highlight the burden of cannabis use disorder on COVID-19 related outcomes, including higher likelihood of ventilatory support and hospitalization in individuals with cannabis use disorder. This presentation will also include positron imaging studies of reduced synaptic density with cannabis use disorder and the potential for modulation of endocannabinoid signaling as novel treatments. The third presentation will include exploratory findings from a large clinical trial of naltrexone and bupropion combination that was shown to be superior to placebo in attaining response, i.e., three out of four methamphetamine negative sample over a two week evaluation period, in individuals with methamphetamine use disorder. Specifically, this presentation will demonstrate how distinct dysregulations in immune response are associated with poorer outcomes with the naltrexone-bupropion combination. The fourth and final presentation will

focus on neural underpinnings of childhood maltreatment in individuals with cocaine use disorder and how they can be used as foundation for personalizing treatment of substance use disorders. This presentation will focus on structural and functional neuroimaging studies of individuals with cocaine use disorders and healthy controls, and how childhood trauma influences dysfunctions in brain circuits. Together, these represent exciting new translational data that can guide development of novel treatments for substance use disorders and precision approaches to use the currently available ones.

Learning Objectives:

1. Recognize the burden of substance use disorders and how lack of effective treatments has contributed to it.
2. Identify novel mechanisms that can serve as treatment targets and guide development of new treatments and precision approaches to using current treatments.

PROTECTION AGAINST COCAINE-SEEKING VIA ENHANCEMENT OF SEROTONERGIC AVERSIVE RESPONSE TO COCAINE

Thomas Jhou, Medical University of South Carolina

Individual Abstract: Cocaine produces strong rewarding effects that drive abuse potential, but also delayed aversive “crashes” that oppose its rewarding effects and are less well understood. In rats, we found that cocaine’s aversive effects are intrinsically stronger in a subset of individuals in whom they confer resilience to drug-seeking during both acquisition and relapse. This resilience derives from cocaine’s ability to increase serotonin levels in the rostromedial tegmental nucleus (RMTg), depolarizing these neurons via serotonin 2C receptors (5HT2CRs) and driving aversive learning. In a subset of animals, RMTg neurons lose these depolarizing responses due to receptor dephosphorylation, resulting in increased drug-seeking during acquisition and relapse, while blockade of this dephosphorylation restores the aversive component of the response to cocaine, protecting against drug-seeking. Our findings that 5HT2CR function is downregulated in drug-vulnerable animals may explain why prior 5HT2CR agonists have not been effective addiction treatments, while also providing a novel therapeutic target (phosphorylation mechanisms) that can circumvent the shortcomings of earlier treatment attempts. Therefore, phosphorylation mechanisms of serotonin 2C receptors represent potentially nove.

Learning Objectives:

1. Understand the role of cocaine's aversive effects in regulating drug-seeking. Recognize mechanisms related to serotonin.
2. C receptor that underpin individual differences in cocaine-seeking behavior

Literature References:

1. Parrilla-Carrero J, Eid M, Li H, Chao Y, and Jhou T, Synaptic Adaptations at the Rostromedial Tegmental Nucleus Underlie Individual Differences in Cocaine Avoidance Behavior. Journal of Neuroscience, 2021, 41 (21) 4620-4630.
2. Ma L, Cunningham KA, Anastasio NC, Bjork JM, Taylor BA, Arias AJ, Riley BP, Snyder AD, Moeller FG. A serotonergic biobehavioral signature differentiates cocaine use disorder participants administered mirtazapine. Transl Psychiatry. 2022 May 6;12(1):187.

IMPACT OF CANNABIS USE ON COVID-19 OUTCOMES AND NEW TREATMENT TARGETS FOR CANNABIS USE DISORDER

Rajiv Radhakrishnan, Yale School of Medicine

Individual Abstract: Background and purpose: The COVID-19 pandemic has disproportionately impacted people with mental health diagnoses. However, less is known about the impact of cannabis use on COVID-19 outcomes. Interestingly, medical cannabis businesses were considered to be an "essential business" during COVID-19. In this session, we will discuss new data examining the impact of cannabis use on COVID-19 outcomes using electronic health record (EHR) data, the effect of cannabis use on an in vivo brain molecular target, SV2A and discuss preliminary data on the efficacy of fatty-acid amide hydrolase (FAAH) inhibition in cannabis use disorder.

Methods: Data from Yale New Haven Healthsystem EHR was analyzed to identify all patients who tested positive for COVID-19 between Jan 1, 2020, and Dec 31, 2021. COVID-19–relevant outcomes included mortality, need for intensive care unit (ICU) admission, need for ventilatory support, length of hospitalization, and number of hospitalizations. Multivariable logistic regression was performed controlling for potential confounders such as age, sex, ethnicity, race, disability, medical comorbidity (Charlson Comorbidity Index), tobacco use, and insurance status. In an independent sample, cannabis-use disorder subjects (n=12) and matched healthy controls, underwent positron emission tomography (PET) imaging with [11C] UCB-J, a radioligand for the synaptic vesicle glycoprotein 2A (SV2A) and a proxy measure of brain synaptic density. Hippocampal function was assessed using a verbal memory task.

Results: 17,423 patients were admitted for COVID-19 during the study period. Cannabis use was associated with increases in the need for ventilatory support (OR 1.54, p=0.008), number of hospitalizations (mean difference =0.76, p=<0.001), and total duration of hospitalization (mean difference = 15.18, p<0.001). In an independent sample, cannabis-use disorder subjects (n=12) and matched healthy controls, underwent positron emission tomography (PET) imaging with [11C]UCB-J PET imaging study, relative to healthy controls, cannabis-use disorder subjects showed significantly lower hippocampal synaptic density (~10%, p = 0.008, effect size 1.2) and also performed worse on the verbal memory task. The preliminary results of FAAH inhibition on cannabis use disorder (D'Souza et al, 2019) will also be discussed.

Importance to the field: Rates of cannabis use have been increasing in the US as states continue to legalize its use for medical and recreational purposes. The impact of cannabis use on COVID-19 is hence important for clinicians. Additionally, there are currently no FDA approved treatments for cannabis-use disorder. There is hence a great need to identify new molecular targets and develop new treatments for this condition.

Learning Objectives:

1. To provide knowledge about the impact of cannabis use of COVID-19 and the effects of cannabis on brain synaptic density.
2. To provide preliminary insights into the efficacy of FAAH inhibition on cannabis use disorder.

Literature References:

1. D'Souza DC, Cortes-Briones J, Creatura G, et al. Efficacy and safety of a fatty acid amide hydrolase inhibitor (PF-04457845) in the treatment of cannabis withdrawal and dependence in men: a double-blind, placebo-controlled, parallel group, phase 2a single-site randomised controlled trial. Lancet Psychiatry. 2019;6(1):35-45

2. D'Souza DC*, Radhakrishnan R*, Naganawa M, et al. In vivo Evidence of Lower Hippocampal Synaptic Density in Cannabis Use Disorder. Molecular Psychiatry. 2021;26(7):3192-3200

IMMUNE MECHANISMS OF RESPONSE TO NALTREXONE-BUPROPION COMBINATION IN METHAMPHETAMINE USE DISORDER: FINDINGS FROM THE ADAPT-2 STUDY

Madhukar Trivedi, UT Southwestern Medical Center

Individual Abstract: Background: There are no approved pharmacological treatments for methamphetamine use disorder (MUD). We recently showed that while response to naltrexone-bupropion combination was 5-fold higher than placebo, only 13.6% of individuals with MUD were able to attain response. Here, we evaluated the association of immune dysregulation with response to naltrexone-bupropion in individuals with MUD.

Methods: Participants of Accelerated Development of Additive Treatment for Methamphetamine Disorder [ADAPT-2] study with plasma samples available at week-6 were included. Immune markers were assayed with the BioRad 27-plex kit. Principal component analysis was used to identify latent factors of immune function. Logistic regression analyses were used for association between immune factors and response (defined as 3 out of 4 negative urine sample over a 2-week evaluation period). Covariates included age, sex, race, and ethnicity. Post hoc analyses evaluated percentage of individuals with negative urine drug sample based on the levels of immune markers (high versus low, median split).

Results: N=49 and N=119 were randomized to naltrexone-bupropion and placebo in Stage 1 of ADAPT-2, respectively. The first two principal components were retained and explained over 75% variance in the immune markers. First principal component (PC1) markers included interferon γ, interleukin (IL) 1β, IL-17A, and IL-2. Second principal component (PC2) markers included IL-4, IL-9, macrophage inflammatory protein 1 beta, and tumor necrosis factor alpha. At week-6, higher levels of PC2 were associated with lower likelihood of response at week-6 to naltrexone-bupropion [odds ratio (OR) = 0.28, 95% confidence interval (CI) = 0.09, 0.90; p = 0.032). No similar association were noted for placebo group. The association between higher levels of PC2 at week-6 and lower likelihood of response to naltrexone-bupropion combination was significant at week-12 (OR = 0.17, 95% CI = 0.04, 0.70; p = 0.013). Low vs. high levels of PC2 were associated with higher proportion of methamphetamine-negative urine samples with naltrexone-bupropion by week-2 and this difference was maintained until week-12.

Conclusion: We found that distinct immune-related dysfunctions were associated with poor response to naltrexone-bupropion combination. Future studies are needed to understand the cellular and molecular mechanisms of this association.

Learning Objectives:

1. Recognize the need for developing effective treatments for individuals with methamphetamine use disorder.
2. Understand the immune mechanisms that are associated with poorer response to naltrexone-bupropion combination in individuals with methamphetamine use disorder.

Literature References:

1. Trivedi MH, Walker R, Ling W, Dela Cruz A, Sharma G, Carmody T, Ghitza UE, Wahle A, Kim M, Shores-Wilson K, Sparenborg S, Coffin P, Schmitz J, Wiest K, Bart

G, Sonne SC, Wakhlu S, Rush AJ, Nunes EV, Shoptaw S. Bupropion and Naltrexone in Methamphetamine Use Disorder. N Engl J Med. 2021 Jan 14;384(2):140-153.
2. Davidson M, Mayer M, Habib A, Rashidi N, Filippone RT, Fraser S, Prakash MD, Sinnayah P, Tangalakis K, Mathai ML, Nurgali K, Apostolopoulos V. Methamphetamine Induces Systemic Inflammation and Anxiety: The Role of the Gut-Immune-Brain Axis. Int J Mol Sci. 2022 Sep 23;23(19):11224.

SETTING THE STAGE FOR PERSONALIZING TREATMENT OF SUBSTANCE USE DISORDER: NEURO-PSYCHOSOCIAL DETERMINANTS

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

Individual Abstract: Background and purpose: Despite the enormous medical and societal burden of substance use disorders, little has changed in developing treatments that consider multidimensional psychosocial and clinical factors to facilitate and improve personalized care for subgrouping patients. Childhood maltreatment, a major psychosocial impact on addiction, is known to alter the reward system including mesocorticolimbic-nigrostriatal-dopaminergic pathways, which are core pathways in addiction. Limited information is, however, known regarding social-neural effects of childhood maltreatment in addiction. We examined neural underpinnings of childhood maltreatment in individuals with cocaine use disorder, to provide an initial foundation for personalizing treatment of substance use disorders.

Methods: Individuals with cocaine use disorder (CUD) and healthy controls (HC) were grouped in those with low and high trauma using the Childhood Trauma Questionnaire: 20 HC with low trauma (HC-); 20 HC with high trauma (HC+); 12 CUD low trauma (CUD-); 17 CUDS with high trauma (CUD+). The groups did not differ on demographic variables. Groups were evaluated using fMRI in regard to neural effects of childhood trauma on: 1) Gray matter concentration using whole-brain flexible factorial model in voxel-based morphometry; 2) Blood oxygenation level dependent during social choice using the Social Navigation fMRI task with analysis of covariance, followed by group classification with average accuracy from leave one out method with 1000 permutations; and 3) Circuit connectome in 44 social brain regions of interest using network-based statistics. Correction for multiple comparisons was applied to all analyses.

Results: Morphologically, we observed trauma effects (HC-, CUD- vs. HC+, CUD+) in the left caudate (qcor.<.05) and right secondary visual cortex (qcor.<.05). In addition, CUD+ had increased gray matter in the right amygdala (qcor.<.001) and left temporal pole (qcor.<.001) compared to CUD-. Functionally, during social choice, the greater the childhood trauma the lower the hippocampus activation (Pcor.<.05). In addition, the activation in the left hippocampus, accurately classified the CUD versus HC groups (L hippocampus: P<.001). On the connectome level, we observed a drug effect where HC had greater connectivity in limbic (NAcc, vmPFC) and executive (dmPFC) nodes as compared with CUD (54 edges, pcor. = .06; trend). Trauma effects (HC-, CUD- vs. HC+, CUD+) were evident in limbic (vmPFC, Amyg) and parietal (precuneus) nodes (63 edges, pcor. = .02). The strongest effect was the interaction of drug x trauma with nodes in ventrolateral corticolimbic regions (insula, IFG) and visuosensory cortex (V5, fusiform gyrus; 74 edges, pcor. = .002).

Importance to the field: Childhood maltreatment has enduring impact on the structural integrity and neural function in executive (prefrontal), limbic, and visual-sensory networks—regions with key roles in cognitive and social-affective regulation—that is evident despite the recency

of drug use. These findings emphasize the long-term neural impact of psychosocial factors that should be considered in the development of a neurobiologically-informed staging approach that crosses current diagnostic silos to bring clarity to the heterogeneity of course and outcome across substance use disorders.

Learning Objectives:

1. Provide knowledge about the enduring social-neural underpinnings of psychosocial factors (childhood maltreatment) on substance use disorders.
2. Glean insights for the development of a neurobiologically-informed staging approach that crosses current diagnostic silos to bring clarity to the heterogeneity of course and outcome across substance use disorders.

Literature References:

1. Bachi, K., et al. Reduced Orbitofrontal Gray Matter Concentration as a Marker of Premorbid Childhood Trauma in Cocaine Use Disorder. Front Hum Neurosci 2018; 12(51). Front. Hum. Neurosci. doi: 10.3389/fnhum.2018.00051
2. Sahani, V., Hurd, Y.L., and Bachi, K. Neural Underpinnings of Social Stress in Substance Use Disorders. Curr Top Behav Neurosci. 2022; 54: 483–515. doi:10.1007/7854_2021_272.

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

Panel Sessions

*#IRRITABILITY ACROSS THE LIFESPAN: CAUSES, ASSESSMENTS, TREATMENTS

Maurizio Fava, Massachusetts General Hospital

Overall Abstract: Irritability is a common reason for referral to a treatment provider and is a risk factor for depression, suicide, significant functional impairment, and substance use later in life. The speakers will present data from recent studies on investigation of causes, assessment and treatment across the lifespan.

Dr. Jha will present data from 3 related studies on neurocircuit mechanisms underlying irritability and suicidal ideation across the lifespan. Study 1 was cross-sectional and included individuals from primary care and psychiatric clinics (N=2248). Study 2 included repeated measures of irritability and suicide from individuals in the Texas Resilience Against Depression study who completed monthly surveys (N=454 with 3429 observations). In the first two studies, age was found to significantly affect irritability and its relationship to suicidality across the lifespan. Additionally, data from the Establishing Moderators and Biosignatures of Antidepressant Response in Clinical Care (EMBARC) study (N=274) was queried to examine association between resting-state functional connectivity in the striatum and irritability and suicide.

Dr. Baweja, will present results from a systematic review of the literature on irritability in youth with attention-deficit/hyperactivity disorder (ADHD) as well as related constructs including impulsive aggression, severe mood dysregulation (SMD) and disruptive mood dysregulation disorder (DMDD). Data regarding use of pharmacotherapy and behavioral interventions will be reviewed. A multimodal treatment approach integrating both pharmacological and

psychosocial interventions were found to be the most efficacious for improving irritability in youth with ADHD. Adjunctive treatment with atypical antipsychotic and mood stabilizer targeting these symptoms may offer additional benefit if these initial treatments are insufficient but tolerability needs to be closely monitored to ensure a favorable risk/benefit profile.

Dr. Trivedi will present a study of individuals from the ongoing Texas Youth Depression and Suicide Research Network (TX-YDSRN) with self- and informant-rated versions of the 10-item extended Concise Associated Symptom Tracking-Irritability scale (CAST-IRRe) (N=658). In this large sample of youths, significant differences in self- (youth) versus informant- (parent/guardian) report of irritability were found. Additionally, the informant report of irritability was higher than self-report of irritability in males but lower in females.

Dr. Fava will lead the discussion about the relevance of these results for clinicians and researchers. As a trans-diagnostic symptom, irritability is impairing and careful attention to assessment and treatment is vital for improvement in functioning. This panel will provide the audience with updates from the field on patient and family-rated measures of irritability, associated neurocircuitry and treatment recommendations.

Learning Objectives:

1. Participants will be able to define the construct of irritability.
2. Participants will be able to identify two evidence-based treatments for irritability.

IRRITABILITY AND SUICIDAL IDEATION IN DEPRESSIVE DISORDERS ACROSS LIFESPAN: CLINICAL SIGNIFICANCE AND POTENTIAL NEUROCIRCUIT MECHANISMS

Manish Jha, University of Texas Southwestern Medical Center

Individual Abstract: Background: Recent reports have linked irritability to suicidal ideation (SI) in adults with major depression. Here, we seek to evaluate age-related differences in association between irritability and SI and identify the neurocircuit mechanisms that mediate association of irritability with SI.

Methods: Study 1 was cross-sectional and included individuals from primary care and psychiatric clinics who completed irritability [Concise Associated Symptom Tracking irritability domain (CAST-IRR)]and SI [Concise Health Risk Tracking suicidal thoughts factor (CHRT-SUI)] measures (N=2248). Linear regression analysis with age-by-CAST-IRR interaction was used to evaluate whether association between irritability and SI differed based on age. Covariates included overall depression, gender, race, and ethnicity.

Study 2 included repeated measures of CAST-IRR and CHRT-SUI from individuals in Texas Resilience Against Depression study who completed monthly surveys (N=454 with 3429 observations). Repeated-measures mixed model analysis with age-by-CAST-IRR interaction and overall depression, gender, race, and ethnicity as covariates was used.

Study 3 included participants of the Establishing Moderators and Biosignatures of Antidepressant Response in Clinical Care (EMBARC) study with magnetic resonance imaging (MRI), CAST-IRR and CHRT-SUI data available (N=274). Resting-state functional connectivity (FC) among 121 cortical and subcortical regions were computed and linear regression analyses were used to identify FC pairs that were associated with irritability. Baron

and Kenny approach was used to evaluate whether these FC pairs mediated the association between irritability and SI. Covariates included age, sex, race, ethnicity and site.

Results: In Study 1, N=1677 and N=571 individuals were between ages of 12-17 (pediatric) and 18-64 (adult) years, respectively. The age-by-CAST-IRR interaction was significant ($p=0.0003$) where the association between CAST-IRR and CHRT-SUI was higher in pediatric ($\beta=0.25$, SE=0.03) versus adult ($\beta=0.13$, SE=0.03) group.

In Study 2, N=41, N=370, and N=43 individuals were between ages of 12-17 (pediatric), 18-64 (adult) and 65+(elderly) years, respectively. The age-by-CAST-IRR interaction was significant ($p=0.009$) where the association between CAST-IRR and CHRT-SUI was higher in pediatric ($\beta=0.10$, SE=0.03) and elderly ($\beta=0.15$, SE=0.02) groups versus adult ($\beta=0.05$, SE=0.01) group.

In Study 3, fifteen FC pairs were associated with irritability at $p<0.0005$ threshold of which nine FC pairs included the striatum. Functional connectivity of dorsal striatum to lingual and superior temporal regions significantly mediated ($p<0.05$) the association between symptoms of irritability and SI.

Conclusion: Association between irritability and SI was stronger in youths as compared to adults. Dysfunctions within the striatum may mediate this association and serve as targets for developing novel circuit-specific treatments.

Learning Objectives:

1. Recognize the association between irritability and suicidal ideation and how it may differ based on age.
2. Understand the potential neurocircuit mechanisms that may link irritability to suicidal ideation.

Literature References:

1. Jha MK, Minhajuddin A, Chin Fatt C, Kircanski K, Stringaris A, Leibenluft E, Trivedi MH. Association between irritability and suicidal ideation in three clinical trials of adults with major depressive disorder. Neuropsychopharmacology. 2020 Jul 14. doi: 10.1038/s41386-020-0769-x.
2. Jha MK, Trivedi MH. Identifying Novel Mechanisms and Treatment Targets for Irritability and Aggression in Psychiatric Disorders. Neuropsychopharmacology. 2021 Sep 20. doi: 10.1038/s41386-021-01166-4

AN UPDATE ON IRRITABILITY IN YOUTH WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER

Raman Baweja, Penn State College of Medicine

Individual Abstract: Objectives: Irritability is one of the most common reasons for referral to mental health professionals and is a risk factor for depression, suicide, significant functional impairment, and substance use later in life. Irritability is commonly associated with attention-deficit/hyperactivity disorder (ADHD) as up to half of youth with ADHD have prominent symptoms of irritability. Comorbid irritability causes meaningful increases in impairment beyond that seen with ADHD alone. The objective of this presentation is to share current evidence about management of ADHD and comorbid irritability.

Methods: We will review all published and presented works from January 2009 to September 2022 on irritability in youth with ADHD as well as related constructs including impulsive

aggression, severe mood dysregulation (SMD) and disruptive mood dysregulation disorder (DMDD). Existing literature was ascertained in the English language, published across 5 databases, namely, Medline, PsychInfo, Embase, Cochrane Register of Controlled Trials, and Web of Science Core Collection. We conducted searches using the following categories: ADHD, DMDD, SMD, irritability, oppositional defiant disorder, aggression, children, adolescence, youth, nonstimulant, pharmacotherapy, drugs, stimulants, and medication.

Results: CNS stimulants were well-tolerated among youth with comorbid irritability. Optimization of CNS stimulants using structured ratings of tolerability and efficacy led to appreciable reductions in irritability. Data supported that joint use of behavioral parenting interventions with CNS stimulant optimization eliminates the need for adjunctive pharmacotherapy for aggression or other behavioral problems in approximately half of youth with ADHD and impairing levels of irritability. When aggression persists, there was evidence that risperidone, and to a lesser degree, divalproex augmentation led to further improvements. There was one controlled trial to support SSRIs for severe irritability and for molindone to reduce impulsive aggression, one open label trial to support aripiprazole, and none for nonstimulants or other medications where irritability was specifically reported as an outcome.

Conclusions: Children with ADHD often exhibit persistent irritability and impulsive aggression that are associated with significant impairment. A multimodal treatment approach integrating both pharmacological and psychosocial interventions are the most efficacious for improving these issues in youth with ADHD. Adjunctive treatment with atypical antipsychotic and mood stabilizer targeting these symptoms may offer additional benefit if these initial treatments are insufficient but tolerability needs to be closely monitored to ensure a favorable risk/benefit profile.

Learning Objectives:

1. To describe the irritability and related constructs in youth with ADHD.
2. To discuss evidence-based pharmacological and psychosocial interventions for irritability in youth with ADHD.

Literature References:

1. Baweja R, Waxmonsky JG. Updates in pharmacologic strategies for emotional dysregulation in attention deficit hyperactivity disorder. Child and Adolescent Psychiatric Clinics. 2022 Jul 1;31(3):479-98.
2. Breaux R, Baweja R, Eadeh HM, et al. Systematic Review and Meta-analysis: Pharmacological and Non-Pharmacological Interventions for Persistent Non-episodic Irritability. Journal of the American Academy of Child and Adolescent Psychiatry, 2022; DOI: 10.1016/j.jaac.2022.05.012

INFORMANT EFFECTS ON MEASURES OF IRRITABILITY IN YOUTHS AND POTENTIAL SEX DIFFERENCES: FINDINGS FROM THE TX-YDSRN STUDY

Madhukar Trivedi, UT Southwestern Medical Center

Individual Abstract: Background: Irritability if a common yet often understudied feature of psychiatric disorders across the lifespan. Among youths and young adults, irritability has been linked to poorer functioning and greater severity of anxiety symptoms and suicidal ideation. Emerging evidence also suggests discrepancies between informant (parent/guardian) report of irritability versus self (youth) report of irritability. Here, we evaluated the psychometric

properties of a new 10-item scale of irritability that was completed by both youths and parent/guardians along with differences in the self- vs. informant-rated versions and how they relate to other symptom measures (especially suicidal ideation) and measures of school and interpersonal functioning.

Methods: Individuals from the ongoing Texas Youth Depression and Suicide Research Network (TX-YDSRN) with self- and informant-rated versions of 10-item extended Concise Associated Symptom Tracking-Irritability scale (CAST-IRRe) were included (N=658). Exploratory factor analysis and item response theory (IRT) analysis were used to evaluate the factor structure, and Cronbach's alpha was used to measure internal consistency. Correlations with other clinical measures were used to inform construct validity.

Results: Both self- and informant-rated versions of CAST-IRRe have a single-factor structure on exploratory factor analyses. In polychoric correlation matrices from IRT analyses, only the first factor had an eigenvalue exceeding 1.00 in both self- and informant-rated versions, supporting the unidimensionality of this measure. Furthermore, the slope of all items exceeded 1.0 (excluding the first item of the anxiety domain), indicating that these items provided adequate discrimination. There was poor agreement between self- and informant-rated times with Kappa statistics ranging from 0.07 to 0.24. Additionally, 9 out of 10 individual items were statistically different on chi-square test between self- and parent-rated version (all $p < 0.005$). Self-rated version were more strongly associated with other self-rated versions of depression (including suicidal ideation), anxiety, school functioning, and interpersonal functioning. Similarly, informant-rated version had a stronger association with other informant-rated measures. When evaluated for sex differences, self-rated irritability was significantly higher in females as compared to males (Cohen's $d = 0.4$, $p < 0.0001$) whereas scores of informant-rated CAST-IRRe were similar in males and females. Notably, informant-report of irritability was higher than the self-report of irritability in males. Conversely, in females, the informant-report of irritability was lower than the self-report of irritability.

Conclusion: In this large sample of youths, we found significant differences in self- (youth) versus informant- (parent/guardian) report of irritability. Additionally, the informant report of irritability was higher than self-report of irritability in males but lower in females.

Learning Objectives:

1. Recognize the differences in self-report versus informant report of irritability in youths with depression.
2. Understand the potential sex differences in how irritability is reported by youths and their parents/guardians.

Literature References:

1. Stringaris A, Vidal-Ribas P, Brotman MA, Leibenluft E. Practitioner Review: Definition, recognition, and treatment challenges of irritability in young people. J Child Psychol Psychiatry. 2018 Jul;59(7):721-739. doi: 10.1111/jcpp.12823. Epub 2017 Oct 30. PMID: 29083031.
2. Zik J, Deveney CM, Ellingson JM, Haller SP, Kircanski K, Cardinale EM, Brotman MA, Stoddard J. Understanding Irritability in Relation to Anger, Aggression, and Informant in a Pediatric Clinical Population. J Am Acad Child Adolesc Psychiatry. 2022 May;61(5):711-720. doi: 10.1016/j.jaac.2021.08.012. Epub 2021 Aug 23. PMID: 34438022; PMCID: PMC8863995.

+EXPANDING CLINICAL TRIAL DIVERSITY: LGBTQIA+ INCLUSION

Francisco Moreno, University of Arizona

Overall Abstract: The Food Drug Administration (FDA) along with other agencies continue to develop guidance aimed at improving enrollment and representation of clinical trials participants from underrepresented racial and ethnic populations. As organizations begin to implement strategies focused on increasing awareness of the value of diversity and need for enhanced clinical trial participation by members of racial and ethnic groups traditionally underrepresented, it is important to challenge ourselves as clinicians and investigators to expand this discussion to include other underserved individuals like the LGBTQIA+ community. The LBGTQIA+ community is remarkably diverse and representative of every race, ethnicity, age, religion, and socioeconomic groups. Multiple studies have reported that the LGBTQIA+ populations face numerous and ongoing barriers to attain physical health and mental health treatment services, and quality of care. There is also lack of LGBTQIA+ individuals in clinical research and their limited representation implies that the benefits of potential interventions may not be generalized this and other populations. The lack of inclusivity in clinical research has drawn the attention of advocacy groups, pharmaceutical organizations, federal agencies, and academia due to its moral and scientific implications.
This panel will describe social, political, and service factors that contribute to health and mental disparities in the LGBTQIA+ community and discuss how these persistent disparities lead to poor health outcomes and identify opportunities to enhance diversity and inclusion in clinical trial recruitment and research.

The panel will discuss: How effective diversity, equity, and inclusion programs have allowed for improvements in community outreach, engagement, experience design, and return of value to optimize clinical trial inclusivity and intersectionality may enhance representation in the underserved and underrepresented people inclusive of individuals from sexual and gender minorities. Best practices for affirming approaches in the management and treatment of underserved populations including the LGBTQIA+ community.

Learning Objectives:

1. After the presentation, attendees will have up-to-date information regarding inclusive and affirming practices for engagement, recruitment, and research experience for work with underrepresented groups.
2. Participants will have an increased appreciation for the value of diversity in research and the role each must play to advance this important variable.

EXPANDING CLINICAL TRIAL DIVERSITY BEYOND RACE & ETHNICITY

Brian Rothman, Otsuka Pharmaceutical Development and Commercialization, Inc., Princeton, NJ, USA

Individual Abstract: The Food Drug Administration (FDA) along with other agencies continue to develop guidance aimed at improving enrollment and representation of clinical trials participants from underrepresented racial and ethnic populations. As organizations become more aware and actively working to implement strategies focused on increasing awareness and need for enhanced clinical trial diversity with respect to race and ethnicity; it is important to challenge ourselves as clinicians and investigators to expand this discussion to include all underserved cohorts.

People in the LGBTQIA+ community face numerous and ongoing barriers to attain physical health and mental health treatment, services, and quality of care. There is also likely a relative under-representation of LGBTQIA+ individuals in clinical research. This under- representation in clinical research could mean that outcomes and interventions may not be generalized to all populations.

The need to increase inclusivity in clinical research has drawn the attention of advocacy groups, pharmaceutical organizations, federal agencies, and academia due to its moral and scientific implications.

The objective of the panel is to educate the mental health community on the factors that contribute to health and mental disparities and discuss how these persistent disparities lead to poor health outcomes and identify opportunities to enhance diversity and inclusion in clinical trial recruitment and research. The panel will discuss:

- How effective diversity, equity, and inclusion programs have allowed for improvements in clinical trial recruiting to include underserved and underrepresented people.
- Outcomes from strategies implemented to improve and enhance diversity in clinical trial recruitment in pharmaceutical research and development.
- How principles and strategies of inclusivity and intersectionality may enhance representation in the underserved and underrepresented people
- Challenges with managing and treating the underserved community including the LGBTQIA+ community.

After the presentation, attendees will have up-to-date information regarding recent outcomes from strategies implemented in clinical trials recruiting, best practices, opinions, and potential solutions to address challenges related to lack of inclusivity within clinical research. The attendees will have an opportunity to discuss and interact with panelists to share their success stories and further enhance knowledge in this area.

Learning Objectives:

1. What are outcomes from pharmaceutical research that have been successful in identifying the areas where people are underrepresented?
2. What are practical strategies that can be implemented in the research community to enhance recruitment of underserved and underrepresented people?

Literature References:

1. Boehmer, Ulrike. Twenty Years of Public Health Research: Inclusion of Lesbian, Gay, Bisexual, and Transgender Populations. Am J Public Health. 2002; 92:1125–1130.
   Mapes BM, Foster CS, Kusnoor SV, Epelbaum MI, AuYoung M, Jenkins G, et al. (2020) Diversity and inclusion for the All of Us research program: A scoping review. PLoS ONE 15(7): e0234962. https://doi.org/10.1371/journal. pone.0234962

EXPANDING CLINICAL TRIAL DIVERSITY BEYOND RACE & ETHNICITY

Candace Saldarini, Otsuka (OPDC)

Individual Abstract: The Food Drug Administration (FDA) along with other agencies continue to develop guidance aimed at improving enrollment and representation of clinical

trials participants from underrepresented racial and ethnic populations. As organizations become more aware and actively working to implement strategies focused on increasing awareness and need for enhanced clinical trial diversity with respect to race and ethnicity; it is important to challenge ourselves as clinicians and investigators to expand this discussion to include all underserved cohorts. People in the LGBTQIA+ community is one such cohort. This community demonstrates diversity in sexual orientation and gender identity as well as in race, ethnicity, socioeconomic status and other dimensions of diversity.

People in the LGBTQIA+ community face numerous and ongoing barriers to attain physical health and mental health treatment, services, and quality of care. There is also likely a relative under-representation of LGBTQIA+ individuals in clinical research. This under- representation in clinical research could mean that outcomes and interventions may not be generalized to all populations.

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- How principles and strategies of inclusivity and intersectionality may enhance representation in the underserved and underrepresented people
- Challenges with managing and treating the underserved community including the LGBTQIA+ community.

After the presentation, attendees will have up-to-date information regarding recent outcomes from strategies implemented in clinical trials recruiting, best practices, opinions, and potential solutions to address challenges related to lack of inclusivity within clinical research. The attendees will have an opportunity to discuss and interact with panelists to share their success stories and further enhance knowledge in this area.

Learning Objectives:

2. How can advocacy, the community, academia, and others work together to address these issues and concerns?
3. What are practical strategies that can be implemented in the research community to enhance recruitment of underserved and underrepresented people?

Literature References:

1. Mapes BM, Foster CS, Kusnoor SV, Epelbaum MI, AuYoung M, Jenkins G, et al. (2020) Diversity and inclusion for the All of Us research program: A scoping review. PLoS ONE 15(7): e0234962. https://doi.org/10.1371/journal. pone.0234962
2. Boehmer, U. Twenty Years of Public Health Research: Inclusion of Lesbian, Gay, Bisexual, and Transgender Populations. American Journal of Public Health. July 2002, Vol 92, No. 7 |

EXPANDING CLINICAL TRIAL DIVERSITY BEYOND RACE & ETHNICITY

Mitchell Lunn, Stanford University School of Medicine

Individual Abstract: The Food Drug Administration (FDA) along with other agencies continue to develop guidance aimed at improving enrollment and representation of clinical trials participants from underrepresented racial and ethnic populations. As organizations become more aware and actively working to implement strategies focused on increasing awareness and need for enhanced clinical trial diversity with respect to race and ethnicity; it is important to challenge ourselves as clinicians and investigators to expand this discussion to include all underserved cohorts.

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- How effective diversity, equity, and inclusion programs have allowed for improvements in clinical trial recruiting to include underserved and underrepresented people.
- Outcomes from strategies implemented to improve and enhance diversity in clinical trial recruitment in pharmaceutical research and development.
- How principles and strategies of inclusivity and intersectionality may enhance representation in the underserved and underrepresented people
- Challenges with managing and treating the underserved community including the LGBTQIA+ community.

After the presentation, attendees will have up-to-date information regarding recent outcomes from strategies implemented in clinical trials recruiting, best practices, opinions, and potential solutions to address challenges related to lack of inclusivity within clinical research. The attendees will have an opportunity to discuss and interact with panelists to share their success stories and further enhance knowledge in this area.

Learning Objectives:

1.) Attendees will understand the societal and health care experiences that limit current research participation by LGBTQ+ community members.
2.) Attendees will learn specific strategies to welcome, affirm, and include LGBTQ+ people in all research studies.

Literature References:

1.) Streed CG Jr, Lunn MR, Siegel J, Obedin-Maliver J. Meeting the Patient Care, Education, and Research Missions: Academic Medical Centers Must Comprehensively

Address Sexual and Gender Minority Health. Acad Med. 2021 Jun 1;96(6):822-827. doi: 10.1097/ACM.0000000000003703. PMID: 32852319.
2.) Lunn MR, Lubensky M, Hunt C, Flentje A, Capriotti MR, Sooksaman C, Harnett T, Currie D, Neal C, Obedin-Maliver J. A digital health research platform for community engagement, recruitment, and retention of sexual and gender minority adults in a national longitudinal cohort study--The PRIDE Study. J Am Med Inform Assoc. 2019 Aug 1;26(8-9):737-748. doi: 10.1093/jamia/ocz082. PMID: 31162545; PMCID: PMC6696499.

***AN EVIDENCE-BASED APPROACH TO PSYCHOPHARMACOLOGY FOR POSTTRAUMATIC STRESS DISORDER (PTSD) - 2023 UPDATE**

David Osser, VA Boston Healthcare System, Brockton Division

Overall Abstract: Algorithms for posttraumatic stress disorder were published by this team in 1999 and 2011. Developments since then warranted revision. New studies and review articles from January 2011 to November 2021 were identified via PubMed and analyzed for evidence supporting changes. Following consideration of variations required by special patient populations, treatment of sleep impairments remained as the first recommended step. Nightmares and non-nightmare disturbed awakenings are best addressed with the anti-adrenergic agent prazosin, with doxazosin and clonidine as alternatives. First choices for difficulty initiating sleep include hydroxyzine and trazodone. If significant non-sleep PTSD symptoms remain, an SSRI should be tried, followed by a second SSRI or venlafaxine as a third step. Second generation antipsychotics can be considered, particularly for SSRI augmentation when PTSD-associated psychotic symptoms are present, with the caveat that positive evidence is limited, and side effects are considerable. Anti-adrenergic agents can also be considered for general PTSD symptoms if not already tried, though evidence for daytime use lags that available for sleep. Regarding other pharmacological and procedural options, e.g., transcranial magnetic stimulation, cannabinoids, ketamine, psychedelics, and stellate ganglion block, evidence does not yet support firm inclusion in the algorithm. In this presentation, the three authors of the algorithm will each review some of the findings and recommendations, and then a discussant will comment and offer a critique of the work.

Learning Objectives:

1.) Participants will obtain a nuanced understanding of the full body of evidence that has accumulated on the effectiveness of prazosin in relationship to other medications that have evidence for usefulness for symptoms of PTSD.
2.) Participants will have knowledge of a range of psychopharmacology options for treatment-resistant cases of PTSD.

AN EVIDENCE-BASED APPROACH TO PSYCHOPHARMACOLOGY FOR POSTTRAUMATIC STRESS DISORDER (PTSD) - 2022 UPDATE

Laura Bajor, Veterans Affairs Medical Center

Individual Abstract: Evidence Based Algorithm for PTSD, Abstract Part II:
The next step of the algorithm involves evaluating for and attempting to address difficulties with sleep. This begins with ruling out and addressing contributing factors to include sleep apnea, excessive use of caffeine, problems with sleep hygiene, restless leg syndrome, pain,

nocturia, and nicotine withdrawal. Sleep problems with PTSD may involve hyperarousal linked to difficulties initiating or maintaining sleep, trauma-related to nightmares, and/or disturbed awakenings without nightmare recollection. As a first step, we recommend determining whether wakings are due to nightmares or hyperarousal, in which case we recommend the alpha-1 antagonist prazosin as a first option. Existing evidence, including 9 RCTs, demonstrates an effect size for this medication that is more impressive than for either FDA-approved medication (sertraline, paroxetine). If at this point sleep is reported as improved, we recommend moving to the next phase of the algorithm. If sleep maintenance is still problematic, and/or if sleep initiation is problematic, we then recommend trials of hydroxyzine, followed by trazodone or clonidine.

Learning Objectives:

1. Be able to modify treatment approach based on comorbidities present.
2. Understand reasoning behind beginning treatment of PTSD with optimization of sleep.

Literature References:

1.) Bajor, L. A., Balsara, C., and Osser, D. N. (2022). An Evidence-based Approach to Psychopharmacology for Posttraumatic Stress Disorder (PTSD)—2022 Update. Psychiatry Research, 114840.

2.) Raskind, M. A., Peskind, E. R., Chow, B., Harris, C., Davis-Karim, A., Holmes, H. A., ... and Huang, G. D. (2018). Trial of prazosin for post-traumatic stress disorder in military veterans. New England Journal of Medicine, 378(6), 507-517.

UPDATE OF THE LATEST TREATMENTS FOR POSTTRAUMATIC STRESS DISORDER (PTSD)

Charmi Balsara, HCA FL Aventura Hospital

Individual Abstract: Having discussed diagnosis and comorbidity in PTSD, and then the approach to insomnia, this presentation focuses on medication treatment of core symptoms. Here an SSRI would be the first consideration. Paroxetine and sertraline are FDA approved for PTSD, though evidence for all SSRIs is weak. The evidence for sertraline is particularly weak in males and veterans, and this SSRI is not approved for men in the England or Australia. In the guidelines of the National Institute for Clinical
Excellence (NICE), the low effect sizes of SSRIs are emphasized. However, there are a few new studies of sertraline published since these guidelines and our previous algorithm and these added modest support for PTSD in civilian populations. If there is no response to the selected SSRI and the patient is experiencing PTSD-related psychosis, consider augmenting with an antipsychotic. Risperidone has the best evidence in that it has the only placebo-controlled randomized trial of this usage. Quetiapine monotherapy was also found to be effective in PTSD symptoms, especially the reexperiencing and hyperarousal clusters with improvements in insomnia. Some of these patients had psychotic symptoms. If side effects from risperidone or quetiapine would be unacceptable, consider aripiprazole which has some open-label reports. If the patient does not have psychosis and does not respond to the first SSRI trial, consider a second SSRI or an SNRI such as venlafaxine or duloxetine. Evidence suggests no reason to prefer them to an SSRI for first-line treatment and hyperarousal symptoms are not improved. Mirtazapine may be considered as an augmentation of the first trial, especially with sertraline and paroxetine, but mirtazapine monotherapy did not show efficacy for PTSD in a randomized

trial. For a third trial, consider another SSRI, SNRI, or daytime prazosin or clonidine. In treatment resistant cases, one may consider some other options; evidence support ranges from unconvincing to sometimes fairly robust. The following will be briefly discussed: transcranial magnetic stimulation, cannabidiol, ketamine/esketamine, stellate ganglion block, and some psychedelic drugs, but none has sufficient evidence to have an earlier spot in the algorithm. Valproate and bupropion are ineffective. Cannabis has some evidence of causing increased difficulties with irritability and anger management and is best avoided, but it is often difficult to persuade enthusiastic users to discontinue it.

Learning Objectives:

1. Evaluate medication options for PTSD symptoms after sleep has been addressed.
2. Determine antipsychotic options for those with PTSD related psychosis.

Literature References:

1. Naylor D, Kilts D, Bradford D, et al A pilot randomized placebo-controlled trial of adjunctive aripiprazole for chronic PTSD in US military Veterans resistant to antidepressant treatment. International clinical psychopharmacology, 2015; 30(3), 167–174.
2. Davis L, Pilkinton P, Lin C, Parker, et al. A Randomized, Placebo-Controlled Trial of Mirtazapine for the Treatment of Posttraumatic Stress Disorder in Veterans. The Journal of clinical psychiatry. 2020; 81(6), 20m13267.

INTRODUCTION: DUCTION, METHODS OF ALGORITHM DEVELOPMENT, CONSIDERATIONS WITH COMORBIDITIES THAT COULD AFFECT THE ALGORITHM, AND INITIAL STEPS.

David Osser, VA Boston Healthcare System, Brockton Division

Individual Abstract: PTSD is associated with significantly decreased quality of life and high levels of disability and comorbidity. These considerations enhance the importance of having up-to-date evidence-derived heuristics to assist with clinical decision-making in the psychopharmacology of the disorder. The panelists will present an updated algorithm for the treatment of PTSD from the Psychopharmacology Algorithm Project at the Harvard South Shore Program based at VA Boston. Previous versions were published in 1999, 2011, and 2022. The group reviewed previous algorithms and new evidence and prepared an opinion-based qualitative distillation of the evidence base, determining appropriate changes to previous versions. Peer review of the algorithms in the process leading to acceptance for publication adds some validation of the authors' interpretation of the literature: when reviewers disagree with reasoning employed in the drafts, changes are made to reach consensus with the reviewers or additional support for the authors' opinion is added. In this initial presentation, there will be an overview of comorbidities and other circumstances for which evidence supports taking actions different from the recommendations in the main algorithm. Substance use disorders heads that list, and here we recommend a minimum of one week of abstinence before applying the algorithm, avoiding benzodiazepines, and topiramate may deserve earlier consideration. For bipolar disorder, avoid antidepressants. For psychosis that is related to the PTSD, augmentation of an antidepressant with risperidone has the best evidence. For major depression comorbid with PTSD, antidepressants may be used earlier than recommended in the algorithm but note that prognosis is reduced compared to depressed patients without PTSD comorbidity. Patients with dissociative symptoms are less responsive to medication treatments but paroxetine may have an edge. For women with the potential to become pregnant, avoid

paroxetine and other medications with known teratogenicity. For smokers, utilize varenicline and bupropion for smoking cessation and manage this use disorder by members of the PTSD treatment team rather than referring out to other specialist clinicians.

Learning Objectives:

1. Listeners will understand the process by which these algorithms are created which will hopefully enhance their credibility.
2. Listeners will understand the importance of diagnosing relevant comorbidities before making treatment decisions on patients with PTSD.

Literature References:

1. Bajor LA, Balsara C, Osser DN. An evidence-based approach to paychopharmacology for PTSD - 2022 upddate. Psychiatry Res. 2022;317:114840
2. Bajor LA, Ticlea AN, Osser DN. The psychopharmacology algorithm Project at the Harvard South Shore Program; An update on posttraumatic stress disorder. Harvard Rev Psychiatry. 2011;19(5):240-259

+*#IMPROVING THE QUALITY OF PSYCHOPHARMACOLOGIC TREATMENT FOR CHILDREN, ADOLESCENTS, AND ADULTS

Ira Glick, Stanford University School of Medicine

Overall Abstract: Although psychopharmacology integrated with psychotherapy is now the predominant intervention in clinical practice, there is a significant lag in both the teaching and the prescribing of effective, quality psychopharmacology. This panel will focus on methods, techniques, and strategies of improving outcomes for children, adolescents, and adults with a focus on developmental disorders, depressive disorders, and schizophrenia.

Dr. Ghaemi will present common fallacies and truths of psychopharmacology. Specifically, the concept of symptom improvement (as opposed to disease modification) is examined, with specific examples based on research and practice with antidepressants.

Dr. Joshi will explore the relational aspects of psychopharmacologic work with youths and families. He will review motivational and therapeutic strategies for engaging psychiatrically impaired youth in treatment, with an emphasis on adherence to treatment with psychotropic medication. Current knowledge about adolescent development will be reviewed in support of these strategies, which ultimately help a young person discover their particular answer to the question: “What’s in this for me?” Three evidence-based treatment models will be explored for tools to help psychopharmacotherapists engage their patients and their families.

Dr. Glick will examine the science underlying psychopharmacology practice which has become roughly equal to that of the science and efficacy underlying medical illness. The level of quality clinical care and competence in practice has become more difficult for clinicians to achieve. This presentation suggests ways to improve teaching to raise the quality level by describing the core tasks for prescribing clinical psychopharmacology. We describe the reasons why the quality is low, why the most common clinical practices are not being done, and most importantly, delineate the necessary core elements for ongoing follow-up visits. We detail clinical psychopharmacology “pearls” that underline global, integrative, long-term practice.

Learning Objectives:

1. At the conclusion of this panel, participants will have improved their psychopharmacology skills integrating core tasks into their clinical practice of child and adolescent disorders.

2. At the conclusion of this session, participants will be aware of how to include core psychopharmacology elements for ongoing followup into clinical practice in long-term management of psychiatric disorders for adults.

TRUTHS AND FALLACIES OF PSYCHOPHARMACOLOGY

Nassir Ghaemi, Tufts University/Harvard Medical School

Individual Abstract: This lecture will describe aspects of the art and science of psychopharmacology, with special emphasis on correcting common misconceptions. It will be explained that medications can be used in one of two ways, either symptomatically or disease modifying. Almost all psychiatric medications are symptomatic and have no effect on the long term diseases that underlie many psychiatric presentations. This fact will be explored in the context of the general philosophy of clinical medicine derived from Hippocrates, which has nothing to do with the false concept of "First do no harm, but rather is based on the view that symptom-oriented treatment is to be discouraged in favor of disease-oriented treatment. Implications of these observations for the use of psychiatric medications in clinical practice will be explored.

Learning Objectives:

1. To examine whether psychiatric medications are symptomatic or disease-modifying.
2. To apply the historically accurate Hippocratic approach to medical practice, which discourages symptom-oriented treatment.

Literature References:

1. SN Ghaemi, Clinical Psychopharmacology: Principles and Practice, New York: Oxford Univ Press, 2019
2. Ghaemi SN. Symptomatic versus disease-modifying effects of psychiatric drugs. Acta Psychiatr Scand. 2022 Sep;146(3):251-257.

THINKING ABOUT PRESCRIBING: THE PSYCHOLOGY OF PSYCHOPHARMACOLOGY WITH DIVERSE YOUTH AND FAMILIES

Shashank Joshi, Stanford University School of Medicine

Individual Abstract: This presentation will explore the relational aspects of psychopharmacological work with youth and families. While technical and scientific knowledge can be taught and examined during medical education, the therapeutic skills also known as "nonspecific" treatment factors, or "common factors" are more elusive and harder to describe. Yet, based on a recent literature review (2), these common factors benefit children receiving psychotropic medications as well as their families and their clinicians.

We will review strategies for engaging impaired youth in treatment, with an emphasis on adherence to treatment with psychotropic medication. Current knowledge about adolescent development will be reviewed in support of these strategies, which ultimately help a young person discover their particular answer to the question: "What's in this for me?" Three evidence-based treatment models will be described to help pharmacotherapists engage with their patients.

Even less is understood about psychological factors when prescribing to a culturally diverse youth population. Culture plays a pivotal role in how children with mental disorders function,

and in how children are subsequently understood and treated. Differences in culture between the clinician and the patient/family often lead to differing perspectives and, if not explored, can interfere with the treatment alliance and subsequently with treatment adherence and/or resistance. In particular, racial discordance between patient and physician almost always predicts poorer communication in the domains of satisfaction, information-giving, partnership building, participatory decision-making, visit length, and supportiveness and respect of conversations. In keeping with the adage, the formulation must always precede the prescription (1), recent work has highlighted the use of the DSM-5 Cultural Formulation Interview as an important tool to more fully understand a young person in the context of their daily life, as part of comprehensive treatment planning (5).

We child and adolescent psychiatrists must extend our roles beyond just psychopharmacology to be truly effective. In this presentation, we propose that the term 'med check' is not only a misnomer that simply doesn't exist in child and adolescent psychiatric treatment (as if the patient just comes to us wanting to 'talk about their meds'), but more importantly it is a disservice to the nature and intention of our work with youth and families. For such time-limited visits where the medication issues are a primary focus, we propose the term, 'brief pharmacotherapy visits', which allows us to retain our role as therapists (as an inextricable part of psychopharmacology). An effective pharmacotherapy appointment necessitates the appreciation of many things that inform treatment, and thus pharmacotherapy decisions, including the intricacies of an individual's culturally informed, biopsychosocial story. It has consistently been shown that strong therapeutic alliances between a patient and their mental health provider, as well as empathy demonstrated by the latter, lead to more positive clinical and functional outcomes- and thus to the primary goal of evaluating and promoting mental health and well-being (1).

In summary, this presentation seeks to address the practice gap associated with the child psychiatrists desire to maintain a therapeutic stance in all interactions with patients and families, while managing the time and billing pressures that come with modern psychiatric practice. We will incorporate adult learning principles to facilitate active learning, including audience participation, stories from real life cases, and small group discussion to reinforce concepts and share ideas.

Learning Objectives:

1. List the essential features of the Y-model of psychotherapy, and appreciate how relational aspects of pharmacotherapy are key to child and adolescent psychiatric practice, even for brief visits.
2. Describe how to best utilize the 30-minute Brief Pharmacotherapy Visit (BPV), so that the alliance is nurtured, and time is most efficiently utilized. Discuss why the term "med-check" is no longer applicable in psychiatry.

Literature References:

1. Joshi SV and Martin A (eds; 2022). Thinking about Prescribing: The Psychology of Psychopharmacology with Diverse Youth and Families; Washington DC, American Psychiatric Association Press
2. De Nadai AS, Karver MS, Murphy TK, et al. Common Factors in Pediatric Psychiatry: A Review of Essential and Adjunctive Mechanisms of Treatment Outcome. J Child Adolesc Psychopharmacol. 2017;27(1):10-18. doi:10.1089/cap.2015.0263

RAISING THE QUALITY OF PSYCHOPHARMACOLOGY CLINICAL PSYCHIATRIC PRACTICE

Ira Glick, Stanford University School of Medicine

Individual Abstract: As the science underlying psychopharmacology practice has become roughly that of the science underlying other medical illnesses, the level of quality clinical care, competence and practice has become more difficult for clinicians to achieve. This report aims to suggest ways to improve teaching to raise the quality level by describing the core tasks for practicing quality clinical psychopharmacology. We describe the reasons why the quality is low and why the most common clinical practices are not being done, and most importantly, we delineate the necessary core elements for ongoing follow-up visits. We detail clinical psychopharmacology "pearls" that underlie global, integrative, long-term clinical practice.

Learning Objectives:

1. At the conclusion of this presentation, clinicians will be aware of core elements necessary to do quality psychopharmacology practice.
2. At the conclusion of this presentation, clinicians will be aware of clinical pearls in doing quality psychopharmacology practice.

Literature References:

1. Glick ID, Balon R, DeBattista C: Raising the Quality of Psychopharmacology Clinical Psychiatric Practice: Elements of Good Psychopharmacology Care. J Clin Psychopharmacology, 2021
2. Glick ID Balon RJ, Ballon J Teaching pearls from the lost art of psychopharmacology. J Psychiatric practice 2009 15:423-426

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

Pharmaceutical Pipeline Session

A PHASE 2 RANDOMIZED CONTROLLED ADJUNCTIVE TREATMENT TRIAL WITH CLE-100 ESKETAMINE TABLET FOR PATIENTS WITH MAJOR DEPRESSIVE DISORDER AND INADEQUATE RESPONSE TO ANTIDEPRESSANTS DURING THE COVID-19 PANDEMIC

Maurizio Fava[1], Oren Berkowitz[2], Sanjay J. Mathew[3], Michael E. Thase[4], Andrew Nierenberg[5], Dan V. Iosifescu[6], L. Alison McInnes[7], Cristina Cusin[1], Robert Berman[8], Eli Eyal[2], Ari A. Gershon[2], Esther Lukasiewicz-Hagai[2], Maurizio Fava*[5]

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Maurizio Fava, Massachusetts General Hospital*

Abstract Introduction: CLE-100 is an oral esketamine tablet formulated with abuse-deterrent technology for daily use at home as an adjunctive treatment for Major Depressive Disorder (MDD) patients with an inadequate response to antidepressants (AD). CLE-100 is a NMDAR antagonist metabolized to active metabolites with AD activity. This Phase 2 US trial assessed home-dosing of CLE-100 40mg vs. placebo and enrolled subjects from August 2020 to August 2022. This coincided with an acute phase of the COVID-19 pandemic, followed by a post-acute phase beginning in 2022, when most of the population had been vaccinated, masking and isolation diminished, and the US government declared to move forward without shutting down schools and businesses. We did a post-hoc analysis to test the hypothesis that recruitment during these two phases would yield differences in CLE-100 vs. placebo responses.

Methods: The study was a randomized, double-blind, placebo-controlled, parallel-arm trial in moderate to severe MDD subjects [Montgomery-Asberg Depression Rating Scale (MADRS) score ≥ 24] with inadequate response to ≥ 2 ADs. Subjects were randomized (1:1) to 4 weeks of daily CLE-100 40mg or placebo added to their current AD. The primary endpoint (PEP) was change in MADRS score from baseline at Week 4. A mixed model repeated measures (MMRM) analysis was used to estimate the difference in the estimated Least Square Means (LSM) at week 4 between the CLE-100 and the placebo groups. To evaluate the cohort effect of the acute (2020-2021) vs. post-acute (2022) phases of the pandemic on the PEP, a post-hoc analysis was performed by adding it to the MMRM model.

Results: The study randomized 130 subjects across 32 US sites; 125 subjects were included in the primary analysis. The mean (SD) age was 44.3 (13.3) with 72.3% females. Mean baseline MADRS was 32.9 (4.9). The LSM [SE] difference of CLE-100 from placebo for change in MADRS at Week 4 in the overall cohort was not statistically significant (−1.26 [1.69], 95% CI: [-4.93 to 1.58] P = 0.46; Cohen's d effect size of 0.14). The post-hoc cohort analysis was performed with 60 subjects in the 2020-2021 cohort and 65 subjects in the 2022 cohort. No meaningful differences were found in baseline characteristics between the two cohorts. No statistically significant difference was seen on the PEP between CLE-100 vs. placebo in the 2020-2021 cohort (2.92 [SE 2.40], 95% CI: [-1.85 to 7.68]; P = 0.227) while in the 2022 cohort CLE-100 was statistically superior to placebo (PEP difference −5.28 [2.34], 95% CI: [-9.91 to -0.65]; P = 0.026; Cohen's d = 0.62). There were no deaths or serious adverse events, or discontinuations due to adverse events in the CLE-100 group. The most common treatment-emergent adverse events (TEAE) occurring more frequently than placebo were dizziness (13.9% vs. 1.8%), headache (12.5% vs. 8.8%), and somnolence (11.1% vs. 1.8%). TEAEs of dissociation occurred in 2.8% of CLE-100 vs. 1.8% of placebo subjects. Drug abuse, dependence, or withdrawal were not observed.

Conclusions: The trial did not meet its PEP in the overall cohort. CLE-100 was well-tolerated, and its safety profile was compatible with at-home dosing. We observed a strong cohort effect related to subjects randomized during the acute (2020-2021) vs. post-acute (2022) phases of the pandemic, with CLE-100 statistically significantly better than placebo in the post-acute pandemic cohort. We hypothesize that these temporal differences were due to the disruptive impact of the pandemic which may have, among other factors, produced an enrollment bias along with possible adjustment reactions that diverge in the pattern of placebo-drug responses. Additional studies of CLE-100 are warranted to confirm the positive results observed in the post-acute pandemic phase.

SAFETY AND EFFICACY OF KARXT IN PATIENTS WITH SCHIZOPHRENIA IN THE RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PHASE 3 EMERGENT-2 AND EMERGENT-3 TRIALS

Stephen Brannan*[1], *Angel Angelov*[1], *Colin Sauder*[1], *Inder Kaul*[1]

[1]*Karuna Therapeutics*

Stephen Brannan, Karuna Therapeutics

Abstract A high unmet medical need exists for more effective, better tolerated treatments for schizophrenia with novel mechanisms of action. All currently approved treatments for schizophrenia have dopamine D2 receptor blocking activity; the efficacy and tolerability limitations of these therapies are well known. KarXT is a novel combination of the dual M1/M4 preferring muscarinic receptor agonist xanomeline and the peripherally restricted anticholinergic trospium. KarXT is designed to preserve the beneficial central nervous system effects of xanomeline, while mitigating the cholinergic adverse events observed previously due to peripheral muscarinic receptor activation. In a 5-week, randomized, double-blind, placebo-controlled, phase 2 study (EMERGENT-1; NCT03697252), KarXT met the primary endpoint of a significant reduction in Positive and Negative Syndrome Scale (PANSS), improved other key secondary efficacy measures, and was generally well tolerated.

EMERGENT-2 (NCT04659161) and EMERGENT-3 (NCT04738123) were 5-week, randomized, double-blind, placebo-controlled phase 3 trials of KarXT in people with schizophrenia with acute psychosis in an inpatient setting. Key inclusion criteria were recent worsening of positive symptoms warranting hospitalization, Positive and Negative Syndrome Scale (PANSS) total score 80, and Clinical Global Impression–Severity (CGI-S) score ≥4. Eligible participants were randomized 1:1 to KarXT or placebo. KarXT dosing (mg xanomeline/mg trospium) started at 50 mg/20 mg twice daily (BID) and increased to a maximum of 125 mg/30 mg BID. The primary efficacy endpoint was change from baseline to week 5 in PANSS total score. Other efficacy endpoints included change from baseline to week 5 in PANSS positive, PANSS negative, and PANSS Marder negative factor subscale scores.

EMERGENT-2 and EMERGENT-3 enrolled 252 and 256 people, respectively. In EMERGENT-2, KarXT demonstrated a statistically significant and clinically meaningful 9.6-point reduction in PANSS total score compared with placebo at week 5 (-21.2 KarXT vs -11.6 placebo, P<0.0001; Cohen's d effect size=0.61). KarXT met other key efficacy endpoints, demonstrating a significant reduction in both positive and negative symptoms. Compared with placebo at week 5, KarXT demonstrated a 2.9-point reduction in PANSS positive subscale score (-6.8 KarXT vs -3.9 placebo, P<0.0001), 1.8-point reduction in PANSS negative subscale score (-3.4 KarXT vs -1.6 placebo, P=0.0055), and 2.2-point reduction in PANSS Marder negative factor subscale score (-4.2 KarXT vs -2.0 placebo, P=0.0022). KarXT was generally well tolerated. Overall discontinuation rates were similar in KarXT and placebo groups (25% vs 21%). The most common (5%) treatment-emergent adverse events with KarXT were all mild to moderate in severity and included constipation, dyspepsia, nausea, vomiting, headache, increases in blood pressure, dizziness, gastroesophageal reflux disease, abdominal discomfort, and diarrhea. KarXT was not associated with common problematic side effects of current therapies such as motor symptoms, weight gain, prolactin elevation, or somnolence. Study data from the EMERGENT-3 program are currently being analysed and will be available at the time of presentation.

KarXT has the potential to be the first in a new class of schizophrenia treatments based on muscarinic receptor agonism and a promising alternative to direct dopamine D2 receptor antagonists.

PHARMACEUTICAL PIPELINE OF BI 1358894: CLINICAL EVIDENCE FOR AN EMERGING DRUG FOR THE TREATMENT OF MENTAL HEALTH CONDITIONS

Brittney Starling*[1], *James Cronican[1], Stefan Just[2], Lauren Liss[2], Irina Adamczyk[2], Sigurd Suessmuth[2], Jennifer Dwyer[1]*

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Brittney Starling, Boehringer Ingelheim Pharmaceuticals Inc

Abstract Introduction: Dysregulated emotional processing and strong negative emotions are core symptoms of borderline personality disorder (BPD), major depressive disorder (MDD), and posttraumatic stress disorder (PTSD) and are correlated with amygdala hyperreactivity. BI 1358894 may provide a novel mechanism of attenuating amygdala hyperreactivity to improve emotion regulation and reduce core symptoms in mental health conditions. Here we provide an overview of early BI 1358894 research in the treatment of conditions such as BPD, MDD, and PTSD, where emotional dysregulation and mood control play an important role.

Methods: Five Phase I studies of BI 1358894, in healthy male volunteers, were performed to determine the safety, tolerability, and pharmacokinetics (PK) of BI 1358894. The pharmacodynamic effects of BI 1358894 versus placebo were also assessed following the administration of cholecystokinin tetrapeptide (CCK-4) to induce anxiety/panic symptoms in healthy volunteers. A functional magnetic resonance imaging (fMRI) study of patients with MDD investigated the effects of BI 1358894 on cortico-limbic brain regions during faces and scenes tasks.

Results: Across the clinical studies, BI 1358894 ≤200 mg was generally well tolerated, with headache, dizziness, and fatigue reported as the most frequent adverse events. PK analysis of BI 1358894 indicated that exposure increased dose-dependently, but less than dose-proportionally, after single doses in the fed state and multiple doses in the fasted state. Positive food effect with increased exposure was observed with single doses of 50 mg and 100 mg. Compared with placebo, BI 1358894 reduced the physiological and psychological response to CCK-4 in healthy volunteers, as measured by the Panic Symptom Scale and the Emotional Faces Visual Analog scale, as well as by levels of stress biomarkers (adrenocorticotropic hormone and serum cortisol), indicating target engagement and functional mechanistic effects. A fMRI study in people with MDD demonstrated that BI 1358894 attenuated activity in several cortico-limbic brain regions, including the amygdala bilaterally, during a task where participants viewed negative emotional faces and scenes.

Conclusion: BI 1358894 was well tolerated across the clinical Phase I studies; BI 1358894 attenuated amygdala hyperactivation in response to negative faces and scenes. These data support further investigation of this mechanism of action for patients with symptomatology associated with amygdala hyperreactivity. A Phase II study in BPD was recently clinically completed. Further Phase II studies are ongoing for MDD and PTSD.

Literature References:

1. ClinicalTrials.gov. A Study to Test Different Doses of BI 1358894 and Find Out Whether They Reduce Symptoms in People With Borderline Personality Disorder. Available from: https://clinicaltrials.gov/ct2/show/NCT04566601. Accessed on: 09 February, 2023.
2. ClinicalTrials.gov. A Study to Test the Effect of Different Doses of BI 1358894 and Quetiapine in People With Depression. Available from: https://clinicaltrials.gov/ct2/show/NCT04521478. Accessed on: 09 February, 2023.

A PHASE 1, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, SAFETY, TOLERABILITY, AND PHARMACOKINETIC STUDY OF ESCALATING SINGLE AND MULTIPLE DOSES OF CVN766, AN OX1R HIGHLY SELECTIVE ANTAGONIST IN HEALTHY SUBJECTS

Nicola Brice[1], Kim Matthews[1], Lee Dawson[1], April Purcell[2], Ricardo Soto[2], Martin Bexon[3], Philip Ryan[4], Mark Carlton[1], Ottavio Vitolo*[1]

[1]Cerevance, [2]Halloran Consulting Group, [3]Bexon Clinical, [4]Nucleus Network

Ottavio Vitolo, Cerevance

Abstract: Orexin-A and orexin-B are two neuropeptides produced in the lateral hypothalamus from the same gene (HCRT) and bind to orexin 1 receptors (Ox1R) and orexin 2 receptors (Ox2R). Ox1R and Ox2R are G-protein coupled receptors that regulate intracellular calcium levels. While orexin-A is equipotent at both receptors, orexin-B shows a 10-fold selectivity for Ox2R. Ox1R is expressed in key brain areas important in regulating reward, motivation, emotions, stress responses and memory, whereas Ox2R is mainly involved in controlling sleep-wake cycles.
CVN766 is a potent and highly selective small-molecule Ox1R antagonist with no significant off-target activity. Nonclinical PK and toxicology studies have established its pharmacological characteristics and probable safety profile. CVN766 is currently in development for the treatment of negative and cognitive symptoms of schizophrenia.

Here we report the findings of a Phase 1, single and multiple ascending doses study to characterize the safety, tolerability, and pharmacokinetics of CVN766.

A total of 64 healthy subjects were enrolled and completed the study. 40 subjects entered the SAD portion of the study and were randomized to either placebo or one of 5 ascending dose levels, from 5 to 250 mg. Each cohort consisted of 8 subjects randomized to CVN766 or placebo in a 6:2 ratio. The 45 mg dose level was tested in fasted and fed conditions. In the MAD portion of the study, 24 subjects were assigned to one of three dose groups: 45 mg, 125 mg or 250 mg once a day for 7 days. In each cohort, subjects were randomized 6:2 to receive either CVN766 or placebo, respectively.

Overall, the demographic distribution among the groups was balanced for age with a slight prevalence of male subjects. All subjects completed the treatment period. Most of the adverse events (AEs) reported were mild. The most frequent treatment related AEs (TEAEs) were nausea and dizziness. There appeared to be no dose-relationship in the frequency and severity of AEs. Individuals exposed to CVN766 did not experience increased somnolence.

No clinically significant changes in vital signs, laboratory values and ECG parameters were observed.

Pharmacokinetics analysis revealed good dose proportionality with repeated exposures and steady state achieved by day 4-5.

There was minimal food effect detected in the 45 mg SAD cohorts.

Cerebrospinal fluid collected 3 hours post dose on day 1 in the 45 mg SAD cohort and at day 7 in the 45 mg MAD cohort enabled the calculation of a CSF/plasma ratio similar to that determined in rats (0.52 vs. 0.4), thus confirming good brain penetrance.

Overall, the findings from this Phase 1 study confirm the favorable safety and tolerability profile observed in the pre-clinical studies and support continuing the development of CVN766.

We are currently preparing a Phase 2 study for the treatment of negative and cognitive symptoms of schizophrenia. Based on the predicted receptor occupancy (RO), we expect doses 45 mg to 250 mg to reach RO between approximately 85% and 97%, which, based on the animal modes, should be more likely efficacious.

Given its mechanism of action and the functions of orexin A, it is possible that CVN766 could also improve aspects of the metabolic syndrome caused by antipsychotics, thus further contributing to an improvement in morbidity and quality of life for individuals suffering from schizophrenia.

THE THERAPEUTIC POTENTIAL OF EVX-101 TO AMPLIFY SEROTONIN SYNTHESIS FOR THE ADJUNCTIVE TREATMENT OF MDD AND OTHER MENTAL ILLNESS: EMERGING PROFILE AND POST-PHASE 1 UPDATE

Jacob Jacobsen*[1], *Rebecca Klein[1], Jennifer Hart[1], David Carpenter[1]*

[1]Evecxia Therapeutics

Jacob Jacobsen, Evecxia Therapeutics

Abstract The therapeutic potential of EVX-101 to amplify serotonin synthesis for the adjunctive treatment of MDD and other mental illness: Emerging profile and post-Phase 1 update.

Background: Serotonin transporter (SERT) inhibitors (e.g., SSRIs, SNRIs) treat depression by elevating brain extracellular serotonin aka 5-hydroxytryptamine (5-HTExt), but only 1/3 patients adequately respond. Evidence suggests this could in part be due to inadequate 5-HTExt elevation. Adjunctive administration of the 5-HT precursor 5-hydroxytryptophan (5-HTP) elevates 5-HText beyond the SERT inhibitor effect and may thereby augment antidepressant efficacy. However, native, immediate-release (IR) 5-HTP is limited as a therapeutic due to poor absorption and short half-life. EVX-101 is a novel gastro-retentive (GR) sustained-release (SR) tablet formulation of 5-HTP plus low-dose carbidopa (CD). It is designed to remedy 5-HTP's PK limitations, enabling sustained 5-HTP plasma exposures. Low doses of CD delivered in close spatial and temporal juxtaposition with 5-HTP to the upper intestine inhibits 5-HTP conversion to 5-HT in the intestine, thereby enhancing 5-HTP bioavailability (BA). Used adjunctively, EVX-101 is theorized to elevate brain 5-HTExt levels beyond the SSRI/SNRI effect and consequently augment the antidepressant effect. Here we update on EVX-101 clinical development.

Methods: Two Phase 1 clinical studies were conducted to investigate the safety, tolerability, PK and pharmacodynamic effect of EVX-101 in healthy subjects. Study 101 was an open-label study to evaluate if EVX-101 could enhance 5-HTP BA and produce prolonged plasma exposures. Study 102 was a double-blind, placebo (PBO)-controlled, 2-part single ascending dose (SAD) and multiple ascending dose (MAD) study in healthy subjects dosed with escitalopram for 21 days pre-randomization and during randomized treatment. The 5-HTP total daily dose (TDD) was fixed at 500 mg (250 mg BID); plasma 5-HTP levels were increased by escalating the CD dose level (DL). In SAD Part 1, 2 cohorts (CD TDD 0.625 mg and 1.25 mg) were dosed BID for 1 day with PK profiling for 48h. In MAD Part 2, subjects in a single cohort were up-titrated weekly: CD TDD by week = 0.625 mg (DL1) → 0.1.25 mg (DL2) → 2.50 mg (DL3) →5.0 mg (DL4). PK profiling occurred on Day 1 and at steady state (SS) at each DL (Days 6, 13, 20, 27). Safety/tolerability were assessed via AEs, VS, ECGs, labs, PE, C-SSRS, and Hunter Criteria for Serotonin Toxicity.

Results: 16 subjects received EVX-101 in Study 101 and 34 subjects received > 1 dose of EVX-101 or PBO in Study 102 (SAD n=16; MAD n=18). In Study 101, co-administration of 250 mg 5-HTP with all CD DLs tested significantly increased the relative BA of 5-HTP (up to ≈ 900% for AUC0-24 for 250 mg + 15 mg CD compared to 5-HTP IR alone). In Study 102, sustained target plasma 5-HTP levels were achieved at all 4 DLs (Cavg [0-12 and 0-24] ≈100-300 ng/mL). Serum cortisol increased in a dose-dependent manner in EVX-101-treated subjects, indicative of target engagement. GI-related AEs were the most frequent AE type in both studies; however, the up-titration approach in the 102 MAD study appeared to improve tolerability, allowing escalation to DL4 in 61% of subjects despite much higher SS 5-HTP levels upon repeated dosing (Rac≈3-5, DL1 D1 vs D6). No safety signals of concern were apparent, and no serious AEs were reported in either study.

Discussion: The novel drug delivery technology utilized in EVX-101 appears to overcome the PK shortcomings of native, IR 5-HTP and may enable the full therapeutic potential of 5-HTP to be realized. Thus, adjunctive EVX-101 could emerge as a critical new therapy for patients suffering from depression.

EFFICACY AND SAFETY OF ATICAPRANT, A KAPPA OPIOID RECEPTOR ANTAGONIST, ADJUNCTIVE TO ORAL SSRI/SNRI ANTIDEPRESSANT IN MAJOR DEPRESSIVE DISORDER: RESULTS OF A PHASE 2A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY

Mark Schmidt*[1], *Iva Kezik*[2], *Vanina Popova*[2], *Peter Van Der Ark*[2], *Darrel J. Pemberton*[2], *Guy Mareels*[2], *Wayne C. Drevets*[2]

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Mark Schmidt, Janssen Pharmaceutica N.V.

Abstract Background: Aticaprant is a small molecule, high-affinity, selective kappa opioid receptor (KOR) antagonist. KOR antagonism has demonstrated meaningful effects in animal models of depression and anhedonia that may translate to therapeutic benefit in humans.
Methods: This was a multicenter, double-blind (DB), placebo-controlled, randomized study of adults (18-64 years old) with a DSM-5 diagnosis of major depressive disorder (MDD) and anhedonia (defined by Snaith-Hamilton Pleasure Scale [SHAPS; range 0 - 56] ≥ 20) at baseline.

Eligible participants had inadequate response to antidepressant treatment at screening (i.e., Montgomery Åsberg Depression Rating Scale [MADRS] ≥25 after 6 continuous weeks to ≤ 12 months of SSRI/SNRI). Patients who had failed ≥3 antidepressants treatments, including the current SSRI/SNRI, during the current depressive episode were excluded.

The study consisted of a 5-week screening phase and an 11-week DB treatment phase, the latter consisting of 3 periods: 1) a placebo lead-in period (up to 3 weeks); 2) a 6-week DB treatment period; and, 3) for patients who completed DB treatment, a withdrawal period during which they received placebo for the remaining time of the treatment phase.

Patients were randomly assigned (1:1) to receive either aticaprant 10 mg or to continue placebo, each once daily during the DB treatment period. Patients were maintained on their SSRI/SNRI, without change, throughout the study.

Results: Of 184 patients enrolled, 169 were included in the safety analyses and 166 were included in the full ITT (fITT) analyses, 121 (73%) of whom were lead-in placebo non-responders (i.e., <30% reduction in MADRS total score from lead-in baseline) (enriched eITT population [eITT]) and 45 (27%) were lead-in placebo responders. The mean (SD) age (fITT) was 42.6 (12.7) years, 72.3% were female, and mean (SD) MADRS at baseline was 25.3 (7.86). All but 1 of the patients had anhedonia at baseline.

Improvement (LS mean [SE] difference vs. placebo) in MADRS total score at week 6 for aticaprant was significant compared to placebo in the eITT analysis set (-2.1 [1.25] with 1-sided 80% CI upper limit of -1.09; p=0.044, observed effect size 0.23). The treatment effect was larger in the fITT analysis set (-3.1 [1.05] with 1-sided 80% CI upper limit of -2.21; p=0.002, observed effect size=0.36).

Among patients with high anhedonia at treatment baseline (defined by SHAPS ≥38), larger differences between aticaprant and placebo at week 6 were observed (effect size: 0.38 eITT, 0.51 fITT) than in those with low anhedonia level (treatment baseline SHAPS ≥20 and <38) (effect size: 0.11 eITT, 0.29 fITT).

Study drugs were well tolerated: Few patients (1 [1.2%] in each treatment group) had adverse events that led to discontinuation of study drug. The most common adverse events reported for aticaprant and placebo, each combined with SSRI/SNRI, were headache (11.8%/7.1%, respectively), diarrhea (8.2%/2.4%), pruritus (5.9%/0%), and nasopharyngitis (5.9%, 2.4%). One serious adverse event (acute cholecystitis in the placebo group) and no deaths were reported.

Conclusions: In this first clinical study of aticaprant for patients with MDD and anhedonia, inadequately treated with SSRI/SNRI antidepressants, adjunctive treatment with aticaprant led to significantly greater reduction in depressive symptoms severity on the MADRS compared to placebo. The safety profile of aticaprant was favorable. These results support further investigation in larger trials.

PHASE 2 STUDY DESIGN AND NEW DATA FROM THE PHASE 1 SAD/MAD TRIAL OF LHP88, A SECOND-GENERATION GINGIPAIN INHIBITOR FOR THE TREATMENT OF P. GINGIVALIS-ASSOCIATED DEMENTIA

Michael Detke*[1], *Marwan Sabbagh*[2], *Leslie Holsinger*[1], *Joanna Bolger*[1], *Jianhong Wang*[1], *Mark Ryder*[3], *Suzanne B Hendrix*[4], *Samuel P Dickson*[4], *Craig Mallinckrodt*[4], *Casey Lynch*[1], *Stephen Dominy*[1]

[1]*Lighthouse Pharma,* [2]*Barrow Neurological Institute,* [3]*UCSF,* [4]*Pentara Corporation*

Michael Detke, Lighthouse Pharma

Abstract Objectives: The novel mechanism of action of LHP588 is based on the discovery of gingipains, toxic protease virulence factors from the bacterial pathogen Pg, in postmortem brains of patients with a pathologic diagnosis of Alzheimer's disease (AD). Gingipain levels correlated with tau and ubiquitin pathology, and oral infection of wild-type mice with Pg resulted in an A□1-42 response, consistent with evidence that A□1-42 is an antimicrobial peptide. In addition, Pg-induced brain inflammation and neurodegeneration in wild-type mice after oral Pg infection was blocked by gingipain inhibitors.

LHP588 is an orally bioavailable and brain-penetrant lysine-gingipain inhibitor that reduces the toxicity of Pg and the bacterial load. A first-generation molecule (atuzaginstat) previously showed reduction of cognitive decline in prespecified cohorts defined by their infection load, but it was discontinued due to a hepatic safety signal.

We will review data from the prior study, data demonstrating the improved selectivity and ADME-PK of LHP588 along with data from the new Phase I SAD/MAD, and show how these inform the design of the Phase 2b study of LHP588 starting later this year.

Methods: The previous Phase 2/3 study with atuzaginstat was a 3-arm, randomized, double-blind, placebo-controlled study in 643 subjects with baseline MMSE scores of 12-24. The Phase 1 study of LHP588 enrolled 32 individuals in the SAD component with 4 cohorts and concurrent placebo (25 mg, 50 mg, 100 mg, 200 mg) and 24 healthy subjects in the 10-day MAD portion, with 3 cohorts and concurrent placebo (50, 100 mg, and 200 mg).

Results: In the study of atuzaginstat, significance was not observed in the full intent-to-treat population, however, prespecified subgroup analyses indicated efficacy in patients with Pg detected in saliva (Pg+), slowing cognitive decline compared with placebo on the ADAS-Cog11 approximately 50% ($p = 0.02$). These findings were consistent across multiple biomarkers of Pg load, including anti-Pg antibodies in CSF, and across statistical sensitivity analyses. Changes in Pg DNA in saliva from weeks 0-24 correlated significantly with changes on multiple clinical scales, including ADAS-Cog, CDR-SB, and MMSE.

LHP588 was well-tolerated in both the SAD/MAD study, and no liver enzyme elevations outside normal ranges were observed. Adverse events in the active arms were mild and sporadic. PK was consistent with once-daily dosing reaching target concentrations equivalent or greater than 80 mg BID of atuzaginstat at >25 mg QD of LHP588. LHP588 was also detected in the CSF of all subjects tested, at expected levels. LHP588 has improved selectivity, including for the bile salt export pump, and projected 10x lower liver metabolite levels. Chronic toxicology studies show that large multiples of exposures did not produce clinical pathology or histopathology findings, supporting advancement into Phase 2.

Conclusions: LHP588 was well tolerated in healthy volunteers without evidence of hepatic safety signals to date, and its PK profile was supportive of once daily dosing, with 10x lower liver metabolite levels. Chronic toxicology and rodent metabolite studies are also supportive of safety and progression to Phase 2.

Clinical results with the first generation gingipain inhibitor atuzaginstat informed the new study design for precision enrollment and efficacious exposures. The Phase 2 trial of LHP588 starting later in 2023 will be similar in design but will be restricted to subjects with Pg+ saliva.

AN OPEN-LABEL TRIAL ASSESSING SHORT- AND LONG-TERM TOLERABILITY AND EFFICACY OF ZYN002 (CANNABIDIOL) ADMINISTERED AS A TRANSDERMAL GEL TO CHILDREN AND ADOLESCENTS WITH 22Q11.2 DELETION SYNDROME (INSPIRE) AND LONG-TERM SAFETY AND SUSTAINED EFFICACY OF ZYN002 CANNABIDIOL TRANSDERMAL GEL IN THE TREATMENT OF BEHAVIORAL SYMPTOMS IN CHILDREN AND ADOLESCENTS WITH FRAGILE X SYNDROME (ZYN2-CL-017)

Stephen O'Quinn*[1], *Nancy Tich[1], Anthony Thibodeau[1], Terri Sebree[1], Thomas Dobbins[2], Helen Heussler[3], Jonathan Cohen[4], Caroline Buchanan[5], Carol O'Neill[1], Terri Sebree[1]*

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Stephen O'Quinn, Zynerba Pharmaceuticals

Abstract Background: 22q11.2 deletion syndrome (22q), caused by a microdeletion of region11.2 of chromosome 22, is the most common recurrent contiguous gene deletion syndrome. 22q is associated with developmental anomalies including heart defects, palate and pharyngeal defects and immunodeficiency. Behavioral problems, autism spectrum disorder (ASD), attention deficit
hyperactivity disorder (ADHD), and mood disorders occur frequently in patients with 22q. ZYN002 is a pharmaceutically produced cannabidiol transdermal gel in development for treatment of the behavioral symptoms in 22q and Fragile X syndrome. INSPIRE was an open-label, phase 2 trial to evaluate the safety/tolerability and efficacy of ZYN002, in children and adolescents ages 4 to <18 years, in the treatment of behavioral and anxiety-related symptoms in 22q.

Methods: Males and females with 22q having a Clinical Global Impression-Severity (CGI-S) score≥4 and a Pediatric Anxiety Rating Score-Revised (PARS-R) score ≥10 were enrolled. Patients received 250 mg/day or 500 mg/day of ZYN002 (weight-based) added to current therapy for 14 weeks (Period 1). Patients with <25% improvement from baseline in the Aberrant Behavior Checklist-Community (ABC-C) Irritability subscale at week 6 could have their dose increased to either 500 mg/day or 750 mg/day. Patients with ≥35% improvement in the ABC-C irritability subscale at week 14 could continue treatment for an additional 24 weeks (Period 2). Safety assessments included adverse events, vital signs, laboratories, and electrocardiograms (ECGs). Primary efficacy assessments included change from baseline on the PARS-R, Anxiety, Depression and Mood Scale (ADAMS), ABC-C and the CGI-Improvement (CGI-I).

Results: Twenty patients, 60% males, with a mean age of 9.9 years were enrolled. Seventeen patients completed Period 1 and 13 patients entered Period 2. Statistically significant improvements were seen in the PARS-R, ADAMS and ABC-C scales at Week 14. Mean change and percent improvement from baseline were PARS-R: Total Score -6.2, 40.6%,

p=0.0005; ADAMS: Total Score -18.4, 45.3%, p=0.0005; General Anxiety -5.4, 43.6%, p=0.0005; Depressed Mood -4.3, 50.3%, p=0.0033; Social Avoidance -4.4, 41.3%, p=0.0084; Obsessive/Compulsive Behavior -1.9, 1 2023 ASCP Annual Meeting 64%, p=0.0037; Manic/Hyperactive Behavior -3.1, 38.2%, p=0.0032; and ABC-C: Social Withdrawal -6.4, 27.6%, p=0.011; Inappropriate Speech -1.8, 18.3%, p=0.0166; Stereotypic Behavior -2.3, 52.1%, p=0.0155; Irritability -8.4, 36.3%, p=0.0055; Hyperactivity -7.6, 16.5%, p=0.0091. Twelve of 16 patients (75%) were rated as "improved", "much improved" or "very much improved" at week 14, with 62.5% being "much improved" or "very much improved" on the CGI-I. The improvements in all endpoints at Week 14 were sustained in patients who completed Period 2. Over 38 weeks, 3 patients reported treatment related adverse events which were all mild application site adverse events which were transient and resolved with continued dosing. One patient discontinued treatment due to adverse events not related to ZYN002. Four non-treatment-related serious adverse events were reported in 3 patients. No clinically significant changes in vital signs, ECGs or laboratories were reported.
Conclusions: INSPIRE provides initial evidence suggesting a positive risk–benefit profile for ZYN002 in improving behavioral and anxiety-related symptoms in children and adolescents with 22q when added on top of stable standard of care. Further studies are warranted.

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

Objectives: To assess the long-term safety and efficacy of ZYN002 in patients with FXS.

Methods: Interim analyses were conducted with data through 23-January-2023. Safety data for all patients, up to 45 months since entry into the study, and efficacy data through 24 months for patients with 100% FMR1 gene methylation who completed CONNECT-FX are reported. Patients screened for CONNECT-FX were eligible for entry, including patients ineligible for randomization, and patients who were randomized to 12-weeks of ZYN002 (250 mg or 500 mg daily [weight-based]) or placebo. Patients from FAB-C also entered the trial. Safety assessments included adverse events, vital signs, laboratories, and electrocardiograms (ECGs). The primary efficacy endpoint was change in the Social Avoidance (SA) subscale of the Aberrant Behavior Checklist–Community FXS (ABC–CFXS).

Results: 240 patients were enrolled; 197 who completed CONNECT-FX, 33 ineligible for randomization from CONNECT-FX and 10 from FAB-C. 110 patients received ZYN002 prior to entry. Mean age was 9.7 years (range 3 to 17 years at entry); 76.3% were male. 176 patients and 101 patients completed at least 12 and 24 months of treatment respectively (median 20 months). Treatment-related adverse events were reported in 13.3% of patients. The most common treatment-related event and only event reported by ≥ 5% of patients was application site pain (6.7%), which was short-lasting and reported as mild in 15 and moderate in 1 patient. Eight patients experienced 11 non-treatment related serious adverse events. Seven patients discontinued due to an adverse event. No clinically significant changes in vital signs or ECGs were reported. There was no evidence of ZYN002-related changes in liver function or any other laboratory tests. At the end of 1 2023 ASCP Annual Meeting CONNECT-FX, completely methylated ZYN002 treated patients had a median improvement of 40% in SA verses 20% in

placebo treated patients (p=0.027); 62% of ZYN002 treated patients and 41% of placebo treated patients reported a clinically meaningful improvement in SA (≥ 3 points) for at least 2 consecutive visits. Placebo treated patients who began ZYN002 in the OLE demonstrated a similar response profile to patients originally treated with ZYN002 in regard to improvement in SA; the effect was maintained through 24 months in both groups. 81% of these patients reported clinically meaningful improvement in SA for at least 2 consecutive visits by 9 months.

Conclusions: ZYN002 was well tolerated over a median of 20 months. In patients with complete FMR1 gene methylation, ZYN002 led to sustained improvement in Social Avoidance, a key behavioral symptom of FXS, following initial improvement seen after 12 weeks of double-blind therapy. The results from this OLE trial continue to support the effectiveness of ZYN002 in patients with complete FMR1 gene methylation.

THE EMERGING SAFETY PROFILE OF ULOTARONT: PRECLINICAL AND CLINICAL EVIDENCE

Heather Dworak[1], Seth C. Hopkins*[1]

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Seth C. Hopkins, Sunovion Pharmaceuticals, Inc.

Abstract Background: Treatment with the current class of dopamine D2 antipsychotic drugs (APDs) is associated with safety and tolerability issues that significantly reduce medication adherence and may be exacerbate health-related morbidity and mortality due to adverse metabolic effects and weight gain. Ulotaront is a non-D2 compound that is a trace amine-associated receptor 1 (TAAR1) agonist with serotonin 5-HT1A agonist activity that has demonstrated efficacy and safety in the treatment of acute exacerbation of schizophrenia in a double-blind, placebo-controlled short-term Phase 2 trial, with changes in metabolic parameters similar to placebo, and in a 6-month extension phase. Here we update ongoing research, highlighting preclinical findings suggesting that ulotaront may have beneficial effects on weight and metabolic parameters; and new clinical findings that further characterize the distinctive safety profile of this non-D2 compound.

Methods: Summarized are preclinical studies of the effect of ulotaront on weight and metabolic parameters in rodent models, including effect on weight gain in rats fed a high fat diet (HFD), rats with olanzapine-induced weight gain, and mice with corticosterone-induced weight gain. Assessment of the effect of ulotaront on gastric emptying in mice, assessment of oral glucose tolerance (oGTT) in naive and diabetic db/db mice; and 3D whole-brain c-fos imaging of ulotaront-treated mice to assess the effects of ulotaront on brain regions associated with the regulation of food intake. Phase I placebo-controlled crossover studies in humans are summarized that examined metabolic biomarkers (C-peptide, insulin, and glucose) after ulotaront treatment. We also present detailed safety results from a recently completed 52-week, double-blind study in adult outpatients with a DSM-5 diagnosis of schizophrenia who were randomized to ulotaront or quetiapine-XR.

Results: HFD rats showed a dose-dependent reduction in body weight, food intake and triglycerides; ulotaront rapidly reversed both olanzapine- and corticosterone-induced weight gain in rats and mice, respectively. Assessment of oGTT showed a dose-dependent reduction

of glucose excursion in response to acute ulotaront in naive and diabetic db/db mice. Acute ulotaront also delayed gastric emptying in mice. 3D whole-brain c-fos imaging of ulotaront-treated mice revealed increased neuronal activity in brain regions associated with the regulation of food intake and integration of peripheral metabolic signals (i.e., arcuate, and paraventricular nucleus of the hypothalamus, and dorsal vagal complex). In crossover studies in subjects with schizophrenia, following administration of a meal, ulotaront lowered insulin and C-peptide levels compared to placebo with large effect sizes (0.8–1.0), indicating a potentially clinically significant effect of ulotaront on glycemic control. The results of the double-blind 52-week study provides further information about the long-term side effects of ulotaront, extrapyramidal symptoms, and safety outcomes including the effect of ulotaront on prolactin, HbA1c, lipids, and body weight.

Discussion: These data indicate that ulotaront, consistent with preliminary clinical data, lacks metabolic liabilities and weight gain effects, and may in fact provide benefit for metabolic disorders via a TAAR1 mechanism. The 52-week study provides the first one-year data on the safety and tolerability profile of ulotaront.

Supported by funding from Sunovion Pharmaceuticals Inc. and Otsuka Pharmaceutical Development and Commercialization Inc.

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

Individual Research Reports: Recent Advances in the Treatment of Schizophrenia

INVESTIGATING THE RELATIONSHIP BETWEEN THE KYNURENINE PATHWAY AND TREATMENT RESISTANCE IN SCHIZOPHRENIA.

Jacopo Sapienza[1], Marco Spangaro[1], Giulia Agostoni[1], Margherita Bechi[1], Mariachiara Buonocore[1], Francesca Martini[1], Marchesi Anna[1], Stefania Sut[2], Sofia Nasini[2], Stefano Dall'Acqua[2], Antonella Bertazzo[2], Federica Cocchi[1], Roberto Cavallaro[1], Marta Bosia[1], Stefano Comai*[2]

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Abstract The neurobiology of schizophrenia is highly complex and multifaced, and the multitude of interactions between different biological systems contribute further to such complexity. Several attempts to disentangle the heterogeneity of the disease were made over the years and, gradually, a more detailed knowledge has been achieved, despite several issues still represent a challenge for research. Two cardinal elements in the pathophysiology of schizophrenia are with no doubts neuroinflammation and the dysregulation of neurotransmission, and interestingly, the kynurenine pathway of tryptophan is at the crossroad between them, constituting a potential causal link and a therapeutic target. However, the possible relationship between changes in biomarkers of the kynurenine pathway and psychopharmacotherapy in schizophrenia is still to be examined. Given such premises, the current study aims at evaluating the link between circulating biomarkers of the kynurenine pathway and the condition of pharmaco-resistance to first-line treatments in schizophrenia. We examined plasma biomarkers related to the metabolism of tryptophan via kynurenine (Kyn)

pathway in 75 patients with schizophrenia, 43 treated with first generation antipsychotics (FGA) or second-generation antipsychotics (SGA) except clozapine, and 32 treated with clozapine after failure of at least two trials of adequate length and dosage with at least one SGA, and thus considered treatment resistant. Psychopathology was assessed using Positive and Negative Syndrome Scale (PANSS) and, in addition to the standard sub-scores, PANSS MARDER factors were used in the analysis. ANOVA analysis (age and duration of illness as covariates) showed increased levels of Kyn in treatment resistant patients compared to first-line responders (p=0.024), highlighting a greater activation of the kynurenine pathway related to pharmaco-resistance. We then investigated possible differential effects of downstream metabolites of Kyn on psychopathology using multiple Separate Slope Models and found differential effects only in first-line responder patients. Specifically, quinolinic acid levels resulted inversely associated with PANSS general score (β=0.603; p=0.005), PANSS total score (β=0.525; p=0.016) and MARDER anx/depr factor (β=0.442; p=0.045). Moreover, the kynurenic acid/quinolinic acid ratio resulted positively correlated with PANSS general score (β=0.451; p=0.0002), PANSS total score (β=0.299; p=0.019), MARDER anx/depr factor (β=0.373; p=0.003) and MARDER positive factor (β=0.304; p=0.016). Our findings show a significant relationship among circulating biomarkers of the Kyn pathway, psychopathology and response to pharmacotherapy in schizophrenia confirming the hypothesis that this metabolic pathway may be at the crossroad of pathophysiology and pharmacotherapy of the disorder, and that Kyn pathway biomarkers may be further investigated for a possible role in the personalized therapy of individuals with schizophrenia.

Learning Objectives:

1. Metabolites of tryptophan along the kynurenine pathway are differently associated with psychopathology in individuals with schizophrenia depending on the presence of treatment resistance.
2. The kynurenine pathway could be at the crossroad between pathophysiology and pharmacotherapy of schizophrenia, and biomarkers of this metabolic pathway may deserve to be further investigated for a personalized approach of the disorder.

Literature References:

1. Sapienza J, Spangaro M, Guillemin GJ, Comai S, Bosia M. Importance of the dysregulation of the kynurenine pathway on cognition in schizophrenia: a systematic review of clinical studies. Eur Arch Psychiatry Clin Neurosci. In press
2. Comai S, Bertazzo A, Brughera M, Crotti S. Tryptophan in health and disease. Adv Clin Chem. 2020; 95:165-218.

IDENTIFYING PREDICTORS OF CLOZAPINE-INDUCED WEIGHT GAIN THROUGH A NATURALISTIC RETROSPECTIVE CHART REVIEW

Nicolette Stogios*[1], *Kateryna Maksyutynska[1], Marcos Sanches[2], Valerie Powell[2], Philip Gerretsen[2], Ariel Graff-Guerrero[2], Araba Chintoh[2], Gary Remington[1], George Foussias[1], Margaret Hahn[1], Sri Mahavir Agarwal[1]*

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Abstract Background: Antipsychotic (AP)-induced weight gain is a distressing and concerning side-effect for patients treated with these medications. Clozapine (CLZ), which is presently the only AP with an approved indication for treatment refractory schizophrenia, carries the greatest

risk for weight gain of all APs. However, it is unclear whether patients who have already gained a substantial amount of weight during the course of their illness and treatment with other APs will continue to experience significant weight gain after starting CLZ. As such, the goal of this study was to stratify patients according to their pre-CLZ BMI and track their weight trajectories after CLZ initiation. Furthermore, this study also mapped the weight trajectory of patients from their pre-diagnosis weight to post-CLZ weight to explore if pre-CLZ weight gain predicts the amount of post-CLZ weight gain that is experienced.

Methods: This is a secondary analysis of a retrospective chart review of patients newly initiated on CLZ at the Centre for Addiction and Mental Health in Canada. To address the first question, patients were stratified according to their baseline (pre-CLZ) BMI: a) normal weight (BMI 18-24.9 kg/m^2), b) overweight (BMI 25-29.9 kg/m^2), and c) obese (BMI 30+ kg/m^2). A mixed model analysis with subjects as random effects was used to assess how weight changes differently over time between BMI classifications. Time (baseline, 6-, 12-months post-CLZ), group (normal, overweight, obese), and the interaction between group and time were included as predictor variables, while controlling for age and sex. To answer the second question, an ANCOVA model was performed in which weight at 6- and 12-months post-CLZ was the dependent variable, and pre-CLZ weight gain was the predictor of interest, while controlling for baseline (pre-CLZ) weight.

Results: This chart review included 396 patients (males: 71.5%, mean age: 42.8 +/- 15.2 years) initiated on CLZ (mean dose: 286.4 mg/day +/- 92.6). The following number of patients were in each BMI category: a) normal: n = 118, b) overweight: n = 123, c) obese: n = 120. In the full sample, there was a significant interaction effect between baseline BMI categories and time, indicating that change in weight depends on baseline BMI. At both timepoints, the greatest increase in body weight was observed in the overweight group (6 months: 4.50 (0.99) kg, $p<0.001$; 12 months: 8.00 (1.19) kg, $p<0.001$) compared to the normal weight (6 months: 3.44 (1.06) kg, $p<0.001$; 12 months: 2.34 (1.39) kg, $p=0.093$) and obese groups (6 months: -0.81 (1.02) kg, $p=0.43$; 12 months: -0.61 (1.22) kg, $p=0.62$). Pre-diagnosis weight was available for 25 patients and was used to calculate pre-CLZ weight gain (pre-CLZ weight – pre-diagnosis weight). Among this subgroup of patients, pre-CLZ weight gain was a significant predictor of body weight 6- ($R^2=0.37$, $B=-0.52$, $p=0.02$) and 12-months ($R^2=0.61$, $B=-0.87$, $p=0.012$) post-CLZ initiation.

Conclusions: This analysis revealed that patients with an increased metabolic risk and propensity to gain weight are more likely to experience significant weight gain after CLZ initiation than those who are normal weight or already obese. Furthermore, those who gained the most weight during their illness and treatment before CLZ experienced a lesser degree of weight gain post-CLZ initiation compared to those who did not gain as much weight during their previous AP trials. Understanding predictors of weight gain could allow for early identification of the minimum metabolic threshold and clinical profile that would warrant and benefit from adjunctive metabolic interventions to prevent significant weight gain with CLZ.

Learning Objectives:

1. To stratify patients according to their pre-clozapine BMI and track their weight trajectories after clozapine initiation to identify a subgroup of patients at greatest risk of gaining weight with clozapine.
2. To map the weight trajectory of patients from their pre-diagnosis weight to post-clozapine weight to explore if pre-clozapine weight gain predicts the amount of post-clozapine weight gain that is experienced.

Literature References:

1. Pillinger T, McCutcheon RA, Vano L, et al. Comparative effects of 18 antipsychotics on metabolic function in patients with schizophrenia, predictors of metabolic dysregulation, and association with psychopathology: a systematic review and network meta-analysis. Lancet Psychiatry. 2020; 7:64-77.
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THE DYNAMIC CHANGE IN CEREBRAL BIOENERGECTICS IN SCHIZOPHRENIA PATIENTS

Muharrem Baytunca*[1], *Xiang Feng[1], Colleen Fitzgerald[1], Danielle Boxer[1], Deborah Yurgelun-Todd[2], Perry Renshaw[2], Douglas Kondo[1]*

[1]University of Utah, [2]George E. Wahlen Department of Veterans Affairs Medical Center, VA VISN 19 Mental Illness Research, Education and Clinical Center (MIRREC), Salt Lake City, UT, USA Department of Psychiatry, University of Utah School of Medicine, Salt Lake City, UT, USADiagnostic Neuroimaging, University of Utah, Salt Lake City, UT, USA

Muharrem Baytunca, University of Utah

Abstract Schizophrenia is a heterogeneous mental disorder with complex cellular biology. Several leading hypotheses including dopamine overflow, NMDA receptor hypofunction cannot fully explain the etiology of schizophrenia. Bioenergetics focuses on the metabolic pathways of the production, transformation, storage, and consumption of high energy phosphates (HEP) including phosphocreatine (PCr), adenosine triphosphate (ATP) and inorganic phosphate (Pi) in cells. A potential shift from mitochondrial oxidative phosphorylation toward increased glycolysis leading up to the accumulation of lactate, and perturbation in mitochondrial oxidative phosphorylation (OXPHOS) supported by genetic and post-mortem studies have been reported. Noteworthy, Du et al reported 22% reduction in CK (creatine kinase) forward rate in schizophrenia patients, which transfers phosphate (Pi) from PCr to ADP to generate ATP to be utilized for ongoing neuronal functions (PCr + ADP <--->CK enzyme <---> Cr + ATP) when higher energy relative to baseline is demanded. This has also been reported in subjects with first episode psychosis too. To the best our knowledge, the dynamic change in cerebral bioenergetics when schizophrenia brain is challenged by stress inducing test (hypoxia) via 31P-MR spectroscopy has not been assessed before. Methodology: We enrolled 11 patients with schizophrenia or schizoaffective disorder (SCZ/SA) (2 females, mean age 31) vs 11 HC (3 females, mean age 29) ($p>0.05$ for gender and mean age). An MRI compatible hypoxia chamber, connected to a generator, enveloping the upper part of the individuals was placed before the scan. Participants inspired air with 13% oxygen (FiO2) for 30 mins in the first part the scan, and FiO2 25% in the second part with same duration. We reduced blood oxygen levels, measured by fingertip pulse oximeter, to 86 (spO2) to induce hypoxic stress in the first part of scan (spo2 levels were %100 in the second part of scan). It is

a well replicated finding that PCr reduces, and Pi increases in skeletal muscle during physical exercise to maintain steady levels of ATP, which shows the natural process during a state requiring higher energy demand than baseline. Results: PCr, Beta-ATP, PCr/Beta-ATP levels did not significantly differ between the groups in both states (hypoxia and hyperoxia). Pi levels were significantly lower in the prefrontal cortex (PFC, p=0.02) and anterior cingulate cortex (ACC, p=0.03) cortices of SCZ/SA subjects during hypoxia scan, not in hyperoxia scan. PCr/Pi ratios were also higher in the PFC (p= 0.01), ACC (p=0.04), whole brain (WB, p=0.04) in SCZ/SA in hypoxic state. PDE levels were higher in the PFC (p=0.01), posterior occipital cortex (POC, p=0.01), the WB (p<0.01) in hypoxia and hyperoxia conditions. pH levels were lower in WB analysis during hypoxia in SCZ subjects. Discussion: This study shows that the dynamic response in cellular bioenergetics to a higher energy demanding state is impaired in the PFCs of schizophrenia subjects, which seems consistent with hypofrontality theory. Significantly lower levels of Pi in the PFC, ACC during hypoxia challenge display a perturbation in compensatory energy production, which might be a consequence of impaired mitochondrial OXPHOS and/or CK forward rate. PCr is the energy buffer that maintain steady levels of ATP for neural homeostasis. Higher levels of PCr/Pi, an indicator of energy production capacity/energy load of cells, in the PFC, ACC and whole brain analyses during hypoxia scan also support the metabolic impairment in compensatory energy production the patients during energy demanding stress. More acidic pH levels in SCZ/SA might be related to more reliance on glycolysis. Limitations: small sample size, medication status.

Learning Objectives:

1. Cerebral bioenergetics seems to be impaired in those with schizophrenia, particularly in the prefrontal cortex, which raises the necessity of pharmacological intervention to this system.
2. There seems to be a widespread catabolic process in neural membranes in whole brain, predominantly in PFC and posterior occipital cortex.

Literature References:

1. Du, Fei, Alissa J. Cooper, Thida Thida, et al. In vivo evidence for cerebral bioenergetic abnormalities in schizophrenia measured using 31P magnetization transfer spectroscopy."JAMA psychiatry 2014; 71, no. 1: 19-27.
2. Henkel, Nicholas D., Xiajoun Wu, Sinead M et al. "Schizophrenia: a disorder of broken brain bioenergetics." Molecular Psychiatry 27; 2022, no. 5: 2393-2404.

THE EFFICACY OF ROLUPERIDONE ON NEGATIVE SYMPTOMS AND SOCIAL FUNCTIONING: ARE THERE QUALITATIVELY DISTINCT PATTERNS OF TREATMENT RESPONSE?

Anthony Ahmed*[1], *Jay Saoud*[2], *Ramana Kuchibhatla*[2], *Gregory Strauss*[3], *Philip Harvey*[4], *Michael Davidson*[2]

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Anthony Ahmed, Weill Cornell Medical College/NewYork-Presbyterian Hospital

Abstract Background: The identification of drugs that can improve negative symptoms in schizophrenia remains a priority for pharmacological development. Roluperidone is a novel cyclic amide derivative with primary antagonistic properties for 5-hydroxytryptamine 2A (5-HT2A) and sigma-2 receptors and added affinity for α1A-adrenergic receptors. The current study uses latent variable modeling to 1) depict the effect of roluperidone on the trajectory of

negative symptoms and social functioning over the 12-week Phase 2b and Phase 3 trials; and 2) illuminate the heterogeneity of response in negative symptoms during the trials.
Method: In the 2 RCTs, participants with predominantly negative symptoms were randomized to receive in 1:1:1 ratio either roluperidone 32 mg/day, roluperidone 64 mg/day, or placebo for 12 weeks. In Phase 2b (N=244), participants were recruited from 36 sites and 6 European countries. The Phase 3 trial (N=513) recruited from 60 sites and 8 countries including the United States. Both trials assessed negative symptoms using the Positive and Negative Syndrome Scale (PANSS) and social functioning with the Personal and Social Performance (PSP) scale. Assessments were completed at baseline, Week 2, Week 4, Week 8, and Week 12 (endpoint). Latent growth curve models were fitted to the data sequentially. First, the most appropriate model of change was determined by fitting intercept only, linear, and then quadratic models to negative symptoms and social functioning data. Second, external variables including treatment group, age, sex, country, were evaluated as predictors of the longitudinal change function. Next, a categorical latent variable was imposed on the preferred model of change to identify subsamples within the data that may differ in their change trajectory over the 12-week trial.

Results: Goodness-of-fit indices frequently favored a quadratic model of change for negative symptoms in both studies, and social functioning in the Phase 3 trial. In Phase 2b, roluperidone treatment was a significant predictor of improved PANSS NSFS (slope=-0.269, $p<0.001$) but its effect on non-linear change was not significant ($q=0.156$, $p=0.134$). Treatment drove reductions in both the PANSS emotional expression (EXP) (slope = -0.289, $p<0.001$) and marginally in motivation and pleasure (MAP) items (slope = -0.164, $p=0.067$).

In Phase 3, treatment predicted reductions in negative symptoms (slope= -0.184, $p<0.001$) non-linear change ($q=0.165$, $p<0.001$). Treatment effects were domain-specific with linear (slope= -0.270, $p<0.0001$) and non-linear ($q=0.264$, $p<0.001$) change in MAP items. In Phase 2b, treatment group was associated with improved PSP composite score (slope= 0.196, $p <0.001$) and PSP total score (slope= -0.177, $p <0.001$). In Phase 3, treatment group was similarly associated with improved PSP composite score linear (slope= 0.115, $P<0.05$) and the PSP total score (slope = -189, $p<0.001$).

Growth mixture modeling favored a two-class quadratic growth model with class varying intercepts and slopes, suggesting 2 trajectories of change in the clinical trial. The first trajectory (class 1 = 23.8%) was characterized by rapid and steep response to treatment that threshold at around week 8. The second trajectory (class 2=76.2%) comprised slow responders. The roluperidone 64 mg (37%) and 32 mg (24%) groups had greater odds off belonging to Class 1 than the placebo group (10.8%) [$\chi 2$ (2, 496) = 31.28, $\varphi=0.251$, $p<0.0001$].

Discussion: Roluperidone is associated with reduced negative symptoms and improved social functioning. There are distinct trajectories of change in negative symptoms in the clinical trial that reflect the impact of the compound and underlying intraindividual variability.

Learning Objectives:

1. Participants will evaluate evidence of roluperidone's effects on negative symptoms and social functioning.
2. Participants will discover the utility of latent growth and latent growth mixture models for illuminating the nature and heterogeneity of response to negative symptoms.

Literature References:

1. Davidson M, Saoud J, Staner C, et al. Efficacy and Safety of MIN-101: A 12-Week Randomized, Double-Blind, Placebo-Controlled Trial of a New Drug in Development for the Treatment of Negative Symptoms in Schizophrenia. Am J Psychiatry. 2017;174(12):1195-1202. doi: 10.1176/appi.ajp.2017.17010122
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4:15 p.m. - 5:30 p.m.

Individual Research Reports: Innovations in Biomarkers and Treatment Targets for Precision Medicine

FROM RELAXED BELIEFS UNDER PSYCHEDELICS (REBUS) TO REVISED BELIEFS AFTER PSYCHEDELICS (REBAS)

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Abstract Psychedelic therapy shows potential as a transdiagnostic therapeutic intervention for a range of psychiatric presentations. The Relaxed Beliefs Under pSychedelics (REBUS) model proposes that serotonergic psychedelics decrease the precision weighting of neurobiologically-encoded beliefs. We conducted a preliminary examination of two psychological assumptions of REBUS: (a) psychedelics foster acute relaxation and post-acute revision of confidence in mental-health-relevant beliefs, which (b) facilitate positive therapeutic outcomes and are associated with the entropy of EEG signals. Healthy individuals (N=11) were administered 1 mg and 25 mg psilocybin 4-weeks apart. Confidence ratings for personally held beliefs were obtained before, during, and 4-weeks post-psilocybin. Acute entropy and subjective experiences were measured, as was well-being (before and 4-weeks post-psilocybin). Confidence in negative self-beliefs decreased following 25 mg psilocybin. Entropy and subjective effects under 25 mg psilocybin correlated with decreases in negative self-belief confidence (acutely and at 4-weeks). Particularly strong evidence was seen for a relationship between decreases in negative self-belief confidence and increases in well-being. We report the first empirical evidence that the relaxation and revision of negative self-belief confidence mediates psilocybin's positive psychological outcomes, and provide tentative evidence for a neuronal mechanism, namely, increased neuronal entropy. Replication within larger and clinical samples is necessary.

Learning Objectives:

1. Understand how psilocybin effects negative and positive beliefs.
2. Understand how psilocybin's effects on negative self-beliefs relate changes in well-being and neural entropy.

Literature References:

1. Carhart-Harris, R. L., and Friston, K. (2019). REBUS and the anarchic brain: toward a unified model of the brain action of psychedelics. Pharmacological Reviews, 71(3), 316-344.
2. Alamia, A., Timmermann, C., Nutt, D. J., VanRullen, R. and Carhart-Harris, R. L. DMT alters cortical traveR. g waves. Elife, 9, e59784 (2020).

BEHAVIORAL AND NEURAL CORRELATES OF SUICIDE RISK: A ROLE FOR KETAMINE IN SUICIDE PREVENTION?

Steven Lamontagne*[1], *Jessica Gilbert[1], Carlos Zarate[1], Elizabeth Ballard[1]*

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Abstract Background: Suicide rates are increasing globally, yet risk mitigation strategies have been largely unsuccessful. These efforts are hindered by (1) a paucity of objective measures that probe suicidal states, (2) limited understanding of the neurobiology of suicide, and (3) considerable heterogeneity in the characterization of suicide risk across clinical trials and neuroimaging studies. There is an urgent need to identify neural correlates associated with varying levels of suicide risk, as well as develop novel fast-acting therapeutics to modulate activity within these neural networks.

Methods: Seventy-five adults were recruited through a suicide-focused research protocol (NCT02543983). Participants were assigned to the following risk categories: (1) those with a suicide attempt in the past two weeks and/or lifetime suicidal ideation with intent (High Risk; HR) (n=15), (2) those with a history of attempt, but no suicidal behavior or ideation with intent in the past year (Moderate Risk; MoR) (n=18) (3) those with anxiety or mood symptoms, but no suicide history (Low Risk; LR) (n=19), and (4) those without psychiatric or suicide history (Minimal Risk; MinR) (n=23). We used a CTF 275-channel whole-head magnetoencephalography (MEG) scanner to examine electrophysiological correlates of suicide. During MEG scanning, participants completed a modified Life-Death Implicit Association Task, which is a computer task measuring associations of oneself to either life or death based on reaction times to words that represent each category (Nock et al., 2010). The behavioral outcome of interest was the D-score, defined as the difference in mean reaction times between self-death and self-life trials. MEG data were source-localized in the gamma (30-58 Hz) frequency, a proxy measure of excitation-inhibition balance. In a proof-of-concept open-label pilot study (N=5 HR participants), we examined changes in gamma power following subanesthetic-dose ketamine, a N-methyl-D-aspartate (NMDA) receptor antagonist known to have rapid anti-suicidal ideation properties.

Results: Behavioral results showed that D-scores in the HR group did not differ from zero ($p=0.78$), but were significantly higher compared to the MoR, LR, and MinR groups ($ps<0.01$). D-scores for the latter three groups did not differ from each other ($ps>0.43$) and were significantly lower than zero ($ps<0.001$), denoting a self-life bias. A significant group-by-condition interaction ($p<0.05$) revealed group differences in gamma power within the posterior cingulate cortex (PCC), right insular cortex, and orbitofrontal cortex (OBF). Higher gamma power for self-death compared to self-life trials was found in the OBF for the HR group ($p<0.01$) and the insula and PCC for the MinR group ($ps<0.05$). D-scores were not affected by ketamine administration ($p=0.57$); however, a session-by-condition interaction ($p<0.05$)

revealed enhanced gamma power for self-death trials in the left insula after ketamine administration compared to baseline ($p<0.001$). Post-ketamine insular gamma power for self-death trials inversely correlated with D-score ($r=-0.89$, $p<0.05$), suggesting the insula might be an important biomarker for implicit cognitions about death in HR individuals.

Conclusion: These findings point to differential implicit cognitive processing of life and death depending on suicide risk, highlighting the need for objective measures of suicidal states. Our findings also implicate a role for pharmacotherapies that modulate gamma activity, particularly in the insula, in risk mitigation. Toward this end, our preliminary data show promising effects of ketamine in modulating neural correlates of suicide-related cognitive processing.

Learning Objectives:

1. Examine whether varying levels of suicide risk are linked to differential implicit self-associations with death and distinct electrophysiological profiles.
2. Determine whether ketamine administration alters both implicit self-associations with death and neural correlates of suicide among individuals with a recent suicide attempt.

Literature References:

1. Ballard E, Gilbert J, Fields J, et al. Network changes in insula and amygdala connectivity accompany implicit suicidal associations. Frontiers in Psychiatry. 2020;11: 577628.
2. Nock M, Park J, Finn C, et al. Measuring the suicidal mind: Implicit cognition predicts suicidal behavior. Psychological science. 2010;21(4): 511-517.

PREFRONTAL FUNCTIONAL DYSCONNECTIVITY IN DELIRIUM MEASURED BY DIFFUSE OPTICAL TOMOGRAPHY

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Abstract Background: Delirium is the most common neuropsychiatric syndrome in the hospital, yet it remains understudied. Most of the published data is focused on clinical manifestations and not underlying pathophysiology or mechanisms. Functional neuroimaging would be beneficial; however there has been no device that can capture three-dimensional data at bedside. The primary objective of this study was to determine if diffuse optical tomography (DOT) can be used to portably obtain resting-state and task-based functional data during and after an episode of delirium. Secondary objectives include correlating regional dysfunction with severity scores and clinical variables.

Methods: This single-center exploratory study was conducted at a tertiary hospital. Two groups of patients were recruited: a delirium group and a non-delirious group matched for age/gender/hand/admission setting. The delirium group included patients with ongoing delirium formally diagnosed by a consultation-liaison psychiatrist (Diagnostic and Statistical

Manual of Mental Disorders, Fifth Edition, [DSM-V] criteria) and documented by a positive 4AT (general ward) or CAM-ICU score (ICU).

Subjects were evaluated daily by a consultation-liaison psychiatrist and delirium resolution was defined as at least two consecutive days of negative screening. The Delirium Rating Scale-R-98 (DRS-R-98) was used to measure severity of delirium. Subtypes were classified based on DSM-V and Liptzin-Levkoff criteria. The APACHE III and the Charlson Comorbidity Index were used to quantify acute illness severity and burden of chronic disease, respectively.

A custom-built DOT system was employed. Continuous-wave measurements of data were captured through a 48-photo source-detector head interface. Regions of interest were identified based on Montreal Neurological Institute coordinates centered on the bilateral prefrontal cortices. The DOT protocol consisted of a two-minute resting state scan, followed by a one-minute task-based sequence (Months Backwards Test), and then concluded after another two-minute resting scan. Imaging data was collected at time of enrollment and then after resolution of delirium. Seed-based correlation analysis with the left dorsolateral prefrontal cortex (DLPFC) set as the seed region was conducted as well.

Results: 25 delirious subjects and 25 non-delirious subjects were recruited (n=50). In all prefrontal regions, the total hemoglobin values were statistically significantly decreased in the delirium group, even after resolution of delirium ($p=0.015$; 95% CI [0.5, 0.92] and $p=0.023$; 95% CI [1.2, 2.05]. The time to peak hemoglobin value and return to resting state was also delayed ($p=0.027$). DRS-R-98 scores correlated with hemoglobin values in all brain regions. Seed-based correlation analysis revealed that left DLPFC activity was more strongly associated with right DLPFC and bilateral dorsomedial prefrontal cortex (DMPFC) activity post-resolution and in non-delirious subjects relative to during an episode of delirium. Furthermore, the reciprocal relationship of left DLPFC to DMPFC activity was found to have stronger functional connectivity in more severely delirious subjects.

Conclusion: To date, this is the largest delirium functional neuroimaging study with a matched control group that reveals marked prefrontal functional dysconnectivity during and even after an episode of delirium. These findings demonstrate the feasibility of a portable three-dimensional functional imaging system for biomarker studies in delirium. Future studies will focus on post-delirium neurocognitive impairment and the relationship between delirium and subsequent Alzheimer's disease and related dementias.

Learning Objectives:

1. Review functional neuroimaging studies in delirium; share pilot data on the use of diffuse optical tomography in delirium.

Literature References:

2. Dai X, Zhang T, Yang H, Tang J, Carney PR, Jiang H. Fast noninvasive functional diffuse optical tomography for brain imaging. J Biophotonics. 2018;11(3):10.1002/jbio.201600267.
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EFFECT OF LEMBOREXANT TREATMENT ON POLYSOMNOGRAPHIC SLEEP MEASURES IN OLDER ADULTS WITH INSOMNIA AND OBJECTIVE SHORT SLEEP DURATION

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Margaret Moline, Eisai Inc.

Abstract Introduction: duction: Subjects with insomnia and objective short-sleep duration (I-SSD), defined by polysomnography as total sleep time (TST) <6 h, may have lessened response to cognitive behavior therapy for insomnia (CBT-I). Thus, we evaluated sleep parameters with lemborexant (LEM) versus zolpidem tartrate extended release 6.25 mg (ZOL) and placebo (PBO) in subjects with I-SSD. LEM is a dual-orexin antagonist approved in the United States, Japan, Canada, Australia, and several Asian countries for the treatment of adults with insomnia. Methods: In Study E2006-G000-304 (NCT02783729), subjects (females age ≥55 years; males age ≥65 years) were randomized to LEM 5 mg (LEM5) or 10 mg (LEM10), placebo (PBO), or ZOL. Latency to persistent sleep (LPS) and wake after sleep onset (WASO) were assessed using polysomnograms (PSG) and averaged from paired PSG during single-blind PBO run-in, Nights (NT)1/2 and NT29/30. Change from baseline was analyzed using mixed-effect model repeated measurement analysis.

Results: The I-SSD subgroup comprised 710 of 1006 (70.6%) subjects. Mean (SD) baseline LPS was similar across treatments in this subgroup: LEM5 54.28 (39.30); LEM10 53.31 (34.45); PBO 52.80 (35.73); ZOL 54.77 (40.93). At NT1/2, LEM5 and LEM10 led to significantly larger ($P<0.05$) mean (SD) decreases from baseline versus PBO and ZOL: LEM5 −22.02 (31.62); LEM10 −25.42 (34.73); PBO −9.65 (36.52); ZOL −17.78 (36.34). At NT29/30, LEM5 and LEM10 led to significantly larger ($P<0.0005$) mean decreases (SD) from baseline versus PBO and ZOL. LPS with ZOL did not differ from PBO: LEM5 −25.37 (37.06); LEM10 −28.20 (34.75); PBO −11.88 (35.09); ZOL −12.57 (38.50). Mean (SD) baseline WASO was similar across treatments: LEM5 128.14 (37.52); LEM10 129.07 (37.98); PBO 123.79 (37.21); ZOL 128.37 (38.94). At NT1/2, LEM5 and LEM10 led to significantly larger ($P<0.0001$) decreases from baseline versus PBO, and LEM10 led to larger differences from baseline versus ZOL ($P<0.0001$), least squares mean (SE): LEM5 −60.58 (2.45); LEM10 −69.35 (2.41); PBO −23.52 (2.74); ZOL −54.74 (2.47). At NT29/30, LEM5 and LEM10 led to significantly larger ($P<0.0001$) decreases from baseline versus PBO and LEM10 decreases were significantly larger versus ZOL ($P<0.05$), least squares mean (SE): LEM5 −52.67 (2.74); LEM10 −55.37 (2.70); PBO −29.62 (3.09); ZOL −46.86 (2.80).

Conclusions: These results support LEM as an effective therapy for older patients with I-SSD and suggest LEM may be more beneficial than ZOL in these patients, especially when a behavioral therapy may have limited efficacy.

Support: Eisai Inc.

Learning Objectives:

1. To increase awareness of the specific impact of insomnia and objective short-sleep duration.

2. To increase awareness of the potential for lemborexant as an effective treatment for insomnia with objective short -sleep duration in older adults.

Literature References:

1. Vgontzas AN, et al. Insomnia with objective short sleep duration: the most biologically severe phenotype of the disorder. Sleep Med Rev. 2013 Aug;17(4):241-54.
2. Pal A, et sl. Management of Chronic Insomnia Using Cognitive Behavior Therapy for Insomnia (CBT-I) During COVID-19 Pandemic: Does One Shoe Fit All? Sleep Vigil. 2022;6(1):56-60.

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

Individual Research Reports: Novel Treatments and Comprehensive Evaluation for Depression and PTSD

AXS-05 (DEXTROMETHORPHAN-BUPROPION) SIGNIFICANTLY IMPROVED FUNCTIONING IN MAJOR DEPRESSIVE DISORDER: ANALYSIS OF THE DOMAINS OF THE SHEEHAN DISABILITY SCALE

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Abstract Background: Major depressive disorder (MDD) is the leading cause of disability worldwide (World Health Organization, 2017). Workplace cost accounts for the largest portion of the growing economic burden of MDD and approximately two-thirds of individuals with MDD report marked impairment in at least one of the domains evaluated by the Sheehan Disability Scale (1,2).

AXS-05 [dextromethorphan-bupropion (Auvelity® extended-release tablet)] is a novel, oral, NMDA receptor antagonist with multimodal activity approved by U.S FDA for the treatment of MDD in adults. The dextromethorphan component of AXS-05 is an antagonist of the NMDA receptor (an ionotropic glutamate receptor) and a sigma-1 receptor agonist. The bupropion component of AXS-05 is an aminoketone and CYP450 2D6 inhibitor, which serves primarily to increase the bioavailability of dextromethorphan.

Objective: To explore the effects of AXS-05 on patient function, post-hoc analysis evaluated functional disability assessed by Sheehan Disability Scale (SDS) subdomain scores over 6 and 52 weeks in two phase 3 studies in MDD.

Methods: Functional disability was measured by the SDS in two clinical trials evaluating AXS-05 (dextromethorphan 45 mg-bupropion 105 mg) in MDD: GEMINI, a randomized, double-blind, placebo-controlled, 6-week trial (Iosifescu DV, et al. J Clin Psychiatry. 2022; 83:21m14345) and COMET, an open-label study evaluating AXS-05 treatment for up to one year (NCT04039022). The SDS consists of 3 domains: Work/School, Social Life, and Family Life/Home Responsibilities. Each domain is scored from 0 to 10, with higher scores representing greater disability. GEMINI enrolled 327 patients. COMET enrolled 609 patients who did not previously participate in an AXS-05 study.

Results: In both studies, patients reported moderate-to-marked disability on each domain at baseline: Work/School (GEMINI: 6.2 for AXS-05 and 5.5 for placebo; COMET: 6.1 for AXS-05), Social Life (GEMINI:7.2 for AXS-05 and 6.8 for placebo; COMET: 7.0 for AXS-05), and Family Life/Home responsibilities (GEMINI: 6.7 for both AXS-05 and placebo; COMET: 6.7 for AXS-05).

In GEMINI, treatment with AXS-05 resulted in significant improvement on all SDS domains at Week 6. Improvements (change from baseline, AXS-05 vs placebo) were -2.6 vs -1.8, p=0.043, in the Work/School domain; -3.3 vs. -2.2, p=0.001 in the Social Life domain; and -3.0 vs -2.3, p=0.029, in the Family Life/Home Responsibilities domain. Functional improvement across these domains was rapid, achieving improvement starting at Week 2.

In the COMET trial, treatment with AXS-05 improved SDS scores across all the domains starting at Week 1 and improvements were maintained for up to one year.

The most commonly reported adverse reactions (≥5% and more than twice the rate of placebo) in the GEMINI trial were: dizziness, headache, diarrhea, somnolence, dry mouth, sexual dysfunction, and hyperhidrosis. Long-term safety in the COMET open-label study was generally consistent with the results observed in the controlled trials.

Conclusions: Treatment with AXS-05 significantly improved functional disability in the SDS domains of Work/School, Social Life and Family Life/Home Responsibilities in patients with MDD.

Sponsorship: This research was supported by Axsome Therapeutics.

Learning Objectives:

1. Describe the impact of AXS-05 (dextromethorphan-bupropion) treatment on the individual domains for the Sheehan Disability Scale.
2. Understanding the impact of major depressive disorder on functioning and disability.

Literature References:

1. Greenberg PE, Fournier AA, Sisitsky T, et al. The Economic Burden of Adults with Major Depressive Disorder in the United States (2010 and 2018). Pharmacoeconomics. 2021;39:653-665.
2. Substance Abuse and Mental Health Services Administration. (2021). Key substance use and mental health indicators in the United States: Results from the 2020 National Survey on Drug Use and Health (HHS Publication No. PEP21-07-01-003, NSDUH Series H-56). Rockville, MD.

RELIABILITY AND VALIDITY OF THE DIFFICULT TO TREAT DEPRESSION QUESTIONNAIRE

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Abstract Background: It has recently been recommended that treatment resistant depression be reconceptualized and renamed as difficult to treat depression (DTD). A consensus statement by an expert panel identified multiple variables that are associated with DTD and emphasized

the importance of conducting a comprehensive evaluation of patients to identify possible contributors to inadequate treatment response. The broader conceptualization of DTD attends to longitudinal course, both the number and types of treatments to which the patient did not respond, and the possibility of identifying patients with DTD prior to initiating treatment based on clinical, social, and biological factors However, comprehensive evaluations are time-consuming and expensive, and thus unlikely to be conducted in routine clinical practice. For practical reasons, it would therefore be desirable to develop a self-report scale that can be easily incorporated into clinical practice that identifies the patient, clinical, and treatment risk factors for DTD.

Methods: Nine hundred twenty depressed patients in a partial hospital program completed the Difficult to Treat Depression Questionnaire (DTDQ). The items of the DTDQ were derived from reviews of the literature of the factors predicting poorer outcome in the treatment of depression and the factors identified as characteristic of difficult to treat depression. Each item is rated on a 5-point scale (0-4), with greater scores reflecting greater levels of pathology/severity (e.g., higher scores on the depression severity item reflect greater levels of depression; higher scores on the financial strain item reflect greater financial difficulty). Anchor point descriptions for each level are provided.

A subset of patients completed the scale a second time.

Because the outcome of DTD should consider nonsymptom as well as symptom domains, the broad-based Remission from Depression Questionnaire (RDQ) was the outcome measure. The RDQ assesses depressive symptoms, nondepressive symptoms, coping ability, positive mental health, impaired functioning, and quality of life. The RDQ was completed at admission and discharge from the program.

Results: The DTDQ demonstrated excellent internal consistency and test-retest reliability.

At both admission and discharge, higher DTDQ scores were associated with higher levels of depressive and nondepressive symptoms, poorer coping, greater impairment in functioning, reduced positive mental health, and lower quality of life. Because of the significant pre-treatment correlations, we computed partial correlations with the post-treatment RDQ scores while controlling for pre-treatment scores. The pattern of findings remained identical, with all partial correlation coefficients being statistically significant.

Both the total DTDQ and the number of prior failed medication trials predicted outcome. However, the DTDQ continued to be significantly associated with outcome after controlling for the number of failed trials, whereas the number of failed trials did not predict outcome after controlling for DTDQ scores.

Conclusions: The DTDQ is a reliable and valid measure of the recently discussed concept of difficult to treat depression. The DTDQ captures important prognostic information beyond that accounted for by the number of medication trial failures.

Learning Objectives:

1. Understand the distinction between treatment resistant depression and difficult to treat depression.
2. Become familiar with the reliability and validity of a new scale designed to assess the clinical factors associated with difficult to treat depression.

Literature References:

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

2. Mcallister-Williams, R.H., Arango, C., Blier, P., Demyttenaere, K., Falkai, P., Gorwood, P., Hopwood, M., Javed, A., Kasper, S., Malhi, G.S., Soares, J.C., Vieta, E., Young, A.H., Papadopoulos, A., Rush, A.J., 2020. The identification, assessment and management of difficult-to-treat depression: An international consensus statement. J. Affect. Disord. 267, 264-282.

CARIPRAZINE AS AN ADJUNCTIVE TREATMENT FOR MAJOR DEPRESSIVE DISORDER: ASSESSMENT OF BENEFIT AND RISK USING NUMBER NEEDED TO TREAT AND NUMBER NEEDED TO HARM

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Abstract Background: Cariprazine (CAR) is an FDA-approved antipsychotic used to treat schizophrenia, bipolar mania/mixed episodes, depressive episodes associated with bipolar I disorder, and in 2022 received approval for adjunctive use in major depressive disorder (MDD). This post hoc analysis investigated the efficacy and tolerability of adjunctive CAR in patients with MDD using the evidence-based medicine metrics of number needed to treat (NNT), number needed to harm (NNH), and likelihood to be helped or harmed (LHH).

Methods: Data sources were five completed Phase II/III, 6-8 week, randomized, double-blind, placebo-controlled studies, including the two informative studies of adjunctive CAR (NCT01469377 and NCT03738215) that were supportive of its approval for MDD in the United States, and three other studies that provided additional tolerability data (NCT00854100, NCT01715805, and NCT03739203). Efficacy outcomes included acute response (≥50% decrease from baseline on the Montgomery-Åsberg Depression Rating Scale [MADRS] total score). Tolerability outcomes included commonly occurring adverse events (AEs) and rates of discontinuation because of an AE, with data pooled across all studies for the CAR 1-2 mg/day plus 1.5 mg/day dose groups, 2-4.5 mg/day plus 3 mg/day dose groups, and for all groups where CAR dose was ≥1 mg/day. NNT and NNH were calculated for adjunctive CAR vs. adjunctive placebo. All subjects received open-label antidepressant treatment.

Results: In study NCT01469377, MADRS response rates at Week 8 for CAR 2-4.5 mg/day vs. placebo were 134/271 (49.4%) vs. 101/264 (38.3%), resulting in a NNT of 9 (95% CI 6-36). In study NCT03738215, MADRS response rates at Week 6 for CAR 1.5 mg/day vs. placebo were 110/250 (44.0%) vs. 87/249 (34.9%), resulting in a NNT of 11 (95% CI 6-193). For the pooled CAR ≥1 mg/day group, MADRS response rates at Week 6 were 765/1887 (40.5%) for CAR vs. 354/1101 (32.2%) for placebo, resulting in a NNT of 12 (95% CI 9-21). For the pooled CAR ≥1 mg/day group, rates of akathisia vs. placebo were 209/1893 (11.0%) vs. 25/1108 (2.3%) for placebo, resulting in a NNH of 12 (95% CI 10-14). This appears to be dose related as the NNH for akathisia vs. placebo was 24 (95% CI 17-43) for the 1-2 mg/day plus 1.5 mg/day dose groups, and 9 (95% CI 7-11) for the 2-4.5 mg/day plus 3 mg/day dose groups. For the pooled CAR ≥1 mg/day group, rates of discontinuation because of an AE vs. placebo were 122/1893 (6.4%) vs. 26/1108 (2.3%) for placebo, resulting in a NNH of 25 (95% CI 19-38). This too appears to be dose related as the NNH for discontinuation because of an AE vs. placebo was 94 (ns) for the 1-2 mg/day plus 1.5 mg/day dose groups, and 17 (95% CI 13-28) for the 2-4.5 mg/day plus 3 mg/day dose groups. For the pooled CAR ≥1 mg/d group, rates of

weight gain ≥7% from baseline vs. placebo were 35/1893 (1.8%) vs. 12/1108 (1.1%) for placebo, resulting in a NNH of 131 (ns). LHH comparing MADRS response vs. discontinuation because of an AE is >1, and >>1 for the lower dose range. Indirect comparisons of the above results with that of the effect sizes seen in positive studies of other adjunctive antipsychotic treatments vs. adjunctive placebo in MDD demonstrate similar values for NNT for response, and when the lower dose range of CAR is used, a more favorable NNH regarding discontinuation because of an AE.

Conclusion: The benefit-risk profile of CAR is favorable for the indication of adjunctive treatment of MDD.

Learning Objectives:

1. At the conclusion of this presentation, attendees will know that cariprazine is a new adjunctive therapy that is administered with an ongoing antidepressant to treat adult patients with major depressive disorder.
2. At the conclusion of this presentation, attendees will understand the benefit-risk profile of cariprazine as an adjunctive treatment option for major depressive disorder.

Literature References:

1. Durgam S, Earley W, Guo H, et al. Efficacy and safety of adjunctive cariprazine in inadequate responders to antidepressants: A randomized, double-blind, placebo-controlled study in adult patients with major depressive disorder. J Clin Psychiatry. 2016;77:371-378.
2. Citrome L. Number needed to treat: what it is and what it isn't, and why every clinician should know how to calculate it. J Clin Psychiatry. Mar 2011;72(3):412-3.

EFFICACY AND SAFETY RESULTS FROM THE CONFIRMATORY PHASE 3 RANDOMIZED, PLACEBO-CONTROLLED TRIAL OF MDMA-ASSISTED THERAPY FOR TREATMENT OF CHRONIC PTSD WITH AT LEAST MODERATE SEVERITY

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Abstract Introduction: duction: Post-traumatic stress disorder (PTSD) is a debilitating neuropsychiatric illness for which novel treatment options are urgently needed. This randomized, double-blind, placebo-controlled, multi-site Phase 3 trial (NCT04077437) was designed to assess the efficacy and safety of MDMA-assisted therapy (MDMA-AT) versus placebo plus therapy in participants with moderate or severe chronic PTSD.

Methods: Participants met DSM-5 criteria for current PTSD diagnosis with a symptom duration ≥6 months and a Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) total severity score ≥28 at Baseline. Participants were recruited at 13 sites in the US and Israel. Exclusion criteria included diagnosis of various mental illnesses, pregnancy, lactation, and any medical condition that could make receiving a sympathomimetic drug harmful due to increased blood pressure or heart rate. A split dose of MDMA HCl (80 mg + 40 mg in Session 1; 120 mg + 60 mg in Sessions 2/3) or placebo was administered 3 times during the ~12-week treatment period with therapy in blinded monthly dosing sessions. The treatment period was preceded by 3 preparatory therapy sessions and each dosing session was followed by 3 integrative therapy sessions. PTSD symptoms, measured with the CAPS-5 total severity score (primary endpoint), and functional impairment, measured with the Sheehan Disability Scale (SDS; key secondary endpoint) item scores, were evaluated at Baseline (Visit 3) through 18 weeks post-Baseline (Visit 19). Endpoints were assessed by a central, blinded Independent Rater Pool by live video conferencing. Vital signs were measured during dosing sessions. Adverse events (AEs), concomitant medications, and suicidal ideation/behavior as measured by the Columbia Suicide Severity Rating Scale were tracked throughout the study.

Results: A total of 104 participants were randomized 1:1 to MDMA-AT or placebo plus therapy; the average (SD) PTSD duration was 16.2 (13.3) years. Baseline demographic data were generally similar between groups. The average (SD) participant age was 38.2 (11.0) years and 40 (9.6) years in the MDMA-AT and placebo plus therapy groups, respectively. More than 50% of the enrolled participants identified as people of color. Average (SD) CAPS-5 score at baseline was 39.4 (6.6) and 38.8 (6.6) in the MDMA-AT and placebo plus therapy groups, respectively. Compared to placebo plus therapy, CAPS-5 scores in the MDMA-AT group were significantly reduced (P=0.0004; d=0.7) as were SDS Total Scores (P=0.0271; d=0.4). The LS mean change (95% CI) in CAPS-5 scores from Baseline in participants completing treatment was −23.69 (−26.94, −20.44) in the MDMA-AT group and −14.78 (−18.28, −11.28) in the placebo plus therapy group (LS Mean [95% CI] for treatment difference, −8.91 [−13.70, −4.12]), as estimated from an MMRM model adjusted for baseline CAPS-5, dissociative subtype (Y/N), and investigational site. No serious AEs were reported. As expected, some treatment emergent AEs (TEAEs) occurred at a greater frequency for the MDMA-AT group during and after Dosing Sessions; MDMA-AT was sympathomimetic. No increase in suicidality-related AEs was observed in the MDMA-AT group versus the placebo with therapy group. There were 9 dropouts, with 0 discontinuations due to TEAEs in the MDMA-AT group and 2 in the placebo plus therapy group.

Conclusions: MDMA-AT met its primary and key secondary endpoints of superiority over placebo with therapy and was generally well-tolerated with a low dropout rate.

Learning Objectives:

1. Understand the primary and key secondary efficacy endpoints for the confirmatory Phase 3 clinical trial of MDMA-AT for treatment of chronic PTSD.
2. Understand the top-line safety profile for the confirmatory Phase 3 clinical trial of MDMA-AT for treatment of chronic PTSD.

Literature References:

1. Mitchell JM, Bogenschutz M, Lilienstein A, et al. MDMA-assisted therapy for severe PTSD: a randomized, double-blind, placebo-controlled phase 3 study. Nat Med. 2021;27(6):1025-1033.
2. Mithoefer MC, Feduccia AA, Jerome L, et al. MDMA-assisted psychotherapy for treatment of PTSD: study design and rationale for phase 3 trials based on pooled analysis of six phase 2 randomized controlled trials. Psychopharmacology (Berl). 2019;236(9):2735-2745.

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

Individual Research Reports: Recent Advances in Treatment of Substance Use Disorders and Eating Disorders: Clinical Trials and Epidemiologic Studies

THE INFLUENCE OF SEX ON CANNABINOID-OPIOID INTERACTIONS: SEX-DEPENDENT EFFECTS OF THC AMONG PERSONS RECEIVING METHADONE THERAPY FOR OPIOID USE DISORDER

Joao De Aquino*[1], *Julia Meyerovich[1], Mohini Ranganathan[1], Brian Pittman[1], Mehmet Sofuoglu[1]*

[1]Yale University School of Medicine

Joao De Aquino, Yale University School of Medicine

Abstract Background: In the grip of the opioid crisis, a growing number of U.S. states have authorized the medicinal use of cannabinoids to treat pain and opioid use disorder (OUD). These rapid policy changes are not based on systematic evidence from clinical trials examining the effects of cannabinoids among persons with OUD. While preclinical and human studies have shown that the anti-nociception induced by cannabinoids varies by sex, it is unknown whether these findings extend to humans with OUD — who exhibit profound analgesic tolerance and a high sensitivity to pain (hyperalgesia).

Objective: We sought to investigate the sex-dependent effects of delta-9-tetrahydrocannabinol (THC), the main analgesic and psychoactive constituent of cannabis, among persons receiving methadone, the most commonly used opioid agonist therapy for OUD.

Methods: We conducted a secondary analysis of a Phase I within-subject, crossover design human laboratory study. A total of 27 persons with OUD who were receiving methadone therapy were randomly assigned to receive single doses of oral THC (10 mg or 20 mg), administered as dronabinol; or placebo, across three test sessions, each lasting for five hours. Pain sensitivity in response to THC administration was measured by the Cold Pressor Test (CPT) at 4 °C, and by the McGill Pain Questionnaire (MPQ). The abuse potential of THC was measured by the Drug Effects Questionnaire (DEQ). Cognitive performance was indexed by the Hopkins Verbal Learning Test (HVLT). We used mixed-effects models to examine the main effects of sex and THC dose, in addition to interactions between sex and THC dose (10 mg, 20 mg). At a significance level of 0.05, this exploratory study had 80% power to detect medium effect sizes ($d \geq 0.56$).

Results: Participants were aged 47.3 ± 12.2 years old. Approximately 76% (n=20) of participants were self-identified as men and 24% (n=7) as women. Results suggest a sex by

dose interaction for pain sensitivity, indexed by the MPQ total pain score, which assesses the overall severity of the pain experience ($F(2,38)=2.76$, $p=0.07$). Post-hoc analyses indicate that, among women, lower doses of THC (10 mg) produced a greater reduction of pain sensitivity than higher doses of THC (20 mg) ($t(5,38) = -2.43$, $p = .001$) and placebo ($t(5,38) = -2.43$, $p = .002$). Conversely, among men, only higher doses of THC (20 mg) produced a reduction of pain sensitivity relative to placebo ($t(3,38) = -2.42$, $p = .002$). We also observed main effects of sex ($F(1,21)=6.06$, $p=0.02$) and THC dose ($F(2,38)=5.11$, $p=0.01$) for cognitive performance, indexed by the HVLT total recall score. Post-hoc analyses showed that, among women only, both 10 mg THC ($t(5,38) = -2.43$, $p = .002$) and 20 mg THC ($t(5,38) = -2.43$, $p = .002$) produced verbal learning deficits relative to placebo. Finally, there was no evidence of sex-dependent effects of THC for abuse potential, indexed by the DEQ.

Importance of the Findings for Advancing the Field: Our findings provide preliminary evidence that, among persons receiving opioid agonist therapy for OUD, women experience analgesic effects under lower doses of THC than men — albeit at the cost of greater verbal learning deficits. Notably, no sex differences were observed for measures of abuse potential. These data support sex differences in the response to cannabinoid agonists among persons with OUD, as women may be more sensitive to the analgesic and cognitive impairing effects of THC than men. Collectively, these findings provide key clinical, methodological, and mechanistic insights for future studies examining whether the risk/benefit ratio of cannabinoids among persons with OUD varies by sex, and whether sex determines if cannabinoids may be leveraged to reduce opioid-related harm, including overdose deaths.

Learning Objectives:

1. To understand how opioids may produce profound neuroadaptations, affecting the efficacy of analgesics, and the risk/benefit ratio of drugs that have addictive potential.
2. To describe how sex might determine the analgesic and cognitive effects of delta-9-tetrahydrocannabinol (THC), the main antinociceptive and psychoactive component of cannabis, among persons with opioid use disorder (OUD).

Literature References:

1. Voelker, R. (2018). States move to substitute opioids with medical marijuana to quell epidemic. JAMA, 320(23), 2408-2410.
2. Cooper, Z. D., and Haney, M. (2014). Investigation of sex-dependent effects of cannabis in daily cannabis smokers. Drug and alcohol dependence, 136, 85-91.

INVESTIGATION OF SELF-TREATMENT WITH LYSERGIC ACID DIETHYLAMIDE (LSD) AND PSILOCYBIN MUSHROOMS: FINDINGS FROM THE GLOBAL DRUG SURVEY 2020

Emma Kopra*[1], *Jason Ferris[2], Adam Winstock[3], Kim Kuypers[4], Allan Young[1], James Rucker[1]*

[1]King's College London, [2]The University of Queensland, [3]University College London, [4]Maastricht University

Emma Kopra, King's College London

Abstract Investigation of Self-Treatment with Lysergic Acid Diethylamide (LSD) and Psilocybin Mushrooms: Findings from the Global Drug Survey 2020

Background: Increasing publicity of psychedelics' therapeutic potential is attracting growing numbers of people to use these substances for personal psychotherapy outside clinical settings, but research on such use is scarce (1,2). This study investigated the patterns of use, self-reported outcomes, and outcome predictors of psychedelic 'self-treatment' of mental health conditions or specific worries/concerns in life.

Methods: We use data from the Global Drug Survey 2020, a large online survey on drug use collected between November 2019 and February 2020 (total N=113,284). 3,364 respondents reported on their self-treatment experiences with lysergic acid diethylamide (LSD; N=1,996) or psilocybin mushrooms (N=1,368) as part of a specialist section of the survey. The primary outcome of interest was the 17-item self-treatment outcome scale, items reflecting aspects of wellbeing, psychiatric symptoms, social-emotional skills, and health behaviours. Each item was rated on a 7-point scale ranging from -3 (strongly negative) to +3 (strongly positive outcomes), and a grand mean was calculated by averaging values across all items. Besides, respondents rated the occurrence of 10 negative outcomes (none/mild/moderate/severe); and indicated the duration of most positive and most negative outcomes (12-option ordinal scales). Descriptive data on self-treatment patterns and outcomes are presented, besides four regression analyses assessing the effect of demographics and treatment patterns on each outcome variable.

Results: The mean age of the sample was 25.4 years, with 72.0% identifying as male, and 80.3% as white. Most common indications treated were depression (40.2%), anxiety (20.0%), and relationship problem (9.3%). Nearly half of respondents (48.8%) used doses to induce an intense psychedelic experience, and most (80.2%) had obtained advice or information before self-treatment. Positive changes were observed across all 17 outcome items, with a grand mean of 1.42 reflecting mild-to-moderate improvements. The strongest benefits were on items related to insight and mood; and for half of the respondents, most positive effects lasted beyond three weeks. Negative effects were reported by 22.5%, most of which were related to emotional states, feelings, and cognition. For the majority, negative effects resolved within a week, but lasted beyond three weeks for 30.2% of those reporting negative outcomes. High intensity of psychedelic experience, seeking advice before treatment, treating with psilocybin mushrooms, and treating post-traumatic stress disorder were associated with higher scores on the 17-item outcome scale; and higher intensity of experience also predicted longer duration of positive effects. Younger age, high intensity of experience, and treating with LSD predicted increased number of negative outcomes; with younger age also predicting longer duration of these.

Conclusions: This study brings important insights into self-treatment practices with psychedelics in a large international sample. Outcomes were generally favourable, but negative effects appear more frequent than in clinical settings. Our findings can help inform safe practices of psychedelic use in the public, and inspire clinical research. The main limitations relate to sampling and response biases. Future research can be improved with inclusion of additional predictive variables of interest, and utilisation of prospective designs including measurement of baseline symptoms.

Learning Objectives:

1. LSD and psilocybin mushrooms are used for independent self-treatment of a wide range of indications, and most individuals report favourable and holistic therapeutic outcomes.

2. Persisting negative effects however appear more frequent than in clinically supervised settings, bearing implications for harm reduction policies and healthcare.

Literature References:

1. Pilecki B, Luoma JB, Bathje GJ, et al. Ethical and legal issues in psychedelic harm reduction and integration therapy. Harm Reduction Journal. 2021;18(1):1-4.
2. Matzopoulos R, Morlock R, Morlock A, et al. Psychedelic mushrooms in the USA: knowledge, patterns of use, and association with health outcomes. Frontiers in Psychiatry. 2022;12:2403.

NALTREXONE PLUS BUPROPION COMBINATION MEDICATION MAINTENANCE TREATMENT FOR BINGE-EATING DISORDER FOLLOWING SUCCESSFUL ACUTE TREATMENTS: RANDOMIZED DOUBLE-BLIND PLACEBO-CONTROLLED TRIAL

Carlos Grilo*[1], *Janet Lydecker[1], Ralitza Gueorguieva[2]*

[1]Yale University School of Medicine, [2]Department of Biostatistics, Yale School of Public Health

Carlos Grilo, Yale University School of Medicine

Abstract Background: Certain treatments have demonstrated acute efficacy for binge-eating disorder (BED) but there is a dearth of controlled research examining pharmacotherapies as maintenance treatments for responders to initial interventions. This gap in the literature is particularly critical for pharmacotherapy for BED which is associated with relapse following discontinuation. The current study tested the efficacy of naltrexone/bupropion maintenance treatment amongst responders to acute treatments for BED.

Methods: Prospective randomized double-blind placebo-controlled single-site trial, conducted August 2017-December 2021, tested naltrexone/bupropion as maintenance treatment for responders to acute treatments with naltrexone/bupropion and/or behavioral weight-loss therapy for BED with comorbid obesity. Sixty-six patients (84.8% women, mean age 46.9, mean BMI 34.9 kg/m2) who responded to acute treatments were re-randomized to placebo (N=34) or naltrexone/bupropion (N=32) for 16 weeks; 86.3% completed posttreatment assessments. Mixed models and generalized estimating equations comparing maintenance treatments (naltrexone/bupropion versus placebo) included main and interactive effects of acute treatments.

Results: Intention-to-treat binge-eating remission rates following maintenance treatments were 50.0% (N=17/34) for placebo and 68.8% (N=22/32) for naltrexone/bupropion. Placebo following response to acute treatment with naltrexone/bupropion was associated with significantly decreased probability of binge-eating remission, increased binge-eating frequency, and no weight loss. Naltrexone/bupropion following response to acute treatment with naltrexone/bupropion was associated with good maintenance of binge-eating remission, low binge-eating frequency, and significant additional weight loss.

Conclusions: Adult patients with BED with co-occurring obesity who have good responses to acute treatment with naltrexone/bupropion should be offered maintenance treatment with naltrexone/bupropion.

Learning Objectives:

1. Participants will recognize evidence-based treatments for binge-eating disorder in adults with obesity.
2. Participants will recognize the utility of pharmacological maintenance treatment for responders to acute treatments and the moderating effects of different initial treatments.

Literature References:

1. Grilo CM, Lydecker JA, Fineberg SK, et al. Naltrexone-bupropion and behavior therapy, alone and combined, for binge-eating disorder: randomized double-blind placebo-controlled trial. Am J Psychiatry. 2022; 179:927-937.
2. Reas DL, Grilo CM. Psychotherapy and medication for eating disorders: better together? Clin Ther 2021; 43:17-39.

Wednesday, May 31, 2023

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

Regulatory Plenary

REGULATORY PLENARY: PEDIATRIC DRUG DEVELOPMENT IN PSYCHIATRY.

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

Overall Abstract There is increasing evidence of time trends in the epidemiologic burden of US pediatric mental health conditions. Despite the overall number of pediatric clinical trials has increased worldwide, there are still a number of unmet needs in terms of the pharmacological treatment of pediatric psychiatric disorders and conditions for which no approved therapy is available.

The lack of well-established safety and efficacy data for this population often results in off-label prescription practices, leaving children vulnerable to potential adverse effects and poor treatment outcomes. Additionally, many psychiatric medications are not developed with pediatric-specific formulations, making accurate dosing and administration difficult.

Conducting clinical trials in the pediatric population presents unique difficulties due to various factors. Obtaining informed consent from both the child and their legal guardian can be challenging, and can be a barrier to enrollment into clinical studies. The heterogeneity within the pediatric population, with developmental stages ranging from infancy to adolescence, further complicates study design and data interpretation. Lastly, clinical trial endpoints and outcome measures may not be as well-established in pediatric populations as in adult populations, making it difficult to assess the efficacy of interventions accurately. The FDA has released guidance documents on pediatric study plans, including content and process requirements, to streamline the development and approval of pediatric medications. Dr. Tiffany Farchione will provide a landscape of unmet needs and the actions taken to address these unmet needs.

The US Government has taken several steps to increase the availability of safe and effective psychiatric medications for the pediatric population. The Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA) are two key legislative initiatives aimed at promoting pediatric drug research and development. BPCA offers incentives, such as extended market exclusivity, to pharmaceutical companies that voluntarily conduct pediatric studies on their products, while PREA requires companies to submit pediatric study plans for

new drugs or biologics, which may have potential use in children. The FDA has established the Pediatric Review Committee (PeRC) to provide expert consultation on pediatric study plans and facilitate the development of age-appropriate clinical trial designs. Dr. John Alexander, vice chair of PeRC, will talk about his experience with psychiatric study plans for various indications in psychiatry, such as ADHD, Autism Spectrum Disorder, depression and schizophrenia.

REGULATORY PLENARY: PEDIATRIC DRUG DEVELOPMENT IN PSYCHIATRY.

Tiffany Farchione, US Food and Drug Administration

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Learning Objectives:

1. The role of the regulatory agencies in fostering drug development in children and adolescents with mental illnesses.
2. The need for appropriately designed clinical investigations in children adolescents.

REGULATORY PLENARY: PEDIATRIC DRUG DEVELOPMENT IN PSYCHIATRY.

John Alexander, FDA

Abstract There is increasing evidence of time trends in the epidemiologic burden of US pediatric mental health conditions. Despite the overall number of pediatric clinical trials has increased worldwide, there are still a number of unmet needs in terms of the pharmacological treatment of pediatric psychiatric disorders and conditions for which no approved therapy is available. The lack of well-established safety and efficacy data for this population often results in off-label prescription practices, leaving children vulnerable to potential adverse effects and poor treatment outcomes. Additionally, many psychiatric medications are not developed with pediatric-specific formulations, making accurate dosing and administration difficult.

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2. The need for appropriately designed clinical investigations in children adolescents.

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

ASCP Awards Ceremony and ASCP Lifetime Awardee Talk

THE SHAPE OF DISCOVERY: KETAMINE FOR TREATMENT RESISTANT DEPRESSION

Dennis Charney, Icahn School of Medicine At Mount Sinai

Abstract: The discovery of ketamine raises questions about the process of discovery. What types of environments facilitate discovery? What is the optimal size of research groups? How did the science come together that led to the initial trials? What opposition existed? What was the initial reaction?

Recent studies indicate that large teams develop and small teams disrupt science and technology. Smaller teams have tended to disrupt science and technology with new ideas and opportunities, whereas larger teams have tended to develop existing ones.

That was the case with our discovery of ketamine. The research groups at Yale, NIMH, and Mount Sinai were and are characterized by being small in size, encouraging bold scientific thinking in a psychological, safe, scientific environment that tolerated failure – as long as something was learned.

Large Teams Develop and Small Teams Disrupt Science and Technology

These results demonstrate that both small and large teams are essential to a flourishing ecology of science and technology, and suggest that, to achieve this, science policies should aim to support a diversity of team sizes.

Every once in a while a new idea comes along – a shift in thinking that challenges the status quo. These innovations require us to accept the change and adapt. This was true for ketamine.

Therapeutic discovery for mental illness needs a paradigm change consistent with Kuhn's conceptions of scientific revolution. As described by Kuhn, normal science begins, in which puzzles are solved within the context of the dominant paradigm, which in the case of depression was the monoamine hypothesis of depression and antidepressant action. There are similar dominant paradigms for other psychiatric diseases that have not resulted in breakthrough therapies.

Over time, progress in "normal science" reveals facts that are difficult to explain within the context of the existing paradigm such as why don't existing therapies have better effectiveness and why haven't new medicines of novel mechanism and better efficiency been discovered.

The major pharmacological treatments for major psychiatric disorders such as schizophrenia, bipolar disorder, multiple anxiety disorders, and attention deficit disorder are only partially effective and were discovered decades ago. We believe there needs to be an intense focus on drug discovery for these conditions. We suggest that multiple small groups of scientists, thinking out of the box, need to discover new hypotheses, moving beyond the long held traditional hypotheses. There have been too few novel treatment approaches and too little funding for innovative clinical trials. Progress has been too slow compared to other serious diseases such as cancer and heart disease, the lack of progress in treatment development for mental illness stands out.

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

***Clinical Updates in Neurotherapeutics**

*CLINICAL UPDATES IN NEUROTHERAPEUTICS

Lee Cohen, Massachusetts General Hospital, Ammon-Pinizzotto Center for Women's Mental Health, Boston, MA

Overall Abstract: This session will feature three leading psychopharmacologists who will review the treatment of depression with rapidly-acting approaches, Alzheimer's Disease and functional neurologic disorders. Dr. Sanacora will describe the advances in both pharmacologic and non-pharmacologic approaches to achieving rapid antidepressant effect in the context of possible converging mechanisms of action /clinical response. Dr Small will address both currently available treatments for Alzheimer's Disease and those in development as well as strategic interventions for optimization of brain health. Lastly, Dr LaFrance will speak to the reconceptualization of functional neurologic disorders from a bio-psycho-social-spiritual model along with a multidisciplinary model of treatment for this long misunderstood illness.

SALTATIONAL EVOLUTION IN THE TREATMENT OF DEPRESSION: THE DEVELOPMENT OF RAPIDLY ACTING ANTIDEPRESSANT APPROACHES

Gerard Sanacora, Yale

Abstract Saltational evolution in the treatment of Depression: The development of Rapidly Acting Antidepressant Approaches.

Until recently it was widely accepted that the effective treatment of depression requires weeks or months to have meaningful benefits. However, over the last two decades we have seen the rise of several treatments with putative rapid onset antidepressant action. Starting with the discovery of ketamine's rapid antidepressant effects there has been a string of studies providing evidence of rapid onset antidepressant effects associated with diverse mechanisms of action. Ketamine, the first of the newer group of rapid acting antidepressants to be developed is believed to primarily target the glutamatergic neurotransmitter system. Brexanolone, demonstrated to have rapid antidepressant effects in postpartum depression is a neurosteroid targeting the GABAA receptor. While treatments including psilocybin, MDMA and novel brain stimulation modalities such as accelerated TMS in earlier stages of development are believed to exert rapid onset of antidepressant effects through the serotonergic system or by directly targeting neurocircuit function independent of individual neurotransmitter systems. This presentation will review the data demonstrating rapid onset of antidepressant action for these treatments and compare and contrast the various treatment approaches in an attempt to identify converging mechanisms associated with the seemingly new ability to generate sustainable, rapid onset antidepressant treatments. Pharmacological, physiological, and non-specific effects associated with the treatments will all be discussed.

Learning Objectives:

1. For attendees to review the relative extent of the existing and emerging data demonstrating the ability of several novel treatments to generate rapid onset of antidepressant effects.
2. To familiarize attendees with potential mechanisms that could be underlying the of rapid on set antidepressant action.

Literature References:

1. McIntyre RS, Rosenblat JD, Nemeroff CB, Sanacora G, Murrough JW, Berk M, Brietzke E, Dodd S, Gorwood P, Ho R, Iosifescu DV, Lopez Jaramillo C, Kasper S, Kratiuk K, Lee JG, Lee Y, Lui LMW, Mansur RB, Papakostas GI, Subramaniapillai M, Thase M, Vieta E, Young AH, Zarate CA Jr, Stahl S. Synthesizing the Evidence for Ketamine and Esketamine in Treatment-Resistant Depression: An International Expert Opinion on the Available Evidence and Implementation. Am J Psychiatry. 2021 May 1;178(5):383-399.
2. Johnston JN, Kadriu B, Allen J, Gilbert JR, Henter ID, Zarate CA Jr. Ketamine and serotonergic psychedelics: An update on the mechanisms and biosignatures underlying rapid-acting antidepressant treatment. . Neuropharmacology. 2023 Mar 15; 226:109422

DETECTION AND TREATMENT OF ALZHEIMER'S DISEASE

Gary Small, David Geffen School of Medicine at UCLA

Abstract: An estimated 10 percent of people age 65 or older suffer from Alzheimer's disease, the most common cause of cognitive impairment that disrupts functional independence (i.e., dementia). The brains of patients with this disease show the accumulation of abnormal brain protein deposits (amyloid plaques and tau tangles) in regions controlling memory and thinking, as well as evidence of heightened inflammation and neurotransmitter dysfunction. Currently recommended clinical assessment strategies provide reasonable diagnostic accuracy, and biomarkers in development aim to further improve diagnostic precision. Several symptomatic drugs temporarily benefit symptoms; most disease-modifying treatments clear brain amyloid but have little symptomatic impact. This presentation will review available pharmacologic treatments as well as those in development. Dementia usually progresses gradually as the brain ages. For most people non-genetic factors have a greater impact on brain aging and Alzheimer's disease risk than genetic factors. This presentation also will highlight strategic interventions to optimize brain health as people age and highlight research focused on early intervention to delay cognitive decline.

Learning Objectives:

1. Available medicines available for Alzheimer's disease and treatments in development.
2. Non-pharmacological strategies that can complement medical treatments.

Literature References:

1. Small GW. Updates in the management of mild cognitive impairment and Alzheimer disease. The Journal of Family Practice. 2022:17(6): S77-S82.
2. Small GW. Detection and prevention of cognitive decline. American Journal of Geriatric Psychiatry. 2016 Dec;24(12):1142-1150. doi: 10.1016/j.jagp.2016.08.013.

ADVANCES IN FUNCTIONAL NEUROLOGICAL DISORDERS/CONVERSION DISORDERS.

W. Curt LaFrance, Rhode Island Hospital/Brown University

Abstract Psychiatrists frequently encounter patients with Conversion (Functional Neurological) Disorders (CD/FND). CD/FND presentations include psychogenic nonepileptic seizures, functional (psychogenic) movement disorders, weakness, and other semiologies. Accurate diagnosis is the first step in treatment. Long considered a diagnosis of exclusion, the DSM-5 diagnostic criteria for CD/FND now no longer requires the identification of a proximal psychological stressor or the exclusion of feigning. In this "rule-in" approach, CD/FND is diagnosed based on the presence of specific examination signs and semiologic characteristics. Assessing CD/FND from a bio-psycho-social-spiritual model allows for a formulation identifying predisposing vulnerabilities, acute precipitants and perpetuating factors. Evidence-based treatments now exist for treatment of CD/FND. Benefits of this new emerging standard of care include increased diagnostic sensitivity and specificity, improved patient acceptance, and opportunities for early multidisciplinary collaborations. With inpatient and outpatient engagement, early initiation of evidence-based treatments facilitate successful transitions to outpatient care. In this symposium, a dually-boarded and certified neurologist-psychiatrist will discuss the state-of-the-art regarding diagnosis, case formulation, and management principles in CD/FND.

Learning Objectives:

1. Learners will define CD/FND as a "rule-in" diagnosis based on clinical and neurologic examination findings and semiologic characteristics.
2. Attendees will employ an updated approach to the delivery of a FND/CD diagnosis and to acute management in the inpatient and outpatient setting.

Literature References:

1. Perez, D.L., M. J. Edwards, G. Nielsen, K. Kozlowska, M. Hallett and W. C. LaFrance, Jr., Decade of progress in motor functional neurological disorder: continuing the momentum. J Neurol Neurosurg Psychiatry, 2021. 92: p. 668-677.
2. Beimer, N.J. and W.C. LaFrance, Jr., Evaluation and Treatment of Psychogenic Nonepileptic Seizures. Neurol Clin, 2022. 40(4): p. 799-820.

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

Workshops

HOW CAN I WRITE MORE? TIPS AND TRICKS

Rishab Gupta, Brigham and Women\'s Faulkner Hospital, Elizabeth Ballard, National Institute of Mental Health, Augustus Rush, Duke University School of Medicine

Overall Abstract: Productive writing is the currency of a scientific career. Publications are vital to convey innovative viewpoints, showcase one’s expertise in specific areas of research, highlight gaps in literature for grant submissions, and feel accomplished as a researcher by the way of “giving back” to science.

However, writing scientific papers and proposals may not be easy, especially for early career researchers. It is common to hear and witness trainees/early career researchers' writer's block while drafting a research proposal or a manuscript. This is in addition to other well-documented challenges faced by early-career psychiatrists like lack of protected time, funding, mentorship, and research skills. Lack of confidence in their writing skills may trap individual researchers in a self-defeating vicious cycle because without manuscripts it can be difficult to apply for research grants and lack of grants will be an obstacle to completing the studies that will ultimately translate into manuscripts. Therefore, efficient, and productive scientific writing is an essential skill for early career researchers.

This practical workshop will focus on productive academic writing for career advancement, teach skills to write scientific manuscripts and research proposals while engaging participants in an interactive activity of developing a specific aims page and biosketch.

The first hour of the workshop will focus on the individual experiences of early career researchers in scientific writing that will be followed by brief presentations from two senior researchers on mechanics of writing manuscripts (Dr. A. John Rush) and scientific proposals (Dr. Nina Schooler). The second hour will be dedicated to hands-on interactive exercise focusing specifically on how to write a specific aims page and develop a biosketch for early career researchers who are balancing clinical duties and research demands. This activity will be supported by examples from the members of the Early Career Committee of the ASCP who will also facilitate the hands-on activity. During this workshop, individual participants will also have opportunities to receive feedback from the senior researchers on the panel (Drs. Rush, Schooler, and Zarate). The workshop will be concluded by Dr. Zarate who will serve as discussant. Overall, this workshop will serve the needs of early career researchers and engage three leaders of psychopharmacology who have extensively trained and mentored early career researchers.

Learning Objectives:

1. Understand the challenges faced by early career researchers in starting a research career.
2. Recognize the broad outline of writing original manuscript.
3. Implement strategies to overcome barriers in writing manuscripts.
4. Identify the individual components of research proposals involving human subjects.
5. Gain confidence in writing specific aims section of the research proposal.
6. Develop a biosketch that showcases researcher's expertise and addresses the needs of a research proposal.

+*FACILITATING RAPID DEVELOPMENT OF MEDICATIONS FOR SUBSTANCE USE DISORDERS AND PTSD: THE DOD-PHARMACOTHERAPIES FOR ALCOHOL AND SUBSTANCE USE DISORDERS ALLIANCE (PASA)

Thomas Kosten, Baylor College of Medicine

Overall Abstract: The US military has nearly twice the rate of substance use disorders (SUD) compared to the general population, particularly alcohol and opioid disorders. Alcohol has a prominent place in military life, making complete abstinence a challenging goal of treatment. Similarly, opioid dependence is often iatrogenically induced during the management of pain and injury, to include mild to moderate traumatic brain injury (mTBI), and becomes difficult

to address after military discharge to the VA. In addition, SUD comorbid with post-traumatic stress disorder (PTSD) is common, and this comorbidity exacerbates SUD symptoms. Several FDA-approved medications address alcohol abuse, opioid abuse, and PTSD but, no FDA-approved pharmacotherapies address these combined disorders. Abuse potential can make some currently FDA-approved medications such as methadone and buprenorphine for opioids less-than-ideal options for Service Members. In the military population specifically, pharmacotherapy-based treatments tend to have limited implementation. Overall, abstinence-based interventions are the core military approaches, although this is not a limitation within the VA care setting, where most of the DoD-funded Pharmacotherapies for Alcohol and Substance use disorders Alliance (PASA)- studies are conducted. Thus, innovative medication approaches for substance use disorder in particular also need to be considered for improving PTSD, mTBI, and other psychological disorders. Furthermore, research in military populations and at VA centers present unique challenges along with opportunities.

PASA is designed to conduct research that provides clinically relevant answers and interventions for Service members and Veterans with SUD comorbid with PTSD or other psychological disorders; however, results are also applicable to the general population. The program uses a state-of-the-art translational approach (pre-clinical, clinical and non-clinical) to understand the complex interaction of substance abuse with comorbid PTSD and other psychological disorders. Under the consortium model, the management core focuses on facilitating rapid development of research by utilizing multidisciplinary SUD expertise and experience. Funding supports protocol development for discovery (new chemicals via pre-clinical and chemical repurposing via non-clinical) and Phase 1 and 2 clinical trials, statistical and data management functions, regulatory assistance, and administrative resources. These resources and efforts produce FDA-compliant product development of new and novel treatments evaluated in pre-clinical and clinical trials to set the stage for these treatments to be integrated into clinical practice.

The goal of this workshop is to Introduction: duce more clinical investigators to the PASA funding mechanism (and DoD funding in general) for SUD together with PTSD or other psychological disorders. In addition to PASA-funded investigators, industry representatives who have been particularly active in the PASA grant development processes will present in this workshop. Topics include:

1. DoD grant mechanisms related to SUD and overview of PASA.
2. Multi-site Phase 2 study of treatments for SUD+PTSD in VAMCs conducted during COVID-19
3. Successes in translation: rapid medication development for PTSD, alcohol and opioid use disorders
4. Industry support for clinical trials
5. Industry collaboration with early translation into clinical studies
6. In silico drug re-purposing

Learning Objectives:

1. Describe the challenges in identifying cutting edge treatments for SUD and co-morbid PTSD or other psychological disorders in order to keep pace with novel drug development efforts using experiences from the PASA pre-clinical and clinical efforts/studies.
2. Understand how the PASA-supported efforts on these studies to overcome these challenges to meet the goal of integrating new and novel treatments into clinical practice.

DOD GRANT MECHANISMS RELATED TO SUBSTANCE USE DISORDERS AND OVERVIEW OF PASA

Tracy Nolen, RTI International

Individual Abstract: In 2010 the Department of Defense (DoD) and Congress expressed strong concerns about increasing problems associated with alcohol and drug disorders among military personnel and established the Alcohol and Substance Use Disorders Research Program (ASUDRP). The 2013 Institute of Medicine report, Substance Use Disorders in the U.S. Armed Forces, characterized prevalence of heavy drinking at 20% and prevalence of illicit drug use at 12%. Findings indicate the increasing medical burden on the Military Health System by alcohol and substance use disorders (ASUDs). It recommended DoD assume leadership to ensure consistency and quality of treatment services available to those with ASUDs.

The ASUDRP established a consortium to explore integrated approaches to address ASUD, especially comorbid ASUD with post-traumatic stress disorder (PTSD) and other psychological disorders and reduce the number of opioid and other substance use-related deaths using multidisciplinary, team-based research efforts that translate basic knowledge into enhanced clinical pharmacological treatment protocols and enhanced quality of life for Service Members, Veterans, and the American public. Translational research approaches are used to understand complex interactions of ASUDs with comorbid PTSD and other psychological disorders. Study selection is done in collaboration with the ASUDRP Programmatic Panel (PP) composed of military, VA, consumer, and NIH ASUD experts and representatives.

Three research aims guide PASA efforts:

1. Discover: Test new chemical entities and repurpose existing medications in strictly pre-clinical and non-clinical models of ASUD with comorbid PTSD and other psychological disorders.
2. Phase 1 First-in-Human Safety: Conduct clinical trials (CTs) of potential medications that include assessment of medical safety and doses for potential efficacy in subjects with ASUD and comorbid PTSD and other psychological disorders.
3. Phase 2 Efficacy: Conduct multiple site CTs to test preliminary efficacy and safety of potential medications or medication combinations in humans with ASUD and comorbid PTSD and other psychological disorders, and to also explore precision medicine tools for matching patients to these medications.

To date, 7 rounds of Requests for Applications were completed approximately yearly since 2016. Applications undergo external scientific review along with programmatic review by the ASUDRP PP. Beginning 2018, PASA required a two-stage funding process for all CTs. Stage 1 funds a "planning grant" where the PI works with PASA to draft a clinical development plan (CDP) and protocol. The program assists the PI with obtaining FDA IND approval/exemption, site selection, and developing a budget.

Stage one offers these advantages:

- Assistance with obtaining pharmaceutical collaboration.
- Understanding FDA requirements for Phase 1 studies of an investigational new drug (IND) for ASUDs before funding a CT

- Confirmation of supportive data for compounds and sample size estimates using pilot data
- More accurate cost estimates for CTs to meet FDA requirements and yield statistically significant results.

In stage 2 the CDP is independently reviewed for scientific merit and programmatically reviewed by the ASUDRP PP where it can receive a full study grant. Challenges this approach addressed include: 1. gaining access to a military population for enrollment in studies 2. equipping academic investigators with knowledge/tools required for FDA regulated clinical research 3. unifying research methods/assessments across studies to allow cross-study analyses and 4. improving study recruitment/retention. Overall, this reduces program risk and maximizes opportunities for success.

Learning Objectives:

1. At the conclusion of the presentation, the learner will better understand the funding available for ASUD with comorbid PTSD and other psychological disorders research available via ASUDRP in general and PASA in particular.
2. At the conclusion of the presentation, the learner will take away the benefits of conducting such ASUD research within PASA.

Literature References:

1. Institute of Medicine. (2013). Returning home from Iraq and Afghanistan: Assessment of readjustment needs of veterans, service members, and their families. Washington, D.C.: National Academies Press.
2. Center for Behavioral Health Statistics and Quality. (2015). Behavioral health trends in the United States: Results from the 2014 National Survey on Drug Use and Health (HHS Publication No. SMA 15-4927, NSDUH Series H-50). Retrieved from http://www.samhsa.gov/data/

A MULTI-SITE, PLACEBO-CONTROLLED PHASE 2 STUDY OF BUPRENORPHINE AND NALTREXONE EXTENDED-RELEASE FOR THE TREATMENT OF COMORBID ALCOHOL USE AND POST-TRAUMATIC STRESS DISORDERS CONDUCTED DURING COVID-19

Lori Davis, Veterans Affairs Medical Center

Individual Abstract: Kappa opioid receptor (KOR) antagonism represents a novel potential mechanism of treatment of comorbid alcohol use (AUD) and post-traumatic stress (PTSD) disorders. Endogenous opioid systems in the brain are involved in regulation of mood, stress modulation, and cravings. The combination of buprenorphine, which acts as an antagonist at kappa and partial agonist of the mu receptors, and naltrexone, which blocks the mu receptor, yields a pharmacological net effect of a KOR antagonist. Several clinical trials have been conducted safely and effectively using buprenorphine combined with naltrexone, including one in comorbid cocaine and opioid use disorder sample, as well as novel KOR antagonists in major depression. From July 2019 through March 2022, our group conducted a multisite, double-blinded, Phase 2, randomized placebo-controlled trial to evaluate the effectiveness of sublingual buprenorphine (SL-BUP) combined with extended-release naltrexone (XR-NTX) for the treatment of comorbid AUD and PTSD. The primary outcome response was defined as a decrease from baseline of ≥10 points on the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) and a reduction of ≥1 risk level of alcohol use, as defined by World Health Organization (WHO) using the Alcohol Timeline Follow-Back (TLFB), at the week 8. Several methodologic amendments were needed to cope with the COVID-19 pandemic that began in

March 2020, and its impact persisted throughout the course of the study. A total of 121 individuals were screened, of which 75 met eligibility criteria and were randomized to active drug (n=35) or placebo combination (n=34). In March 2022 the study was prematurely discontinued due to an interim futility analysis that indicated lack of efficacy. For each outcome measure at week 8 primary timepoint, the low dose arm consistently showed lower odds of a better outcome compared to the placebo arm, although none were statistically significant. There were no statistically significant differences in the proportion of adverse event severity, relationship, or system organ class between the active and placebo arm. In addition to an overview of these disappointing results, the lead investigator will discuss challenges to and mitigations in recruitment and retention in this comorbid patient population, especially during times of COVID.

Learning Objectives:

1. Understand the theoretical premise of kappa opioid receptor antagonism in the treatment of AUD and PTSD.
2. Describe the results of a phase 2, randomized placebo-controlled trial of buprenorphine and naltrexone.
3. Appreciate the recruitment and retention challenges in a study involving comorbid AUD-PTSD participants during COVID.

Literature References:

1. Ling, W., Hillhouse, M. P., Saxon, A. J., Mooney, L. J., Thomas, C. M., Ang, A., Matthews, A. G., Hasson, A., Annon, J., Sparenborg, S., Liu, D. S., McCormack, J., Church, S., Swafford, W., Drexler, K., Schuman, C., Ross, S., Wiest, K., Korthuis, P. T., Lawson, W., Brigham, G. S., Knox, P. C., Dawes, M., and Rotrosen, J. (2016). Buprenorphine + naloxone plus naltrexone for the treatment of cocaine dependence: the Cocaine Use Reduction with Buprenorphine (CURB) study. Addiction (Abingdon, England), 111(8), 1416-1427
2. Seal, K. H., Maguen, S., Bertenthal, D., Batki, S. L., Striebel, J., Stein, M. B., Madden, E., and Neylan, T. C. (2016, 2016/03/01). Observational Evidence for Buprenorphine's Impact on Posttraumatic Stress Symptoms in Veterans With Chronic Pain and Opioid Use Disorder. The Journal of Clinical Psychiatry, 77(09), 1182-1188. https://doi.org/10.4088/jcp.15m09893
3. Verplaetse, T. L., McKee, S. A., and Petrakis, I. L. (2018). Pharmacotherapy for Co-Occurring Alcohol Use Disorder and Post-Traumatic Stress Disorder: Targeting the Opioidergic, Noradrenergic, Serotonergic, and GABAergic/Glutamatergic Systems. Alcohol Res, 39(2), 193-205.

SUCCESSES IN TRANSLATION: RAPID MEDICATION DEVELOPMENT FOR PTSD, ALCOHOL AND OPIOID USE DISORDERS

Colin Haile, University of Houston

Individual Abstract: PASA has funded preclinical studies that have translated to clinical trials potentially affecting human health positively within a reduced timeframe.

Three examples of PASA-funded pre-clinical studies that have resulted in achieving significant medication development milestones will be presented. These examples will include: 1) CERC-501, a kappa antagonist owned by the pharmaceutical company Cerecor, was assessed in predator odor-induced place aversion (POIPA) an animal model of PTSD; 2) the impact of ASP8062, a GABAb allosteric modulator was assessed using operant alcohol self-administration (model of alcohol use disorder); and 3) the effects of an anti-fentanyl vaccine

(FEN-CRM) formulated with components contained in vaccines presently on the market was assessed in analgesic tests (e.g. tail flick, hotplate), schedule-controlled responding, FEN-induced overdose and brain distribution.

CERC-501 significantly blocked POIPA and the development of anxiety associated with this model providing evidence this compound may be useful in treating PTSD. Johnson and Johnson subsequently procured the rights to CERC-501 from Cerecor for further development. ASP8062 dose dependently decreased alcohol self-administration that was not due to non-specific effects (e.g., sedation). These data significantly contributed toward Astellas pursuing ASP8062 as a potential treatment for alcohol use disorder. Multi-site clinical trials assessing ASP8062 for AUD are underway (NCT05096117). The adjuvanted FEN-CRM vaccine generated high levels of anti-FEN antibodies that completely blocked FEN-induced analgesia, disruption of schedule-controlled responding and FEN-induced decreases in oxygen saturation, heart rate and activity. FEN-CRM was also associated with significantly lower FEN levels in brain compared to un-vaccinated animals. Clinical-grade FEN-CRM is now being manufactured for toxicology testing and subsequent Phase 1 clinical trials.

The PASA funding mechanism has supported pre-clinical studies that have had immediate impact on moving potential treatments for disorders that heavily impact the veteran community into the clinical arena.

Learning Objectives:

1. At the conclusion of the presentation, the learner will know more about promising novel treatments for ASUDs.
2. At the conclusion of the presentation, the learner will have a better understanding of pre-clinical studies critical to establishing potential efficacy prior to assessing these treatments in human clinical trials.

Literature References:

1. Haile CN, Carper BA, Nolen TL, Kosten TA. The GABAB receptor positive allosteric modulator ASP8062 reduces operant alcohol self-administration in male and female Sprague Dawley rats. Psychopharmacology (Berl). 2021 Sep;238(9):2587-2600.
2. Haile CN, Baker MD, Sanchez SA, Lopez Arteaga CA, Duddupu-di AL, Cuny GD, Norton EB, Kosten TR, Kosten TA, An Immunconjugate Vaccine Alters Distribution and Reduces the Antinociceptive, Behavioral and Physiological Effects of Fentanyl in Male and Female Rats. Pharmaceutics 2022, 14 (11), 2290, https://doi.org/10.3390/pharmaceutics14112290 26 Oct 2022.

INDUSTRY SUPPORT FOR CLINICAL TRIALS

Sarah Akerman, Alkermes, Inc.

Individual Abstract: Collaboration between academic institutions, federal agencies, patient advocacy groups and the pharmaceutical industry can accelerate advances toward shared goals in research and drug development, improving outcomes for patients. While the pharmaceutical industry routinely sponsors multisite clinical trials, opportunities exist to support independent or collaborative research such as with PASA and DoD. The two areas of focus for PASA on substance use disorders and PTSD have been relatively underfunded through industry initiatives, but can be rich for interaction. Such industry interactions afford researchers funding or other resources such as medications and placebo, and access to technical information or

support. These arrangements offer industry opportunities to support pilot studies and Phase 2 proof of concept studies that may inform future larger research programs.

One such research opportunity from industry is an Investigator Sponsored Studies (ISS) program, which can provide medications, placebo, and/or funding for research independently designed and conducted by clinicians and scientists that aligns with defined areas of research interest established by the company. Areas of interest often aim to address important research gaps for a treatment or a disease state and may be publicized by companies so that researchers can understand if their idea fits within scope. Submissions may be accepted on a rolling basis, at specific timepoints, or through a request for proposal (RFP) process. Criteria for selection of ISS proposals include the scientific rigor and scientific value, feasibility of completion within specified timeframe, absence of known conflicts of interest, and likelihood that the outcome will be published. In general, supported research projects are awarded to experienced researchers who have an established history of successfully receiving independent funding.

In addition, industry may establish other types of competitive research award programs. An example is a junior investigator research award program to support the next generation of researchers. Research proposals can be reviewed and selected by an independent review committee consisting of experts in the field. Awardees carry out their research under the guidance of a research mentor and typically have not yet received an NIH RO1 grant as an independent investigator.

Another avenue for partnership with industry is the collaborative research study, where independent investigators work closely with industry research scientists to design protocols with shared research interests. Types of support provided by industry may include medical writing support, scientific/medical support for protocol development, and supply of medication and/or placebo.

An additional industry funding mechanism is through a competitive grant program for non-profit organizations such as patient advocacy groups or grassroot organizations aiming to address unmet patient and caregiver needs. Examples include the development of educational materials to support clinical trial participation or survey-based research aiming to understand the perspectives of patients and caregivers.

This wide range of initiatives represent productive interactions between industry and independent investigators which serve to advance the field scientifically, generate clinically relevant data, and, consistent with the goals of PASA, may lead to the development of new treatment approaches.

Learning Objectives:

1. At the conclusion of the presentation, the learner will understand what types of support are available from industry in research.
2. At the conclusion of the presentation, the learner will be better informed of possible avenues for obtaining such industry support of clinical trial research supported primarily through PASA-DoD funding.

Literature References:

1. Ramsey, B. W., Nepom, G. T., and Lonial, S. (2017). Academic, foundation, and industry collaboration in finding new therapies. New England Journal of Medicine, 376(18), 1762-1769.
2. Elsevier. (January 27, 2021). University-industry collaboration: A closer look for research leaders. https://www.elsevier.com/research-intelligence/university-industry-collaboration/

MODULATION OF NORADRENERGIC SIGNALING FOR THE TREATMENT OF ALCOHOL USE DISORDER IN PATIENTS WITH PTSD

Michael De Vivo, BioXcel Therapeutics

Individual Abstract: Substance use disorders (SUDs), including alcohol and opioid use disorders (AUD, OUD), constitute a major public health challenge among US veterans. The US Department of Veterans Affairs (VA) annually manages the care of over a million veterans diagnosed with psychiatric disorders or SUDs. A sobering reality is that over 30% of VA inpatients suffer from either SUDs or psychiatric disorders. The number of veterans treated for an SUD in an outpatient setting increased by 52.7% between 2005 and 2012, and this number remains on the rise in recent years.

Norepinephrine (NE) release in the central amygdala (CeA) is proposed to be a major neural mechanism for the emergence of alcohol use disorder (AUD) (Varodayan et al., 2022). Receptors for norepinephrine, the beta- and alpha1- adrenergic post-synaptic receptors, are expressed in the CeA. Beta-adrenergic antagonists (propranolol) and alpha1-adrenergic receptors antagonists (prazosin) may be beneficial in treating AUD. The alpha2-adrenergic receptor is a pre-synaptic receptor that regulates release of norepinephrine from neurons projecting from the locus coeruleus (LC). Stress activates the LC and increases NE release from these neurons. Alpha2-adrenergic receptors modulate the activity of LC neurons. Therefore, it is possible that BXCL501 will modulate the effect of stress on norepinephrine levels, rendering it a promising drug for the treatment of AUD.

BXCL501 is a sublingual formulation of dexmedetomidine approved for the acute treatment of agitation associated with schizophrenia and bipolar disorders. BXCL501 demonstrated efficacy and safety in 2 Phase 3 studies by acutely treating agitation in patients with schizophrenia or bipolar disorder (Preskorn et al., 2022). Several alpha2-adrenergic receptor agonists, including clonidine, guanfacine and lofexidine, are approved for indications related to a highly aroused and agitated state, such as ADHD, opioid withdrawal and hypertension. Dexmedetomidine is more potent and efficacious than other alpha2-adrenergic agonists that are used therapeutically. It is approved for the use of pre-procedural anesthesia as an intravenous infusion drug (Precedex). Because of its poor oral bioavailability, dexmedetomidine was never used as an oral drug. By administering dexmedetomidine using a sublingual film, oral bioavailability was increased robustly. Dexmedetomidine is well suited for the acute treatment of agitated episodes because of its high potency, high intrinsic activity at the receptor, and fast onset of action. The hemodynamic effects of dexmedetomidine are resolved within 6 hours unlike clonidine and guanfacine which have longer plasma half-lives. Because of its high potency, circulating plasma concentrations of dexmedetomidine are low meaning that drug: drug interactions are unlikely.

BioXcel Therapeutics is supporting evaluation of BXCL501 in AUD in patients with PTSD by providing drug supplies for a PASA-funded study conducted by the VA Connecticut Healthcare System. This is a phase 1, double-blind, placebo-controlled, within subject study. The study is evaluating BXCL501 in 10 heavy drinker participants with comorbid PTSD. The primary aims of this study of BXCL501 in individuals with AUD and PTSD will be to evaluate whether pretreatment: 1) attenuates stress (PTSD) reactivity, 2) attenuates alcohol cue

reactivity, 3) is medically safe in altering subjective effects like sedation and vital signs when combined with ethanol in a laboratory setting. is medically safe i sedation and vital signs when combined with ethanol.

Learning Objectives:

1. At the conclusion of the presentation, the learner will understand the structure of the collaborative research conducted by BioXcel and Yale University as part of PASA and how the PASA research consortium is supporting both BioXcel's pipeline development alongside supporting the development of a promising new therapeutic for Veterans.
2. At the conclusion of the presentation, the learner will understand the results of this early clinical study of BXCL501 and the next steps in research of BXCL501 as a potential treatment for ASUD.

Literature References:

1. Varodayan FP, Patel RR, Matzeu A, Wolfe SA, Curley DE, Khom S, Gandhi PJ, Rodriguez L, Bajo M, D'Ambrosio S, Sun H, Kerr TM, Gonzales RA, Leggio L, Natividad LA, Haass-Koffler CL, Martin-Fardon R, Roberto M. The Amygdala Noradrenergic System Is Compromised With Alcohol Use Disorder. Biol Psychiatry. 2022 Jun 15;91(12):1008-1018. doi: 10.1016/j.biopsych.2022.02.006. Epub 2022 Apr 13. PMID: 35430085; PMCID: PMC9167785.
2. Citrome L, Preskorn SH, Lauriello J, Krystal JH, Kakar R, Finman J, De Vivo M, Yocca FD, Risinger R, Rajachandran L. Sublingual Dexmedetomidine for the Treatment of Acute Agitation in Adults With Schizophrenia or Schizoaffective Disorder: A Randomized Placebo-Controlled Trial. J Clin Psychiatry. 2022 Oct 3;83(6):22m14447. doi: 10.4088/JCP.22m14447. PMID: 36198061.

IN SILICO IDENTIFICATION OF CANDIDATE COMPOUNDS FOR SUBSTANCE USE DISORDER REPURPOSING STUDIES BY LEVERAGING MULTI-OMIC DATA AND RESOURCE INTEGRATION

Bradley Webb, RTI International

Individual Abstract: Military service members and veterans are at increased risk for opiate use disorder (OUD). Recent discoveries in genome wide association studies (GWAS), protein-protein interactions, and gene expression research domains are increasing the understanding of the biology of OUD. However, a gap exists between translating this biological insight into effective therapies. To address this gap, we are constructing a framework to integrate cross-domain research evidence to identify and prioritize new biological targets for repurposing approved or clinically advanced medications for treatment of OUD.

Background: Recently, specific genetic loci influencing opiate use disorder (OUD) risk have begun to be identified. Gene expression and network analyses offer additional insight beyond risk. However, even multi-domain investigations rarely focus on producing prioritized targets for translational studies. To address this gap, we constructed a framework to identify biological targets and pharmacotherapies for clinical repurposing studies. This is accomplished by 1) leveraging extant results, 2) performing cross-omic network-based analysis, 3) creating an integrated catalogue of results and biological targets, and 4) generating a prioritized list of existing candidate compounds for expert review and selection for future repurposing studies.

Methods: OUD results were collected including two large (n=304,507, n=79,729) independent genome-wide association studies (GWAS) and four post-mortem human brain gene expression

(332 independent samples). Network analyses were performed using dense module GWAS (dmGWAS) to identify human brain specific protein-protein interaction (PPI) modules. Drug repurposing databases Pharos, Open Targets, Therapeutic Target Database (TTD), and DrugBank were queried for clinical status, safety, and target selectivity. Cross-omic and drug query results were integrated for all genes in the genome, allowing flexible filtering to identify candidate compounds for follow-up review.

Results: Gene expression meta-analysis and gene-level GWAS analyses revealed 2698 and 3 genes (FDR <0.05), respectively. Network analysis detected 22 PPI modules containing 71 genes showing enrichment. For pilot drug repurposing analysis, we selected genes showing robust expression differences ($q<0.01$, n=605), suggestive GWAS evidence ($q<0.16$, n=115), and is in an enriched PPI module. Using expression, GWAS, or network evidence alone detected 78, 15, and 84 genes targeted by 560, 383, and 958 approved compounds, respectively. Of the 958 compounds targeting these genes, 70 were found in a single drug database. Finally, 15 genes showed evidence across more than one domain and at least one approved drug including known targets OPRM1 an DRD2.

Discussion: This study leveraged existing results and multiple resources to identify approved compounds that target genes associated with OUD. By querying multiple lines of evidence, the approach allows a) querying many genes of interest, b) detecting candidates missed using a single domain or resource, c) and produces a succinct summary to facilitate efficient expert review. Identifying larger pools of candidate pharmacotherapies and summarizing the supporting biological evidence bridges the gap between discovery and translational studies.

Learning Objectives:

1. To show how integrating evidence across multiple domains can identify known and novel gene targets with converging evidence.
2. To show how querying multiple drug repurposing databases is needed for comprehensive detection of approved compounds targeting genes of interest.
3. To teach how integrating, ranking, and filtering discovery results and repurposing candidates can accelerate the path to translational studies by producing succinct summaries for efficient expert review.

Literature References:

1. Nelson, M. R. et al. The support of human genetic evidence for approved drug indications. Nat. Genet. 47, 856–860 (2015).
2. King, E. A., Davis, J. W. and Degner, J. F. Are drug targets with genetic support twice as likely to be approved? Revised estimates of the impact of genetic support for drug mechanisms on the probability of drug approval. PLoS Genet. 15, e1008489 (2019).
3. Gaddis N, Mathur R, Marks J, Zhou L, Quach B, Waldrop A, Levran O, Agrawal A, Randesi M, Adelson M, Jeffries PW, Martin NG, Degenhardt L, Montgomery GW, Wetherill L, Lai D, Bucholz K, Foroud T, Porjesz B, Runarsdottir V, Tyrfingsson T, Einarsson G, Gudbjartsson DF, Webb BT, Crist RC, Kranzler HR, Sherva R, Zhou H, Hulse G, Wildenauer D, Kelty E, Attia J, Holliday EG, McEvoy M, Scott RJ, Schwab SG, Maher BS, Gruza R, Kreek MJ, Nelson EC, Thorgeirsson T, Stefansson K, Berrettini WH, Gelernter J, Edenberg HJ, Bierut L, Hancock DB, Johnson EO. Multi-trait genome-wide association study of opioid addiction: OPRM1 and beyond. Sci Rep. 2022 Oct 7;12(1):16873. doi: 10.1038/s41598-022-21003-y. PMID: 36207451; PMCID: PMC9546890.

4. Jia P, Zheng S, Long J, Zheng W, Zhao Z. dmGWAS: dense module searching for genome-wide association studies in protein-protein interaction networks. Bioinformatics. 2011 Jan 1;27(1):95-102. doi: 10.1093/bioinformatics/btq615. Epub 2010 Nov 2. PMID: 21045073; PMCID: PMC3008643.

IN PRESS: HOW TO BE A MORE EVIDENCE-BASED AUTHOR AND REVIEWER OF THE PEER-REVIEWED LITERATURE

Marlene Freeman, Massachusetts General Hospital, Ammon-Pinizzotto Center for Women's Mental Health

Overall Abstract Publication and service to the field are both major priorities in career development and academic promotion. This workshop, developed by members of the ASCP-Journal of Clinical Psychiatry Liaison Task Force, is aimed at both early career and junior/mid-career clinical-investigators who wish to become more interactive members of the academic publishing community. We will demystify the mechanics of how to publish and review papers in the peer reviewed literature, explain the review process, and offer practical tips for authorship and reviewership. Journal editors will discuss the qualities most sought in submissions, including the likely impactfulness of a submitted paper, how to choose where to submit a paper and its match with the "identity" of a journal, and targeting pertinent journal subsections (e.g., the Early Career Psychiatrist, Focus on Geriatric Psychiatry, and ASCP Corner subsections of the Journal of Clinical Psychiatry). We will offer strategies for preparing compelling original research papers, reviews and meta-analyses that are likely to draw favorable reviewer and editorial responses, and ways to obtain mentorship as both an author and reviewer. From the reviewer's perspective, core concepts with illustrative examples will be discussed for recognizing strengths and weaknesses of study designs, hypothesis testing, and evaluating the merits of a study's results and conclusions. An interactive panel of editors will share their career development stories, and provide insider tips on how to engage with editors, contribute productively to the field, and influence the scope and direction of the empirical literature in clinical psychopharmacology and related interventions.

Learning Objectives:

1) To enhance knowledge about the peer review process.
2) To provide information about the academic publication process.

HOW THE PEER REVIEW PROCESS WORKS: TIPS ON REVIEWING A RESEARCH PAPER

Joseph Goldberg, Icahn School of Medicine at Mount Sinai

Individual Abstract: This presentation will focus on core concepts and the mechanics behind the peer-review process for research papers, reviews, and meta-analyses submitted for journal publication. Attendees will understand how peer reviews are conducted and editorial decisions are made to accept, revise or reject manuscripts. Alignment between a study topic and its fit with the nature and readership of a particular journal will be discussed. We will discuss reasons to serve or not serve as a reviewer (based on factors such as expertise or conflicts of interest) and the general criteria reviewers should adopt when evaluating a manuscript. Key points will be reviewed around issues related to study methodologies and hypothesis-generating versus hypothesis-testing designs, sample selection and power, detecting bias and confounding factors, citing appropriate references, interpreting findings without drawing unjustified

conclusions, and recognizing study strengths and weaknesses. Participants will understand how to write reviews that can improve the quality of a submitted paper and help editors and authors appreciate whether a manuscript is not merely acceptable for publication but, moreover, holds impact for the field within the context of the existing literature on a given topic.

Learning Objectives:

1. To improve participants' understanding about the mechanics and logistics of the peer review process for papers submitted for journal publication.
2. To enhance participants' skills for critically reviewing and critiquing the methodology and findings of studies submitted to the peer-reviewed literature.

Literature References:

1. Andrade C. How to read a research paper: reading between and beyond the lines. Ind J Psychiatry 2011; 53: 362-366
2. Stiller-Reeve M. How to write a thorough peer review. www.nature.com/articles/d41586-018-06991-0?utm_source=briefing-dy and utm_medium=email and utm_campaign=briefing and utm_content=20181009

HOW TO GET PUBLISHED

Leslie Citrome, New York Medical College, Susan Kornstein, Virginia Commonwealth University, Holly Swartz, University of Pittsburgh School of Medicine

MID-CAREER WORKSHOP: LOOKING AT AN OPPORTUNITY FOR RE-FOCUSING, PIVOTING OR RE-INVENTING

Scott Aaronson, Sheppard Pratt

Overall Abstract This year's program will feature the reflections of several senior members who each navigated mid-career transformations—some staying in academic roles but shifting focus, some moving to regulatory or administrative positions and some making the transition to research from full time practice. Mid career offers an important time for reflection on what is working and not working in one's professional and personal journey. The session will be divided into two parts. The first hour will be each of our panelists sharing their personal journey and lessons learned. The second hour we will break into smaller groups for an opportunity to engage in discussions with each of our panelists.

Learning Objectives:

1. Identify one aspect of your professional life that needs to be changed and one aspect you wish to retain.
2. Identify the two strongest skills you have that you want to make the best use of in the next phase of your career.

Thursday, June 1, 2023

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

Keynote Plenary

THE CHANGING LANDSCAPE OF CLINICAL PSYCHIATRY: NOVEL THERAPEUTICS, METHODS AND ASSESSMENTS

Susan Kornstein, Virginia Commonwealth University

Overall Abstract This Keynote Plenary Session will focus on the 2023 annual meeting theme about the changing landscape of clinical psychiatry: novel therapeutics, methods and assessments. First, Dr. Ranga Krishnan will provide an overview of the transformation in health care delivery from hospital-based to outpatient and telehealth with a focus on value-based care, and implications for the adoption of new treatments. Dr. Andrew Nierenberg will describe plans to develop a Bipolar Learning Health Network and its potential to transform the care of people with bipolar disorder. Finally, Dr. John Torous will discuss the evolving use of smartphone apps in psychiatry for both research and patient care.

MIND OVER MATTER: CHANGING LANDSCAPE OF HEALTHCARE DELIVERY IMPLICATIONS FOR MENTAL HEALTH THERAPEUTICS

K. Ranga Krishnan, Rush

Abstract We are in the middle of a rapid transformation of health care delivery in the United Sates.

There is a shift from hospital focused delivery systems to outpatient, telehealth and home based care delivery systems and a change in payments to a Value based care payment system. These changes have profound implications on how adoption of new treatments happen, what outcomes are of interest with a focus on value and cost effectiveness, some factors that need to be kept in mind include: Mental health and substance abuse affect cost and outcomes of medical conditions.

This is both an opportunity and a risk for new therapies. The presentation will focus on

What outcomes should we focus on in this environment?

For adoption of new treatment what do we need?

Implications for pragmatic trials

Learning Objectives:

1. Understand concepts of value-based care as it applies to mental health.
2. Understand the critical importance of substance abuse and mental health for value-based care of medical conditions.

Literature References:

1. Knickman J, Krishnan R, Pincus H. Improving Access to Effective Care for People With Mental Health and Substance Use Disorders. JAMA. 2016 Oct 25;316(16):1647-1648. doi: 10.1001/jama.2016.13639. PMID: 27668948.March JS, Silva SG, Compton S, Shapiro M, Califf R, Krishnan R. The case for practical clinical trials in psychiatry. Am J Psychiatry. 2005 May;162(5):836-46. doi: 10.1176/appi.ajp.162.5.836. PMID: 15863782.

A BIPOLAR LEARNING HEALTH NETWORK: A MODEL FOR IMPROVING OUTCOMES IN PSYCHIATRY

Andrew Nierenberg, Massachusetts General Hospital

Abstract While treatments for bipolar disorder have changed over the past 20 years, outcomes have not. Furthermore, clinicians' diagnosis and assessment of people with bipolar disorder tend to be unreliable and inconsistent, leading to sometimes diagnosing people with bipolar disorder who do not have it and missing the diagnosis in those who do. Treatments vary widely, and few clinicians follow best practice guidelines. Care for comorbid medical conditions is fragmented and premature death, mostly from cardiovascular disease, occurs all too often. Overall, we generally don't know the outcomes of our patients with bipolar disorder. To address these seemingly intractable challenges, we propose to develop a Bipolar Learning Health Network based on a successful model developed by the James M Anderson Center for Health Systems Excellence at Cincinnati Children's Hospital.

The Learning Health Network is an actor-oriented network organizational model in which participants (actors) actively collaborate to identify critical issues, test and validate methods to improve those issues systematically and reproducibly, develop best practices and evidence and then disseminate the resulting knowledge and know-how continuously. People with bipolar disorder and their families, clinicians, researchers, data analysts, administrators, insurance companies, and pharmaceutical companies collaborate with a single focus to get better outcomes that matter. The Network develops a culture of curiosity, humility, generosity, and trust so that "All teach. All Learn."

This presentation will describe the plan to develop the bipolar learning health network as well as a vision of how it has the potential to transform the care of people with bipolar disorder.

Learning Objectives:

1. The participant will be able to describe the substantial challenges that exist for people with bipolar disorder, their families, clinicians, and the researchers who focus on bipolar disorder.
2. The participant will know the key components of a Learning Health Network model.

Literature References:

1. He H, Hu C, Ren Z, et al. Trends in the incidence and DALYs of bipolar disorder at global, regional, and national levels: Results from the global burden of Disease Study 2017. J Psychiatr Res 2020; 125: 96-105. 2020/04/07. DOI: 10.1016/j.jpsychires.2020.03.015.
1. 2.Britto MT, Fuller SC, Kaplan HC, et al. Using a network organisational architecture to support the development of Learning Healthcare Systems. BMJ Qual Saf 2018; 27: 937-946. 2018/02/14. DOI: 10.1136/bmjqs-2017-007219.

DIGITAL MEASUREMENTS AND THERAPEUTICS

John Torous, Beth Israel Deaconess Med. Ctr. and Harvard Medical School

Abstract As the use of telepsychiatry in mental health via video/phone visits soars, it is important to also consider how asynchronous telepsychiatry tools like smartphone apps can also advance care. This talk will focus on the evolving field of smartphone digital phenotyping and consider the potential of real-time data capture via smartphones, methods necessary to analyze such data, and practical clinical applications of these tools. Looking at the evolving smartphone mental health ecosystem, the talk will also cover the topic of app evaluation and

supporting research for making informed choices related to smartphone apps for use in research or patient care.

Learning Objectives:

1. Assess which digital phenotyping data streams could be most useful in helping understand your patients' clinical trajectories and list three risks and benefits of this method of data collection.
2. Apply a digital literacy frame to be able to evaluate which of your patients may most benefit from digital health and which first require training / support.

Literature References:

1. Langholm C, Kowatsch T, Bucci S, Cipriani A, Torous J. Exploring the potential of Apple SensorKit and digital phenotyping data as new digital biomarkers for mental health research. Digital Biomarkers. 2023 Mar 27.
2. Langholm C, Byun AJ, Mullington J, Torous J. Monitoring sleep using smartphone data in a population of college students. npj Mental Health Research. 2023 Mar 17;2(1):3.

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

Update From Federal and Other Funding Agencies

UPDATE FROM FEDERAL AND OTHER FUNDING AGENCIES

Joseph Goldberg, Icahn School of Medicine at Mount Sinai

Overall Abstract Continuing with long-standing tradiiton, this is the much-anticipated 2023 Update From Federal and Other Funding Agencies Plenary. Alphabet soup never tasted so good! Hear updates from NIMH, PCORI, NIDA, and the VHA.

TOWARDS A PRECISION PSYCHIATRY

Josh Gordon, National Institute of Mental Health

Abstract Effective treatments for mental illnesses exist, yet tailoring treatment for individuals is often a trial-and-error process that can lead to unacceptable delays in receiving effective treatment. NIMH plans to launch a new Precision Psychiatry Initiative, a research program that will focus on two parallel areas of need: biomarker development and precision diagnostics. Research conducted as part of this effort will also focus on developing and testing quantitative, clinically relevant tools for use by clinicians in making treatment recommendations for individual patients, leading to better understanding and more effective treatments for mental illnesses.

Learning Objectives:

1. Describe the importance of advancing precision medicine research.
2. Learn about innovative computational approaches to identify and validate novel mechanisms, biomarkers, and treatment targets relevant to the prevention and treatment of mental illnesses.

Literature References:

1. Drysdale AT, Grosenick L, Downar J, et al. Resting-state connectivity biomarkers define neurophysiological subtypes of depression. Nat Med. 2017;23(1):28-38. (PMID: 27918562)

2. Wu W, Zhang Y, Jiang J, et al. An electroencephalographic signature predicts antidepressant response in major depression. Nat Biotechnol. 2020;38(4):439-447. (PMID: 32042166)

CHANGING THE CONVERSATION AROUND ALCOHOL: NIAAA UPDATE

George Koob, National Institute of Health – NIAAA

Abstract Alcohol misuse and alcohol use disorder (AUD) are endemic societal problems that have been willingly absorbed into the social fabric of our society for generations. They cause an enormous amount of medical pathology, human suffering, loss of productivity and cost to our medical care system and the nation's economy. Alcohol misuse accounts for 30 million individuals with alcohol use disorder, 5% of cancers, 50% of liver disease deaths, and up to 25 % of pancreatitis. While efforts to employ screening, brief intervention and referral to treatment have successfully initiated screening in many situations, brief intervention and referral to treatment remain underused. Missed screening opportunities especially for some subgroups and the more widespread lack of follow up after screening contribute to a significant treatment gap: less than 10% of individuals in need of treatment receive treatment for AUD. Less than 2% receive one of the three FDA approved and effective medications for treatment of AUD. In addition, the COVID-19 pandemic has exposed some long-neglected drivers of AUD: increased drinking to cope with stress, interaction of alcohol with mental health, the role of alcohol in women's health, alcohol and health in older adults, and understanding recovery from AUD. In the face of these challenges, a cultural change is underway as highlighted by movements to reevaluate our relationship with alcohol such as Dry January, Sober October, and the broader Sober Curious movement. Current NIAAA priorities and challenges include providing resources for the public to facilitate prevention among young adults (College Aim), to help individuals evaluate their own relationship with alcohol (Rethinking Drinking), and to assist those seeking treatment (NIAAA Treatment Navigator). Also, the Healthcare Professional Core Resource on Alcohol, launched in 2022, provides healthcare professionals with evidence-based knowledge and resources to address alcohol misuse in clinical practice.

Learning Objectives:

1. To understand what are the causes of the treatment gap in alcohol use disorder.
2. To understand the resources available from the National Institute on Alcohol Abuse and Alcoholism with particular emphasis on the Health Care Professional's Core Resource on alcohol

Literature References:

1. Koob GF, Powell P, White A. Addiction as a coping response: hyperkatifeia, deaths of despair, and COVID-19. American Journal of Psychiatry, 2020, 177:1031-1037. PMID: 33135468. PMC: none. DOI: 10.1176/appi.ajp.2020.20091375.

UPDATE OF THE MEDICATIONS DEVELOPMENT PROGRAM AT NIDA

Ivan Montoya, DHHS/National Institute on Drug Abuse

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

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

Learning Objectives:

2. Learn about the NIDA Therapeutics Development Program for SUDs, including opioid, cocaine, methamphetamine and cannabis use disorders.
3. Become familiar with the pipeline of medications and other therapeutics currently investigated to treat SUD and overdose.

Literature References:

1. Rasmussen K, White DA, Acri JB. NIDA's medication development priorities in response to the Opioid Crisis: ten most wanted. Neuropsychopharmacology. 2019 Mar;44(4):657-659. doi: 10.1038/s41386-018-0292-5. Epub 2018 Dec 7. PMID: 30538289; PMCID: PMC6372702.
2. Aklin WM, Walton KM, Antkowiak P. Digital therapeutics for Substance Use Disorders: Research priorities and clinical validation. Drug Alcohol Depend. 2021 Dec 1;229(Pt A):109120. doi: 10.1016/j.drugalcdep.2021.109120. Epub 2021 Oct 9. PMID: 34740068.

2023 UPDATE ON PCORI RESEARCH PRIORITIES AND FUNDING OPPORTUNITIES IN MENTAL HEALTH

Elisabeth Houtsmuller, PCORI

Abstract About 1 in 5 adults and 1 in 6 youth experience a mental health disorder in the U.S. each year, and more recent estimates for depression, anxiety, and suicidality have been alarming, especially for youth. While evidence-based treatments are available, what and how much works best for whom is often not clear. The Patient-Centered Outcomes Research Institute (PCORI) funds a large portfolio of mental/behavioral health studies designed to provide evidence to help patients, caregivers, and other stakeholders make more informed decisions about mental health care.

This presentation will provide an overview of this portfolio and discuss PCORI's mission to fund comparative effectiveness research (CER), our patient-centered research focus, and our emphasis on meaningful stakeholder engagement throughout the entire research process. The presentation will also highlight PCORI's research priority topic themes that are relevant to psychiatric researchers, including improving mental and behavioral health, addressing substance use, violence and trauma, and improving outcomes for people with intellectual or developmental disabilities. Finally, the presentation will conclude with an overview of research funding announcements that invite investigator-initiated CER topics in mental/behavioral health.

Learning Objectives:

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

Literature References:

1. Frank L, Basch E, Selby JV, For the Patient-Centered Outcomes Research Institute. The PCORI Perspective on Patient-Centered Outcomes Research. JAMA. 2014;312(15): 1513–1514. doi:10.1001/jama.2014.11100
2. Luce BR, Simeone JC. How different is research done by the Patient-centered Outcomes Research Institute, and what difference does it make? J Comp Eff Res. 2019;8(14):1239-1251. doi:10.2217/cer-2019-0054
3. Mental Health by the Numbers. National Alliance on Mental Illness. Updated April 2023. Accessed May 1, 2023. https://nami.org/mhstats

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

Panels

*REPEATED PSILOCYBIN ADMINISTRATION IN PATIENTS WITH TREATMENT RESISTANT OBSESSIVE COMPULSIVE DISORDER

Francisco Moreno, University of Arizona

Overall Abstract Introduction: duction: Obsessive-compulsive disorder (OCD) leads to great disability and suffering because of limitations in efficacy of available treatments. Anecdotal reports [1] and results from a preliminary study [2] suggest that Psilocybin may benefit OCD patients when used under safe clinical supervision, in the absence of structured psychotherapeutic interventions.

Methods: Fifteen psychotropic free patients with OCD who failed to improve after at least one adequate trial of guideline concordant care were tested in a two-phase study that included: Phase 1, four sessions of double-masked, active-placebo controlled design with a) low dose psilocybin (100 mcg/kg), b) high dose psilocybin (300 mg/kg), or c) Lorazepam 1 mg PO (Ativan ®), separated by one week. Phase 2, included four sessions with high dose psilocybin (300 mg/kg) one-week apart. Psychophysiological, neuroimaging, clinical, and behavioral effects were measured at baseline, and various points throughout testing, and prospectively up to six-month follow up. Efficacy, safety and tolerability are being measured with standard clinical trial methodology.

Results: Katja Allen will present clinical safety and efficacy data. The results show that both doses of psilocybin were safe and well tolerated, and both reduced OCD symptoms better than lorazepam. Long term follow up data will be completed by the date of this panel, the preliminary assessment shows benefits observed during acute treatment phase are maintained for six month.

John Allen will present findings from an event-related brain potential investigation of error monitoring. At baseline -- prior to any sessions -- and again after the 4th and after the 8th session, participants completed a flanker's task designed to create a motor response conflict, and errors. Prior work has found that the response-locked error-related midfrontal negative

voltage potential (the error-related negativity or ERN) is larger in individuals with OCD compared to healthy controls and is related to symptom severity among individuals with OCD. This task and measure can provide an index of the extent to which this biomarker of OCD was impacted by the intervention.

Diheng Zhang will present findings on resting state network connectivity with fMRI. Aberrant Default-mode Network (DMN) activity has been observed in OCD patients compared to controls and can identify a treatment resistant subgroup of patients with OCD. Our preliminary results show changes in DMN network connectivity that scale in magnitude with OCD symptom reduction.

Conclusion: Preliminary findings suggest that psilocybin is well tolerated and may improve OCD symptoms. Biomarkers such as changes in event related potentials and functional connectivity may serve as surrogate indicators of clinical response.

Robin Carhart-Harris will discuss the relevance of these findings, potential implications for treatment of OCD and related disorders, putative mechanisms of change, and potential for benefits from supportive psilocybin ingestion without structured psychotherapy.

Learning Objectives:

1. 1.- Review safety and efficacy signal of psilocybin in clinical research for people with OCD.
2. 2.- Discuss potential mechanisms of action for efficacy of psilocybin when used without psychotherapy in patients with OCD.

EFFICACY AND SAFETY OF PSILOCYBIN IN THE TREATMENT OF OCD

Katja Allen, University of Arizona

Individual Abstract: Obsessive-compulsive disorder (OCD) is a chronic and debilitating condition with a lifetime prevalence of 2 to 3%, and one with very high disease burden. Existing treatments, while helpful for some, leave many with little or no lasting relief. Our research thus examines whether psilocybin may provide a safe and effective intervention for OCD. To determine the acute efficacy, safety and tolerability of two different doses of psilocybin, we studied 15 patients with symptomatic OCD in two study phases.

Study phase 1 was a four-week randomized controlled trial (RCT) during which participants were randomly assigned to one of the following groups a) low dose (100 µg/kg) psilocybin, b) high dose (300 µg/kg) psilocybin, or c) lorazepam (1 mg). Five subjects per group took the assigned study drug a total of four times, separated by a week. During the four-week Phase 2, all participants received high doses of psilocybin.

Symptom severity was assessed with the Yale-Brown Obsessive Compulsive Scale (YBOCS) at Baseline and weekly thereafter until one week after the final study session. Follow-up YBOCS scores were collected for another 6 months after participants completed the trial.

Psilocybin sessions were conducted with no severe drug-related adverse events (SAEs) during or following administration. Moreover, no psychotic symptoms emerged, and no increase in acute suicidality occurred.

With this small sample size and limited statistical power, we present descriptive statistics. At baseline, patients presented with severe OCD (YBOCS mean = 28.8), and at the end of phase 1, patients receiving psilocybin showed larger reduction in symptoms than those receiving

Lorazepam (High 38%, Low 22%, Lorazepam 11% reduction). At the conclusion of the full 8 weeks, after all patients had received psilocybin, symptom reduction was similar across groups (High-High 53%, Low-High 47%, Lorazepam-High 56% reduction). By end of treatment, using conservative criteria of YBOCS reduction > 35% for response and YBOCS < 12 for remission, 73% of patients were responders and 40% achieved remission. At baseline 14 patients had severe OCD and 1 had moderate, whereas at end of treatment 2 had severe, 7 mild, and 6 in remission. At 6 months following end of treatment, 80% of those in remission remained in remission, and 77% of responders maintained their response.

These results suggest the promise of psilocybin for the acute and durable treatment of OCD, and support the merit of a larger clinical trial. Moreover, during supervised clinical research, both doses of psilocybin were safe and well tolerated, and reduced OCD symptoms to a greater extent than the active control lorazepam.

Learning Objectives:

1. To understand new approaches to treat mental disorders like OCD.
2. To describe a safe and efficacious treatment protocol using psychedelics.

Literature References:

1. Ehrmann, K., Allen, J. J., and Moreno, F. A. (2021). Psilocybin for the Treatment of Obsessive-Compulsive Disorders. Disruptive Psychopharmacology, 247-259.
2. Moreno, F. A., Wiegand, C. B., Taitano, E. K., and Delgado, P. L. (2006). Safety, tolerability, and efficacy of psilocybin in 9 patients with obsessive-compulsive disorder. Journal of clinical Psychiatry, 67(11), 1735-1740.

ERROR-RELATED BRAIN ELECTRICAL ACTIVITY IN OCD BEFORE AND AFTER TREATMENT WITH PSILOCYBIN

John Allen, The University of Arizona

Individual Abstract: Hyperactive cortico-striatal circuits, including the anterior cingulate cortex (ACC), are implicated in obtrusive thoughts and repetitive behaviors in obsessive–compulsive disorder (OCD). Meta-analyses support the finding of larger error-related negativities (ERNs) in OCD patients during simple flanker tasks, which have been proposed to reflect an amplified error signal in these hyperactive circuits. Such amplified error signals typically are associated with an adaptive change in response, yet in OCD these same repetitive responses persist to the point of distress and impairment. Although ERN magnitude scales with symptom severity in OCD, some evidence suggests that enhanced ERN amplitudes persist in OCD following treatment. Given that many OCD patients do not respond to treatment, we investigated whether ERN amplitudes at baseline would predict treatment response, and whether psilocybin-induced changes in OCD symptoms would be reflected in decreased ERN amplitudes.

Our recently concluded RCT of 15 participants with OCD involved assignment to receive low dose (100 μg/kg) psilocybin, high dose (300 μg/kg) psilocybin, or lorazepam (1 mg) for each of 4 weekly sessions, followed by 4 additional weekly sessions of high dose (300 μg/kg) psilocybin for all participants. At baseline -- prior to any sessions -- and again after the 4th double-blind session, and after the 8th session, participants completed a flankers task designed to create a motor response conflict, and errors, while EEG was recorded. Preliminary completed findings with 4 participants reveal decreased error-related brain activity following the completion of 8 weeks of psilocybin treatment in OCD, during which time substantial

symptom reductions were observed. Data from the entire trial will be presented. If ERN amplitude is impacted by repeated psilocybin sessions in OCD, this would differ from other interventions and suggest that psilocybin may produce enduring changes within cortico-striatal circuits and reduce risk for future episodes.

Learning Objectives:

1. To describe the nature of error-monitoring alterations in OCD.
2. To describe how brain electrical indices of error monitoring change with psilocybin-induced symptom reduction in OCD.

Literature References:

1. Cavanagh, J.F., Gründler, T.O.J., Frank, M.J., and Allen, J.J.B. Altered cingulate sub-region activation accounts for task-related dissociation in ERN amplitude as a function of obsessive-compulsive symptoms. Neuropsychologia, 2010; 48, 2098–2109. PMCID: PMC2876228
2. Gründler, T.O.J., Cavanagh, J.F., Figueroa, C.M., Frank, M.J., and Allen, J.J.B. Task-related dissociation in ERN amplitude. Neuropsychologia 2009; 47, 1978-1987. PMCID: PMC2680784

PSILOCYBIN-INDUCED DECREASES IN DEFAULT-MODE NETWORK CONNECTIVITY PREDICT GREATER SYMPTOM REDUCTION IN OBSESSIVE COMPULSIVE DISORDER.

Diheng Zhang, The University of Arizona

Individual Abstract: Obsessive-compulsive disorder (OCD) is a chronic mental health condition characterized by repetitive anxiety-inducing intrusive thoughts (obsessions) and compulsive behaviors (compulsions), affecting 2.3% of the population in the U.S (Grant et. al., 2012). OCD is debilitating and brings personal distress, impaired daily functioning, social isolation, poor quality of life and even suicide attempts. Resting state fMRI studies have revealed a connection between default mode network connectivity and symptoms of OCD. Kwak et. al. (2020) showed that increased connectivity within DMN differentiates OCD subjects from HC (similar to other disorders like MDD), and the level of increased connectivity within DMN signifies a treatment resistant subgroup.

Despite the significant cost to individuals and to society, previous research showed that up to 40 – 60% of patients do not have a satisfactory outcome with Serotonin Reuptake Inhibitor (SRIs) treatment (Pallanti et. al., 2002). Our recently concluded randomized control trial tested the effects of repeated psilocybin treatment for OCD. Fifteen OCD subjects received eight weeks of treatment in of two phases: phase one was a double-blind trial with 5 individuals assigned to each of three groups (high-dose (300 μg/kg) psilocybin, low-dose (100 μg/kg) psilocybin, Lorazepam (1 mg)) for four weeks; in phase two, all 15 subjects received four more weeks of high dose psilocybin. Resting state fMRI data were collected before the beginning of phase one (baseline), after four weeks between phase one and phase two (week 4), and again after eight weeks at the conclusion of the acute phase treatment (week 8). We could thus assess whether the clinical impact of repetitive psilocybin treatment is related to changes in functional connectivity within DMN.

Our preliminary fMRI data analysis used a seed-to-voxel region of interest (ROI) approach, focusing on the anterior-medial prefrontal cortex (amPFC) as the ROI, given its well-

established role as a core hub in the DMN, one that is particularly associated with self-related processing. We were particularly interested in changes in connectivity between this amPFC and the other core regions of the DMN: the posterior cingulate cortex, the precuneus, and the angular gyrus. We thus examined the relationship between subjects' symptom reduction over eight weeks of treatment and the change of their pre-and-post functional connectivity between these ROIs within the default mode network, using PCC (left and right) and aMPFC (left and right) as seeds. Results showed that decreased of connectivity between left amPFC and right Angular Gyrus, and between right amPFC and both left and right angular gyrus, is significantly correlated to decrease in YBOCS scores following 8 weeks of intervention. Of additional interest is whether changes DMN connectivity over the 8-week active treatment phase could predict longer-term symptom change. Greater decreases from baseline to end of treatment in connectivity between amPFC (both left and right) and angular gyrus (right) were associated with greater symptom reduction at 6 months. Surprisingly, increased treatment-related connectivity between amPFC (left) and precuneus predicted greater symptom reduction at 6 months (based on 12 subjects who had completed the 6 month follow up assessment).

These preliminary results indicate that psilocybin-induced decoupling of brain areas within the DMN is associated with a reduction of OCD symptom severity, both at end of active-phase treatment as well as 6 months later, and support the promise of psilocybin to alter neural networks that underlie OCD symptoms. Full data analysis will be presented in the panel discussion.

Learning Objectives:

1. To investigate the nature of aberrant DMN connectivity in OCD.
2. To investigate the effects of psilocybin on DMN connectivity and its relationship to OCD symptom reduction.

Literature References:

1. Kwak, S., Kim, M., Kim, T., et al. Defining data-driven subgroups of obsessive–compulsive disorder with different treatment responses based on resting-state functional connectivity. Translational psychiatry. 2020;10(1), 1-11.
2. Moreno FA, Wiegand CB, Taitano EK, Delgado PL. Safety, tolerability, and efficacy of psilocybin in 9 patients with obsessive-compulsive disorder. Journal of clinical Psychiatry. 2006;67(11):1735-40.

RECENT UPDATES ON ASSESSMENT AND OUTCOMES IN RESEARCH ON SUICIDAL BEHAVIORS IN YOUTH

Madhukar Trivedi, UT Southwestern Medical Center

Overall Abstract Depression and suicide in youth are critical public health problems, and both are on the rise in the United States (US). Among adolescents, rates of past-year major depressive episodes increased 52% between 2005 and 2017 (from 13.1% to 19.9%) (Twenge et al., 2019). Suicide is the second leading cause of death in persons aged 10-24 years in the US. A recent Centers for Disease Control and Prevention report that focused on this age group highlighted that after a stable trend in suicide rates from 2000 to 2007, the rate sharply increased from 6.8 to 10.6 per 100,000 persons from 2007 to 2017 (Curtin and Heron, 2019). As a result, there is dire need for research to improve our understanding of assessment and treatment for youth with suicidal ideation and behaviors (Busby et al., 2020). This session will

explore late-breaking advances in research for depression and suicidal behaviors in youth. Dr. Elizabeth Ballard will give a general update on announced funding initiatives into youth suicide, as well as highlights from NIMH-funded research. Dr. Michael Bloch will present data on a recent trial examining ketamine in youth with depression. Dr. Madhukar Trivedi will present two new studies, including one that examines immune dysfunction in suicidal youth and one randomized controlled trial of ketamine versus midazolam in youth with recent suicidal behaviors. Dr. Jill Harkavy-Friedman will serve as Discussant for the panel.

Learning Objectives:

1. Explain recent research updates on assessments and novel treatments for adolescents with depression and suicidal behaviors.
2. Understand potential biological markers to guide in assessment and treatment of youth with suicidal behaviors.

UPDATE ON NIMH-FUNDED RESEARCH INTO YOUTH SUICIDE

Elizabeth Ballard, National Institute of Mental Health

Individual Abstract: This presentation will give a general update on announced funding initiatives into youth suicide as well as highlights from NIMH-funded research.

Learning Objectives:

1. At the end of the presentation, participants will be able to describe recent NIMH funding announcements related to youth suicide.
2. At the end of the presentation, participants will be able to summarize recent findings from NIMH funded research on suicide and youth.

Literature References:

1. Sheftall AH, Vakil F, Ruch DA, Boyd RC, Lindsey MA, Bridge JA. Black Youth Suicide: Investigation of Current Trends and Precipitating Circumstances, J Am Acad Child Adolesc Psychiatry. 2022 May;61(5):662-675.
2. Brent DA, Horowitz LM, Grupp-Phelan J, et al. Prediction of Suicide Attempts and Suicide-Related Events Among Adolescents Seen in Emergency Departments. JAMA Netw Open. 2023 Feb 1;6(2): e2255986

KETAMINE AS A NOVEL ANTIDEPRESSANT FOR TREATMENT-RESISTANT DEPRESSION IN ADOLESCENTS

Michael Bloch, Yale Child Study Center

Individual Abstract: Background: Adolescent depression is a major public health problem with suicide being the second leading cause of death in the age group in the United States. Although intravenous ketamine has shown efficacy in adult treatment-resistant depression, its efficacy in pediatric populations is unknown.

Methods: We conducted a proof-of-concept randomized, double-blind, single-dose crossover clinical trial, 17 adolescents (ages 13-17) with major depressive disorder received a single intravenous infusion of either ketamine (0.5 mg/kg over 40 minutes) or midazolam (0.045 mg/kg over 40 minutes), and the alternate compound 2 weeks later. All participants had previously tried at least one antidepressant medication and met the severity criterion of a score

>40 on the Children's Depression Rating Scale-Revised. The primary outcome measure was score on the Montgomery-Åsberg Depression Rating Scale (MADRS) 24 hours after treatment. In secondary analysis we also examined the relationship between ketamine metabolites, dissociative symptoms as measured on the CADSS scale and treatment response.

Results: A single ketamine infusion significantly reduced depressive symptoms 24 hours after infusion compared with midazolam (MADRS score: midazolam, mean=24.13, SD=12.08, 95% CI=18.21, 30.04; ketamine, mean=15.44, SD=10.07, 95% CI=10.51, 20.37; mean difference=-8.69, SD=15.08, 95% CI=-16.72, -0.65, df=15; effect size=0.78). A significantly greater proportion of participants experienced a response to ketamine during the first 3 days following infusion as compared with midazolam (76% and 35%, respectively). Ketamine was associated with transient, self-limited dissociative symptoms that affected participant blinding, but there were no serious adverse events. There was no significant association between dissociative symptoms and depression treatment response.

Conclusions: In this first randomized placebo-controlled clinical trial of intravenous ketamine in adolescents with depression, the findings suggest that it is well tolerated acutely and has significant short-term (2-week) efficacy in reducing depressive symptoms compared with an active placebo. We will also describe ongoing studies that are designed to examine the safety and efficacy of repeated-doses of ketamine for treatment-refractory depression with suicidal ideation in adolescents.

Learning Objectives:

1. Understand the limitations of currently available pharmacological treatments for adolescent depression.
2. Review preliminary data examining the effects of ketamine for treatment-resistant adolescent depression.

Literature References:

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

NOVEL TREATMENTS AND BIOMARKERS TO IMPROVE OUTCOMES FOR YOUTH WITH SUICIDAL BEHAVIORS

Madhukar Trivedi, UT Southwestern Medical Center

Individual Abstract: Background: Depression and suicide in youth are on the rise in the United States (US), and suicide is now the second leading cause of death in persons aged 10-24 years in the US. As a result, there is dire need for research to improve our understanding of assessment and treatment for youth with suicidal ideation and behaviors. Two ongoing studies aimed at improving our understanding of identification and treatment for adolescents with suicidal ideation and behaviors will be presented.

Methods: Two studies will be reviewed. The first study, funded by the American Foundation for Suicide Prevention (AFSP), aims to map immune dysfunction to suicidal behavior and

establish a reliable immune signature of suicide risk that can 1) guide future research into fundamental pathophysiology and 2) identify targets for drug development. Blood samples and a comprehensive array of clinical measures are collected from three groups of adolescents: (1) with suicidal behavior [recent (within 3 months) suicide attempt or suicidal ideation warranting urgent evaluation,] (2) at risk for mood disorders, and (3) who are healthy (no psychiatric history). The second study, funded by the National Institute of Mental Health, aims to examine whether ketamine will result in greater symptomatic improvement in the short-term and lower likelihood of repeat suicidal event in the long-term as compared to midazolam (placebo condition).

Results: Both studies are underway. Preliminary outcomes will be reviewed.

Conclusions: These studies will help elucidate mechanisms that may play a causal role in suicide and potential impact of current treatments and future therapeutic development.

Learning Objectives:

1. Understand the potential immune markers associated with suicidal ideation and behaviors in adolescents.
2. Describe current available treatments and potential novel treatments for youth with suicidal ideation and behaviors.

Literature References:

1. Chin Fatt C, Ayvaci ER, Jha MK, Emslie G, Gibson S, Minhajuddin AT, Mayes TL, Farrar JD, Trivedi MH. Characterizing inflammatory profiles of suicidal behavior in adolescents: Rationale and design. J Affect Disord; 2023; 325:55-61. doi: 10.1016/j.jad.2022.12.114.
2. Chin Fatt CR, Farrar JD, Jha MK, Minhajuddin A, Mayes T, Foster JA, Trivedi MH. Immune characterization of suicidal behavior in female adolescents. Brain Behav Immun Health; 2022; 25:100499. doi: 10.1016/j.bbih.2022.100499

ANHEDONIA: TRANSLATIONAL TARGETS AND CLINICAL IMPLICATIONS

Susannah Tye, The University of Queensland

Overall Abstract Anhedonia is a debilitating, transdiagnostic symptom of treatment-resistant mood disorders, and is significantly associated with suicidality and poor functioning. Through complementary clinical and translational approaches, we are gaining a better understanding of the biological processes underpinning anhedonia. In turn, biological and behavioral markers of anhedonia for targeted precision medicine approaches to patient care are emerging. This panel will integrate complementary results from laboratory animal and in vitro human cellular models with data from clinical trials to illuminate the biological and clinical correlates of anhedonia, their role in driving clinical outcomes, and viability for therapeutic target engagement. A key emerging mechanism of interest is immunometabolism and its control of corticostriatal dopamine systems. The panel will discuss new data from studies in depressive disorders demonstrating the relationship between anhedonia, immunometabolism, and antidepressant outcomes. Implications for precision medicine and novel therapeutics will also be reviewed. The symposium Chair, Dr. Susannah Tye, will first provide a brief Introduction: duction to the topic and overview of the translational goals of the panel. Dr. Balwinder Singh will then lead with new, unpublished data demonstrating ketamine's antianhedonic effects in a heterogeneous group of patients with treatment-resistant depression (TRD), its relationship with overall clinical outcomes, and mTOR target engagement in peripheral immune cells. Dr.

Jennifer Kruse will discuss new clinical data on the association of immune and metabolic markers and clinical features of anhedonia among the TRD patients. Dr. Mandakh (Mandy) Bekhbat will next describe new data on the molecular and bioenergetic phenotypes of monocytes, highlighting the relationship between immunometabolic shifts toward glycolysis and symptoms of anhedonia in depressed patients with high inflammation. Finally, Dr. Susannah Tye will complete the session with new data from animal models and clinical subjects with TRD, presenting evidence that immunometabolic shifts associated with anhedonic phenotype underpin biological and behavioral responses to ketamine and other classes of antidepressants. The Discussant, Professor Mark Frye, will then review key findings and summarize how the emerging biological basis and readily identifiable clinical indicators of anhedonia can be used to improve precision medicine approaches in psychiatry, enabling treatments to more effectively be matched to the patients who need them. Given conventional monoaminergic antidepressants have delayed therapeutic efficacy and limited antianhedonic properties, identifying novel biomarker and therapeutic approaches with antianhedonic properties is a high priority.

Learning Objectives:

1. 1: Understand the relationship between anhedonia and immunometabolism.
2. 2: Understand the relationship between anhedonia and antidepressant outcomes.

KETAMINE ASSOCIATED CHANGE IN ANHEDONIA AND MTOR EXPRESSION IN TREATMENT-RESISTANT DEPRESSION

Balwinder Singh, Mayo Clinic

Individual Abstract: Background: Ketamine has been shown to rapidly reduce anhedonia in preliminary studies. However, the biologicals mechanism underlying the antianhedonic effects is unknown. In this post hoc analysis of two independent cohorts, we aimed to replicate the evidence for ketamine's anti-anhedonic action. We evaluated the association between in-vivo change in mTOR protein expression as a predictive biomarker for antianhedonic effect of acute ketamine response.

Methods: Adult patients with treatment-resistant depression (TRD) who received racemic intravenous ketamine in an acute series of up to six infusions (twice/thrice-weekly, dosed at 0.5mg/kg) at the Emory TRD clinic (n=44) in Atlanta, Georgia, and at the Mayo Clinic (n=12), Rochester, Minnesota, were included. Simple linear regression was carried out to investigate the relationship between percent change in anhedonia and percent change in modified total depression score (baseline to end point), measured using PHQ-9/MADRS. We investigated a correlation between percent change in anhedonia (MADRS #8), core-depression phenotype scores (MADRS #1+#2+#8), and interest+activity phenotype scores (MADRS #6+#7+#8) (baseline to 24h) and percent change in mTOR, pmTOR, and mTOR/pmTOR (baseline to end of infusion).

Results: Ketamine treatment significantly reduced anhedonia scores in both cohorts. The percentage change in anhedonia (baseline to the end of acute series) significantly correlated with percentage change in modified total PHQ-9 score ($r=0.67$, $p<0.001$). These findings were similar to the Mayo study (n=12) where the percentage change in anhedonia (baseline to 24-hr post first infusion) significantly correlated with percentage change in modified total MADRS score ($r=0.72$, $p=0.008$).

There was a significant correlation between change in anhedonia, N=10, (baseline and at 24h) and in vivo increases in mTOR protein expression in peripheral blood mononuclear cells (baseline and at the end of infusion). This was evident with anhedonia itself (MADRS #8, r=0.70, p=0.03), core depression (r=0.57, p=0.08), and with interest+ activity (r=0.59, p=0.07).

Conclusion: These data demonstrate ketamine's antianhedonic action in a heterogeneous group of TRD patients, independent of general depressive symptoms. We further showed an in-vivo increase in peripheral immune cell mTOR protein expression correlates with this antianhedonic effect. These novel findings suggest peripheral immune mTOR expression may serve as a predictor biomarker for ketamine's rapid antianhedonic effects, warranting replication in a larger, independent sample.

Learning Objectives:

1. To highlight ketamine's antianhedonic action in a heterogeneous group of TRD patients, independent of general depressive symptoms, at two different sites.
2. To evaluate the association between in-vivo change in mTOR protein expression as a predictive biomarker for antianhedonic effect of ketamine response.

Literature References:

1. Singh B, Vande JL, Riva-Posse P, Pazdernik V, Frye MA, Tye SJ. Ketamine associated change in anhedonia and mTOR expression in treatment-resistant depression. Biological Psychiatry. 2022 (In Press)
2. Abdallah CG, Averill LA, Gueorguieva R, Goktas S, Purohit P, Ranganathan M, et al. (2020): Modulation of the antidepressant effects of ketamine by the mTORC1 inhibitor rapamycin. Neuropsychopharmacology. 45:990-997.

INFLAMMATION, THYROID HORMONE METABOLISM, AND REWARD DEFICITS, AMONG PATIENTS WITH TREATMENT RESISTANT DEPRESSION

Jennifer Kruse, University of California, Los Angeles

Individual Abstract: Background: Higher inflammation in depression is related to greater reward deficits, e.g., anhedonia and amotivation, and is associated with disruptions in dopamine related reward circuitry. However, the mechanisms underlying these relationships are not fully understood and may involve the impact of inflammation on hormonal and metabolic processes. It is established in the nonthyroidal illness syndrome that inflammation leads to changes in the metabolism of thyroid hormone, causing a decrease in the relative availability of the active thyroid hormone (triiodothyronine, T3), important for mood and for dopaminergic behavioral responses. However, this has not been studied in the setting of depression. It is unknown whether high inflammation is associated with shifts in thyroid hormone metabolism (as indexed by ratios of T3:rT3 and T3:T4) among depressed patients, and whether this in turn relates to reward system deficits.

Methods: Among patients with treatment resistant depression (TRD, n=90; 58% female; mean age 39.4 years), we evaluated baseline relationships between CRP, thyroid hormone metabolism (as indexed by ratios of T3:rT3 and T3:T4), and reward system deficits.

Results: Higher CRP levels were associated with lower relative availability of the active thyroid hormone, T3, as indexed by a lower ratio of T3:rT3 (r= -0.26, p=.01). Similarly, when evaluated by "high" CRP (> 3 mg/L) vs "lower" CRP (< 3 mg/L), the high CRP group had lower mean T3:rT3 ratio: [t (88) =2.04, p=0.04] and a trend toward lower mean T3:T4 ratio [t(88)=1.52, p=0.13]. In examination of reward deficits (covarying for age, sex, and BMI),

lower T3:rT3 ratio was associated with lower positive affect (B= 0.260, p=.02; NIH Toolbox Positive Affect measure) and with lower scores on two subscales of the Behavioral Activation Scale (BAS), indicating lower propensity to seek fun (B = 0.248, p=.02) or to respond positively to reward (B= 0.236, p=.03).

Conclusions: Higher inflammation was related to lower T3 availability among TRD patients, which in turn was associated with reward system deficits. It is critical to identify targetable mechanisms related to elevated inflammation that can be translated into effective treatments for depression. Future mechanistic interrogation of the role of T3 in "high" versus "low" inflammation depression may aid in the development of precision medicine strategies.

Learning Objectives:

1. Describe the impact of inflammation on the relative availability of active thyroid hormone (T3) among depressed patients.
2. Consider the potential impact of subtle, subclinical decreases in the relative availability of active thyroid hormone on depression phenotype, including reward system deficits.

Literature References:

1. Wajner SM, Goemann IM, Bueno AL, et al. IL-6 promotes nonthyroidal illness syndrome by blocking thyroxine activation while promoting thyroid hormone inactivation in human cells. J Clin Invest. 2011;121(5):1834-45.
2. Lee E-H, Kim S-M, Kim C-H, et al. Dopamine neuron induction and the neuroprotective effects of thyroid hormone derivatives. Scientific reports. 2019;9(1):13659.

CELLULAR IMMUNOMETABOLIC SIGNATURES ARE ASSOCIATED WITH ANHEDONIA IN DEPRESSION WITH HIGH INFLAMMATION

Mandakh Bekhbat, Emory University School of Medicine

Individual Abstract: Inflammation is implicated in the pathophysiology of major depression (MD) and its core feature anhedonia; yet the immune cell mechanisms and related metabolic programing that fuel inflammation to impact the brain and behavior are largely unknown. Using microarray, single cell RNA-Sequencing (scRNA-Seq), and Seahorse cellular bioenergetic assessments, we investigated transcriptomic and immunometabolic pathways within immune cells that underlie increased inflammation, and their relationship with anhedonia in MD outpatients. In unmedicated, medically-stable MD patients (n=62), we found relationships between anhedonia and a whole-blood gene expression pattern consistent with monocytic glycolysis, but only among patients with high inflammation (C-reactive protein [CRP]>3 mg/L; n=19). scRNA-Seq in PBMCs from six patients – three with high inflammation (CRP>3 mg/L) before and after anti-inflammatory challenge with infliximab and three with low inflammation (CRP □3mg/L) – further revealed that CD14+ and CD16+ monocytes were more abundant in MD patients with high inflammation, and 29% and 55% reduced after infliximab. Genes upregulated in patients with high compared to low inflammation enriched inflammatory (phagocytosis, complement, chemotaxis) and immunometabolic pathways (hypoxia-inducible factor [HIF]-1, aerobic glycolysis). Following infliximab, changes in the number of CD14+ monocytes predicted improvements in anhedonia (r=1.0, p<0.001). Real-time bioenergetic profiling of intact monocytes from four additional MD patients and one healthy control showed that monocytic glycolysis was associated with CRP levels (r=0.85, p=0.06) and greater anhedonia (r=0.9, p=0.03). Our results indicate that MD patients with

increased inflammation have enrichment of circulating monocyte populations. These monocytes exhibited greater glycolysis and immunometabolic reprograming needed to sustain cellular activation, in association with symptoms of anhedonia. Together, these findings begin to elucidate the cellular and molecular pathways associated with high inflammation in MD, which may lead to novel monocyte-targeted immunomodulatory treatment of psychiatric illnesses with increased inflammation.

Learning Objectives:

1. Recognize the role of cellular metabolic programing in immune cell activation as well as systemic inflammation and its effects on the brain and motivated behavior.
2. Evaluate the potential of novel immunometabolic approaches to reverse the effects of inflammation on the brain and symptoms of anhedonia.

Literature References:

1. Bekhbat M, Ulukaya GB, Bhasin MK, Felger JC, Miller AH. Cellular and immunometabolic mechanisms of inflammation in depression: Preliminary findings from single cell RNA sequencing and a tribute to Bruce McEwen. Neurobiol Stress. 2022; 19:100462.
2. Bekhbat M, Treadway MT, Goldsmith DR, Woolwine BJ, Haroon E, Miller AH, Felger JC. Gene signatures in peripheral blood immune cells related to insulin resistance and low tyrosine metabolism define a sub-type of depression with high CRP and anhedonia. Brain Behav Immun. 2020; 88:161-5.

IMMUNOMETABOLIC MODERATORS OF ANHEDONIA AND TREATMENT RESISTANT DEPRESSION: THERAPEUTIC TARGETS AND PRECISION MEDICINE PATHWAYS

Susannah Tye, The University of Queensland

Individual Abstract: Treatment-resistant depression (TRD) is defined by the failure to respond to at least two antidepressant treatments given at adequate dose and duration during a current depressive episode. The presence of anhedonia in TRD is associated with suicidal ideation and poorer clinical outcomes. The mechanisms governing antidepressant treatment resistance are not known, however a role for inflammation and insulin-dependent metabolic dysfunction in anhedonia is now established. Using a rodent model of TRD elicited via daily hypothalamic pituitary adrenal (HPA) axis stimulation with adrenocorticotropic hormone (ACTH), we have characterized insulin-dependent immunometabolic mechanisms contributing to antidepressant resistance in the forced swim test, anhedonia-like phenotypes in the effort-related choice behavioral task and dopamine deficits in the ventral striatum. Under the stress of the forced swim test we found that rates of insulin-dependent glucose uptake and glycolysis increase significantly in peripheral blood mononuclear cells (PBMCs) from TRD animals ($p<0.001$; n=8-16). This immunometabolic shift, together with impaired insulin signaling in brain and PBMC tissue, was significantly correlated with resistance to commonly prescribed antidepressants ($p<0.05$; n=8-14). Conversely, insulin-activation of the downstream molecular target mammalian target of rapamycin (mTOR), which has both neurotrophic and immunometabolic actions, was robustly associated with response to ketamine and/or lithium augmentation in this rodent model ($p<0.01$; n=10-16) and in human TRD subjects ($p<0.05$; n=12). Application of ketamine to brain cell cultures from TRD and control animals ex vivo evoked local brain-derived insulin efflux to stimulate insulin signaling and glucose uptake locally. In TRD animals, relative to control, significantly more insulin was evoked in response to ketamine application, yet with reduced activation of insulin signaling and glucose uptake

observed ($p<0.05$; n=6). This suggests that central insulin resistance develops in response to ACTH treatment. Similarly, PBMC insulin resistance was associated with ketamine non-response in rodent and human TRD subjects. Augmentation of insulin signaling with lithium or metformin, or inflammatory stimulation with lipopolysaccharide (LPS), increased response rates to >90%, effectively eliminating ketamine non-response in these animals ($p<0.01$; n=10-16). Notably, these same immunometabolic phenotypes were associated with an anhedonia-like phenotype in the effort-related choice behavioral paradigm, together with decreased tyrosine hydroxylase expression and phasic dopamine release in the ventral striatum nucleus accumbens. Collectively, these data demonstrate that insulin-sensitive immunometabolic mechanisms moderate striatal dopamine, anhedonia-like behavioral phenotypes and antidepressant response in TRD, offering novel therapeutic and biomarker targets.

Learning Objectives:

1. To understand the effects of hypothalamic pituitary adrenal axis dysfunction on immunometabolism, dopamine neurotransmission, and dopamine-dependent behaviors
2. To understand the moderating role of immunometabolism in therapeutic response to antidepressants

Literature References:

1. Tye SJ, Borreggine K, Price JB, et al. Dynamic insulin-stimulated mTOR/GSK3 signaling in peripheral immune cells: Preliminary evidence for an association with lithium response in bipolar disorder. Bipolar Disord. 2022 Feb;24(1):39-47.
2. Price JB, Bronars C, Erhardt S, et al. Bioenergetics and synaptic plasticity as potential targets for individualizing treatment for depression. Neurosci Biobehav Rev. 2018 Jul;90:212-220.

ENHANCING RELEVANCE FOR PUBLIC HEALTH: A FOCUS ON DIVERSITY AND INCLUSION

Bernard Fischer, U.S. Food and Drug Administration

Overall Abstract Race, ethnicity, age, sex, gender, and other aspects of human identity intersect critically with mental health. These factors impact an individual's presentation, resources, and interactions with healthcare systems. Recognition of the influence of human diversity on public health is a relatively recent phenomenon. The U.S. Food and Drug Administration (FDA) recognizes the public health benefit of diversity in clinical trial participation and prescription drug labeling. In this panel, speakers will discuss the importance of a more inclusive approach to enrollment in phase 3 trials using the example of major depressive disorder. We will describe FDA guidances and draft guidances for industry that have focused on clinical trial diversity and discuss opportunities for increasing inclusion in clinical trials and drug labeling.

Learning Objectives: At the conclusion of this session, the participants will be able to:

1. Identify and discuss the benefits to public health from enhancing diversity of drug trials.
2. Identify and discuss the benefits to public health from inclusive drug labeling.

DIVERSITY IN CLINICAL TRIALS: INTRODUCTION: DUCTION

Cathy Southammakosane, FDA/CDER/DPP

Individual Abstract: Despite the increasing diversity of the American population and the persistence of health disparities, clinical trials often fail to enroll important subgroups, often those with the greatest medical need. The U.S. Food and Drug Administration's (FDA) public health mission involves granting marketing authorization and the labeling of new drugs based upon evidence consisting of adequate and well-controlled clinical trials in populations representative of the United States. Improving study quality by ensuring that the subjects enrolled in trials better reflect the population most likely to use the drug is important to enhance understanding of the drug's benefit-risk profile across the target patient population. In turn, a more representative study population and more inclusive language in labeling can disseminate the benefits of research participation across the U.S. population, assist in identifying meaningful clinical trial outcomes, and enhance treatment acceptance for the broadest range of relevant patients. Diversity involves the intersection of many different aspects of an individual's identity, of which our panel will focus upon a few: race and ethnicity; sex, gender, and sexuality; and age. We will briefly review the Agency's current thinking on specific strategies to enhance diversity in clinical trials: inclusive trial design and methodology, inclusive enrollment and retention practices, and decreased subject burden during trial participation. We will also discuss strategies for more inclusive language in drug labeling and why it matters.

Learning Objectives:

1. Participants will understand why inclusive enrollment of diverse populations in clinical trials is important.
2. Participants will be able to describe current Agency thinking on trial design elements that could enhance diversity in clinical trial populations.

Literature References:

1. National Academies of Sciences, Engineering, and Medicine; Policy and Global Affairs; Committee on Women in Science, Engineering, and Medicine; Committee on Improving the Representation of Women and Underrepresented Minorities in Clinical Trials and Research. 2022. Improving Representation in Clinical Trials and Research: Building Research Equity for Women and Underrepresented Groups. Washington (DC): National Academies Press (US).
2. Guidance for industry Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment Practices, and Trial Designs (November 2020)

RACIALLY AND ETHNICALLY INCLUSIVE CLINICAL TRIALS

Martine Solages, Center for Drug Evaluation and Research, Food and Drug Administration

Individual Abstract: The U.S. Food and Drug Administration (FDA) recommends enrollment practices that facilitate the recruitment of clinical trial populations that reflect the population of patients likely to use the drug. The Division of Psychiatry recognizes the value of incorporating racially and ethnically diverse patient voices throughout drug development. Studies intended to support labeling should include populations that are racially and ethnically representative of the population impacted by the condition.

Potential benefits of racially and ethnically inclusive clinical trials include promotion of equitable access to the potential benefits of research; identification of treatment targets and clinical outcome assessments that are relevant and clinically meaningful across the intended clinical population; and development of treatments that are trusted and acceptable to a broad range of patients. Race and ethnicity are sociopolitical constructs and should not be interpreted

as biological in nature. However, participation of diverse populations may help capture effects of social determinants of health that are associated with self-identified racial or ethnic categories and that may impact clinical presentation and treatment. This session will review published FDA guidance on the collection and reporting of race and ethnicity data and on strategies to enhance the inclusion of diverse populations in clinical trials.

Learning Objectives:

1. Participants will understand the current statutory requirements and FDA guidance for the reporting of race and ethnicity data in regulatory submissions.
2. Participants will recognize factors that may impede recruitment of racially and ethnically representative clinical trial populations and identify strategies that may facilitate more inclusive enrollment.

Literature References:

1. Collection of Race and Ethnicity Data in Clinical Trials - Guidance for Industry and Food and Drug Administration Staff (October 2016)
2. Kelsey MD, Patrick-Lake B, Abdulai R, et al. Inclusion and Diversity in Clinical Trials: Actionable Steps to Drive Lasting Change. Contemp. Clin. Trials. Published online March 29, 2022, doi: 10.1016/j.cct.2022.106740.

SEX, GENDER, AND SEXUALITY IN CLINICAL TRIALS

Anna Weissman, FDA

Individual Abstract: For decades, there has been concern that the drug development process does not produce adequate information about population-based differences in drug effects. During this time, constructs of sex, gender, and sexuality have evolved into separate concepts with distinct definitions. Honing our understanding of these concepts creates an opportunity for reconsideration of how to facilitate inclusion in clinical trials and labeling. Such inclusion is critical for trials to be representative of the relevant clinical population and for advancing health equity.

This session will explore concepts and definitions of sex, gender, and sexuality. We will review the currently available U.S. Food and Drug Administration guidance on these topics. We will consider how population-based differences in sex, gender, and sexuality may or may not impact various drugs and indications. We will discuss whether and how information about sex, gender, and sexuality is currently being collected and reported. We will consider potential approaches to improving inclusion in clinical trials and drug labeling.

Learning Objectives:

1. Participants will understand the differences between sex, gender, and sexuality.

2. Participants will recognize current limitations to recruiting representative clinical trial populations and consider future strategies for improving inclusion.

Literature References: References:

1. National Academies of Sciences, Engineering, and Medicine. "Measuring sex, gender identity, and sexual orientation." (2022).
2. Pardue, Mary-Lou, and Theresa M. Wizemann, eds. "Exploring the biological contributions to human health: does sex matter?" (2001).

INCLUSION OF OLDER ADULTS IN CLINICAL TRIALS
Roberta Rasetti, FDA/CDER/DP

Individual Abstract: The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH), a global initiative that guides scientific and technical aspects of drug development, issued the guidance E7 Studies in Support of Special Populations: Geriatrics, to provide recommendations on clinical trials of drugs that are likely to have significant use in older adults. Since the ICH guidance was finalized in 1993, the importance of older adult data in a drug evaluation program has increased, given the increasing size of the older adult population and advances in pharmacokinetic and pharmacodynamic assessments.

Older adult patients can respond differently than younger patients to drug therapy in a number of ways, and such differences can be greater in patients 75 years and older. Age-related physiological changes can affect pharmacokinetic and pharmacodynamic response to drug therapy. Older adult patients are more prone to adverse effects because they often have comorbidities and are taking concomitant therapies that may interact with the study drug. Adverse effects can be more severe, less tolerable, and have more serious consequences than in the younger adult population.

Reviews of clinical trial databases indicate that older adult populations are not represented in pivotal clinical trials in proportion to the U.S. treatment populations. This session will discuss current U.S. Food and Drug Administration guidance on the representation of older adult patients in clinical trials and considerations for their inclusion to adequately characterize the safety and efficacy of a drug for a marketing application.

Learning Objectives:

1. Participants will understand the various age-related factors that can impact the response of older adult patients to drug therapy.
2. Participants will be able to describe the FDA's current guidance on inclusion of older adults in clinical trials.

Literature References:

1. Guidance for industry E7 Studies in Support of Special Populations: Geriatrics: Questions and Answers (February 2012).
2. Lau SWJ, Huang Y, Hsieh J, et al. Participation of Older Adults in Clinical Trials for New Drug Applications and Biologics License Applications From 2010 Through 2019. JAMA Netw Open. 2022;5(10): e2236149. doi:10.1001/jamanetworkopen.2022.36149.

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

Workshops

+BEST PRACTICES TO REDUCE SUBJECT AND INVESTIGATOR BIAS IN CLINICAL TRIALS
Timothy Rogier, Lotus Clinical Research

Overall Abstract Placebo-controlled clinical trials with primary endpoints based suffer from a high degree of variability secondary to inflated placebo response and inaccurate patient reporting. Over decades, researchers from industry and academia have developed multiple tools to identify potential high placebo responders, educate study subjects and staff, and analyze data from ongoing trials in an effort to reduce this variability and increase experimental assay sensitivity (i.e., the likelihood that an actually efficacious study treatment will separate from placebo). In this workshop, several experts who have studied the placebo problem and/ or developed successful approaches to reducing unnecessary variability in clinical trials will present their findings. They will discuss how and why placebo response is a significant problem, what techniques have been successful in recent trials, and new methods that could be developed in the future.
Each speaker will present for approximately 15 minutes followed by panel discussions and Q and A from the audience. Attendees involved in ongoing or planned clinical trials are welcome to ask specific questions about their programs.

A list of presenters is below:

3. Moderator/ presenter: Neil Singla, MD, Founder and Chief Scientific Officer, Lotus Clinical Research.
    - Dr. Singla is a board-certified anesthesiologist who frequently speaks and publishes on methods to minimize the inherent variability in subjective endpoint clinical trials. He developed Lotus' placebo response mitigation training program, which has been deployed in over 50 clinical trials.
4. Presenter: Dominique Demolle, PhD, CEO, Cognivia
    - Dr. Demolle and Cognivia develop tools that leverage disease-specific AI-based predictive models to deliver insights on patient psychology. Cognivia offers a clinical trial solution called Placebell, which is used for predicting each clinical trial patient's placebo response.
5. Presenter: Steve Targum, PsyD, Scientific Director, Clintara
    - Dr. Targum is an expert in psychiatric clinical trials who has published widely on clinical trial methodology.
6. Presenter: Elan Cohen, PhD, Hassman Research Institute
    - Dr. Cohen has taken a leadership role in the clinical trial industry in researching strategies for managing the placebo and nocebo effects. He developed the widely used Placebo-Control Reminder Script (PCRS) tool.

Learning Objectives:

1. Understand how and why placebo response and other sources of data variability can cause false negative results in clinical trials.
2. Have access to a series of potential techniques to employ in clinical trials that may reduce bias from study staff and study subjects, and produce more accurate data.

PLACEBO RESPONSE MITIGATION IN PAIN STUDIES

Neil Singla, Lotus Clinical Research

Individual Abstract: Placebo-controlled clinical trials with primary endpoints based on subjective measures suffer from a high degree of variability secondary to inflated placebo

response and inaccurate patient reporting. This is especially problematic in analgesic studies, where formulations of drugs known to work often fail to separate from placebo in clinical trials. Dr. Singla will discuss a placebo response mitigation strategy he has deployed in over 50 analgesic clinical trials, designed to mitigate both placebo response among subjects and study bias among investigators. He'll provide a detailed overview of the material and share insights from 10 years of refining the program.

Learning Objectives:

1. Understand how and why placebo response and other sources of data variability can cause false negative results in clinical trials.
2. Have access to a series of potential techniques to employ in clinical trials that may reduce bias from study staff and study subjects, and produce more accurate data.

Literature References:

1. Evans K, Colloca L, Pecina M, Katz N. What can be done to control the placebo response in clinical trials? A narrative review. Contemp Clin Trials. 2021; 107:106503. doi: 10.1016/j.cct.2021.106503
2. Vachon-Presseau E, Berger SE, Abdullah TB, et al. Brain and psychological determinants of placebo pill response in chronic pain patients. Nat Commun. 2018;9(1):3397. Published 2018 Sep 12. doi:10.1038/s41467-018-05859-1

LEVERAGING MACHINE LEARNING TO PREDICT INDIVIDUAL PATIENTS' PLACEBO RESPONSE

Dominique Demolle, Services provider

Individual Abstract: The placebo response has posed a significant challenge to demonstrating efficacy of novel therapies for decades despite the best efforts of the industry. Numerous approaches exist, often complementary to each other. In this talk, we will explore how machine learning can be used to mitigate this challenge and how this approach can be implemented to de-risk drug development. The technology (Placebell®) use AI/ML-powered algorithm that calculates a placebo responsiveness score based on a sophisticated assessment of patient psychology, expectations, and other factors. The volume and complexity of these data require AI/ML-based approaches to distill the information into a single score on a continuous scale. This score can then be defined as a baseline prognostic covariate in statistical analyses to mathematically remove the of the impact of placebo response and help statisticians better determine treatment efficacy. Real cases examples will be presented in different indications to illustrate the impact on the precision of the estimated treatment effect.

Learning Objectives:

1. Understand how and why artificial intelligence/ machine learning techniques can be applied to mitigate placebo response in clinical trials.
2. Understand how study subjects' response to placebo can potentially be predicted with testing and AI/ ML techniques.

Literature References:

1. Branders S, Pereira A, Bernard G, Ernst M, Dananberg J, Albert A. Leveraging historical data to optimize the number of covariates and their explained variance in the analysis of randomized clinical trials. Stat Methods Med Res. 2022;31(2):240-252. doi:10.1177/09622802211065246

2. Smith EA, Horan WP, Demolle D, et al. Using Artificial Intelligence-based Methods to Address the Placebo Response in Clinical Trials. Innov Clin Neurosci. 19(1-3):60-70.

EXPLORING THE ROOTS OF PLACEBO RESPONSE IN CNS TRIALS

Steven Targum, Signant Health

Individual Abstract: The placebo controls used in double-blind randomized clinical trials (RCT's) play a critical role in facilitating an estimate of the true drug effect. Although it has been suggested that placebo effects are merely additive to anti-depressive effects in RCTs of major depressive disorder, a higher than anticipated placebo response can compel a study to failure. The response of study participants to placebo is influenced by conditioning, expectations, and several non-specific factors that include the actual consenting process to participate in the study. Some study participants are more susceptible to these influences any may experience an early clinical improvement regardless of the blinded treatment assignment. Early placebo response in RCT's may obscure signal detection at the end of the study. This presentation will review the roots of early placebo response, the effect of early response on study outcome in depression studies and explore some study designs that attempt to manage higher than anticipated placebo response.

Learning Objectives:

1. To identify some of the factors that contribute to placebo response in CNS trials.
2. To explore some of the study designs that have been employed to mitigate higher than anitcipated placebo response.

Literature References:

1. Targum SD, Cameron BR, Ferreira L, MacDonald ID. Early score fluctuation and placebo response in a study of major depressive disorder. J Psychiatric Res. 121: 118-125, 2020.
2. Weimer K, Enck P, Dodd S, Colloca L. Editorial: Placebo and nocebo effects in psychiatry and beyond. Frontiers in Psychiatry. Published 07 Aug 2020. doi: 10.3389/psyt.2020.00801

ACCOUNTABILITY AT RESEARCH SITES: STRATEGIES FOR MINIMIZING PLACEBO AND NOCEBO RESPONSES

Elan Cohen, Hassman Research Institute

Individual Abstract: Given the perpetual and alarmingly high placebo and nocebo responses within various psychiatric and physiological (general medicine) indications (Jones et al., 2021; Khan et al., 2018a, 20018b; Rief et al., 2009; Rutherford et al., 2014), the crucialness for developing interventions to reduce these phenomena cannot be understated. While various methodological approaches have been implemented or recommended to manage these responses (e.g., centralized ratings and data surveillance before subjects are randomized), the purpose of this presentation is to review pertinent strategies that have been implemented, either based on empirical or anecdotal findings, targeted to mitigate placebo and nocebo response particularly at the research site level. This talk will mostly present on the Placebo-Control Reminder Script (PCRS), which a thorough review of the literature has shown to be the only subject-targeted intervention scientifically substantiated to reduce these phenomena (Cohen et

al., 2020) and demonstrate face and content validity (Cohen et al., 2022). As will be detailed during the presentation, the PCRS is a paragraph read by a site staff member (typically the rater) immediately before administering the primary efficacy scale at each study visit and which thoroughly reviews placebo response factors established in the industry, including expectation bias from both the site and participant (Evans et al., 2021; Haflioadottir et al., 2021) as well as participants' poor understanding of the placebo, misconceptions of expected site staff interactions, and uncertainty of their role. The PCRS has been licensed since 2017 in over 24 clinical trials and this presentation will review how the PCRS is seamlessly weaved into study procedures. Other recommended site-participant interaction placebo mitigation approaches will be reviewed, including but not limited to monitoring enthusiasm of the investigational product, engaging in a research alliance versus clinical rapport, 360-degree rater feedback, and the importance of training all staff members on these practices.

Learning Objectives:

1. To articulate how an empirically grounded participant and site mitigation strategy to reduce the placebo and nocebo response in clinical trials, the Placebo-Control Reminder Script (PCRS), can seamlessly implemented into study procedures across psychiatric indications.
2. To understand how several theories related to the causes of placebo and nocebo response factors can be practically implemented into study procedures to manage these phenomena at the crucial research site level.

Literature References:

1. Cohen, E. A., Hassman, H. H., Ereshefsky, L., Walling, D. P., Grindell, V. M., Keefe, R. S. E., Wyka., K., and Horan, W. P. (2020). Placebo response mitigation with a participant-focused psychoeducational procedure: A randomized, single-blind, all placebo study in major depressive and psychotic disorders. Neuropsychopharmacology, 46, 844-850.
2. Hafliðadóttir, S. H., Juhl, C. B., Nielsen, S. M., Henriksen, M., Harris, I. A., Bliddal, H., and Christensen, R. (2021). Placebo response and effect in randomized clinical trials: Meta-research with focus on contextual effects. Trials, 22 (1), 493. https://doi.org/10.1186/s13063-021-05454-8

+FORGING A PATH TO BETTER CLINICAL TRIALS: A DISCUSSION ON ENABLING THE IMPLEMENTATION OF RWE, AIML, AND COLLABORATION TO BETTER CAPTURE PATIENT EXPERIENCE AND IMPROVE SUCCESS IN DRUG DEVELOPMENT

Anthony Cannon, AbbVie, Inc.

Overall Abstract Innovation is required to address the entrenched problems facing CNS drug Development. The prevalence and economic burden of mental illness has continually risen despite record prescriptions of psychotropic medications. The yawning burden of mental illness is compounded by static treatment effects for novel therapies along with an ever-growing placebo response rate, driving a low success-rate in bringing new treatments to patients. The low success rate in delivering new treatments has been continually cited in the need to improve the ways in which efficacy is detected, but a lack of accepted new endpoints and novel methods of study by regulatory authorities has disincentivized innovation. The FDA has recently provided new guidance on the utilization and submission of real-world evidence (RWE), and has also begun a new program to foster the advancement and adoption of RWE. While the Agency's guidance shows an openness to innovation in trial design and efficacy

detection, industry and academia must now develop and adopt the approaches that have long been sought.

Therefore, this panel aims to further characterize a path to widespread adoption and regulatory acceptance of four innovative approaches that can be implemented now. (1) Broadening evidence: new sources of evidence can reveal previously unappreciated value, like using RWE in regulatory decision making or developing new methodologies that define clinically meaningful improvement in psychiatric illness that is simultaneously objective and relevant to patients. (2) Accelerating analysis: Artificial Intelligence/Machine Learning (AIML) can streamline late phase trials and increase precision of treatments, but succinctly incorporating the heterogeneity of patient experiences remains a challenge. (3) Executing inquiry: implementation and adoption of AI/ML, RWE and other innovations can enhance the cohesion of findings in trials, but productive execution requires a definition of how each innovation enhances the richness of the data and deepens the elucidation of the research question. Finally, (4) Fostering collaboration: pre-competitive consortia have been successfully utilized in diverse areas of drug development within and outside of CNS to further innovation, scientific inquiry, and speed treatments to markets; but these require vast amounts of data or intensive cooperation which raises concerns about data confidentiality and intellectual property, constraining collaboration. Therefore, the thoughtful synthesis of these aspects by this panel will help define and inspire the actions required to implement these four innovative approaches, thereby speeding the delivery of new treatments to the patients who need them.

Learning Objectives:

1. The learner will understand the role of four key innovations in improving both the detection of efficacy and relevance of clinical trial results now.
2. The learner will understand how a thoughtful implementation of innovation needs collaboration to gain adoption.

PRE-COMPETITIVE CONSORTIA ACCELERATING THERAPEUTIC INNOVATION

Ramona Walls, Critical Path Institute

Individual Abstract: Pre-competitive efforts have been successfully leveraged and implemented across various neurology therapeutic areas to advance innovation, scientific understanding, and accelerate therapeutic innovation for millions of people living with neurodegenerative diseases and neuropsychiatric disorders. Such cooperation and collaboration between organizations is necessary because the rigorous application of innovative approaches requires a vast amount of data. This part of the panel will describe the ways in which pre-competitive initiatives and consortia can ease the process of collaboration and address concerns about data confidentiality and intellectual property while ensuring that every single data point is maximized for advancing innovation.

Learning Objectives:

1. Precompetitive collaboration and accelerating therapeutic innovation.

Literature References:

1. Tabrizi et al., A biological classification of Huntington's disease: the Integrated Staging System Lancet Neurology, 2022 Jul;21(7):632-644. doi: 10.1016/S1474-4422(22)00120-X.

2. Karpen et al., Effective Data Sharing as a Conduit for Advancing Medical Product Development Ther Innov Regul Sci. 2021 May;55(3):591-600. doi: 10.1007/s43441-020-00255-8. Epub 2021 Jan 4.

PRE-COMPETITIVE CONSORTIA ENABLING ACCELERATED THERAPEUTIC INNOVATION

Seth C. Hopkins, Sunovion Pharmaceuticals, Inc.

Individual Abstract: Pre-competitive efforts have been successfully leveraged and implemented across various neurology therapeutic areas to advance innovation, scientific understanding, and accelerate therapeutic innovation for millions of people living with neurodegenerative diseases and neuropsychiatric disorders. Such cooperation and collaboration between organizations is necessary because the rigorous application of innovative approaches requires a vast amount of data. This part of the panel will describe the ways in which pre-competitive initiatives and consortia can ease the process of collaboration and address concerns about data confidentiality and intellectual property while ensuring that every single data point is maximized for advancing innovation.

Learning Objectives:

1. Precompetitive collaboration and accelerating therapeutic innovation.

Literature References:

1. Tabrizi et al., A biological classification of Huntington's disease: the Integrated Staging System Lancet Neurology, 2022 Jul;21(7):632-644. doi: 10.1016/S1474-4422(22)00120-X.
2. Karpen et al., Effective Data Sharing as a Conduit for Advancing Medical Product Development Ther Innov Regul Sci. 2021 May;55(3):591-600. doi: 10.1007/s43441-020-00255-8. Epub 2021 Jan 4.

CLINICAL TRIAL INNOVATION ENABLES A RICHER UNDERSTANDING OF THE PATIENT EXPERIENCE

Erin Gallagher, This Is My Brave, Inc.

Individual Abstract: Erin Gallagher – executive director of This is My Brave – will speak to leading a national nonprofit dedicated to mental health storytelling where ordinary people share their extraordinary stories of overcoming mental illness and/or substance use disorder through song, spoken word, essay and even comedy and dance. The mission of This is My Brave is to end the stigma associated with mental illness by creating a space where individuals can be heard and understood. Erin can share powerful testimonies the group has heard on stage and share verbatims of the This is My Brave community about what recovery can look like on an individual level that she has been able to gather through qualitative research and the interviewing of individuals with lived mental health experience.

Learning Objectives:

1. The learner will understand that each patient's experience is unique and that innovation is required for a richer characterization of patient experience.

Literature References:

1. Kosyluk,K, Marshall, J, et al. Examining the Impact of This Is My Brave on Mental Illness Stigma and Willingness to Seek Help: A Pilot Study. Community Mental Health Journal 2018; 54 (276-281)

2. Kosyluk, K, Marshall, J, et al. Challenging the Stigma of Mental Illness through Creative Storytelling: a Randomized Controlled Trial of This Is My Brave. Community Mental Health Journal. 2021; 57(147-152)

AI/ML AS A MECHANISM TO STREAMLINE TRIALS

Li Wang, AbbVie

Individual Abstract: Artificial Intelligence/Machine Learning (AIML) can streamline late phase trials and increase precision of treatments, but succinctly incorporating the heterogeneity of patient experiences remains a challenge. Better treatments that address the complexity of mental illness requires an understanding of the genetic, molecular, and neural network changes as well as the specific anatomic localization of pathologies caused by neuropsychiatric illnesses. The proliferation of new methodologies aiming to capture these essential anatomic and biochemical changes, has revealed that traditional efficacy endpoints do not adequately capture the necessary characteristics of drug response, or the range of experiences faced by those living with and recovering from mental illnesses. While modalities such as PET, fMRI, EEG, and parameters in ecological momentary analysis promise to elucidate a clearer picture of treatment response and patient improvement, the immense amount of data produced by these modalities must be extracted and analyzed in an accurate way. Applying AI/ML to psychiatric illnesses, leveraging its capabilities in rendering concise, usable conclusions from vast pools of data, has garnered promise in not only filling the knowledge gaps in understanding the mechanisms that produce mental illnesses, but could also enable a more complete characterization of the lives of patients by expanding data collection beyond study visits. This portion of the panel will discuss how AI/ML has been used successfully in other therapeutic contexts, and how those lessons can be applied to psychiatry, enabling not only the acquisition of data, but also a more nuanced understanding of patient experiences that could spur innovations in patient care that improve adherence and engagement in treatment as well as quality of life.

Learning Objectives:

1. AI/ML, potential use cases in psychiatry

Literature References:

1. Cearns, M., Hahn, T. and Baune, B.T. Recommendations and future directions for supervised machine learning in psychiatry. Transl Psychiatry 9, 271 (2019)
2. Koppe, G., Meyer-Lindenberg, A. and Durstewitz, D. Deep learning for small and big data in psychiatry. Neuropsychopharmacol. 46, 176–190 (2021)

INNOVATION IN CLINICAL TRIAL CONDUCT AND OPERATIONS

Erica Lawson, Otsuka (OPDC)

Individual Abstract: The operational conduct of clinical trials is an important opportunity for innovation. Decentralized trials, novel endpoint collection, and non-traditional clinical trial sites offer greater access to patients and faster data acquisition. Such innovations can likewise increase the diversity of our trial participants ensuring greater applicability of our products in the real world and more meaningful treatments to the patient.

Learning Objectives:

1. The learner will understand the role of four key innovations in improving both the detection of efficacy and relevance of clinical trial results now.

2. The learner will understand how a thoughtful implementation of innovation needs collaboration to gain adoption.

Literature References:

1. Meurer WJ, Lewis RJ, Tagle D, et al. An overview of the adaptive designs accelerating promising trials into treatments (ADAPT-IT) project. Ann Emerg Med. 2012;60(4):451-457. doi:10.1016/j.annemergmed.2012.01.020
2. Swift B, Jain L, White C, et al. Innovation at the Intersection of Clinical Trials and Real-World Data Science to Advance Patient Care. Clin Transl Sci. 2018;11(5):450-460. doi:10.1111/cts.12559

FORGING A PATH TO BETTER CLINICAL TRIALS: A DISCUSSION ON ENABLING THE IMPLEMENTATION OF RWE, AIML, AND COLLABORATION TO BETTER CAPTURE PATIENT EXPERIENCE AND IMPROVE SUCCESS IN DRUG DEVELOPMENT

Yanjun Bao, AbbVie Inc.

Individual Abstract: New sources of evidence, like RWE, can reveal previously unappreciated value. This portion of the workshop aims to characterize how RWE can be used to aid regulatory decision making as well as in developing new methodologies that enable a deeper understanding of clinically meaningful improvement that is more relevant to patients, and more objective than traditional clinician-reported outcome measures that are currently used to establish efficacy and safety of novel treatments.

Learning Objectives:

1. The learner will understand the role of RWE in enabling a better understanding of patient recovery, treatment efficacy, and regulatory decision making.
2. The learner will understand how a thoughtful implementation of innovation needs collaboration to gain adoption.

Literature References:

1. Mofsen AM, Rodebaugh TL, Nicol GE, Depp CA, Miller JP, Lenze EJ. When All Else Fails, Listen to the Patient: A Viewpoint on the Use of Ecological Momentary Assessment inClinical Trials. JMIR Ment Health. 2019;6(5):e11845. Published 2019 Apr 21. doi:10.2196/11845.
2. The Federal Register. Advancing Real-World Evidence Program, A Notice by the Food and Drug Administration. 20-October 2022. https://www.federalregister.gov/d/2022-22795.

*PSILOCYBIN: OPPORTUNITIES ACROSS THE DIAGNOSTIC SPECTRUM

Scott Aaronson, Sheppard Pratt

Overall Abstract Psychedelic therapy has shown promise as a potential intervention across a wide spectrum of psychiatric conditions for which there are few successful interventions. The symposium brings together some of the leading investigators looking into novel uses for psychedelic therapy. The topics covered include an Introduction: duction into the thinking behind the mechanisms of action of psychedelic therapy and why this treatment may have efficacy across a wide span of differing disease targets. This will be followed by presentations

looking at the early evidence for psychedelics having efficacy in obsessive compulsive disorder, treatment resistant depression, and bipolar type II depression.

Learning Objectives:

1. Attendees will be able to describe the current hypothesis about how psychedelics affect the brain.
2. Attendees will be able to identify two illness targets for psychedelics suggested by the proposed mechanism for action.

CONSIDERING THE RANGE OF PSILOCYBIN'S MECHANISMS OF ACTION; POSSIBLE EXPLANATIONS FOR PUTATIVE TRANSDIAGNOSTIC EFFICACY

Gerard Sanacora, Yale

Individual Abstract: This opening presentation will serve as an overview psilocybin's proposed mechanisms of action and how the various mechanisms could be related to transdiagnostic clinical benefits. Examples will be drawn from the literature suggesting how several factors could help account for the purported efficacy of psilocybin treatment across several diagnostic areas. Concepts of diagnostic overlap, cross diagnostic domain and network effects, broad ranging physiological adaptations, and non-specific extra-pharmacological therapeutic effects will all be considered in reference to the psilocybin's apparent clinical efficacy in several neuropsychiatric disorders. The presentation is intended to stimulate discussion and to lay the groundwork for the ensuing presentations.

Learning Objectives:

1. To familiarize attendees with the various hypothesized mechanisms of action associated with psychedelic drugs' purported clinical benefits in the treatment of neuropsychiatric disorders.
2. To develop a conceptual framework to help understand and evaluate the emerging evidence suggesting transdiagnostic clinical benefits associated with psychedelic type medications.

Literature References:

1. Daws RE, Timmermann C, Giribaldi B, et al. Increased global integration in the brain after psilocybin therapy for depression. R.Nat Med. 2022 Apr;28(4):844-851
2. Dupuis D, Veissière S. Culture, context, and ethics in the therapeutic use of hallucinogens: Psychedelics as active super-placebos? Transcult Psychiatry. 2022 Oct 19:13634615221131465.

PSILOCYBIN IN THE TREATMENT OF OCD: EARLY EXPERIENCE

Christopher Pittenger, Yale Medical School

Individual Abstract: Obsessive-compulsive disorder (OCD) affects about one person in 40, over the course of their lifetime. Available treatments are of benefit to about 2 patients in 3, leaving many without meaningful symptom relief even when evidence-based interventions are optimally delivered. Certain antidepressant treatments are of benefit in OCD - specifically, pharmacotherapy with SSRIs or clomipramine - but others are not. The evidence for benefit from ketamine, the paradigmatic rapidly acting antidepressant, is equivocal.

Published case reports and anecdotal evidence suggests that psilocybin can be of benefit to some individuals with OCD, but controlled data are lacking. We are conducting the first

blinded placebo-controlled trial of single-dose psilocybin treatment in OCD (NCT03356483). Adult participants with a primary diagnosis of OCD, without psychosis, autism, or active substance use and without any current psychiatric pharmacotherapy, are randomized to receive a single dose of 0.25 mg/kg psilocybin vs 250 mg niacin. Dosing follows procedures established in earlier studies in other conditions, with psychological support provided by two facilitators in a non-medical room with music and eyeshades. No manualized or OCD-targeting therapy is provided. The primary outcome is improvement in the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) at 48 hours. Blind is broken at 1 week, and subjects randomized to receive niacin are offered open-label psilocybin. Subjects who receive psilocybin, either during the blinded phase or the subsequent open-label phase, are followed for 12 weeks. Secondary measures include ratings safety and tolerability data and measures of depression and anxiety symptoms. Resting-state fMRI scans are performed 24 hrs before and 48 hrs after dosing and pay provide insight into mechanism.

We will share data from an interim analysis of participants who completed the study before it was paused due to the COVID pandemic. Early results are promising, though very preliminary. Participant experiences, which are being analyzed through qualitative analysis of structured interviews, may provide insight into psychological correlates of symptom change. Data collection is ongoing.

Learning Objectives:

1. Participants will identify which antidepressant medications have been shown to be effective in the treatment of obsessive-compulsive disorder (OCD).
2. Participants will understand the early anecdotal evidence that psilocybin treatment can be of benefit in some individuals with OCD

Literature References:

1. Kelmendi B, Kaye A, Pittenger, C, and Kwan AC. Psychedelics. Curr. Biol. 32(2):R63-R67.
2. Kelmendi B, Kichuk SA, DePalmer G, Maloney G, Ching THW, Belser A, and Pittenger C. Single-dose psilocybin for treatment-resistant obsessive-compulsive disorder: A case report. Heliyon, accepted pending minor revision.

GATHERING MOMENTUM: PSILOCYBIN THERAPY FOR TREATMENT RESISTANT DEPRESSION

James Rucker, King's College London, Institute of Psychiatry

Individual Abstract: Psilocybin Therapy for Treatment Resistant Depression was first given to a participant in a clinical trial at Imperial College London, United Kingdom, in 2015. Eight years later we have seen the publication of a positive multicentre RCT in the New England Journal Medicine and, now, the start of phase 3 licensing trials. In this lecture I will cover the evidence surrounding of psilocybin therapy for treatment resistant depression, discussing the hope, the hype and the pitfalls along the road to a licensing decision.

Learning Objectives:

1. Understand how psilocybin therapy may be a treatment for resistant depression.
2. Know the evidence from a recent large muticentre RCT of psilocybin therapy for treatment resistant depression.

Literature References:

1. Carhart-Harris, R. L., et al. (2016). "Psilocybin with psychological support for treatment-resistant depression: an open-label feasibility study." Lancet Psychiatry 3(7): 619-627.
2. Goodwin, G. M., et al. (2022). "Single-Dose Psilocybin for a Treatment-Resistant Episode of Major Depression." N. Engl. J. Med. 387(18): 1637–1648.

SYNTHETIC PSILOCYBIN IN BIPOLAR TYPE II DEPRESSION: AN OPEN LABEL TRIAL

Scott Aaronson, Sheppard Pratt

Individual Abstract: Treatment options are limited for patients with bipolar depression. With accelerating interest in the use of psychedelics in difficult to treat mood disorders and early evidence of efficacy along with safety, the question is raised as to whether some patients with cyclical mood disorders may also benefit.

Methods: Fourteen adults with bipolar type II depression who had failed at least two medications in the current episode, without rapid cycling by history, and no history of mania or psychoses were recruited to be dosed with a single 25 mg dose of a proprietary synthetic psilocybin (COMP360) after withdrawal from psychotropic medication for two weeks prior to dosing. All subjects had three preparatory sessions prior to dosing and three integration session post dosing. Subjects were followed for 12 weeks post dose. The primary outcome measure was the MADRS at three weeks post dose. Response was defined as a MADRS score reduction of >50% since baseline and remission as a score of <10. Trial registration-NCT04433845.

Results: There were no unexpected adverse events. No subjects developed hypomania or mood instability. At one week after dosing 11 of 14 (78.6%) met remission criteria and 12 of 14 (85.7%) met response criteria. At three weeks, 11 of 14 (78.6%) met both remission and response criteria. At 12 weeks 12 of 14 (85.7%)met both remission and response criteria. The Cohen's d effect size was 2.59 at Week 3 and 4.81 at Week 12.

Conclusions: In this small, open-label pilot study, most subjects reported significant improvement in chronic depressive symptoms with durability lasting for the three months they were followed post dosing.

Learning Objectives:

1. Attendees will be able to identify the major risk factor in studying the effect of psilocybin in a cyclical mood disorder.
2. Attendees will be able to describe the target symptoms within mood disorders most likely to respond to psilocybin therapy.

Literature References:

1. Bosch OG, Halm S, Seifritz E. Psychedelics in the treatment of unipolar and bipolar depression. Int J Bipolar Disord. 2022 Jul 5;10(1):18. doi: 10.1186/s40345-022-00265-5. PMID: 35788817; PMCID: PMC9256889.
2. Barber GS, Aaronson ST. The Emerging Field of Psychedelic Psychotherapy. Curr Psychiatry Rep. 2022 Oct;24(10):583-590. doi: 10.1007/s11920-022-01363-y. Epub 2022 Sep 21. PMID: 36129571; PMCID: PMC9553847.

+THE ACADEMIC CLINICAL TRIALIST: SAVING AN ENDANGERED SPECIES

Joseph Goldberg, Icahn School of Medicine at Mount Sinai

Overall Abstract In 2013, NIMH reoriented its focus on clinical trial funding and scientific interests from the pursuit of novel agents or new therapeutic applications toward translational target signal detection – making clinical trials subservient as the means toward an end, rather than the end in itself. This fundamental course change diverged from an earlier heritage that descended from the NIMH-led Early Clinical Drug Evaluation Unit (ECDEU) (later renamed the New Clinical Drug Evaluation Unit (NCDEU) – the precursor umbrella meeting to ASCP), which first and foremost cultivated the science of clinical trial methodology and implementation. Until then, countless federally-funded academic clinical psychopharmacologists organized their careers and scientific endeavors around the pursuit of new therapeutic agents to improve patient outcomes and facilitate their implementation for patient care. Since then, clinician-scientists whose interests coalesce mainly around designing and implementing innovative clinical trials to optimize patient care have had to negotiate a cultural shift. Increasingly, early career clinical investigators have had to consider moving from academia to industry, pursuing privatized models of clinical trial networks, or redesigning their career trajectories to incorporate translational models as a primary, rather than secondary scientific pursuit. Little focus has been paid on the career development, training, and professional identity of early career clinical investigators whose primary goal is to devise and implement intervention studies. Notably, a dearth of early-career, well-trained clinical trialists threatens to imperil testing of novel interventions, particularly as the field seeks to answer salient questions about treatment related outcomes. Pertinent training involves developing a skillset and expertise in formulating and testing clinically-relevant hypotheses, recognizing patient-centered phenotypes and viable intervention targets, addressing the potential value of orphan drugs and nonproprietary compounds, appreciating clinically unmet needs, managing ill patients in the context of a clinical trial and understanding appropriate biostatistical approaches and study design methodologies, alongside the pursuit of extramural funding.
This workshop will present several perspectives on the challenge of preserving the identity and academic professional viability of clinician trialists, with the goal of addressing current clinical trialist pipeline problems. Presenters will share their own experiences in tracing career trajectories within academia, forming relationships with industry, forging a career path that merges translational models with innovative drug therapies, pursing clinical trials through privatization, and providing mentorship around career development for career clinical trialists, alongside strategies to pursue funding. We will have an interactive focus with audience members aimed to answer two core questions: 1) How do we promote and support academic clinical trialist careers in the current post-NCDEU environment? and 2) Should the future of innovative, nontranslational trials rightfully belong more to the realm of academia or industry?

Learning Objectives:

1. To inform participants about the urgent need to assure training and career development of academic clinical trialists as fundamental to the future of novel drug development and patient care.
2. To identify strategies to enhance and foster the training, development and extramural funding of the next generation of academic clinical trialists in psychopharmacology and related interventions.

WHAT ARE CLINICAL TRIALISTS AND WHY DO WE NEED THEM?

Joseph Goldberg, Icahn School of Medicine at Mount Sinai

Individual Abstract: This presentation will provide a brief overview that defines the unique professional identity of an academic clinical trialist and the skillsets they must possess to undertake valid and meaningful treatment intervention studies. Psychopharmacologists who undertake interventional trials assume a unique clinician-scientist role. As practitioners, they must be facile in assessing and managing the disorders they study; this includes gauging illness severity, suicide risk, impulsivity, capacity for consent, diagnostic accuracy, anticipating common comorbidities, and recognizing the pharmacokinetics and pharmacodynamics of co-therapies for safe drug washouts or cross-tapers. As investigators, they must appreciate the clinical and scientific relevance of interventions they undertake; they bear ultimate responsibility for appropriate subject recruitment, study procedures and recognition of adverse events; and at varying levels they are involved in the design and implementation of studies that reflect well-crafted aims and hypotheses. As administrators, trialists often oversee multiple competing studies and directly interface with subjects, referral sources, clinical research staff, study sponsors, clinical research organizations, and institutional review boards. Proper training includes gaining a strong working knowledge of how to design and execute relevant and feasible intervention studies and how to interpret and articulate key findings. Without funding for, and experience with, clinical trials, the field faces a dearth of junior colleagues who will be adequately prepared to assume these duties. And, without properly trained and mentored academic clinical trialists, the field will be ill-prepared to develop and test next-generation patient-oriented psychiatric interventions.

Learning Objectives:

1. To inform participants about the training, skillset and professional identity of academic clinical trialists
2. To alert participants to the deprioritization of academic training in the conduct of clinical trials, and the risk for a shrinking pool of well-trained clinical investigators to conduct treatment intervention studies in psychiatry.

Literature References:

1. March JS, Silva SG, Compton S, et al. The case for practical clinical trials in psychiatry. Am J Psychiatry 2005; 162: 836-846
2. Smyth RMD, Jacoby A, Altman DG, et al. The natural history of conducting and reporting clinical trials: interviews with trialists. Trials 2015; 16: 16

HOW WE GOT HERE: EVOLUTION OF CLINICAL TRIALISTS IN ACADEMIA

Holly Swartz, University of Pittsburgh School of Medicine

Individual Abstract: From its founding in 1949, NIMH established itself as an international leader in psychiatric clinical research funding. With an explicit mission to alleviate suffering in those with mental illness, NIMH invested in many informative clinical trials. Aligning with this mission, NIMH established psychopharmacology research programs to develop and test new medications showing promise to reduce symptoms in individuals with hitherto untreatable psychiatric disorders. Investigators participating in these so-called “Early Clinical Drug Evaluation Units (ECDEU)” were housed in academic medical centers across the US and met annually to discuss new data and methods. These pioneers developed and refined contemporary clinical trials methodologies. The ECDEU annual meeting, subsequently known as New Clinical Drug Evaluation Unit (NCDEU) meeting, brought together academic investigators, industry scientists, and regulators from FDA and EMA to advance the evolving science of clinical trials. In their heyday, NCDEU meetings attracted over 1000 attendees, reflecting the large number of clinical trialists supported by NIMH to conduct this type of research. In 2002,

Thomas Insel, M.D., was appointed Director of NIMH, and everything changed. Over a relatively short time, Insel engineered a shift in the Institute's priorities from clinical research, including clinical trials, to basic science. Approximately 90% of its budget was re-allocated to neuroscience, and funding for clinical trials was relegated to narrowly defined studies that focus on "target engagement" rather than clinical outcomes. In 2011, NIMH asked the American Society of Clinical Psychopharmacology to take responsibility for the NCDEU annual meeting, signaling its waning interest in clinical trials. No other NIH institute has abandoned funding for clinical trials as they remain the gold standard for evaluating treatments. Although neuroscience is important, Insel's single-minded emphasis on neuroscience effectively eliminated treatment research that directly informs patient care. Allen Frances, M.D., professor emeritus of psychiatry at Duke, said in the New York Times (February 22, 2022) that the shift from clinical trials to neuroscience has been "an exciting intellectual adventure, one of the more fascinating pieces of science in our lifetimes, but it hasn't helped a single patient." As the field reckons with failures of NIMH's "Decade of the Brain" agenda to deliver actionable discoveries that concretely advance the practice of psychiatry, it also grapples with the fact that, in the absence of NIMH funding for clinical trials, academia has failed to train a new generation of clinical trialists who are adequately prepared to evaluate new compounds and interventions in real patients. Downstream effects will likely include an academic research community that, in the not too distant future, will be ill-equipped to move neuroscience discoveries from bench to bedside.

Learning Objectives:

1. To recognize the historical factors that contribute to impending shortage of academically trained clinical trialists.
2. To identify reversible and non-reversible factors that place the field at risk for a dearth of clinical trialists.

Literature References:

1. Kane JM, Hill LD, Kinon BJ et al. New Clinical Drug Evaluation Unit (NCDEU) Annual Meeting: A great opportunity for Early Career Psychiatrists. J Clin Psychiatry 2012;73(4):504-505; https://doi.org/ (10.4088/JCP.12com07750)
2. Markowitz JC, Milrod BL. Lost in translation: the value of clinical trials. J Clin Psychiatry 2022;83(6):22com14647

OUTCOMES IN PSYCHIATRIC CLINICAL TRIALS: SYMPTOMS OR TARGETS?

James Murrough, Icahn School of Medicine at Mount Sinai

Individual Abstract: Therapeutic discovery efforts in psychiatry are of critical importance in biomedical research. Yet clinical trials in psychiatry are well-known for their complexity, controversy, and high failure rate. Complicating the problem, there appears to be a drying up of the pipeline of clinical scientists who will be well-suited to lead the psychiatric clinical trials of the future. This presentation will consider the modern state of affairs regarding psychiatric clinical trials, with an emphasis on those conducted within academia. The presentation will take stock of the shift in emphasis by NIMH from funding clinical trials with traditional symptom-based endpoints to trials with mechanistic target endpoints, such as brain receptors and circuits. The promises and challenges arising from this "target engagement" approach to psychiatric clinical trials will be considered, both from the prospective of progress in the field as well as for the career development of would-be clinical trialists in psychiatry. Specific initiatives from the NIMH that have shaped the current clinical trials research environment will be discussed, including the research domain criteria (RDoC) and FAST-FAIL initiatives. The

discussion will be facilitated by considering specific highlights and lowlights from recently completed NIMH-funded experimental medicine studies, including the NIMH FAST Mood and Anxiety Disorders Program (FAST-MAS) and the Developing Neuronal KCNQ Channel Modulators for Mood Disorders NIMH R61/R33 project. Both research projects took an 'RDoC approach' to clinical trials by selecting anhedonia as the primary clinical domain of interest and both featured a readout of target engagement by neuro-circuit activation measured with functional MRI as the primary outcome. The methods, results and lessons learned from these programs will be considered in terms of implication for the field and for aspiring clinical trial researchers in psychiatry. The material considered in the presentation is critical to understanding how to optimize drug discovery efforts in the field moving forward.

Learning Objectives:

1. Understand how the approach to clinical trials in psychiatry has changed over the years, including a shift from traditional symptom-based outcomes to so-called 'target engagement' outcomes.
2. Be able to describe both potential advantages and disadvantages to the modern experimental medicine approach to psychiatric clinical trials.

Literature References:

1. Costi S, Morris LS, Kirkwood KA, et al. Impact of the KCNQ2/3 Channel Opener Ezogabine on Reward Circuit Activity and Clinical Symptoms in Depression: Results From a Randomized Controlled Trial. Am J Psychiatry. 178, 437-446 (2021).
2. Krystal, A.D., Pizzagalli, D.A., Smoski, M. et al. A randomized proof-of-mechanism trial applying the 'fast-fail' approach to evaluating κ-opioid antagonism as a treatment for anhedonia. Nat Med 26, 760–768 (2020).

DEVELOPING CLINICAL TRIAL SPECIALISTS IN PSYCHIATRY: THE ROLE OF THE DEPARTMENT OF VETERANS AFFAIRS

Michael Ostacher, Stanford University School of Medicine

Individual Abstract: Since the NIMH has turned its attention to understanding the underlying pathophysiology and circuitry of mental illness, fewer resources have been devoted to the specific development of specialists in clinical trial design, implementation, and interpretation in psychiatry. Because of this, less time is available to developing scientists to develop the skills necessary to learn the epidemiological and statistical underpinnings of clinical trial methodology. The development of these skills is especially important as novel treatments are developed, most notably in the areas of neuruomodulation, where devices must be systematically studied against sham treatments, and in the development of novel pharmacological treatments, where interventions using ketamine and psychedelic drugs need to be studied in a context in which placebo blinding is impractical or difficult. The development of scientists whose focus is on understanding the potential biases and pitfalls of clinical trials design has been become secondary to their development in target discovery.

Research at the Department of Veterans Affairs has a mission that can insure the development of investigators in mental health and that includes improving Veterans' health and well-being via basic, translational, clinical, health services, and rehabilitative research; applying scientific knowledge to develop effective individualized care solutions for Veterans; and attracting, training, and retaining the highest-caliber investigators, and nurture their development as leaders in their fields.

How the mission of the VA contrasts to that of NIMH, and how it's commitment to its Veteran population provides the structure and opportunities for researchers to develop the skills to become clinical trialists outside of the confines of NIMH will be discussed, including how the Mental Illness Research, Education and Clinical Centers (MIRECCs), established by Congress in 1997, achieve the goal of bringing best practices in mental health care into the clinical settings of the VA, and train clinical researchers in mental health to do so. Several structures within the VA, including the Network of Dedicated Enrollment Sites (NODES) model will be discussed. Examples of clinical trials conducted at multiple sites at the VA that have an impact on care will be presented.

Learning Objectives:

1. Describe how clinic trials methodologists are necessary for the development of interventions in psychiatry.
2. Describe the structure and support of clinical trials research at the Department of Veterans Affairs.

Literature References:

1. Oslin DW, Lynch KG, Shih MC, Ingram EP, Wray LO, Chapman SR, Kranzler HR, Gelernter J, Pyne JM, Stone A, DuVall SL, Lehmann LS, Thase ME; PRIME Care Research Group, Aslam M, Batki SL, Bjork JM, Blow FC, Brenner LA, Chen P, Desai S, Dieperink EW, Fears SC, Fuller MA, Goodman CS, Graham DP, Haas GL, Hamner MB, Helstrom AW, Hurley RA, Icardi MS, Jurjus GJ, Kilbourne AM, Kreyenbuhl J, Lache DJ, Lieske SP, Lynch JA, Meyer LJ, Montalvo C, Muralidhar S, Ostacher MJ, Paschall GY, Pfeiffer PN, Prieto S, Przygodzki RM, Ranganathan M, Rodriguez-Suarez MM, Roggenkamp H, Schichman SA, Schneeweis JS, Simonetti JA, Steinhauer SR, Suppes T, Umbert MA, Vassy JL, Voora D, Wiechers IR, Wood AE. Effect of Pharmacogenomic Testing for Drug-Gene Interactions on Medication Selection and Remission of Symptoms in Major Depressive Disorder: The PRIME Care Randomized Clinical Trial. JAMA. 2022 Jul 12;328(2):151-161. doi: 10.1001/jama.2022.9805. PMID: 35819423; PMCID: PMC9277497.
2. Condon DL, Beck D, Kenworthy-Heinige T, Bratcher K, O'Leary M, Asghar A, et al. A cross-cutting approach to enhancing clinical trial site success: The Department of Veterans Affairs' Network of Dedicated Enrollment Sites (NODES) model. Contemp Clin Trials Commun [Internet]. 2017;6:78–84.

A FUNNY THING HAPPENED ON THE WAY TO BECOMING AN ACADEMIC RESEARCHER: I STARTED A PRIVATE CLINICAL TRIALS SITE

Andrew Cutler, SUNY Upstate Medical University

Individual Abstract: I always wanted to be an academic: a professor, a teacher and a clinical researcher, but my career took an unexpected turn away from academia towards private, industry-sponsored clinical trials. How did this happen, how did it affect my research career, and would I recommend this path? In this presentation I will review my education and training in clinical research, my foray into academia, and why and how I started a private dedicated research site at a very opportune time in the mid-1990s. My goal was to use my research training to do academic quality research while using best business practices. I will review the forces that drove industry towards private sites and the resulting effects on the results of CNS trials over the past 25 years. Is there still room for academic clinical research, or is this now the domain of private sites? Can an investigator have a career in clinical research at a university, or is academic research now limited to preclinical and translational research?

Learning Objectives:

1. Elucidate the reasons for doing research privately vs in academia.
2. Recognize how to do research privately and how it has changed and evolved over 25 years.

Literature References:

1. Beninger P, et al. Bridging the Academia/Industry Chasm: Proposed Solutions. Journal of Clinical Pharmacology. 2016;56(12):1457–1460
2. Getz K. Trends driving clinical trials into large clinical care settings. Nature Reviews Drug Discovery. 2018;17:703–704.

HOW CAN ACADEMIC PROGRAMS MENTOR AND FOSTER THE CAREERS OF CLINICAL TRIALISTS?

Anita H. Clayton, University of Virginia

Individual Abstract: Academic support is critical in the development of career clinical trialists. A structured clinical mentoring program might involve connecting junior faculty with mentors matching their clinical interests, and provide on-boarding and promotion mentorship. A systematized research mentoring program matches junior faculty with research mentors, assists in defining clinical and research focus(es) and integration of research into clinical settings, provides training as a sub-investigator on clinical trials at the academic site, provides opportunities to conduct research such as departmental-provided initial funding on an independent project (assistance with the competitive process), assists in identifying and preparing Investigator-Initiated protocols to industry and other diverse funding sources. Also, departments can utilize Early Career Faculty Mentoring Programs through the School of Medicine.

Academic psychiatric clinical trialists, and psychopharmacology organizations e.g. ASCP also need to work to address systemic impediments to trialist career development and the success of academic clinical psychopharmacologists. Several factors contribute significantly to the problem. NIMH must be pressed to re-establish funding lines/RFPs and prioritize testing of novel interventions, treatment-related predictors and outcomes, and academic trialist careers. Federal funding is no longer focused on direct improvement in clinical care, so has forced this role on industry which may conflict with the development of their drug in design of clinical trials and Investigator-Initiated RFPs. The pharmaceutical industry has ceded running clinical trials and some study design to Clinical Research Organizations which have focused on quick completion of studies over the quality of subjects e.g. funding based on competitive enrollment rather than excellence in enrollment, limitations on the number of academic sites in multicenter trials, requiring repetition of time-wasting and generally unsuccessful “training” and “approval” as a rater on the same commonly used scales for every study (instead need to address interview quality and rater bias), and objecting to increasing F and A rates in academic medical centers (although still about half of the federal rate).

We have the opportunity to make changes in multiple ways to restore the career pathway for psychopharmacological academic trialists.

Learning Objectives:

1. Articulate support appropriate for individual clinical faculty to develop as psychopharmacology trialists – particularly, formal mentoring, developing a focus,

training, departmental funding/supported time for initial research project, and assistance in selection and preparation of research submissions.

2. Actively work to address systemic impediments to career development and success of academic clinical psychopharmacologists including at NIMH, the pharmaceutical industry, and clinical research organizations (CROs).

Literature References:

1. Markowitz JC, Milrod BL. Lost in Translation: The Value of Psychiatric Clinical Trials. J Clin Psychiatry 2022;83(6):22com14647
2. Gruber J, Borelli JL, Prinstein MJ et al. Best practices in research mentoring in clinical science. J Abnormal Psychology. 2020;129(1):70-81

Friday, June 2, 2023

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

Panels

***ANTIPSYCHOTICS, METABOLIC DYSFUNCTION, AND COGNITION IN PSYCHOSIS: NOVEL INSIGHTS INTO BIOLOGICAL CORRELATES, GENETIC PREDICTORS, AND MITIGATION STRATEGIES.**

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

Overall Abstract Severe mental illnesses (SMI) such as schizophrenia are associated with very high rates of metabolic disorders, including obesity, diabetes, and metabolic syndrome. Several factors including inherent biological risk, lower self-care, and poverty, contribute to high rates of obesity and metabolic co-morbidity. Much of this risk is accrued early, with rates of obesity approaching 50%, and prediabetes in excess of 15% within less than 6 months of starting treatment. Beyond increased cardiovascular mortality, weight gain is the most distressing side effect reported by callers to mental health helplines; it is associated with poorer quality of life and stigma, and creates barriers to social engagement. Importantly, metabolic dysfunction can compromise adherence with treatment, leading to relapse and poor mental health outcomes, and can worsen cognition. In spite of the clear importance of metabolic health in determining functional outcomes, rates of treatment for metabolic comorbidities in SMI remain embarrassingly low.

In this symposium, we will discuss 1) epigenetics/proteomics and metabolic changes in patients with psychiatric disorders and healthy volunteers exposed to an antipsychotic, 2) the association and relative contribution of cardiovascular genetic risk and medication exposure to cognitive impairment in psychosis, and 3) a pragmatic data-driven algorithmic approach to prevention and treatment of antipsychotic-induced metabolic dysfunction. The symposium will present data acquired from a variety of settings, approaches, and methodologies including randomized control trials, retrospective chart reviews, and meta-analyses.

Kyle Burghardt will present findings a randomized, double-blind, placebo-controlled pilot trial in healthy volunteers detailing acute changes in skeletal muscle DNA methylation that co-occurred with a decrease in insulin resistance following exposure to atypical antipsychotics, suggesting that antipsychotics can cause insulin resistance by altering gene regulation in the skeletal muscle.

Lusi Zhang will review findings from a large sample of participants from the Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP) study showing both higher cardiovascular genetic risk and medication exposure to be significantly associated with cognitive impairment in psychosis.

Mahavir Agarwal will present data examining the utility of prevention and early intervention approaches in mitigating antipsychotic-induced weight gain and data on the effectiveness of a pragmatic data-driven algorithmic approach focusing on the effect of semaglutide, a novel weight loss agent, in metformin non responders.

Kristen Ward, an expert in using precision medicine techniques, such as metabolomics and pharmacogenomics, to improve the safety and efficacy of psychotropic medications, will serve as discussant and help synthesize and contextualize the presented findings.

Together, the symposium will highlight the speed and intensity of metabolic dysfunction across various participant groups, its consequences beyond cardiovascular health, and how addressing metabolic health proactively can lead to better clinical outcomes.

The symposium brings together women (Drs. Zhang and Ward) under-represented minorities (Drs. Zhang and Agarwal), early career scientists (Drs. Zhang, Agarwal, and Ward), and clinicians (all symposium participants).

Learning Objectives:

1. Biological correlates, predictors, and consequences of antipsychotic-induced metabolic dysfunction
2. Utility of pragmatic data-driven algorithmic approach to prevention and treatment of antipsychotic-induced metabolic dysfunction

THE EFFECT OF OLANZAPINE ON THE SKELETAL MUSCLE EPIGENOME AND PROTEOME

Kyle Burghardt, Wayne State University

Individual Abstract: Purpose: Atypical antipsychotics cause acute and direct insulin resistance independent of significant weight gain and psychiatric disease through a reduction in glucose uptake. Despite the skeletal muscle's essential role in peripheral glucose uptake, this tissue has not been thoroughly investigated for its role in atypical antipsychotic-induced insulin resistance. We aimed to investigate changes in skeletal muscle DNA methylation with a pilot randomized, double-blind, placebo-controlled trial of olanzapine in healthy volunteers.
Content: The presentation will present unpublished findings from the healthy volunteer trial.

Methodology: Healthy volunteers were given blinded placebo or olanzapine for 7 days. Anthropometrics, energy expenditure, an insulin sensitivity test and muscle biopsies were obtained before and after drug administration. Changes in the epigenome were assessed by Illumina EPIC technology and the proteome by mass spectrometry.

Results: Twelve healthy volunteers (6 olanzapine; 6 placebo) completed the trial. The average age of the cohort was 25.8 ± 4.1, 40% were female, 30% were Caucasian and 60% were Asian. The treatment groups did not differ based on demographic factors. The olanzapine group had a significant increase in insulin resistance but no differences were observed for weight, fasting glucose or lipid panel. Both epigenomic and proteomic analyses identified various and diverse

sites with altered levels (methylation or proteomic). A targeted pathway analysis of glucose transport also found several changed epigenomic sites.

Conclusion: Within our study we identified acute changes in skeletal muscle DNA methylation and protein levels with olanzapine treatment. This may suggest that atypical antipsychotics cause insulin resistance by altering gene regulation in the skeletal muscle. Future work will need to expand on these findings through gene-specific analyses and correlations with insulin resistance.

Importance: This work is critical to further identifying the mechanisms of atypical antipsychotic side effects that lead to 2-3x increased risk of diabetes, metabolic syndrome and cardiovascular disease ultimately culminating in elevated medication-associated mortality.

Learning Objectives:

1. Identify the role for skeletal muscle in antipsychotic-associated side effects.
2. Describe how epigenetics and proteomics may play a role in medication outcomes.

Literature References:

1. Burghardt, Kyle J., et al. "Atypical antipsychotics, insulin resistance and weight; a meta-analysis of healthy volunteer studies." Progress in Neuro-Psychopharmacology and Biological Psychiatry 83 (2018): 55-63.
2. Burghardt, Kyle J., et al. "Skeletal muscle DNA methylation modifications and psychopharmacologic treatment in bipolar disorder." European Neuropsychopharmacology 29.12 (2019): 1365-1373.

THE IMPACT OF CARDIOMETABOLIC FACTORS ON COGNITIVE PERFORMANCE IN PSYCHOSIS SPECTRUM DISORDERS: GENETIC RISKS, MEDICATION EXPOSURE AND CHRONIC INFLAMMATION

Lusi Zhang, University of Minnesota

Individual Abstract: Background: Cardiometabolic diseases (CMDs) are highly prevalent in persons with schizophrenia and related psychoses. Epidemiological observations suggest associations between the core cognitive deficits in psychosis and comorbid cardiometabolic risk factors, but the underlying etiology remains unclear. Chronic inflammation is closely related to CMDs and its implications in psychosis has also been suggested by recent studies. The extent to which these relationships are relevant to cognitive function in persons with psychotic disorders remains unclear. Our recent work examined the impact of the cardiometabolic risk factors on cognitive performance in psychotic disorders, with a specific focus on genetic risks, medication exposures, and the implications of inflammation dysregulation.

Methods: Patients with chronic psychosis spectrum disorders on stable antipsychotic treatment (n=403) and healthy controls (n=213) from the Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP) were included in this study. All participants underwent an assessment of neuropsychological performance using the Brief Assessment of Cognition in Schizophrenia (BACS). Concomitant psychotropic and non-psychotropic medications for each participant were collected and categorized. Genetic risk for psychiatric and cardiometabolic traits was quantified from genome-wide DNA data by calculating polygenic risk scores (PRS). A subset of participants underwent further assessment with a panel of 15 cytokine and vascular markers of peripheral inflammation. Factor and clustering analyses were performed on the

inflammatory markers to generate peripheral inflammation index scores and identify discrete high/low inflammation subgroups. Regression analyses examined the relationships between neurocognitive function, PRS, medications, and peripheral inflammation.

Results: Higher PRS for coronary artery diseases (CAD) was associated with lower generalized cognitive performance in individuals with psychosis (beta=-0.069, p=0.001) but not controls (beta=-0.013, p=0.565), primarily driven by verbal memory scores. After controlling for PRS, a greater number of concomitant cardiovascular medications was also associated with worse cognitive performance in psychotic disorders (beta=0.029, p=0.001). In the inflammation cohort, a subgroup of 38% individuals with psychotic disorders was categorized as a higher inflammation subgroup and was found to have lower performance on the BACS (beta=-0.586, p=0.038) as compared to those with lower inflammation. A composite cardiometabolic PRS generated by aggregating the significant signals of GWAS for CAD, type-2 diabetes, lipids and waist-to-hip ratio was related to higher inflammation status in the psychosis group (OR=2.04, p=0.001).

Conclusions and Discussion: Our findings indicate that higher cardiovascular genetic risk and medication exposure were both significantly associated with cognitive impairment in psychosis. These findings highlight a significant contribution of cardiometabolic factors to cognitive deficits that are an important source of functional disability in these patients. Cardiometabolic genetic risks may contribute to inflammation overactivation in some individuals with psychosis which adversely impacts cognition associated with illness. Preemptive strategies to mitigate cardiometabolic risks represent opportunities to minimize illness-associated cognitive impairments. Targeting inflammation dysregulation may be an avenue for novel therapeutic interventions to improve cognitive outcomes in these patients.

Learning Objectives:

1. To review findings of the impact of cardiovascular genetic risk and medication exposure on cognitive impairment in psychosis
2. To appreciate the contribution of cardiometabolic genetics in elevated peripheral inflammation in patients with psychosis associated with clinical phenotypes.

Literature References:

1. Zhang L, Hill SK, Guo B, et al. Impact of polygenic risk for coronary artery disease and cardiovascular medication burden on cognitive impairment in psychotic disorders. Prog Neuropsychopharmacol Biol Psychiatry. 2022;113:110464.
2. Zhang L, Lizano P, Guo B, et al. Inflammation subtypes in psychosis and their relationships with genetic risk for psychiatric and cardiometabolic disorders. Brain Behav Immun Health. 2022;22:100459.

AN ALGORITHMIC PHARMACOLOGICAL APPROACH TO PREVENTION AND TREATMENT OF ANTIPSYCHOTIC-INDUCED WEIGHT GAIN.

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

Individual Abstract: Background: Patients with schizophrenia (SCZ) have a 15–20-year shorter life expectancy than the average population, a finding directly attributable to their increased rates of obesity, cardiovascular disease, and type 2 diabetes. Antipsychotics remain the cornerstone of treatment in schizophrenia but are associated with serious metabolic adverse effects that are often most pronounced in the first few months after their initiation. As such, there is an urgent need for safe and effective adjunctive pharmacological approaches such as

metformin to be implemented at the earliest stages of illness to ameliorate antipsychotic-induced weight gain (AIWG). Simultaneously, it is important to remember that not all patients benefit from metformin, necessitating search for other efficacious agents. Semaglutide is a weekly injectable Glucagon-Like Peptide 1-Receptor Agonists (GLP1-RA) that has recently been approved for obesity management but the efficacy and tolerability of semaglutide in AIWG has not been explored to date. This talk will review the efficacy of an algorithmic pharmacological approach involving metformin and semaglutide for prevention and treatment of antipsychotic-induced weight gain, respectively, in two independent datasets.

Methods: We conducted a retrospective chart review of patients newly initiated on clozapine at Centre for Addiction and Mental Health (CAMH) in Toronto, Canada, from January 2014 to March 2021. We also conducted a separate chart review of all the patients enrolled in the Metabolic Clinic between 2019-2021 at CAMH, who were diagnosed with schizophrenia spectrum disorders, did not respond to metformin, and were started on semaglutide. A mixed model analysis with subjects as random effects, controlling for age, sex, T2D status, and smoking status, was used for our primary outcome measures of body weight and body mass index (BMI) at 6 and 12 months after initiation of intervention.

Results: In the first dataset, among 396 patients (males: 71.5%, mean age: 42.8 years) initiated on clozapine, 69 were on metformin or prescribed it ≤3 months after clozapine initiation. The clozapine+metformin group demonstrated significantly less weight gain compared with the clozapine-only group at 6 months (clozapine+metformin: 0.15 kg [SE = 1.08] vs. clozapine-only: 2.99 kg, SE = 0.54) and 12 months after clozapine initiation (clozapine+metformin: 0.67 kg, SE = 1.22 vs. clozapine-only: 4.72 kg, SE = 0.67). Adaptive changes were also observed for fasting glucose ($F = 3.10$, $p = 0.046$) and triglycerides ($F = 8.56$, $p < 0.001$) in the clozapine+metformin group compared with clozapine only. Patients in the clozapine+metformin group were also significantly more likely to continue taking clozapine at 12 months (clozapine+metformin: 65.2%; clozapine only: 51.1%; $p = 0.03$).

In the second dataset from the Metabolic Clinic, twelve patients who did not respond to metformin and were subsequently started on semaglutide weekly injections (mean dose: 0.71 ± 0.47 mg/week) were included in the analysis. A weight loss of 5.16 ± 6.27 kg (p=0.04) and 8.67 ± 9 kg (p=0.04) was seen at 6 and 12 months respectively after initiation of semaglutide with relatively well-tolerated side effects.

Conclusion: Co-initiation of clozapine and metformin was associated with lesser weight gain at 6 and 12 months after initiation than being on clozapine alone, providing evidence for the effectiveness of metformin in preventing AIWG. Evidence from the Metabolic Clinic cohort suggests that semaglutide may be effective in reducing AIWG in patients not responding to metformin. Randomized control trials are needed to corroborate these findings.

Learning Objectives:

1. To appreciate the feasibility of preventing antipsychotic-induced weight gain
2. To review the effectiveness of an algorithmic approach to prevention and treatment of antipsychotic-induced weight gain

Literature References:

1. Stogios N, Maksyutynska K, et al. Metformin for the prevention of clozapine-induced weight gain: a retrospective naturalistic cohort study. Acta Psychiatrica Scandinavica 2022 (accepted for publication).
2. Agarwal SM, Stogios N, et al. Pharmacological interventions for prevention of weight gain in people with schizophrenia. Cochrane Database of Systematic

Reviews 2022, Issue 10. Art. No.: CD013337. DOI: 10.1002/14651858.CD013337.pub2.

DIGITAL PHENOTYPING AND THERAPEUTICS: ASSESSING THE HYPE VS EVIDENCE

John Torous, Beth Israel Deaconess Med. Ctr. and Harvard Medical School

Overall Abstract Digital Tools to Advance Mechanistic Understanding of Psychopathology and Treatment Response

Understanding the mechanism of mental illnesses and treatment response offers the ability to develop more effective treatments and offer preventive services. Drawing from the ongoing Accelerating Medicines Partnership (AMP) Schizophrenia (SCZ) program, Wellcome Trust supported digital phenotyping research in India, and other clinical examples, this talk will focus on the role of smartphone assessments (both ecological momentary assessment and digital phenotyping) as well as wearables as multimodal assessments towards assessing symptoms and response to treatments.

Learning Objectives:

1. List at least three risks and benefits of digital phenotyping compared to traditional outcomes measurements.
2. Assess the validity of digital phenotyping markers of mood and anxiety as compared to gold standard measurments.

DIGITAL TOOLS AS MEASUREMENT DEVICES TO ASSESS EFFECTS OF TREATMENTS AND DRUGS

John Torous, Beth Israel Deaconess Med. Ctr. and Harvard Medical School

Individual Abstract: Interest in real-world functional outcomes and ecologically valid markers of treatment progress have also accelerated interest in digital endpoints. Ranging from simple ecological momentary assessment to advanced digital phenotyping, this talk will focus on how digital systems are being deployed to monitor and measure treatment outcomes. Challenges around lack of standardization and replicability will be contrasted with innovative solutions to deploy these systems for global mental health at scale.

Learning Objectives:

1. Assess threats to engagement with digital phenotyping and list three means to boost engagement.
2. List three use cases for digital phenotyping and consider the pros/and cons of this approach when deployed for observational vs interventional studies.

Literature References:

1. Torous J, Myrick K, Aguilera A. The need for a new generation of digital mental health tools to support more accessible, effective and equitable care. World Psychiatry. 2023 Feb;22(1):1.
2. Cohen A, Naslund JA, Chang S, Nagendra S, Bhan A, Rozatkar A, Thirthalli J, Bondre A, Tugnawat D, Reddy PV, Dutt S. Relapse prediction in schizophrenia

with smartphone digital phenotyping during COVID-19: a prospective, three-site, two-country, longitudinal study. Schizophrenia. 2023 Jan 27;9(1):6.

DIGITAL TOOLS AS MEASUREMENT DEVICES TO ASSESS EFFECTS OF TREATMENTS

Michele Ferrante, FDA

Individual Abstract: The FDA Digital Health Center of Excellence has an Interest in real-world functional outcomes, ecologically valid markers of treatment progress, and robust digital endpoints. Ranging from simple ecological momentary assessment to advanced digital phenotyping, this talk will focus on how safe and effective digital systems are being deployed to monitor and measure treatment outcomes. Challenges around lack of standardization, regulation, and replicability will be contrasted with innovative solutions to deploy these systems for global mental health at scale.

Learning Objectives:

1. To understand the importance of ecologically valid markers of treatment progress and digital endpoints in the monitoring and measurement of treatment outcomes in mental health, and how they can improve patient care.
2. To gain insights into the challenges surrounding the deployment of digital systems for mental health at scale, including lack of standardization, regulation, and replicability, and learn about innovative solutions to overcome these challenges.

Literature References:

1. List of FDA Guidance Documents with Digital Health Content: https://www.fda.gov/medical-devices/digital-health-center-excellence/guidances-digital-health-content

USING TECHNOLOGY AND DIGITAL PHENOTYPING TO ASSESS FUNCTIONING AND DETECT TREATMENT RESPONSES

Philip Harvey, University of Miami Miller School of Medicine

Individual Abstract: Background: One of the important treatment targets with developing pharmacological interventions is everyday functioning. Deficits in everyday functioning can have several different origins across conditions, from never learning skills to having skills performance inhibited by new onset cognitive impairment or negative symptoms. Direct assessment of everyday functioning bypasses several different biasing factors, including recall deficits or response bias. In this presentation, we demonstrate the use of technology based assessments of the treatment response of everyday functioning in a large-scale treatment study with assessments focused on negative symptoms, using both active and passive digital phenotyping strategies.

Methods: The behavioral indicators of avolition in schizophrenia were examined in a 12-month open label study of a medication in development. Ecological Momentary Assessment (EMA) of moods, location, social context (alone or with someone), location (home vs. away), and productive vs. unproductive activities was conducted 3 times per day, 7 days per week, one week per month and was augmented with daily actigraphy measurement of steps per day (n=340, 18,171 EMA surveys 4411 patient-days with step counts).

Results: Statistically significant reductions over the study period in the number of surveys at home, surveys alone, and unproductive activities were found ($p<.001$). Significant

improvements in positive affect (PA) , productive activities at home and away, and steps per day were found. Significant correlations between improvements in PA and daily steps and productive activities were found, as were significant negative correlations between improvements in PA and reductions in unproductive activities. Clinical ratings of the severity of negative symptoms were found to correlate with both actively collected EMA surveys and passive measurements of steps, including total scores and subscale scores targeting avolition.

Discussion: Differing technology-based strategies can detect treatment effects on everyday functioning associated with medication and device-based interventions across populations. These assessments are momentary and have reduced bias and adherence in our studies was over 65% for the schizophrenia patients. These findings raise the possibility that previous negative results in treatment studies targeting negative symptoms were actually due to limitations in the outcomes assessments, as we previously reported in a comparison of EMA outcomes vs. clinical ratings for the benefits of oxytocin on social functioning in schizophrenia.

Learning Objectives:

1. At the end of this presentation, the attendee will be able to describe active and passive digital phenotyping strategies.
2. At the end of this presentation, the attendee will be able to develop a strategy for assessment of negative symptoms that combines active passive digital phenotyping strategies.,

Literature References:

1. Cohen AS, Schwartz E, Le TP, et al. Digital phenotyping of negative symptoms: the relationship to clinician ratings. Schizophr Bull. 2021;47(1):44-53. doi:10.1093/schbul/sbaa065
2. Strassnig MT, Miller ML, Moore R, Depp CA, Pinkham AE, Harvey PD. Evidence for avolition in bipolar disorder? A 30-day ecological momentary assessment comparison of daily activities in bipolar disorder and schizophrenia. Psychiatry Res. 2021;300:113924. doi:10.1016/j.psychres.2021.113924

+*IDENTIFYING MEANINGFUL TARGETS OF PHARMACOTHERAPY IN MOOD DISORDERS

Joseph Goldberg, Icahn School of Medicine at Mount Sinai

Overall Abstract What are the intended targets of pharmacotherapy in the treatment of mood disorders? Ideally, an efficacious treatment reliably eradicates any and all symptoms associated with syndromal or subsyndromal mania or depression, triggers no mood dysregulation, and prevents recurrences. More pragmatically, clinicians are often forced to accept only partial improvements that may not comprehensively address all symptom domains. Given the limitations of existing drug therapies, practitioners often capitalize on particular pharmacodynamic effects of specific agents to leverage improvement in key symptom areas, such as motivation and hedonic capacity, sleep-wake cycle disruptions, anxiety, agitation, impulsivity, aggression, psychosis, or suicidal thoughts or behaviors. Deliberately treating such dimensions of psychopathology, rather than categorically-defined disease entities, acknowledges both the clinical heterogeneity of mood disorder presentations as well as the imperfections of existing medications as singular antidotes for disorders with multi-faceted symptoms. However, purposefully targeting symptoms rather than diagnoses runs counter to view that diseases are coherently unified entities, detracts from efforts to elucidate underlying

pathophysiological mechanisms, and potentially invites capricious rather than synergistic forms of polypharmacy.
The Introduction: duction of the NIMH Research Domain Criteria (RDoC) in place of DSM-based diagnoses ushered in a new era that has focused more on detecting salient neuroscientific targets of drug delivery linked to presumptive underlying neural circuitry or other biomarkers, rather than on interventions designed to modify illness burden or improve quality of life. Clinical trialists have since struggled with how best to define the goals of intervention trials. This symposium will address unresolved debates about a) efforts to study pharmacotherapies that are disease- versus symptom-modifying; b) the targeting of core psychopathology symptoms versus the use of psychiatric drugs as probes to elucidate putative underlying neural mechanisms; and c) the extent to which persistent residual symptoms despite iterative pharmacotherapy trials may prompt the need for modified treatment goals, as described in palliative care models of chronic illness. Presenters will offer their thoughts and impressions about best practices for clinical trial designs and integrative approaches for future drug development.

Learning Objectives:

1. To analyze two different clinical purposes of drug treatment -- symptomatic vs disease modifying effects -- and to compare and contrast their effects on drug discovery research and clinical practice.
2. To contrast symptom from patient-centered outcomes and to compare the relative value of mechanisms that explain pathophysiological disease versus treatment response.

IMPROVING PSYCHIATRIC DRUG DEVELOPMENT: BEYOND THE CONVENTIONAL WISDOM

Nassir Ghaemi, Tufts University/Harvard Medical School

Individual Abstract: This lecture will describe problems in psychiatric drug discovery, and proposed solutions beyond the conventional wisdom. It will be explained that medications can be used in one of two ways, either symptomatically or disease modifying. Almost all psychiatric medications are symptomatic, and have no effect on the long term diseases that underlie many psychiatric presentations. Psychiatric drug discovery remains almost entirely symptomatic, rather than disease modifying. To make a change to the latter, diseases need to be identified validly, which raises the problem of DSM, which is not a scientifically valid nosology. Disease modification involves improving long-term course of illness. Hence the use of false maintenance clinical trial designs, like the randomized discontinuation trial, is another major problem in psychiatric drug development. Evidence for these claims will be provided, and debate and discussion of alternative viewpoints will be included.

Learning Objectives:

1. To examine how psychiatric medications are symptomatic or disease-modifying and how psychiatric drug discovery remains almost entirely focused on only symptomatic benefit.
2. To analyze the validity or invalidity of DSM nosology for psychopharmacology research

Literature References:

1. Ghaemi SN. 2022a. 'Drug Discovery in Psychiatry: Rethinking Conventional Wisdom Decouverte de medicaments en psychiatrie: Repenser les idees conventionnelles', Can J Psychiatry: 7067437221112907.
2. Ghaemi SN. 2022b. 'Symptomatic versus disease-modifying effects of psychiatric drugs', Acta Psychiatr Scand, 146: 251-57.

MATCHING TARGET SYMPTOMS OF PHARMACOTHERAPY WITH THEIR NEUROBIOLOGICAL SUBSTRATES: ON BABIES AND BATHWATERS

Manpreet Singh, Stanford University School of Medicine

Individual Abstract: Treatments for serious psychiatric disorders offer at best short-term and up to medium treatment effects with limited or unknown potential for long-term or preventative benefit. There are also few empirical studies that have been conducted that compare active treatments to be able to guide which treatments benefit which patients and under what conditions. Funding priorities for new research in psychiatry have shifted from clinical trials in DSM-defined clinical disorders toward mechanistic discovery of novel therapeutics that engage pre-defined neurobiological targets. It remains to be seen whether this shift will yield more effective treatments or successfully guide precision-based treatment matching. Research Domain Criteria (RDoC) aimed to confront the limited efficacy, specificity, and generalizability of investigations of treatments based on traditional DSM diagnostic categories. Many DSM diagnoses are comprised of heterogeneous constructs that are only partially responsive to currently available treatments. Dimensionalizing disorder components using RDoC constructs aims to provide more granularity for treatment targets that might be better modeled across species and perhaps increase translational potential. However, psychiatric conditions in humans can hardly be reduced to component parts, single brain regions, or neurotransmitter systems. Rather, they are highly complex and sensitive to context. Even if we have access to the right validation tools to determine target engagement of an RDoC construct, the path toward translating that validation toward meeting clinical unmet needs may be neither simple nor direct. Moreover, whether through DSM or RDoC, targeting core psychopathology symptoms or using psychiatric drugs as probes to elucidate putative underlying neural mechanisms, the field might benefit from several strategies to accelerate translation, leveraging past lessons learned. This presentation will propose alternative strategies for treatment matching using: 1) comparative effectiveness trials; 2) diverse sampling; 3) examination of the science underlying placebo response; 4) investigation of rational combination strategies (versus polypharmacy); and 5) investigation of symptom/relapse triggers and time course of therapeutic effects.

Learning Objectives:

1. To weigh the relative advantages and disadvantages of drug development in the context of categorical (DSM) and dimensional (RDoC) outcomes.
2. To propose alternative research foci to accelerate translation toward meeting patient unmet needs.

Literature References:

1. Cuthbert BN, Research Domain Criteria (RDoC): Progress and Potential Curr Dir Psychol Sci. Author manuscript; available in PMC 2022 Jun 10. Published in final edited form as: Curr Dir Psychol Sci. 2022 Apr; 31(2): 107–114. Published online 2022 Mar 1. doi: 10.1177/09637214211051363; PMCID: PMC9187047
2. Singh MK, Hu R, Miklowitz DM, Preventing Emotion Dysregulation in Youth by Building Resilience, Clinics of North America: Child and Adolescent Psychiatric Clinics. 2021 Jul;30(3):595-610.

ON REDEFINING THE GOALS OF TREATMENT FOR DIFFICULT-TO-TREAT MOOD DISORDERS: BORROWING FROM THE PALLIATIVE CARE MODEL

Joseph Goldberg, Icahn School of Medicine at Mount Sinai

Individual Abstract: Current antidepressant pharmacotherapies exert only small to medium effect sizes and show almost exponentially declining likelihoods of remission after each successive failed trial. Treatment-resistant mood disorders are often operationally defined as a poor response to one or two adequate and appropriate pharmacotherapy trials, but in actuality many mood disordered patients respond poorly to far more than only two interventions. There has been little empirical study of standard-care pharmacotherapy approaches for multi-drug resistant unipolar and bipolar patients, inasmuch as most existing medications have not been formally studied in mood disorder patients unresponsive to >2 prior medications. Unique issues arise in defining the goals of treatment for such patients – that is, identifying appropriate and tangible targets of pharmacotherapy -- where more fundamental disease modification may not be feasible. Clinicians struggle on the one hand with maintaining realistic expectations and recognizing low probabilities of fundamentally better outcomes when they iteratively cycle through the finite repertoire of standard care options; at the same time, they face challenges for credibly maintaining hope in the face of numerous failed attempted treatment interventions. This presentation will address how clinicians and clinical investigators can and should most reasonably identify the goals of pharmacotherapy in multi-drug-resistant difficult-to-treat forms of mood disorders, including a focus on quality of life, individual target symptoms such as insomnia or anxiety, managing chronic suicidal ideation, simplifying elaborate drug regimens to minimize side effects, targeting comorbidities, and pursuing a focus on chronic disease management. Concepts from the palliative care model will be described when the likelihood of disease-modifying treatments appears remote.

Learning Objectives:

1. To familiarize participants with the limitations of existing pharmacotherapies for bipolar and unipolar mood disorders in terms of magnitude of effect and a narrow spectrum of efficacy for chronic or complex presentations
2. To provide greater understanding about how best to define the tangible goals of pharmacotherapy for difficult-to-treat mood disorders when fundamental disease-modification appears untenable.

Literature References:

1. Goldberg JF. When further pharmacotherapy seems futile. J Clin Psychiatry 2018; 80: 18ac12276
2. Berk M, Berk L, Udina M, et al. Palliative models of care for later stages of mental disorder: maximizing recovery, maintaining hope, and building morale. Aust NZ J Psychiatry 2012; 46: 92-99

***NEW DATA AND NEW STRATEGIES TO IMPROVE TREATMENT FOR SCHIZOPHRENIA**

Ira Glick, Stanford University School of Medicine

Overall Abstract Although there is a dearth of new medications that show better efficacy than clozapine, risperidone, or olanzapine – the actual efficacy of long-term treatment of schizophrenia has improved. This panel will focus on the evidence-based treatment outcome data and new strategies as well as ways of treatment delivery for patients with schizophrenia.

Dr. Lindenmeyer will emphasize the early treatment of first-episode psychosis patients, the early Introduction: duction of clozapine, the concomitant use of computerized cognitive and social remediation interventions, the efficacy of newer long acting depot antipsychotics and new medication delivery methods together with the Introduction: duction of digital adherence and self-monitoring devices. These newer treatment tools will be critically reviewed in terms of available efficacy data, uptake data by both patients and treatment providers and potential barriers for their transition in a typical practice settings.

Dr. Glick will present data from long-term studies of antipsychotic treatment. Results suggest both early intervention and lifetime treatment for many patients, especially involving the family in treatment to improve adherence.

Dr. Marder will discuss managing the side effects of antipsychotics in order to maintain adherence to achieve efficacy. He will focus on three area: abnormal movements, prolactin elevation, and metabolic effects (including obesity, Type 2 Diabetes and abnormal lipids).

Learning Objectives:

1. At the conclusion of this session, clinicians will understand and be able to use in practice new strategies for delivery of long-term treatment of schizophrenia.
2. At the conclusion of this panel, clinicians will understand how to integrate the most effective medications and manage side effects in the long-term treatment of schizophrenia in their clinical practice.

NEW DATA AND NEW STRATEGIES FOR THE TREATMENT CONTINUUM OF SCHIZOPHRENIA PATIENTS

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

Individual Abstract: The aim of this presentation is to systematically review novel treatment strategies for the continuum of patients with schizophrenia. The following illness phases will be discussed:1.First Episode Psychosis Patients: Emphasis will be placed on treatment data on preventing conversion from Ultra-high Risk states to overt psychosis. Data on the use of coordinated specialty care (CSC) in first episode patients (FEP) will be reviewed, including data from the RAISE study and the NYC OnTrack programs. It appears that these multi-element team-based approaches have shown significant advantages over traditional care, including increased treatment engagement, improved quality of life, and greater symptom reduction. New data on treatment algorithms for FEP and on the early Introduction: duction of clozapine based on results from the OPTiMiSE trial (Khan et al., 2017) together with the recommendation for use of Long -Acting Antipsychotics in FEP patients will be discussed.
2.Multi-episode Patients: New data on adherence support interventions will be presented, together with the efficacy of newer and longer acting depot antipsychotics and other new medication delivery methods together with chip enhanced oral antipsychotics and the Introduction: duction of digital adherence and self-monitoring devices. Racial disparities in the prescription patterns of antipsychotic medications in the US will be discussed. Data on the provision of concomitant computerized cognitive and social remediation interventions will be discussed.3.Treatment Resistance Patients (TRS): The TRRP (Howes et al., 2017) criteria will be reviewed together with the limited support for the efficacy of polypharmacy in TRS patients

(Correll et al., 2017; Tiihonen et al, 2019). The paradox of the under-utilization of clozapine with its superior efficacy in treatment resistant patients will be discussed together with proposals for remediation of the status quo. Data from augmentation trials and non-pharmacological novel treatments (e.g. tDCS; DBS) will be reviewed as well.

4.Discussion: These newer treatment tools and strategies will be critically reviewed across the different illness phases in terms of available efficacy data, uptake data by both patients and treatment providers and potential barriers for their transition into typical practice settings together with recommendations for the further development of the most promising newer interventions.

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Learning Objectives:

1. This presentation will help the audience to get an overview of novel multi-dimensional treatment options available for the treatment of the continuum of patients with schizophrenia.
2. This presentation will increase the audience understanding of available new delivery mechanisms of antipsychotics, their uptake by patients any poteniail barriers for their use.

Literature References:

1. Kahn RS, Winter van Rossum I, Leucht S, McGuire P, et al.:; OPTiMiSE study group. Amisulpride and olanzapine followed by open-label treatment with clozapine in first-episode schizophrenia and schizophreniform disorder (OPTiMiSE): a three-phase switching study. Lancet Psychiatry. 2018 Oct;5(10):797-807. doi: 10.1016/S2215-0366(18)30252-9. Epub 2018 Aug 13. PMID: 30115598.
2. Jonathan G. Leung, Pharm D, Jose de Leon, MD, Mark A. Frye, MD,: The Modernization of ClozapineA Recapitulation of the Past in the United States and the View Forward. J Clin Psychopharmacol 2022; epub).

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

Ira Glick, Stanford University School of Medicine

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

Method: These were retrospective, naturalistic, longitudinal (6-53 years) studies of antipsychotic treatment (mean average, 20) follow-ups of a consecutive series of patients from an academic setting, a V-A, a clinical research organization, and a community clinic. Lifetime data were collected on (1) their medication adherence, (2) long-term global outcome, and (3)

life satisfaction. Outcomes were rated by 2 different clinicians, 1 with information on medication adherence (nonblind rater) and 1 without (blind 21 rater). We used linear regression models adjusted for age, family support, substance use disorder, race, marital status, and number of years in treatment to estimate the association between adherence and each outcome.

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

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

Learning Objectives:

1. At the conclusion of this presentation, participants will be aware of the most efficacious psychopharmacologic and psychotherapeutic treatment.
2. At the conclusion of this presentation, participants will be aware of how long to continue treatment.

Literature References:

1. Glick I D, Davis J M, Zamora D et al: Should Antipsychotic Medications for Schizophrenia Be Given for a Lifetime? A Naturalistic Long-Term Follow-up Study, J Clin. Psychopharm, 2017,37:125-130
2. Glick I D, Zamora D, Kamis, D , Davis J: Should Antipsychotic Medications for Schizophrenia Be Given for a Lifetime?: Replication of a Naturalistic, Long-Term, Follow-Up Study of Antipsychotic Treatment" CNS Spectrums, 2019, 24, 557-563.

NEW STRATEGIES FOR MANAGING ADVERSE EFFECTS OF ANTIPSYCHOTICS

Stephen Marder, Semel Institute at UCLA

Individual Abstract: Among the side effects and health challenges for individuals with schizophrenia are long-term neurological effects from antipsychotics, prolactin elevation, and metabolic side effects including diabetes, obesity, and elevated lipids. This talk will review recent findings in each of these areas with a focus on new approaches for side effect management. For tardive dyskinesia, new data has become available regarding the role of VMAT2 inhibitors. This includes information regarding the long-term effects of these agents. For prolactin elevation, recent findings suggest that agents that are potent elevators are associated with a small increase in the risk of breast cancer in women. In addition, antipsychotics that are partial dopamine agonists may play a role in managing this side effect. For metabolic effects, recent findings support the role of life-style interventions, particularly

exercise for improving outcomes. In addition, advances in understanding feeding behavior have suggested new targets for managing these effects. Studies have supported the role of metformin as well as GLP-1 agonists in managing weight gain and diabetes risk.

Learning Objectives:

1. Learn the role of VMAT-2 inhibitors in managing tardive dyskinesia.
2. Understand the role of GLP-1 agonists in managing weight and diabetes risk.

Literature References:

1. Ishoy, P. L., Knop, F. K., Broberg, B. V., Bak, N., Andersen, U. B., Jorgensen, N. R., Holst, J. J., Glenthoj, B. Y., and Ebdrup, B. H. Effect of GLP-1 receptor agonist treatment on body weight in obese antipsychotic-treated patients with schizophrenia: a randomized, placebo-controlled trial. Diabetes Obes Metab, 2017 19(2), 162-171.
2. Scorr, L. M., and Factor, S. A. VMAT2 inhibitors for the treatment of tardive dyskinesia. J Neurol Sci, 2018 389, 43-47.

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

Regulatory Challenges: Ask the Experts

REGULATORY CHALLENGES: ASK THE EXPERTS

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

Overall Abstract This session is intended to facilitate dialogue between expert regulators from the US Food and Drug Administration and conference participants with an interest in drug development and clinical research in psychopharmacology. There will be no pre-submitted questions, but rather regulators will take questions directly from the audience.

REGULATORY CHALLENGES: ASK THE EXPERTS

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Learning Objectives:

1. Participants will be able to ask questions to a panel of FDA representatives.
2. Participants will learn from regulators how to improve quality of clinical research.

REGULATORY CHALLENGES: ASK THE EXPERTS

Tiffany Farchione, US Food and Drug Administration

Abstract This session is intended to facilitate dialogue between expert regulators from the US Food and Drug Administration and conference participants with an interest in drug development and clinical research in psychopharmacology. There will be no pre-submitted. questions, but rather regulators will take questions directly from the audience.

Learning Objectives:

1. Participants will be able to ask questions to a panel of FDA representatives.
2. Participants will learn from regulators how to improve quality of clinical research.

REGULATORY CHALLENGES: ASK THE EXPERTS

Bernard Fischer, U.S. Food and Drug Administration

Abstract This session is intended to facilitate dialogue between expert regulators from the US Food and Drug Administration and conference participants with an interest in drug development and clinical research in psychopharmacology. There will be no pre-submitted. questions, but rather regulators will take questions directly from the audience.

Learning Objectives:

1. Participants will be able to ask questions to a panel of FDA representatives.
2. Participants will learn from regulators how to improve quality of clinical research.

Wednesday, May 31, 2023

Poster Session I with Lunch

W1. A SINGLE ARM PIVOTAL TRIAL TO ASSESS THE EFFICACY OF AKL-T01, A NOVEL DIGITAL INTERVENTION DESIGNED TO IMPROVE ATTENTION, IN ADOLESCENTS DIAGNOSED WITH ATTENTION DEFICIT HYPERACTIVE DISORDER (ADHD)

Catherine Mercaldi[1], Minny Suh[1], Ann Childress[2], Napolean Higgins[3], Scott Kollins[1]*

[1]Akili, Inc., [2]Center for Psychiatry and Behavioral Medicine, Inc., [3]Southeast Behavioral Research Group, Inc.

Abstract: Background: Attention deficit hyperactivity disorder (ADHD) is a common pediatric psychiatric condition, and best practice for treatment includes both pharmacological (usually psychostimulant) and nonpharmacological (e.g., behavioral therapy) components. Limitations of these interventions, including side effects or access, suggest that novel, cost-effective, nonpharmacological interventions for ADHD that are easy to implement could be helpful for many patients. AKL-T01 (EndeavorRx®) is an FDA-cleared digital therapeutic approved to improve attention function in children ages 8-12 years with inattentive or combined-type ADHD who have a demonstrated attention issue. This study assessed AKL-T01 in adolescents with ADHD.

Methods: STARS-ADHD-Adolescents was a multicenter, single-arm trial conducted at 14 US research sites to evaluate objective attention functioning and ADHD symptoms and impairments after 4 weeks of AKL-T01 treatment in adolescents aged 13-17 years. Enrolled patients had a confirmed diagnosis of ADHD (combined or inattentive) and attentional impairment with Test of Variables of Attention (TOVA) Attention Comparison Score (ACS) of -1.8 or below. Participants were asked to complete AKL-T01 treatment at home in combination with their previously established stable regimen, which could include medication and/or nonpharmacological therapies. Treatment with AKL-T01 required approximately 25 minutes of gameplay per day for 5 days per week over 4 weeks. The primary endpoint was 4-week change in the TOVA-ACS. Secondary endpoints of this study were 4-week change in the ADHD RS-5 inattention scale and total scale scores. Safety, tolerability, and compliance were also assessed. Analyses were done on the Efficacy Population consisting of those with complete data on the primary endpoint. This trial was registered with ClinicalTrials.gov, NCT04897074, and completed enrollment in September 2022.

Results: Of the 526 participants who were screened for this study, 162 participants were enrolled between July 29, 2021, and September 1, 2022, and 146 had sufficient data for inclusion in the Efficacy Population. The mean age was 14.3 years, and the majority were male (59%), White (77%), and not Hispanic or Latino ethnicity (82%), with 49% reporting current stimulant use. AKL-T01 met its primary efficacy endpoint with a significant positive mean change after 4 weeks in the TOVA-ACS of 2.6 (95% CI: 2.02, 3.26; $P < 0.0001$). AKL-T01 also demonstrated efficacy across multiple secondary and exploratory endpoints, including significant improvements in ADHD-RS inattention and total scale scores ($P < 0.0001$ for both). In exploratory responder analyses, 24.7% of participants achieved a TOVA-ACS of at least 0, which is in the normative range, and 27.1% had improvement in ADHD-RS total scale of at

least 30%. No serious adverse device effects (ADE) or discontinuations due to ADEs occurred. A total of 4 participants (2.5%) experienced any ADE, including frustration tolerance decreased (3 participants) and headache (1 participant), all of which were anticipated and of mild or moderate severity. Mean overall compliance with AKL-T01 was 72.4%.

Conclusion: Results showed that AKL-T01 demonstrated statistically significant improvement of sustained and selective attention as measured by TOVA-ACS after 4 weeks of treatment. There were also consistent benefits in a range of secondary measures of ADHD-related symptoms and functioning. AKL-T01 was well-tolerated, with no deaths or serious ADEs reported. The magnitude of effects across measures was comparable to or exceeded that of children aged 8-12 years with ADHD and suggest a comparable level of benefit for adolescents.

W2. RETHINKING THE ROLE OF SEROTONIN IN ATTENTION DEFICIT HYPERACTIVITY DISORDER

*Matia Solomon**[1], Brittney Yegla[1], Jeffrey Newcorn[2], Jonathan Rubin[1], Trevor Robbins[3], Vladimir Maletic[4]*

[1]Supernus Pharmaceuticals Inc, [2]Icahn School of Medicine At Mount Sinai, [3]Behavioural and Clinical Neuroscience Institute, University of Cambridge, [4]Department of Psychiatry/Behavioral Science, University of South Carolina School of Medicine

Abstract: Attention deficit hyperactivity disorder (ADHD) is a common neurodevelopmental disorder characterized by inattention and/or hyperactivity-impulsivity. However, for many individuals, it also encompasses emotional dysregulation and executive dysfunction, which further impairs cognitive and socioemotional capacities. Stimulants are a first-line treatment for ADHD; owing to their potent effects on dopamine (DA) and norepinephrine (NE) neurotransmission in critical cognitive and inhibitory brain regions [e.g., medial and dorsolateral prefrontal cortex (PFC); ventral striatum]. However, a substantive literature highlights the importance of a variety of other neurotransmitters in ADHD, including serotonin which has documented effects in the regulation of impulsive behavior, emotional control, and executive function. Of note, amphetamines (AMPs) increase serotonin in ADHD-relevant brain regions including the medial PFC, suggesting the potential role for serotonin in stimulant-mediated effects.

While stimulants are a first line-treatment for ADHD, they carry certain safety risks, including abuse/misuse potential, reduced growth and weight in pediatric populations, and limited duration of effects. Thus, nonstimulant treatment options may be more suitable for some individuals. Viloxazine is a recently approved nonstimulant for ADHD which is classified as a NE reuptake inhibitor. However, its effects on NE reuptake are modest compared with other nonstimulants targeting the NE transporter (i.e., atomoxetine, reboxetine). This suggests that the efficacy of viloxazine may not be solely driven by its effects on NE. Our preclinical findings indicate that viloxazine differentially engages specific serotonin receptor subtypes (i.e., 5HT2C, 5HT2B, 5HT7) and, at a clinically relevant dose, increases serotonin concentrations in the medial PFC. Because of its moderate effects as a NE transporter inhibitor, the possibility exists that the serotonergic modulating properties may contribute to viloxazine's mechanism of action.

This presentation will review evidence from an extensive literature review from preclinical and clinical studies suggesting an important modulatory role for serotonin in the behavioral manifestations and treatment of ADHD. First, we present findings indicating that stimulant

efficacy may be partially mediated by serotonin and highlight several studies demonstrating a dynamic interaction between serotonin and the catecholaminergic system in behavioral characteristics of ADHD. Next, we evaluate the efficacy of drugs with known serotonergic activity (e.g., tricyclic antidepressants, selective serotonin norepinephrine reuptake inhibitors). Finally, the impact of serotonergic signaling in cognitive and emotion-regulatory brain regions on ADHD behavioral phenotypes is discussed.
Given that preclinical studies provide the most evidentiary support for serotonin in the neuropharmacology of ADHD, it is imperative to build upon these findings in human investigations. Overall, the data suggest the need for a broader evaluation/understanding of serotonergic pathways in the manifestation and treatment of ADHD and related comorbidities.

W3. TREATMENT OF OPIOID USE DISORDER IN CORRECTIONAL FACILITIES A REVIEW OF CURRENT PRACTICES

Thersilla Oberbarnscheidt[1]*

[1]*University of Pittsburgh Medical Center, Western Psychiatric Hospital*

Abstract: The opioid epidemic continues to be a major concern in the U.S. and opioid related overdose deaths are at an all-time high. At highest risk of overdose are populations that are incarcerated or recently released from incarceration. The risk of overdose death in the first 2 weeks post incarceration is increased 129-fold compared to the general population.
One-quarter to one-third of all heroin users in the U.S. are incarcerated at least once within a year, as substance use and in particular opioid use disorder is highly associated with illicit activities. Estimates indicate that 80% of all arrests are related to drug or alcohol use and associated lifestyles. The length of heroin use has been shown to increase the likelihood of incarceration. Each additional year of opioid use increases the risk of incarceration by 11%. The risk increases even further among ethnic minorities.

Medication assisted treatment (MAT) options for opioid use disorder (OUD) are available and well researched. Several studies have shown their efficacy in reduction of opioid use and injecting behavior, as well as providing social/health benefits and safety. The first state to incorporate MAT in correctional facilities was Rhode Island in 2016. However, throughout the U.S., MAT for OUD in correctional facilities remains widely underutilized.

To reduce the rate of overdose deaths from opioids, correctional facilities and the ongoing treatment in those settings should become a higher focus of concern. Providing MAT for OUD in correctional settings can reduce the mortality rate, avoid re- incarceration, and improve psycho-social functioning. This review of literature will go over available data for the FDA approved mediation assisted treatment forms: buprenorphine, methadone, naltrexone and illustrate the outcome for relapse, mortality and re-incarceration rate.

Withholding life-saving medications from incarcerated populations also raised ethical concerns as it was pronounced unethical by the National Academies of Science.

This oral presentation will provide a systematic review of available MAT forms for OUD and present the current utilization in the U.S with discussion of the available data.

W4. BMB-101 – A SELECTIVE 5-HT2C RECEPTOR (5-HT2CR) AGONIST THAT MAY HAVE UTILITY IN SUBSTANCE ABUSE DISORDERS

Mark Smith[*1], Kathryn Cunningham[2], Christina Merritt[2], Alan Kozikowski[3], Andrew Cao[4], Hailey Bock[4], Joseph Hennessey[4], John McCorvy[4], Alex Vasilkevich[5], Jesse Damsker[5], Jianmin Duan[5], Alessandro Lovera[5], Ian McDonald[5], Jan Torleif Pedersen[5]*

[1]Mark A. Smith, [2]University of Texas Medical Branch, Galveston, [3]Univ. of Illinois, Chicago, [4]Medical College of Wisconsin, [5]Bright Minds Biosciences, Inc.

Abstract: Background: Serotonin 5-HT2CR agonists have been used to treat obesity and some forms of epilepsy, and more recently have shown promise in substance abuse disorders (SUDs). The efficacy of the anti-obesity medication fenfluramine was based upon its indirect actions as a 5-HT2CR agonist, however its dual action as a 5-HT2BR agonist resulted in its withdrawal due to cardiac toxicity. Studies with the 5-HT2CR agonist lorcaserin suggest efficacy to suppress relapse vulnerability in smoking, cocaine and cannabis, but lorcaserin is not a selective 5-HT2CR agonist. Thus, there is a need for a more selective and safer 5-HT2CR agonist to treat various SUDs. Here, we describe BMB-101 which is a novel cyclopropanemethylamine (1) that is a highly selective, partial agonist at 5-HT2CR (EC50 = 9.1 nM; EMAX = 74%) but only weak partial agonist at 5-HT2BR and 5-HT2A R with 15 and >150-fold selectivity, respectively. Importantly, and in contrast to lorcaserin, BMB-101 is a Gq-biased ligand that shows weak β-arrestin1/2 recruitment and therefore may be less prone to desensitization and tolerance. In the present studies, we tested the hypothesis that BMB-101 would attenuate fentanyl self-administration in rats and describe preliminary safety, tolerability and pharmacokinetic (PK) properties in humans in preparation for proposed Phase 2 studies in SUDs.

Methods: Rat Opioid Use Model (2) - Male, Sprague-Dawley rats were trained to lever press on a fixed ratio (FR) schedule of reinforcement to receive an intravenous infusion of fentanyl (3.2 μg/kg/inf) during daily 3-hour sessions. Rats progressed from the FR1 to an FR5 schedule and were maintained on this final schedule until stable responding was achieved. Vehicle (saline) or BMB-101 (10, 20, 60 mg/kg) was administered s.c., 1 mL/kg, 15-min prior to the test session.

Phase 1 Human Study – We are conducting a randomized, double-blind, placebo-controlled, study of BMB-101 in healthy human subjects at a single center in Australia. This study consists of 3 parts: a single ascending dose (SAD) a food effect, and multiple ascending dose (MAD) in order to investigate the safety and tolerability as well as pharmacokinetic (PK) profiles of BMB-101 following single and multiple oral administration.

Results: Rat Opioid Model - BMB-101 [20 and 60 mg/kg (n=6-9/group)] suppressed fentanyl infusions earned as well as the number of active lever presses without alterations in inactive lever presses. The latency to first response on the active lever was unaltered at any dose of BMB-101 tested. Another BMB 5-HT2CR agonist (10 mg JJ-42a) showed similar effects in this model. Based on the high clearance of BMB-101 in rats, the human equivalent dose of 20 mg/kg in the rat is approximately 1 mg/kg in humans or 70 mg in a typical 70 kg person.

Human Phase 1 Study – All doses in the SAD study were generally well tolerated, with mainly mild AEs reported. The most common AEs were nausea, oral paresthesia and headache. No serious or severe AEs were reported. Plasma half-life is estimated at 4.8-5.7 hrs. Therefore, in the ongoing MAD study, BMB-101 is being administered twice a day.

Conclusion: Based on preclinical evidence described in the opioid use model, as well as the developing safety and tolerability profile in humans, we believe that BMB-101 may be a "best in class" 5-HT2CR agonist suitable for testing in substance abuse and other disorders.

W5. SEX AND DIET-DEPENDENT GENE ALTERATIONS IN HUMAN AND RAT BRAINS WITH A HISTORY OF NICOTINE EXPOSURE

Javier Vargas Medrano[*1], Luis M. Carcoba[2], Guadalupe Vidal-Martinez[3], Zuber D. Mulla[3], Victoria Diaz[3], Alejandra Ruiz-Velasco[3], Fabian Alvarez-Primo[3], Gabriela Colina[3], Sergio D. Iñiguez[2], Peter M. Thompson[3], Laura E. O'Dell[2], Bharathi S. Gadad[3]*

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Abstract: Background: Chronic nicotine exposure induces changes in the expression of key regulatory genes associated with metabolic function and neuronal alterations in the brain. Many bioregulatory genes have been associated with exposure to nicotine, but the modulating effects of sex and diet on gene expression in nicotine-exposed brains have been largely unexplored. Both humans and rodents display motivation for nicotine use and the emergence of withdrawal symptoms during abstinence. Research comparing pre-clinical models with human subjects provides an important opportunity to understand common biomarkers of the harmful effects of nicotine as well as information that may help guide the development of more effective interventions for nicotine cessation.

Methods: Human postmortem dorsolateral prefrontal cortex (DLPFC) tissue BA9 was collected from female and male subjects, smokers and non-smokers (N = 12 per group). Rat frontal lobes were collected from female and male rats that received a regular diet (RD) or a high-fat diet (HFD) (N = 12 per group) for 14 days following implantation of an osmotic mini-pump (Alzet) that delivered nicotine continuously. Controls (control-s) received a sham surgical procedure. RNA was extracted from tissue from human and rat samples and reversed-transcribed to cDNA. Gene expression of CHRNA10 (Cholinergic receptor nicotinic alpha 10), CERKL (Ceramide Kinase-Like), SMYD1 (SET and MYD Domin Containing 1), and FA2H (Fatty Acid 2-Hydrolase) in humans was compared to rats in each subset of groups and quantified by qPCR methods. Additionally, protein expression of FA2H was analyzed by immunohistochemistry (IHC) in human dLPFC.

Results: Humans with a history of smoking displayed decreased CHRNA10 ($p = 0.0005$), CERKL ($p=0.0001$), and SMYD1 ($p = 0.0005$) expression and increased FA2H ($p = 0.0097$) expression compared to non-smokers ($p < 0.05$). Similar patterns of results were observed in nicotine exposed vs. control rats. Interestingly, sex-related differences in gene expression for CERKL and FA2H were observed. In addition, ANCOVA analysis showed a significant effect of nicotine i n a sex-different manner, including an increase in CERKL i n male and female rats with RD or HFD. In rats exposed to an HFD, FA2H gene expression was lower i n nicotine-treated rats compared to RD rats treated with nicotine. Protein expression of FA2H ($p= 0.001$) by IHC was significantly higher in smokers compared to non-smokers.

Conclusion: These results suggest that a history of long-term nicotine exposure in humans alters the expression of sphingolipid metabolism-related (CERKL, SMYD1, and FA2H) and neuronal (CHRNA10) marker genes similarly as compared to rats. Sex- and diet-dependent differences appear in nicotine-exposed rats, critical in regulating sphingolipid metabolism and nicotinic acetylcholine receptors. This research enhances the construct validity of rat models of nicotine usage by showing a similar pattern of changes in gene expression in human subjects with a smoking history.

W6. USING BIG DATA TO UNDERSTAND THE SAFETY PROFILE OF GABAPENTIN IN PEOPLE WITH OPIOID USE DISORDER: AN ANALYSIS OF MULTISTATE ADMINISTRATIVE CLAIMS DATA

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Abstract Background: Gabapentin prescriptions have significantly increased in the United States (U.S.) amid prevalent off-label prescribing for opioid use disorder (OUD) treatment, as well as for the management of co-occurring medical and psychiatric comorbidities. Among people who experience drug-related poisonings, gabapentin is commonly found on toxicology, raising concern about its role in overdose risk. To date, there is limited comprehensive data on the prevalence and associated risks of gabapentin prescribing in OUD treatment. Several U.S. states have acknowledged the potential drug-related poisoning risks associated with gabapentin and have considered placing gabapentin within prescription drug monitoring programs.

Objective: We evaluated 1) predictors of gabapentin receipt in people receiving buprenorphine for OUD and 2) whether the addition of gabapentin conferred increased drug-related poisoning risk in people taking buprenorphine for OUD.

Methods: We used national administrative claims data , spanning both commercial insurance and Medicaid enrollees in 50 U.S. states, from the Merative MarketScan (2006-2016) Databases to investigate the rates of gabapentin initiation within 60 days of buprenorphine initiation in people (n= 109,204) diagnosed with OUD. We used poisson regression models to evaluate the association of gabapentin initiation with age, sex, race, insurance type, and co-occurring medical (chronic pain, insomnia, migraine, diabetes mellitus, fibromyalgia, epilepsy, chronic kidney disease, irritable bowel syndrome) and psychiatric disorders (mood disorders, psychotic disorders, anxiety disorders). We subsequently evaluated the association between gabapentin and emergency room or hospital admission for drug-related poisoning among a subset of buprenorphine recipients who had at least 1 drug-related poisoning event (n=19,553). To mitigate confounding by indication, we used a within-person case-crossover approach, which is analogous to a stratified Cox-regression with recurrent events. Conditional logistic regression models estimated the risk of emergency admission or hospitalization for drug-related poisoning between days without active gabapentin prescriptions and days with active prescriptions, with analyses stratifying by gabapentin dosage (0-900 mg, 900-1800mg, 1800+ mg).

Results: Gabapentin was initiated in 32% of individuals who were starting buprenorphine for the treatment of OUD. Gabapentin was more likely to be prescribed to females (adjusted risk ratio [aRR]: 1.07, 95% CI: 1.04-1.09), those with co-occurring substance use (aRR: 1.35, 1.30-1.40), mood disorders (aRR: 1.34, 1.31-1.37), anxiety disorders (aRR: 1.30, 1.27-1.33), psychotic disorders (aRR: 1.21, 1.13-1.29), and those with comorbid physical illnesses (i.e., chronic pain) (aRR: 1.38, 1.32-1.44). Person-days of gabapentin use without buprenorphine were not significantly associated with hospitalization for drug-related poisoning (OR=0.96, 0.89-1.04). Buprenorphine maintained its protective effect against drug-related poisoning even

when taken together with gabapentin (OR=0.62, 0.59-0.66). Notably, drug-related poisoning risks associated with person-days of gabapentin exposure did not vary based on gabapentin dosage.

Conclusion: Gabapentin is frequently used in people receiving buprenorphine maintenance for OUD, and is associated with a myriad of comorbid medical and psychiatric illnesses. Our data suggest that gabapentin—after accounting for confounding by indication—was not associated with an increased risk of overdose alone, or alongside buprenorphine. More data on the safety profile of gabapentin in OUD settings is urgently needed.

W7. EFFICACY AND SAFETY OF AN ALPHA 7 NICOTINIC ACETYLCHOLINE RECEPTOR AGONIST, VQW-765, IN SUBJECTS WITH PERFORMANCE ANXIETY IN A RANDOMIZED, PLACEBO-CONTROLLED TRIAL

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Abstract: Background: Genetic abnormalities in the alpha 7 Nicotinic Acetylcholine Receptor (α7-nAChR) genomic locus have been implicated in neurological and psychological disorders. This study aimed to investigate the anxiolytic effect of VQW-765, an α7-nAChR agonist, in subjects with performance anxiety.

Methods: We conducted a randomized, double-blind, placebo-controlled trial of 230 adults with the Public Speaking Anxiety Scale (PSAS) total score ≥60 at 15 sites in the United States. Participants were randomly assigned to groups and given a single oral dose of 10 mg VQW-765 (n=116) or placebo (n=114), followed by a Trier Social Stress Test (TSST) with a public speaking challenge. The stress level was assessed by the Subjective Units of Distress Scale (SUDS). Heart rate was monitored during the TSST. The VQW-765 concentration in plasma was measured after the TSST.

Results: Of the 230 participants, 3 (1.3%) reported a history of social anxiety disorder (SAD). 189 (82.2%) of the participants had the Liebowitz Social Anxiety Scale (LSAS) total score ≥60 at baseline, suggesting that most participants may have had SAD but have not been diagnosed yet. Participants receiving VQW-765 showed a trend of improvement in intensity of anxiety as measured by SUDS during the public speaking challenge compared to placebo (p=0.116). Female participants (69% of the total participants) showed a larger magnitude and significant response to the treatment (p=0.034). A significant relationship was also seen between exposure to VQW-765 and clinical response. VQW-765 was safe and well tolerated.

Conclusion: This is the first time that an α7-nAChR agonist has shown an anxiolytic effect in humans. VQW-765 is a promising candidate to be developed as a medicine that can be used on an as needed basis for the treatment of acute anxiety and warrants further clinical studies.

Trial registration: ClinicalTrials.gov NCT04800237.

W8. A PHASE 2, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY FOR BNC210, AN ALPHA7 NICOTINIC RECEPTOR NEGATIVE ALLOSTERIC MODULATOR (NAM) FOR THE ACUTE TREATMENT OF SOCIAL ANXIETY DISORDER (PREVAIL): TOP-LINE EFFICACY AND SAFETY RESULTS

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Abstract: SAD is a serious and prevalent condition characterized by a persistent, intense fear of social and performance-related situations. SAD carries a burden of functional disability, such as reduced workplace productivity, increased financial costs, and reduced health-related quality of life. SAD tends to be chronic if untreated.

BNC210 is a novel experimental alpha7 nicotinic NAM with a differentiated mode of action compared to existing FDA-approved anti-anxiety therapies. In completed clinical trials, acute treatment with BNC210 has reduced panic symptoms in a CCK-4 challenge in HVs and demonstrated inhibition of the amygdalar activity at resting, inhibition of anxiety-relevant neural circuits during the Emotional Faces task, and reduced threat avoidance behavior in patients with generalized anxiety disorder; and with at least equivalent if not better, responses than lorazepam when compared to placebo. These data support BNC210's potential for efficacy in the acute treatment of anxiety disorders. In all studies conducted to date, there is no evidence of sedation, addiction liability (ARCI-based), cognitive or motor impairment (unlike benzodiazepines), or increased suicidal ideation (unlike antidepressants).

PREVAIL aimed to determine the efficacy and safety of BNC210 in patients with moderate to very severe social anxiety disorder (SAD) and was also designed to uncover the best methodological approaches to measure the therapeutic potential of BNC210 in SAD.

The study enrolled 151 adult patients (average age of 36 years) and was completed in December 2022. Subjects were randomized to receive a single dose of 225 mg BNC210, 675 mg BNC210, or placebo (1:1:1 ratio). The Subjective Units of Distress Scale (SUDS, a VAS from 0-100 that measures the self-reported intensity of anxiety and/or distress) was the primary outcome measure to capture effects across different stages of a standardized public speaking task. The State-Trait Anxiety Inventory (STAI) and the Self Statements During Public Speaking–negative self-statements (SSPS-N) were used as secondary outcome measures.

Administration of both 225 mg and 675 mg doses of BNC210 resulted in therapeutic responses of similar magnitude, allowing for the data from the two-dose arms to be combined, enhancing the dataset's statistical power. While PREVAIL did not meet its primary endpoint based on the performance phase of the public speaking task, multiple findings favoring BNC210 were observed across endpoints. Participants who received BNC210 experienced statistically significant less anxiety throughout the two anxiety-inducing phases of the public speaking task (anticipation/speech preparation and speech performance) compared to participants who received placebo as measured by the SUDS ($p=0.044$). Converging findings favoring BNC210 were also observed in the State-Trait Anxiety Inventory (STAI). There were no safety and tolerability findings that altered the favorable profile of BNC210.

Subgroup analyses indicated that the younger participants showed more robust responses to BNC210 with significant separation from placebo ($p=0.023$) on the SUDS. This younger cohort may be particularly relevant given that SAD often exhibits onset during adolescence or early adulthood.

In conclusion, patients who received BNC210 exhibited a statistically significant separation over those receiving placebo across high-anxiety speaking task phases, which was enhanced in younger patients. BNC210 also possesses a favorable safety and tolerability profile compared

to the standard of care, including antidepressants and benzodiazepines. These results are expected to enable late-stage development of BNC210 in SAD.

W9. A PHASE 1, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, SAFETY, TOLERABILITY, AND PHARMACOKINETIC STUDY OF ESCALATING SINGLE AND MULTIPLE DOSES OF CVN766, AN OX1R HIGHLY SELECTIVE ANTAGONIST IN HEALTHY SUBJECTS

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Abstract: Orexin-A and orexin-B are two neuropeptides produced in the lateral hypothalamus from the same gene (HCRT) and bind to orexin 1 receptors (Ox1R) and orexin 2 receptors (Ox2R). Ox1R and Ox2R are G-protein coupled receptors that regulate intracellular calcium levels. While orexin-A is equipotent at both receptors, orexin-B shows a 10-fold selectivity for Ox2R. Ox1R is expressed in key brain areas important in regulating reward, motivation, emotions, stress responses and memory, whereas Ox2R is mainly involved in controlling sleep-wake cycles.

CVN766 is a potent and highly selective small-molecule Ox1R antagonist with no significant off-target activity. Nonclinical PK and toxicology studies have established its pharmacological characteristics and probable safety profile. CVN766 is currently in development for the treatment of negative and cognitive symptoms of schizophrenia.

Here we report the findings of a Phase 1, single and multiple ascending doses study to characterize the safety, tolerability, and pharmacokinetics of CVN766.

A total of 64 healthy subjects were enrolled and completed the study. 40 subjects entered the SAD portion of the study and were randomized to either placebo or one of 5 ascending dose levels, from 5 to 250 mg. Each cohort consisted of 8 subjects randomized to CVN766 or placebo in a 6:2 ratio. The 45 mg dose level was tested in fasted and fed conditions. In the MAD portion of the study, 24 subjects were assigned to one of three dose groups: 45 mg, 125 mg or 250 mg once a day for 7 days. In each cohort, subjects were randomized 6:2 to receive either CVN766 or placebo, respectively.

Overall, the demographic distribution among the groups was balanced for age with a slight prevalence of male subjects. All subjects completed the treatment period. Most of the adverse events (AEs) reported were mild. The most frequent treatment related AEs (TEAEs) were nausea and dizziness. There appeared to be no dose-relationship in the frequency and severity of AEs. Individuals exposed to CVN766 did not experience increased somnolence.

No clinically significant changes in vital signs, laboratory values and ECG parameters were observed.

Pharmacokinetics analysis revealed good dose proportionality with repeated exposures and steady state achieved by day 4-5.

There was minimal food effect detected in the 45 mg SAD cohorts.

Cerebrospinal fluid collected 3 hours post dose on day 1 in the 45 mg SAD cohort and at day 7 in the 45 mg MAD cohort enabled the calculation of a CSF/plasma ratio similar to that determined in rats (0.52 vs. 0.4), thus confirming good brain penetrance.

Overall, the findings from this Phase 1 study confirm the favorable safety and tolerability profile observed in the pre-clinical studies and support continuing the development of CVN766.

We are currently preparing a Phase 2 study for the treatment of negative and cognitive symptoms of schizophrenia. Based on the predicted receptor occupancy (RO), we expect doses 45 mg to 250 mg to reach RO between approximately 85% and 97%, which, based on the animal modes, should be more likely efficacious.

Given its mechanism of action and the functions of orexin A, it is possible that CVN766 could also improve aspects of the metabolic syndrome caused by antipsychotics, thus further contributing to an improvement in morbidity and quality of life for individuals suffering from schizophrenia.

W10. MM-402, R(−)-3,4-METHYLENEDIOXYMETHAMPHETAMINE, DEMONSTRATES PROSOCIAL AND THERAPEUTIC-LIKE EFFECTS IN FMR1 KNOCKOUT MICE, A PRECLINICAL MODEL OF AUTISM SPECTRUM DISORDER (DUE TO FRAGILE X SYNDROME).

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Abstract: Background: S,R(±)-3,4-methylenedioxymethamphetamine (SR-MDMA) is a substituted phenethylamine with structural and functional similarities to amphetamine-like psychostimulants and mescaline-like hallucinogens. Several ongoing and completed clinical trials are investigating SR-MDMA as a treatment for post-traumatic stress disorder along with other conditions. Previous studies of R-MDMA in pharmacodynamics models in wild-type animals have demonstrated its potential prosocial effects and reduced locomotor hyperactivity, though it is unknown whether these effects would be present in animals with phenotypical traits of ASD. We investigated a hypothesis of whether MM-402 (synthetic R(−)-3,4-methylenedioxymethamphetamine) in development for autism spectrum disorder (ASD), is efficacious in an animal model of ASD due to Fragile X syndrome (FXS) in Fmr1 knockout (KO) mice. The Fmr1 KO mouse lacks FMRP protein due to a disruption in its Fmr1 gene and this mouse model is well established for the study of ASD/FXS with symptoms of social deficits and repetitive behaviors. In addition, phenotypic traits such as hyperactivity and altered anxiety are observed in this model.

Methods: The study was conducted in 10-week-old male Fmr1 KO mice. Animals were dosed per os with vehicle, MM-402 (8, 17 and 30 mg/kg) or SR-MDMA (8 mg/kg) with a minimum 3-day washout between doses. Animals were observed in the Open Field Test including a grooming evaluation, Three-Chamber Social Interaction Test as well as an Ultrasonic Vocalization (USV) test. Compounds were administered 30 min prior to each behavioral test. Basic statistical analysis was performed. If more than 2 groups were compared with each other, significance was calculated by One-way or Two-way analysis of variance (ANOVA) followed by the Bonferroni post hoc test. In case of non-normally distributed data, significance was calculated by Kruskal-Wallis test followed by Dunn's multiple comparisons test.

Results: In the Three-Chamber Social Interaction Test, MM-402 dose dependently increased social interaction, measured by several parameters. For Arena Frequency, all three doses of MM-402 produced a significant difference vs vehicle treated animals in interaction with the stranger and empty chamber. Administration of SR-MDMA was not associated with significant

changes. In test endpoints such as Interaction Duration, Arena Frequency and Interaction Index with the stranger were statistically significant for MM-402 at 30 mg/kg with no effect produced by SR-MDMA (8 mg/kg).

In the USV test, male mice were exposed to fresh urine from the females in estrous cycle. Vocal emission was recorded for 5 minutes and analyzed for the total number of vocalizations and the latency to initiate the first call. Treatment with MM-402 and SR-MDMA at any dose significantly reduced the number of vocalizations.

In the Open Field test, MM-402 and SR-MDMA produced hyperactivity and increases in distance moved, with MM-402 resulting in a diminished effect compared to SR-MDMA. The number of grooming occasions, a representative trait of ASD, was decreased by both compounds, with MM-402 active at 17 and 30 mg/kg and less efficacious than SR-MDMA at 8 mg/kg.

Conclusion: This study demonstrated that administration of MM-402 increased social interaction of Fmr1 KO mice, one of the characterized preclinical models of ASD/FXS. MM-402 exhibited a robust effect on social interaction and was more potent than SR-MDMA with reduced hyperactivity effects. Both compounds suppress USV in male mice equipotently.

The results of this study support clinical development of MM-402 in ASD/FXS to determine whether it has similar prosocial effects in humans and the same therapeutic efficacy.

W11. SEX DIFFERENCES IN MITOCHONDRIAL METABOLISM OF ACETYL-L-CARNITINE IN SUBJECTS WITH COGNITIVE IMPAIRMENTS

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Abstract: The current study is an outgrow of mechanistic studies in rodents showing decreased levels of the pivotal mitochondrial metabolite acetyl-L-carnitine (LAC) in relation to cognitive deficits and depressive-like behavior (Neuron 2017, 10.1016/j.neuron.2017.09.020, PNAS 2013, 10.1073/pnas.1216100110). Specifically, the goal of this study was to ascertain the role of this specific mitochondrial signaling pathway in subjects with cognitive impairments (CI), and potential sex differences in these mechanisms. First, we used ultraperformance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS) to measure the levels of LAC and its main derivative free carnitine in available plasma samples (n=61) from a well-characterized cohort, including subjects with CI and age- and sex-matched cognitively healthy controls (HC). Our new findings showed decreased levels of LAC in subjects with CI as compared to age- and sex-matched HC. We also found important sex differences in the levels of carnitine in relation to cognitive function as assessed by using the Mini Mental Status Exam (MMSE). Specifically, the magnitude of carnitine deficiency reflected the severity of cognitive dysfunction in a sex-specific manner. Next, using computational approaches, we found that the integration of these mitochondrial measures with canonical biomarkers improves diagnostic accuracy. The current findings of sex differences in carnitine deficiency in subjects with CI

suggest a possible sex-specific mitochondrial phenotype of vulnerability to cognitive dysfunction and point to LAC-related mitochondrial metabolism as a new signaling pathway of cognitive regulation.

W12. ELECTROPHYSIOLOGICAL CORRELATES OF A KETAMINE INFUSION CAPTURED VIA THE PORTABLE CUMULUS NEUROCOGNITIVE PLATFORM USING REPEATED SAMPLING FROM THE CLINIC AND THE HOME

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Abstract: Background: An extraordinary effort has recently been made to identify valid, reliable and broadly usable biomarkers as potential tools for monitoring target engagement and drug efficacy in neuropsychiatric and other CNS clinical trials, particularly large-scale, real-world studies. Ideally, real world assessments should include both direct measures of neurophysiological mechanisms, and of the higher functions which are impacted by CNS conditions, that ultimately drive patient symptoms and quality of life. Here we describe objective measures of a range of domains including EEG that are user-friendly and suitable for frequent sampling – either in clinic (e.g. to examine pharmacodynamics) or over longer periods of time in the home. For methodological validation, we targeted well established ketamine EEG biomarkers including the mismatch negativity (MMN), gamma and alpha band power modulations. Passive and task-driven EEG recordings yielded metrics of targeted executive functions including error monitoring, working memory, decision making, and attention. A growing body of evidence suggests that gamma activity can be used as an indicator of the cortical-excitation inhibition balance and that ketamine could reverse the imbalances observed in depressed brains (McMillan and Muthukumaraswamy, 2020). Ketamine has also extensively been used as a model of schizophrenia, replicating the well-described deficits in early auditory sensory system observable in the MMN task.

Methods: 30 neurotypical adult males participated in a double-blind cross-over study. Racemic ketamine (0.5 mg/kg) or saline was administered intravenously in the clinic, flanked by two-weeks of at-home measurements, using the Cumulus functional neurophysiology platform (Barbey et al., 2022). Passive recordings during infusion (resting state and passive auditory oddball) were complemented with gamified tasks (2-stimulus visual oddball, Flanker) before and after the infusion, both in-lab (+/- 1 hour) and daily at-home (+/- 7 days).

Results: Over 1000 individual EEG sessions were recorded. Analyses of dissociative symptoms revealed acute, short lived psychomimetic effects of the drug. During ketamine infusion, resting state power-spectral density analyses showed suppression of alpha and beta band activity (8-25Hz), and enhancement of gamma band activity (>25Hz), primarily in the parietal lobe. The mismatch negativity (MMN) during infusion was reduced in amplitude and increased in latency. All EEG and cognitive behavioral points were successfully collected in the home, though without observing clear effects of ketamine.

Conclusion: Pharmacodynamic effects on both resting state and MMN during ketamine infusion indicated the engagement of the drug target. Neuropharmacological effects can be observed with easy-to-use dry EEG technology, both in the laboratory, and over longer baseline

and post-administration periods in the home, opening new possibilities in psychiatric clinical research, particularly in mood related disorders, including major depression disorder and bipolar disorder where gamma-band alterations have been described. The Cumulus platform is currently deployed in clinical trials across several neurodegenerative and neuropsychiatric indications.

W13. USING A TRANSLATIONAL EEG MEASURE OF SYNAPTIC FUNCTION FOR PATIENT STRATIFICATION IN MAJOR DEPRESSIVE DISORDER CLINICAL TRIALS

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Abstract: There is a growing body of evidence that dysregulation in synaptic function can lead to changes in neural plasticity and contribute to the development of mood disorders, including major depressive disorder (MDD). Dysregulation of synaptic function can manifest in changes in neural activity that can be measured using various neuro-biomarker techniques, including quantitative electroencephalography (qEEG), and thus there is potential that qEEG could be used as a biomarker to monitor placebo and treatment response in patients with MDD.
We have identified a translational qEEG tool that indexes synaptic strength in the frontal cortex and can be applied to MDD patients prospectively to differentiate placebo responders and drug responders. Previous studies consistently show that electrical stimulation in the alpha frequency range (6-10 Hz) increases synaptic strength and induces long term potentiation (LTP), whereas delta stimulation (~2 Hz) decreases synaptic strength and induces long-term depotentiation (LTD) as measured by changes in field excitatory postsynaptic potentials (fEPSP). In both rats and humans, we have identified a novel qEEG pattern reflecting a ratio of alpha and delta frequencies that corresponds with both synaptic function and behavior response. This novel qEEG pattern can be used for patient stratification to potentially reduce the overall placebo response in clinical trials, and increase the efficacy signal vs placebo of novel synaptic function-enhancing therapeutics.

Preclinical qEEG: In freely behaving rats, we found that active wake behavior enhanced frontal cortical alpha power and was associated with increased synaptic strength and LTP induction in the medial prefrontal cortex as measured by fEPSP. In contrast sleep deprivation was related to decreased alpha and synaptic strength and increased delta and LTD.

Human qEEG: We examined frontal alpha and delta qEEG and insomnia measures in the Establishing Moderators and Biosignatures of Antidepressant Response for Clinical Care for Depression (EMBARC) subjects were segregated into placebo responder and non-responders, and baseline resting qEEG was analyzed before randomization. Placebo non-responders showed more delta EEG and less alpha, and greater middle insomnia score as compared to the placebo responders. In a prospective analysis of these data, subjects with high delta to low alpha ratio showed a smaller placebo response than the high alpha to low delta ratio subjects.

Conclusion: Depressed subjects that exhibit high delta / low alpha resting EEG and elevated middle insomnia scores are likely have an underlying deficit in synaptic function and have been shown to generally have a lower response to placebo. The data here provide a potential framework for using qEEG as a guiding-biomarker for stratifying patients with reduced synaptic function, and patients that may have a lower placebo response in clinical trials.

W14. ANHEDONIA IS A CONSEQUENCE OF MEMORY CONSTRAINTS AND IS AMELIORATED BY κ-OPIOID ANTAGONISM

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Abstract: Anhedonia, the inability to experience pleasure, is a common symptom in numerous psychiatric conditions. Despite its prevalence and burden, we are limited in our ability to treat it. This is in large part because we lack a basic understanding of how to define anhedonia. Computational psychiatry, a burgeoning new field, offers promise. Just like understanding how the heart functions as a pump allowed for better treatment of cardiac pathologies, understanding how the brain functions as a computer, and how those computations go awry in psychiatric illness, will provide a new path towards treating psychopathology.

We have recently developed a broad theory of decision making, which we call policy compression. This framework assumes agents not only seek to maximize reward, but also seek to minimize cognitive cost, which we formalize as the mutual information between actions and states of the environment. Policy compression explains how we act under memory constraints - when we are forced to operate under severe memory constraints, like those that may exist in psychiatric disease, our behavior suffers in predictable ways. Policy compression has broad explanatory power, including describing perseveration, response times, action chunking, state chunking, and reward sensitivity. We have recently shown that policy compression is applicable to psychiatry by identifying novel cognitive deficits in schizophrenia (Gershman and Lai 2021). Here, we aimed to apply policy compression to explain anhedonia.

Recently, in the first clinical trial to use NIMH's 'fast-fail' approach, a novel κ-opioid receptor (KOR) antagonist was developed and tested to treat anhedonia, with promising results (Krystal et al. 2020). One assay used in this study was the Probabilistic Reward Task, a reward-based perceptual decision-making task. In this task, subjects are asked to categorize two ambiguous stimuli, with one stimulus providing greater reward than the other stimulus. Given this perceptual ambiguity, an adaptive strategy is to form a 'response bias,' or a tendency to pick the more rewarding option more often. Subjects with anhedonia, across diagnostic boundaries, frequently fail to form this response bias, which is taken as a behavioral signature of anhedonia (Pizzagalli et al., 2005, 2008; Luc, Pizzagalli, Kangas 2021). As expected, KOR therapy restored response biases in subjects with high anhedonia. While exciting, this analysis is limited in that it does not provide insight into how anhedonia arises, simply that it has a behavioral signature.

We reanalyzed these data using policy compression, with the goal of developing a novel computational phenotype of anhedonia. We found that subjects with anhedonia have few cognitive resources to allocate to the task, and that KOR antagonism increases their cognitive capacity - effectively increasing the memory that subjects can allocate to harvest reward. We additionally found that subjects with anhedonia are inefficient with their limited cognitive resources, and that KOR antagonism allows them to more efficiently make decisions. Motivated by these findings, we next sought to determine how KOR therapy changed the decision-making strategy implemented by subjects. We developed and fit a reinforcement learning model inspired by policy compression. We found that KOR antagonism modulates learning and decision-making parameters, allowing for more optimal behavior.

Altogether, these preliminary findings support a novel computational interpretation of anhedonia: inefficient utilization of cognitive resources, with restoration by KOR antagonism.

W15. EVALUATION OF MANIA AND HYPOMANIA IN LATE-PHASE CLINICAL TRIALS OF LUMATEPERONE IN THE TREATMENT OF MAJOR DEPRESSIVE EPISODES ASSOCIATED WITH BIPOLAR I OR BIPOLAR II DISORDER

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Abstract: Background: Lumateperone (LUMA) is an FDA-approved antipsychotic to treat schizophrenia and depressive episodes associated with bipolar I or bipolar II disorder as monotherapy and as adjunctive therapy with lithium or valproate. This analysis evaluated mania and hypomania across short- and long-term studies of LUMA 42 mg in patients with bipolar depression.

Methods: Trials enrolled adults (18-75 years) with bipolar I or bipolar II disorder experiencing a major depressive episode (Montgomery-Åsberg Depression Rating Scale Total score≥20 and Clinical Global Impression Scale-Bipolar Version-Severity [CGI-BP-S] score≥4). LUMA 42mg was administered once daily in the evening.

This analysis included 3 groups: (1) data pooled from 2 short-term, 6-week, placebo (PBO)-controlled studies of LUMA 42-mg monotherapy (Study 401 [NCT02600494]; Study 404 [NCT03249376]); (2) a 6-month open-label extension period (OLE) of Study 401 that evaluated long-term effects of LUMA 42-mg monotherapy; (3) a 6-week, PBO-controlled study (Study 402, NCT02600507) that investigated LUMA 42-mg therapy adjunctive with lithium or valproate.

Assessments included the incidence and severity of mania/hypomania treatment-emergent adverse events (TEAEs) in the safety population (all patients who received ≥1 dose of study drug). The Young Mania Rating Scale (YMRS) Total score and CGI-BP-S Mania subscore were measured in the intent-to-treat (ITT) population (patients who received ≥1 dose and had a valid baseline and ≥1 valid post-baseline MADRS assessment) in PBO-controlled studies.

Results: The short-term safety population comprised 746 patients in pooled monotherapy trials (PBO, 374; LUMA, 372) and 352 patients in the adjunctive study (adjunctive PBO, 175; adjunctive LUMA, 177). Mania/hypomania TEAEs were reported in 11 patients (PBO, 5 [1.3%]; LUMA, 6 [1.6%]) in the pooled monotherapy groups and in 2 patients (adjunctive PBO, 1 [0.6%]; adjunctive LUMA, 1 [0.6%]) who received adjunctive treatment. Mania/hypomania TEAEs were mild or moderate in severity. There was 1 serious TEAE of mania in the LUMA monotherapy group and no serious TEAEs of hypomania. The ITT population comprised 719 patients in pooled monotherapy trials (PBO, 365; LUMA, 354) and 348 patients in the adjunctive study (adjunctive PBO, 174; adjunctive LUMA, 174). Mean change in YMRS Total score from baseline to Day 43 was similar with LUMA and PBO in monotherapy trials (least squares mean difference vs PBO [LSMD], −0.5; 95% confidence interval [CI] −1.0, 0.1; P=.10) and the adjunctive study (LSMD, −0.2; 95% CI −0.8, 0.4; P=.56). Change from baseline to Day 43 in CGI-BP-S Mania subscore with LUMA was also similar to PBO for monotherapy trials (LSMD, −0.0; 95% CI −0.1, 0.1; P=0.77) and the adjunctive study (LSMD, 0.0; 95% CI −0.1, 0.1; P=.83).

The long-term OLE safety population comprised 127 patients. One patient (0.8%) had a mild mania TEAE which was not serious. No patients had TEAEs of hypomania. There was not a significant mean change from baseline to end of treatment in YMRS score with LUMA treatment (−0.5; 95% CI −1.7, 0.6; P=.37). LUMA therapy significantly improved CGI-BP-S Mania subscore from baseline to end of treatment (mean change from baseline: 0.2; 95% CI 0.0, 0.4; P<0.05).

Conclusion: In patients with bipolar depression, LUMA 42-mg monotherapy or adjunctive therapy was associated with low rates of treatment-emergent mania and hypomania that were similar to those of PBO-treated patients in both acute and long-term treatment.

W16. CHANGES IN METABOLIC PARAMETERS ASSOCIATED WITH LUMATEPERONE IN LATE-PHASE CLINICAL TRIALS FOR THE TREATMENT OF MAJOR DEPRESSIVE EPISODES ASSOCIATED WITH BIPOLAR I OR BIPOLAR II DISORDER

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Abstract: Background: Atypical antipsychotics are correlated with a range of metabolic adverse effects including weight gain. Lumateperone is an FDA-approved antipsychotic to treat schizophrenia and depressive episodes associated with bipolar I or bipolar II disorder as monotherapy and as adjunctive therapy with lithium or valproate. A robust late phase clinical trial program established the safety and efficacy of lumateperone 42 mg in patients with a major depressive episode (MDE) associated with bipolar I or bipolar II disorder. This analysis evaluated the metabolic impact of lumateperone 42 mg across short- and long-term studies in patients with bipolar depression.

Methods: All trials enrolled adults (18-75 years) with bipolar I or bipolar II disorder experiencing an MDE (Montgomery-Åsberg Depression Rating Scale Total score ≥20 and Clinical Global Impression Scale-Bipolar Version-Severity score ≥4 at screening and baseline). Lumateperone 42 mg was administered once daily in the evening.

This analysis included 3 groups: (1) data pooled from 2 short-term, 6-week, placebo-controlled studies of lumateperone 42-mg monotherapy (Study 401 [NCT02600494]; Study 404 [NCT03249376]); (2) a 6-month open-label extension period (OLE) of Study 401 that evaluated long-term effects of lumateperone 42-mg monotherapy; (3) a Phase 3 placebo-controlled study (Study 402, NCT02600507) that investigated lumateperone 42-mg therapy adjunctive with lithium or valproate.

Metabolic assessments included changes in weight, body mass index (BMI), waist circumference, and cardiometabolic laboratory parameters. Subgroup analyses were conducted in patients who were classified by baseline BMI as underweight, normal weight, overweight, or obese.

Results: The short-term safety population comprised 746 patients in pooled monotherapy trials (placebo, 374; lumateperone 42 mg, 372) and 352 patients in the adjunctive study (adjunctive placebo, 175; adjunctive lumateperone 42 mg, 177). In the short-term studies, mean changes from baseline to end of treatment with lumateperone were similar to placebo for weight, BMI, and waist circumference. No patients treated with lumateperone had potentially clinically

significant (PCS) weight gain (≥7% increase) during treatment. PCS weight loss with lumateperone monotherapy or adjunctive therapy was observed in those who were overweight (2 patients) or obese (2 patients) at baseline. Mean change from baseline to the end of treatment with lumateperone was similar to placebo for total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, glucose, or insulin in the monotherapy and adjunctive therapy trials.

The long-term OLE safety population comprised 127 patients. There was no mean increase from baseline to the end of treatment in weight, BMI, or waist circumference with lumateperone. During the 175-day treatment period, 3.4% of patients (2 normal BMI, 2 obese patients at baseline) experienced PCS weight increase and 6.0% had PCS weight loss (1 normal weight, 3 overweight, 3 obese patients at baseline). There were no clinically significant changes from baseline to end of treatment in total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, glucose, or insulin.

Conclusion: In patients with bipolar I or bipolar II disorder experiencing an MDE, lumateperone 42-mg monotherapy or adjunctive therapy had a favorable metabolic profile for both acute and long-term treatment.

W17. MODIFIABLE BEHAVIORAL TARGETS ASSOCIATED WITH SUBSYNDROMAL SYMPTOMS OF DEPRESSION IN BIPOLAR DISORDER

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Abstract: Background: Bipolar disorder (BD) is a devastating chronic psychiatric illness. Historically, clinical outcomes have centered around treatment response and resolution of acute episodes with the expectation that patients return to normal/pre-morbid functioning. However, emerging evidence suggests that there is substantial individual variability with up to half of all patients with BD experiencing subthreshold symptoms of depression during remitted phases, accompanied by related functional disability. Subsyndromal symptoms of depression also increase an individual's risk for affective relapse and contribute to prolonged episode duration. Subsyndromal symptoms suggest only partial recovery, despite the implementation of standard of care. If we can identify factors that are associated with this incomplete treatment response, we can direct therapeutic efforts toward these as targets for improving quality of life

Methods: We assessed 261 inter-episode individuals with BD for depressive symptoms, sleep quality, coping styles, and psychosocial functioning using standardized scales.

Results: As in prior work, we defined subsyndromal depression as a score on the Hamilton Rating Scale for Depression (HRSD) between 7-17; 40% (n=104) of the sample met this threshold and were compared with asymptomatic (HDRS < 6; n=130) patients and a smaller subset (n=27) who endorsed severe symptoms of depression (HDRS > 18). Compared to asymptomatic individuals, those with subsyndromal symptoms of depression endorsed significantly more functional disability across several domains (all ps < .001), higher levels of sleep disturbance ($F = 16.32$, $p < .001$), less emotional support coping, and more maladaptive and self-blaming coping ($F = 5.25$, $p < .05$; $F = 8.43$, $p < .001$; $F = 16.21$, $p < .001$, respectively). The only significant difference between the subsyndromal group and the severe group was the use of less self-blaming coping ($F = 16.21$, $p < .001$). There were no significant differences between individuals with subsyndromal depression and those with severe depression on

functional disability, emotional support coping, or maladaptive coping between individuals with subsyndromal depression and those with severe depression.

Conclusion: In line with recent estimates, almost 40% of our sample endorsed subsyndromal symptoms of depression and exhibited functional impairment comparable to that seen in more severe depression. Traditional maintenance therapy focused solely on extending the time between acute episodes may not be enough to promote a full recovery and optimize psychosocial functioning for a substantial proportion of individuals with BD. Treating modifiable behavioral targets associated with subsyndromal symptoms of depression such as sleep and coping behaviors may not only help prevent relapse but also improve psychosocial functioning and quality of life.

W18. LONG-TERM LITHIUM-THERAPY AND THYROID DISORDERS IN BIPOLAR DISORDER: A HISTORICAL COHORT STUDY

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Abstract: Background: Lithium has been a cornerstone treatment for bipolar disorder (BD). Despite descriptions in the literature regarding associations between long-term lithium therapy (LTLT) and development of a thyroid disorder (overt/subclinical Hypo/Hyperthyroidism, thyroid nodule, and goiter) in BD, factors such as time to onset of thyroid abnormalities and impact on clinical outcomes in course of illness have not been fully characterized. In this study we aimed to compare clinical characteristics of adult BD patients with and without thyroid disorders who were on LTLT.

Methods: Adult BD patients on LTLT for ≥1 year who enrolled in the Mayo Clinic Bipolar Disorder Biobank were included. Our primary outcome was the development of incident thyroid disorder and investigated sex differences on time of onset to thyroid disorders. Our secondary outcome was response to lithium among patients with and without Thyroid disorders. Cox proportional models were used to find the median time to the development of a thyroid disorder. Kaplan–Meier plots were used to show the time from lithium initiation to the development of Thyroid disorders among sexes. All analyses were performed using R software and a p-value ≤ 0.05 was considered significant.

Results: A total of 154 patients with BD on LTLT of which 18 patients were excluded due to presence either of a preexisting thyroid disorder or missing data. In our primary analysis (N=136) mean age of participants was 40.5, predominantly females (57.4%) and with BD type I (69.9%). Compared to the non-Thyroid disorders group, patients with thyroid disorders had a higher median MCIRS scores (18 vs 21; p=0.01) and borderline increased history of trauma (32% vs 50%, p=0.05). At one year of Li treatment 7% (n=9/131) patients developed a thyroid disorder. Thirty two percent patients (n=43/136) developed a new thyroid disorder by the study

end date, of which 79% (n=34/43) developed overt or subclinical hypothyroidism and 94% (32/34) of these patients (with subclinical/overt hypothyroidism) were on THR receiving treatment with levothyroxine. Only 2 patients discontinued Li due to the development of thyroid disorders. The median time to the development of a Thyroid disorder was significantly lower in females as compared to males (17.0 vs 42.6 years, p=0.04). Compared to males, females had a higher risk for a Thyroid disorder (HR=2.00, 95% CI, 1.02 to 3.95: log-rank p= 0.04). Mean Alda-A scores were also similar among the Thyroid disorders and non-Thyroid disorders group (6.26 vs. 6.38; p=0.92). Limitations are inherent shortcomings of a retrospective study design, smaller cohort size and its limited diversity.

Conclusion: One-third BD patients on LTLT developed a thyroid dysfunction, with similar Li response rates between groups. Our study complements previous literature and suggests closely monitoring thyroid hormone functions during Li treatment for early identification and diagnosis of thyroid disorders.

W19. OLANZAPINE/SAMIDORPHAN EFFECTS ON WEIGHT GAIN: A POOLED ANALYSIS OF PHASE 2 AND 3 RANDOMIZED, DOUBLE-BLIND STUDIES

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Abstract: Background: Olanzapine has established efficacy in patients with schizophrenia (SZ) or bipolar I disorder (BD-I), but associated weight gain and metabolic sequelae have limited its clinical use. Olanzapine/samidorphan (OLZ/SAM; Lybalvi, Alkermes, Inc.) is approved in the United States for the treatment of adults with SZ or BD-I. OLZ/SAM was designed to maintain the established antipsychotic efficacy of olanzapine while reducing the risk of weight gain. This pooled post hoc analysis evaluated differential OLZ/SAM vs olanzapine weight change profiles from studies where change in body weight was a primary or secondary endpoint.

Methods: This pooled analysis included 3 randomized, double-blind studies assessing the weight change profile of OLZ/SAM vs olanzapine: a phase 2, 12-week efficacy and safety study in patients with SZ (NCT01903837); a phase 3, 24-week pivotal weight study in patients with SZ (NCT02694328); and a phase 3, 12-week study in patients with recent-onset SZ, schizophreniform disorder, or BD-I (NCT03187769). Adult patients aged ≥18 years with SZ or BD-I, or those with schizophreniform disorder who were diagnosed with SZ or BD-I by week 12, were included in the analysis. Patients receiving daily OLZ/SAM (olanzapine 5-20 mg + samidorphan 10 mg) or olanzapine (5-20 mg) who had ≥1 postbaseline weight assessment by week 12 were included. The primary outcome evaluated, percent change in body weight at week 12, was analyzed using a mixed effects for repeated measures model. Secondary outcomes assessing the proportions of patients with ≥7% or ≥10% weight gain from baseline at week 12 were analyzed using a generalized linear mixed model. Metabolic changes and adverse events were examined as additional outcomes.

Results: Among the 1336 patients randomized to the 3 studies, 1063 (79.6%; NCT01903837, n=161; NCT02694328, n=538; NCT03187769, n=364) patients who met inclusion criteria and

had ≥1 postbaseline weight assessment by week 12 were included in this pooled analysis. Baseline mean (SD) age was 35.2 (10.7), 308 (29%) were female, 440 (41.4%) were White, and mean (SD) body mass index (BMI) was 24.8 (3.3) kg/m2. At week 12, OLZ/SAM treatment was associated with a lower least-square mean (LSM) percent change in body weight from baseline (3.68%) vs olanzapine (5.43%) (LSM [SE] difference=-1.75% [0.41]; 95% CI=-2.55, -0.94). Fewer patients treated with OLZ/SAM vs olanzapine gained ≥7% of baseline body weight (23.9% vs 34.6%; odds ratio [OR]=0.58; 95% CI=0.43, 0.79) or ≥10% of baseline body weight (13.7% vs 20.4%; OR=0.60; 95% CI=0.42, 0.88). Changes in metabolic parameters were similar between OLZ/SAM and olanzapine treatments at week 12, as were the percentages of patients with adverse events.

Discussion: In this pooled analysis of similarly designed studies evaluating weight gain and associated outcomes between OLZ/SAM and olanzapine, treatment with OLZ/SAM was consistently associated with less weight gain and reduced odds of reaching ≥7% or ≥10% body weight gain from baseline vs olanzapine. These findings highlight the consistency with which OLZ/SAM mitigates olanzapine-associated weight gain, an effect that has been demonstrated across multiple studies.

W20. ASSESSING TEMPORAL PERFORMANCE OF MACHINE LEARNING PIPELINES PREDICTING DATA QUALITY ISSUES IN A SCHIZOPHRENIA CLINICAL TRIAL

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Abstract: Background: Data quality concerns can have a detrimental effect on signal detection (Kott, 2021; Umbricht, 2020). We have previously reported the development of a sequential machine learning pipeline predictive of data quality concerns (Kott, 2022). The process utilizes screening data and updates the prediction as subjects progress through the trial. In the current analysis we assessed the temporal performance of two selected pipelines, predicting within PANSS logical discrepancies and outlying variability in an acute schizophrenia clinical trial.

Methods: Two layered machine learning pipelines were trained across a number of acute schizophrenia clinical trials and implemented into a single trial. For both pipelines the structure is identical. The first layer is a parsimonious model that uses only the most common screening data available. As the patient progresses to baseline, a second more complex model is utilized that includes both screening and baseline data. The third layer implements data from independent audio reviews. Once the patient gets randomized, the fourth layer utilizing study specific data is enabled. One model predicts within PANSS logical inconsistencies, the other outlying data variability. Both models were implemented at the same time and their performance measured over the next 12 months. Both models were trained to maximize prediction and accuracy.

Results: Both models exhibited acceptable levels of accuracy and precision. For the model predicting the high variability, the average accuracy rate was 76.4% with the minimal value of 66.4% and maximal of 85.5%. The average precision rate was 81.1% with the minimal value of 68.1% and maximal 91.3%. For the within PANSS logical inconsistencies model, average

accuracy was 94.9% with the minimal values of 91.7% and maximal value of 97.0%. Average precision was 99.0% with minimal value of 93.3% and maximal value of 100%.

Discussion: The goal of implementing data analytics into clinical trials is to retrospectively identify and address emerging data quality concerns before these become a significant problem for signal detection. The advance of machine learning allows a fundamental shift where future data quality concerns can be predicted before actually happening. We have developed and monitored for a year the performance of two ML pipelines predicting 2 types of common data quality concerns in acute schizophrenia clinical trials, namely outlying PANSS variability and within PANSS logical inconsistencies. Our Results: show promising stability in both accuracy and precision, two indicators the models were trained to maximize. This means that the hits the model predicted actually subsequently appeared in the data and the rate of false positives was very low. The models however did not manage to predict all the data concerns and further work is necessary to improve the performance in this regard.

W21. RISK OF PSYCHIATRIC DISORDERS POST ANTIBIOTIC USE IN INPATIENT ADULTS: A MULTICENTER RETROSPECTIVE COHORT STUDY

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Abstract: Background: Mental illness, affecting 20% of adults in the United States, is a major contributor to disability worldwide. Previous literature shows evidence that antibiotic use may affect mental health by altering the gut microbiome. However, the conclusion is still equivocal. Our study aimed to investigate the relationship between antibiotic exposure and the development of various psychiatric disorders in a historical cohort study.

Methods: A retrospective cohort study using TriNetX (a large database of approximately 69 million patients from 54 large healthcare organizations) was conducted. We included in-patients aged 18-89 who did not receive antibiotics within six months prior to admission between Jan 1st, 2013, to Dec 31, 2015. Patients had at least one follow-up visit after six months post-discharge. Subjects with prior neuropsychiatric diagnoses and C Reactive Protein (CRP) levels > 3 mg/L were excluded. The primary outcome was defined as psychiatric diagnoses, including anxiety, trauma, and stress-related disorders, depression and bipolar disorder, psychosis, self-harm, and suicidality, based on ICD- 10-CM criteria from 6 months to five years post-discharge. Univariate Logistic regression analysis was conducted to assess the association between antibiotic exposure/use and psychiatric diagnoses within 6 months to five years after discharge, adjusting for covariates (age, race, ethnicity, sex, BMI, weight, as well as medications, diagnoses, and procedures that could potentially affect microbiome or mental health). Cox proportional hazards models were used to estimate hazard ratios (HRs) for exposure to outcome.

Results: The cohort included 8594 adult male patients and 16,457 matched controls, the mean age for the treatment and control groups were 57.87 ± 15.02 and 57.28 ± 15.46. In males, antibiotic use was found to be associated with a significantly decreased risk of novel anxiety

(HR [95% CI] = 0.8794 [0.8170, 0.9466]; p=0.0006), mood disorders (HR [95% CI] = 0.8359 [0.7702, 0.9072]; p<0.0001), and Self Harm (HR [95% CI] = 0.7325 [0.5472, 0.9804]; p=0.0364) diagnoses.

The female cohort included 11,620 and 25,098 age-matched controls. The mean ages were 57.87 ± 17.40 and 57.28 ± 16.76. Female patients had a significantly reduced risk of anxiety (HR [95% CI] = 0.929 [0.8815, 0.9790]; p=0.0059) and mood disorder (HR [95% CI] = 0.9396 [0.8859, 0.9965]; p=0.0378) diagnoses in follow-up.

After stratifying age, no significance was found between antibiotic use and any measured outcome in the 18- to 25-year-old group. The 26- to 49-year-old group showed significantly reduced risk of novel anxiety (HR [95% CI] = 0. 904 [0.8398, 0.9730]; p=0.0072) and mood disorder (HR [95% CI] = 0. 8681 [0.7984, 0.9438]; p=0.0009). The 50 or older age group showed significantly reduced risk of novel anxiety (HR [95% CI] = 0. 916 [0.8669, 0.9679]; p=0.0018), mood disorder (HR [95% CI] = 0. 9124 [0.8587, 0.9695]; p=0.0031), psychosis (HR [95% CI] = 0. 8279 [0.6909, 0.9920]; p=0.0407), and self-harm (HR [95% CI] = 0. 6744 [0.4931, 0.9225]; p=0.0137). No mediating effect of CRP on diagnoses was noted.

Conclusion: In this large population-based cohort study, we report that the use of antibiotics during treatment was associated with reduced risks of various neuropsychiatric disorders, specifically in ≥ 50 years of age. Our study findings suggest that antibiotic treatment during inpatient hospital settings may provide some protection against the development of psychiatric disorders post-discharge. Future large cohort studies are required to investigate the relationship between antibiotics use and neuropsychiatric disorders as well as sex differences.

W22. THE IMPACT OF METABOLIC DYSREGULATION ON COGNITION IN MOOD DISORDERS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Abstract: Background: Individuals with mood disorders are predisposed to cardiometabolic comorbidities, including metabolic syndrome and type 2 diabetes. These metabolic disturbances converge on insulin resistance which is strongly associated with greater depressive symptoms, psychosis, and cognitive decline. Therefore, due to their shared pathophysiology, this study aims to explore whether metabolic dysfunction in mood disorders has an impact on cognitive function.

Methods: Ovid MEDLINE, Embase, PsycInfo, CINAHL, Scopus, and Web of Science were searched for articles of populations with comorbid mood disorders and metabolic dysregulation that reported on cognitive outcomes. A random-effects meta-analysis on global cognition was conducted in individuals with mood disorders and a comorbid metabolic abnormality.

Results: Twenty studies were included in this meta-analysis (n=984 with major depressive disorder (MDD), n=1046 with bipolar disorder (BD), n=2352 with self-report depression/depressive symptoms). Comorbid metabolic dysregulation, encompassing type 2 diabetes, metabolic syndrome, and individual components of metabolic syndrome, resulted in significant reduction in cognitive function among individuals with mood disorders (-0.34 Standard Mean Difference (SMD), 95% Confidence Interval (CI) [-0.45, -0.23], p<0.00001,

I2=85%). These effects were significant within each mood disorder subgroup, including diagnosed MDD (-0.30 SMD, 95% CI [-0.50, -0.10], p=0.004, I2=81%, n=5 studies), BD (-0.35 SMD, 95% CI [-0.50, -0.20], p<0.00001, I2=82%, n=10), and self-report depression/depressive symptoms (-0.43 SMD, 95% CI [-0.70, -0.16], p=0.002, I2=88%, n=5).

Conclusion: Overall, metabolic dysregulation appears to have a significant negative impact on cognition in individuals with mood disorders. Further research is required to understand the underlying mechanisms of this interplay between mood disorders, metabolism, and cognition.

W23. STEROID EFFICACY IN ADOLESCENTS WITH COVID-19- ASSOCIATED NEUROPSYCHIATRIC SEQUELAE

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Abstract: Psychosis and catatonia have been reported as neuropsychiatric sequela of COVID-19 infection. COVID-19 can provoke an extensive immune response affecting the striatum, limbic system, and frontal cortex, which is hypothesized to be the underlying mechanism of neuropsychiatric complications. Authors have observed several adolescents with no previous psychotic disorder, presenting with acute psychosis and catatonia following COVID-19.
We describe two adolescents, Patient A (17) and Patient B (16) with recent COVID-19 exposure who presented with rapid-onset psychosis, worsening mentation, and catatonic features. Notable presenting symptoms included paranoid and bizarre delusions, confusion, thought blocking, and significant decline in attention, concentration, fund of knowledge, recent and remote memory, and information processing speed.

Diagnostic workup revealed nonspecific elevated CSF protein and subtle flair hyperintensities on MRI. The remaining workup was negative, including CSF antibodies for autoimmune encephalitis. Due to equivocal response with psychotropic medications, treatment for neurological sequelae of COVID-19 was proposed. Patients received IV methylprednisolone followed by prednisone taper. The patients' psychosis and cognition rapidly improved and they progressed to discharge. Following discharge, Patient B experienced continued improvement; Patient A required readmission and second course of methylprednisolone.

There are limited case reports/series describing new-onset psychosis in adolescents exposed to COVID-19. We encourage the consideration of COVID-19-related neuropsychiatric complications in the differential diagnosis for teens presenting with acute new-onset psychosis. IV Steroids demonstrated efficacy in treating post-COVID neuropsychiatric sequelae in our patients. Empirical steroid treatment in suspected cases can lead to significant improvements and decreased hospital stay.

W24. AGITATION IN ALZHEIMER'S DEMENTIA: DEFINING A MEANINGFUL WITHIN-PATIENT CHANGE FOR THE COHEN-MANSFIELD AGITATION INVENTORY (CMAI)

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Abstract: Background: The Cohen-Mansfield Agitation Inventory (CMAI) is a questionnaire to assess the frequency of agitation behaviors in elderly persons (including those with Alzheimer's dementia) based on caregiver information. The CMAI was the primary efficacy measure in three Phase III, 12-week, randomized, double-blind, placebo-controlled, parallel-arm clinical trials of brexpiprazole in patients with agitation associated with Alzheimer's dementia (AAD) (NCT01862640 [Trial 1], NCT01922258 [Trial 2], NCT03548584 [Trial 3]). The aim of this post hoc analysis was to determine a threshold that would constitute a meaningful within-patient change (MWPC) in CMAI Total score, using data from the three brexpiprazole trials.

Methods: Anchor-based and distribution-based Methods: were used to identify an appropriate range for an MWPC threshold. The Clinical Global Impression – Severity of illness (CGI-S) as related to agitation, and the Clinical Global Impression – Improvement (CGI-I), which were secondary endpoints in the three trials, were used as anchor scales to determine a magnitude of CMAI improvement that clinicians considered as meaningful. The anchor-based analyses were supported by empirical cumulative distribution functions (eCDFs) and probability distribution functions (PDFs), and distribution-based methods which use statistical parameters related to the distribution of scores in a relevant sample. The MWPC analyses were conducted in two phases, initially using pooled data from Trials 1 and 2, followed by a sensitivity analysis using data from Trial 3 (Trial 3 had slightly different inclusion criteria, resulting in higher mean baseline CMAI Total scores than in Trials 1 and 2). A responder analysis determined the proportion of patients who had an improvement in CMAI Total score greater than or equal to the defined threshold for meaningful change. Responder data are reported for the following brexpiprazole doses (pooled): Trial 1, fixed-dose brexpiprazole 2 mg/day; Trial 2, flexible-dose brexpiprazole 0.5–2 mg/day; Trial 3, fixed-dose brexpiprazole 2 or 3 mg/day.

Results: Overall, the change in CMAI Total score showed good correlation with the CGI-S and CGI-I at Week 12 (0.65 and 0.68, respectively; three trials pooled), suggesting that both the CGI-S and CGI-I were good anchors for the analysis. Triangulation of evidence from the anchor-based and distribution-based analyses of the pooled data from Trials 1 and 2 suggested an MWPC threshold for CMAI Total score in the -15 to -20 range. An additional analysis of Trial 3 data confirmed these overall findings and suggested that a slightly higher change in CMAI Total score (-25 points) would constitute a meaningful improvement, providing an MWPC range of -15 to -25 points. The characterization of the meaningful change, as illustrated by eCDFs and PDFs, showed good distribution and good separation of the change in CMAI Total score between the categories defined by the anchors. Using the threshold for MWPC of -20 points, the percentage of responders at Week 12 (i.e., those who had an improvement in CMAI Total score of at least 20 points) across the three trials was 52% for brexpiprazole and 38% for placebo. At the -20 points threshold, response rates in the individual trials ranged from 47–57% for brexpiprazole and 37–41% for placebo.

Conclusion: The MWPC threshold helps with the interpretation of the clinical relevance of clinical trial results. Applying an MWPC threshold to three clinical trials of brexpiprazole in AAD demonstrates that brexpiprazole is consistently associated with more meaningful improvements on the CMAI compared with placebo.

W25. PHASE 2 STUDY DESIGN AND NEW DATA FROM THE PHASE 1 SAD/MAD TRIAL OF LHP88, A SECOND-GENERATION GINGIPAIN INHIBITOR FOR THE TREATMENT OF P. GINGIVALIS-ASSOCIATED DEMENTIA

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Abstract: Background: The novel mechanism of action of LHP588 is based on the discovery of gingipains, toxic protease virulence factors from the bacterial pathogen Pg, in postmortem brains of patients with a pathologic diagnosis of Alzheimer's disease (AD). Gingipain levels correlated with tau and ubiquitin pathology, and oral infection of wild-type mice with Pg resulted in an A□1-42 response, consistent with evidence that A□1-42 is an antimicrobial peptide. In addition, Pg-induced brain inflammation and neurodegeneration in wild-type mice after oral Pg infection was blocked by gingipain inhibitors.

LHP588 is an orally bioavailable and brain-penetrant lysine-gingipain inhibitor that reduces the toxicity of Pg and the bacterial load. A first-generation molecule (atuzaginstat) previously showed reduction of cognitive decline in prespecified cohorts defined by their infection load, but it was discontinued due to a hepatic safety signal.

We will review data from the prior study, data demonstrating the improved selectivity and ADME-PK of LHP588 along with data from the new Phase I SAD/MAD, and show how these inform the design of the Phase 2b study of LHP588 starting later this year.

Methods: The previous Phase 2/3 study with atuzaginstat was a 3-arm, randomized, double-blind, placebo-controlled study in 643 subjects with baseline MMSE scores of 12-24. The Phase 1 study of LHP588 enrolled 32 individuals in the SAD component with 4 cohorts and concurrent placebo (25 mg, 50 mg, 100 mg, 200 mg) and 24 healthy subjects in the 10-day MAD portion, with 3 cohorts and concurrent placebo (50, 100 mg, and 200 mg).

Results: In the study of atuzaginstat, significance was not observed in the full intent-to-treat population, however, prespecified subgroup analyses indicated efficacy in patients with Pg detected in saliva (Pg+), slowing cognitive decline compared with placebo on the ADAS-Cog11 approximately 50% ($p = 0.02$). These findings were consistent across multiple biomarkers of Pg load, including anti-Pg antibodies in CSF, and across statistical sensitivity analyses. Changes in Pg DNA in saliva from weeks 0-24 correlated significantly with changes on multiple clinical scales, including ADAS-Cog, CDR-SB, and MMSE.

LHP588 was well-tolerated in both the SAD/MAD study, and no liver enzyme elevations outside normal ranges were observed. Adverse events in the active arms were mild and sporadic. PK was consistent with once-daily dosing reaching target concentrations equivalent or greater than 80 mg BID of atuzaginstat at >25 mg QD of LHP588. LHP588 was also detected in the CSF of all subjects tested, at expected levels. LHP588 has improved selectivity, including for the bile salt export pump, and projected 10x lower liver metabolite levels. Chronic toxicology studies show that large multiples of exposures did not produce clinical pathology or histopathology findings, supporting advancement into Phase 2.

Conclusion: LHP588 was well tolerated in healthy volunteers without evidence of hepatic safety signals to date, and its PK profile was supportive of once daily dosing, with 10x lower

liver metabolite levels. Chronic toxicology and rodent metabolite studies are also supportive of safety and progression to Phase 2.

Clinical results with the first generation gingipain inhibitor atuzaginstat informed the new study design for precision enrollment and efficacious exposures. The Phase 2 trial of LHP588 starting later in 2023 will be similar in design but will be restricted to subjects with Pg+ saliva.

W26. RAPID IMPROVEMENTS IN MADRS WITH ZURANOLONE IN MAJOR DEPRESSIVE DISORDER AND POSTPARTUM DEPRESSION: RESULTS FROM THE LANDSCAPE AND NEST CLINICAL DEVELOPMENT PROGRAMS

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Abstract: Treatments for major depressive disorder (MDD) and postpartum depression (PPD) are suboptimal for some patients due to slow time to effect and low remission rates.1, 2 Rapid-acting therapies remain an unmet need in the treatment of MDD and PPD. Zuranolone (ZRN) is being evaluated as a once-daily, oral, 14-day treatment course for adult patients with MDD and PPD. Efficacy, as assessed by multiple scales, including the Montgomery-Åsberg Depression Rating Scale (MADRS) total score and safety of ZRN vs placebo (PBO), was evaluated across five completed Phase 2 and 3, placebo-controlled, randomized studies (conducted between the years of 2016 and 2022) in patients with either MDD (MDD-201B [NCT03000530], MOUNTAIN [NCT03672175], and WATERFALL [NCT04442490]) or PPD (ROBIN [NCT02978326] and SKYLARK [NCT04442503]). While other endpoints were examined in these studies, the goal of this additional analysis is to present data focused on patient mood symptoms.

Among adult patients with MDD or PPD receiving ZRN 30 or 50 mg once daily for 14 days, improvement in depressive symptoms was assessed at Days (D)8 and 15 by change from baseline (CFB) in MADRS total score and by rates of patients achieving MADRS response (≥50% improvement from baseline in total score) and remission (total score ≤10). Safety was assessed throughout. Efficacy (MADRS) results were not adjusted for multiplicity; therefore, all p-values and statements of significance reported are nominal. MADRS response and remission was not assessed in the MDD-201B study.

At D8 the least squares mean (LSM) CFB in MADRS total score was numerically greater in patients treated with ZRN vs PBO in MDD-201B, and significantly greater in MOUNTAIN, WATERFALL, ROBIN, and SKYLARK ($p<0.05$). At D8, the proportion of patients who achieved MADRS response in the ZRN arm was numerically greater than the PBO arm in ROBIN and significantly greater in MOUNTAIN, WATERFALL, and SKYLARK ($p<0.05$). The proportion of patients in the ZRN arm who achieved MADRS remission at D8 were numerically greater than the PBO arm in WATERFALL, ROBIN, and SKYLARK and significantly greater in MOUNTAIN ($p<0.05$). The LSM CFB MADRS total score (standard error) treatment difference between ZRN vs PBO at D15 was −7.6 (2.4; p=0.002; MDD-201B), −1.2 (1.3; p=0.323; MOUNTAIN), −2.4 (1.1; p=0.024; WATERFALL), −4.6 (1.9; p=0.018; ROBIN), and −5.1 (1.7; p=0.003; SKYLARK). The proportion of patients who achieved MADRS response at D15 in the ZRN arm was numerically greater than those in the PBO arm in MOUNTAIN (48.3% vs 43.0%) and significantly greater in WATERFALL (51.8% vs

41.4%), ROBIN (73.0% vs 47.9%), and SKYLARK (56.5% vs 37.1%; $p<0.05$). The proportion of patients who achieved MADRS remission at D15 was numerically greater in patients who received ZRN vs PBO in MOUNTAIN (34.7% vs 27.9%) and WATERFALL (34.4% vs 29.5%), and significantly greater in ROBIN (54.1% vs 30.1%) and SKYLARK (41.3% vs 26.7%; $p<0.05$).

ZRN was generally well tolerated, with consistent safety and tolerability profiles observed across the studies. The most common treatment-emergent adverse events (≥5% for ZRN) were headache, somnolence, dizziness, nausea, sedation, diarrhea, upper respiratory tract infection, fatigue, and COVID-19.

In the five completed clinical studies, rapid improvement in depressive symptoms, as assessed by MADRS total score, was consistently observed across studies of adults with MDD and PPD who received a once-daily, oral, 14-day treatment course of ZRN. In all studies, ZRN was generally well tolerated. These data support further development of ZRN as a potential oral, rapid-acting treatment for patients with MDD or PPD.

W27. SAFETY AND EFFICACY OF ZURANOLONE REPEAT TREATMENT USING PHQ-9 DEPRESSION SEVERITY IN PATIENTS WITH MAJOR DEPRESSIVE DISORDER FROM THE SHORELINE STUDY

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Abstract: Background: Current treatment options for major depressive disorder (MDD) may be suboptimal for some patients due to slow time to effect and low rates of remission. Many patients with MDD on currently available antidepressants experience impaired functioning and diminished quality of life. Zuranolone (ZRN) is a positive allosteric modulator of synaptic and extrasynaptic GABAA receptors and a neuroactive steroid in development as an oral, once-daily, 14-day treatment for adults with MDD and postpartum depression. SHORELINE is an ongoing, open-label, longitudinal, Phase 3 study (NCT03864614) assessing safety and efficacy of episodic treatment with ZRN 30 and 50 mg in adults with MDD. Results from the patient-reported 9-item Patient Health Questionnaire (PHQ-9) assessed after initial and repeat treatment courses from SHORELINE for the 30-mg Cohort are reported.

Methods: Eligible patients were aged 18–75 years with MDD and 17-item Hamilton Rating Scale for Depression total score (HAMD-17) ≥20. HAMD-17 responders (≥50% reduction from baseline) at Day (D)15 of treatment period 1 were followed-up for ≤48 weeks. Patients continuing past D28 completed the PHQ-9 at baseline and every 2 weeks (scoring for depression severity: 0–4, minimal; 5–9, mild; 10–14, moderate; 15–19, moderately severe; and 20–27, severe). Patients with PHQ-9 ≥10 and HAMD-17 ≥20 were eligible for repeat treatment with ZRN 50 mg at ≥D70 of each study period.

Results: Patients in the ZRN 30-mg Cohort (n=725) were mostly female (67.4%) with a baseline mean±SD HAMD-17 of 25.3±4.1. The baseline mean±SD PHQ-9 (n=650) was 17.3±5.2 (severity: minimal 0.3%, mild 8.8%, moderate 18.6%, moderately severe 34.3%, and severe 38.0%). Mean±SD change from baseline (CFB) in PHQ-9 at D15 in treatment period 1 was −10.3±7.2 (severity: minimal 40.6%, mild 30.6%, moderate 15.9%, moderately severe

7.8%, and severe 5.1%, respectively). For initial responders, the mean CFB±SD PHQ-9 at D15 of treatment course 2 was −8.3±6.4 (n=249; severity: minimal 32.9%, mild 37.3%, moderate 18.1%, moderately severe 8.4%, severe 3.2%); for treatment course 3, −9.1±6.2 (n=137; severity: minimal 29.2%, mild 38.0%, moderate 15.3%, moderately severe 12.4%, severe 5.1%); for treatment course 4, −11.0±6.6 (n=91; severity: minimal, 34.1%, mild 37.4%, moderate 15.4%, moderately severe 6.6%, severe 6.6%); and treatment course 5, −10.8±7.6 (n=38; severity: minimal 36.8%, mild 26.3%, moderate 15.8%, moderately severe 10.5%, severe 10.5%), respectively. Incidence and severity of treatment-emergent adverse events (TEAEs) were highest in treatment courses 1 and 2; no new trends in TEAEs and no evidence for increased suicidal ideation were identified with any treatment course.

Conclusion: Treatment with ZRN was generally well tolerated and led to improvements in self-reported depressive symptoms across all treatment courses. These results support further development of ZRN as an episodic treatment for MDD.

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W28. COMPARATIVE TREATMENT PATTERNS AMONG MEDICAID-INSURED PATIENTS WITH MAJOR DEPRESSIVE DISORDER WITH INSOMNIA

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Abstract: Background: Insomnia is a key symptom of major depressive disorder (MDD); its presence is associated with increased severity, duration, and other health-related burden of MDD. To understand real-word treatment approaches and unmet needs of patients with MDD with insomnia (MDDIS), treatment use and hospitalizations of United States Medicaid beneficiaries with MDDIS were compared to those with MDD without evidence of insomnia (other MDD) and those without MDD.

Methods: Adults with and without MDD were selected from IBM® MarketScan® Multi-State Medicaid Database (01/2016-06/2021). To be included in the MDDIS and MDD cohorts, patients were required to have at least 1 diagnosis for MDD (index date). Those patients with a diagnosis for insomnia during the 1-year follow-up period were considered to have MDDIS. All cohorts were matched on race and index quarter and propensity score matched on age, sex, and Charlson Comorbidity Index. Rates of treatment utilization and hospitalization based on pharmacy and medical claims were compared among cohorts during the follow-up period using Poisson regressions.

Results: A total of 15,653 patients were included in the MDDIS cohort (mean age: 40.8 years; 73.0% female) and matched to the control cohorts. Proportions of patients claiming ≥3 unique antidepressants were 23.5% in the MDDIS and 7.2% in the other MDD cohort (risk ratio [RR]: 3.25, $p<0.001$). Selective serotonin reuptake inhibitors were the most common antidepressant class claimed in the MDDIS cohort (61.6%) and other MDD cohort (51.4%; RR: 1.20, $p<0.001$). However, trazodone, a sedative serotonin modulator, was the most claimed antidepressant drug in the MDDIS cohort (38.2%) compared to 8.4% in the other MDD cohort

(RR: 4.56, p<0.001). Other psychiatric and neurological medications with sedative effects like gabapentin (MDDIS: 24.5%, other MDD: 16.5%; RR: 1.49, p<0.001) and mirtazapine (MDDIS: 9.7%, other MDD: 4.0%; RR: 2.46, p<0.001) were also more commonly claimed in the MDDIS versus other MDD cohort.

A higher proportion of MDDIS cohort (20.6%) compared to other MDD cohort (15.4%) and non-MDD cohort (2.4%) had mental health-related inpatient admissions (RRs: 1.33 and 8.74, respectively, all p<0.001). Further, higher proportion of MDDIS cohort (11.5%) compared to other MDD cohort (8.5%) and non-MDD cohort (3.4%) had cardiovascular-related inpatient admissions (RRs: 1.35 and 3.35, respectively, all p<0.001). Finally, higher proportion of MDDIS cohort (9.2%) compared to other MDD cohort (7.8%) and non-MDD cohort (2.9%) had metabolic-related inpatient admissions (RRs: 1.18 and 3.19, respectively, all p<0.001).

Conclusion: Among Medicaid beneficiaries, MDDIS compared to other MDD was associated with higher antidepressant and other on-label and off-label psychiatric drugs use, particularly with sedative effects, suggesting physicians may prescribe multiple MDD treatments targeting complex symptomatology of MDD with insomnia. Data on hospitalizations suggests that burden of MDDIS extends beyond mental health and is associated with cardiovascular and metabolic disorders.

W29. INTRANASAL ESKETAMINE VERSUS INTRAVENOUS KETAMINE: AN OBSERVATIONAL STUDY COMPARING THE EFFICACY AND TOLERABILITY OF TWO NOVEL 'STANDARD OF CARE' TREATMENTS FOR TREATMENT RESISTANT DEPRESSION

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Abstract: Background: Intravenous (IV) ketamine and intranasal (IN) esketamine have been studied as novel therapeutic alternatives for the management of treatment resistant depression (TRD). They have demonstrated rapid and potent reduction of depressive symptoms after the administration of both single and multiple subsequent doses. The objective of this observational pilot study is to compare the real-world effectiveness and tolerability of IV ketamine versus IN esketamine in the management of unipolar TRD. The hypothesis of this study is that both ketamine and esketamine treatments will have similar efficacy and tolerability.

Methods: This is a multicenter prospective observational study of naturalistic clinical practice still in progress. Patients (n=60) experiencing moderate to severe TRD referred to receive IV ketamine (n=30) or IN esketamine (n=30) treatments are being recruited. Effectiveness of these treatments is assessed using the Montgomery and Åsberg Depression Rating Scale (MADRS) for depression severity and item 10 of the MADRS for suicidal ideation (SI). Tolerability is assessed by tracking side effects and depersonalization using the 6-item Clinician administered dissociative symptom scale (CADSS-6) depersonalization scale. The data will be analyzed using descriptive statistics, risk ratio (RR) and effect size using Cohen D (d) analysis.

Results: These are preliminary results using the data collected by one research center. 17 patients referred to receive IV ketamine and 7 referred to receive IN esketamine have been recruited so far. Both ketamine (d=3.07, p<0.0001) and esketamine (d=1.39, p=0.0086) groups presented a rapid and significant reduction of depressive symptoms severity at endpoint (4 weeks) with large effect size. Patients receiving IV ketamine treatment experienced a

significant reduction in SI (d=1.14, p=0.0027), had a significantly higher risk of developing side effects (RR=1.62, p=0.0046) and a significantly lower depersonalization score (d=1.306, p=0.013) compared to those receiving IN esketamine. All side effects reported were mild and transient, with the most common side being sedation or drowsiness, present in over 40% of patients.

Conclusion: These preliminary results suggested that both IV ketamine and IN esketamine have similar effectiveness in the management of depressive symptoms. Though, they differed in the management of SI and side effect profile, both treatments were well tolerated. Thus, these results provide additional evidence for the treatment of patients with TRD in real life clinical setting and could serve to guide clinical practice and health policy.

W30. ASSESSING INDIVIDUALS' EXPERIENCES WITH ZURANOLONE FOR MAJOR DEPRESSIVE DISORDER: QUALITATIVE INTERVIEWS WITH PARTICIPANTS FROM THE OPEN-LABEL SHORELINE STUDY

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Abstract: Background: Pharmacological treatments for major depressive disorder (MDD) usually include daily use of antidepressant therapy (ADT) over extended periods of time [1]. Zuranolone is an investigational drug being evaluated as a rapid-acting, once-daily, 14-day oral treatment in adults with MDD. We conducted qualitative interviews to further understand trial participants' experiences with and perceptions of this potential treatment for MDD.

Methods: Two independent researchers conducted interviews using a convenience sample of participants with MDD who received zuranolone 50 mg once-daily for 14 days as part of the SHORELINE open-label study, responded to the initial treatment course, and remained in the study for ≥ 24 weeks [2]. This qualitative study was run in parallel with but was not part of the SHORELINE study. Interview participants were asked about their experiences with MDD, their perceptions of zuranolone, and the meaningfulness and importance of treatment improvements. Interview data were analyzed using a thematic analysis approach. Denominators used for calculating percentages varied based on pretrial reporting of symptoms.

Results: The mean age of the 32 interview participants was 40.6 years (range, 20-66 years) and 56.3% were male. Most participants (78.2%) had a prior history of MDD at enrollment in SHORELINE (mean, 12.6 years; range, 1-40 years); 81.3% had previously received an ADT. Before starting SHORELINE, participants generally reported low energy (96.9%), sleep problems (93.8%), feeling depressed/sad/hopeless (90.6%), fatigue/tiredness (84.4%), and that their MDD-related symptoms affected their work/school (87.5%), daily roles and responsibilities (84.4%), and social lives/activities/relationships (84.4%).

All 32 participants reported an improvement in ≥ 1 MDD-related symptoms after receiving zuranolone, and most participants (87.5%) noticed improvements within the first week of treatment (range, 1 day-1 month). Participants noticed improvements in sleep (90.0%), feeling depressed/sad/hopeless (82.8%), anhedonia/apathy/lack of interest or desire (81.0%), and energy (80.6%). Many participants also noticed improvements in fatigue/tiredness (77.8%),

self-worth/guilt/doubt (75.0%), short-term memory (75.0%), irritability (66.7%), motivation (61.5%), concentration/focus/attention (60.9%), appetite/eating habits (60.9%), and anxiety (59.1%). Furthermore, all participants who reported MDD-related impacts to their social lives, activities, or relationships before receiving zuranolone also reported improvements following treatment. Participants also reported improvements in their daily roles and responsibilities (92.6%) and work/school (82.1%) following zuranolone treatment.

Of the 29 participants who described what they liked about zuranolone as a potential treatment for MDD, 75.9% liked that it helped manage their depression or another specific MDD-related symptom, 62.1% liked the 14-day treatment duration, 27.6% liked that they noticed improvements quickly, and 24.1% liked that they experienced little or no side effects. All participants reported being at least moderately satisfied with zuranolone, and 83.8% reported being "quite" or "very" satisfied.

Conclusion: Interviewed participants from SHORELINE observed rapid improvements in depressive symptoms, improvements in their daily lives and roles, and reported high satisfaction rates with zuranolone.

W31. CONCORDANCE BETWEEN PATIENT-REPORTED OUTCOMES (PROS) AND CLINICIAN-REPORTED OUTCOMES (CLINROS) FOR SUICIDALITY FROM THE SUICIDE IDEATION AND BEHAVIOR ASSESSMENT TOOL (SIBAT) IN TWO PHASE 3 STUDIES

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Abstract: As part of an ongoing effort to incorporate patient-reported outcomes within clinical trials of Major Depressive Disorder (MDD), it is important to assess the relationship between clinician-reported outcomes (ClinROs) and patient-reported outcomes (PROs). Two double-blind, randomized, placebo-controlled studies have been conducted to examine the safety and efficacy of intranasal esketamine for the rapid reduction of symptoms of MDD including suicidal ideation in an adult MDD population at imminent risk of suicide. As part of this effort, a novel assessment tool, the Suicide Ideation and Behavior Assessment Tool (SIBAT), was developed (1). However, the relationship between PROs and ClinROs of suicidality from the SIBAT within the context of these trials has not been fully reported. To assess PRO and ClinRO concordance, we provided Spearman rank correlations and a cross-tabulation analysis of PROs from Patient Module 5 and ClinROs from Clinician Module 7 of the SIBAT that measure similar constructs: passive suicidal ideation (patient) vs severity of suicidality (clinician); active suicidal ideation (patient) vs severity of suicidality (clinician); frequency of suicidal thinking (patient and clinician); and suicide risk (patient and clinician). Our analysis included 451 participants and relationships were assessed at baseline, Day 2 (24 hours post first dose), and Day 25 (end of double-blind treatment phase). Correlations of change from baseline to Day 2 and change from baseline to Day 25 were also assessed. In general, correlations between PROs and ClinROs at baseline, Day 2, and Day 25 ranged from moderately to strongly correlated (baseline: 0.41 to 0.58, Day 2: 0.39 to 0.69, Day 25: 0.55 to 0.82). Correlations of change from baseline to Day 2 and change from baseline to Day 25 ranged from weakly to strongly correlated (change from baseline to Day 2: 0.24 to 0.47, change from baseline to Day 25: 0.44 to 0.67). We also found that PROs and ClinROs were more strongly correlated at Day 25 than at baseline across all relationships assessed. At baseline in three out of the four

comparisons, clinicians rated the patient condition as more severe than the patient rated themselves. A similar trend was also seen at Day 25 in all four comparisons. Our data suggests that there is general concordance between PRO and ClinRO assessments of the SIBAT in the context of these clinical trials. However, as the correlation is not 1, this data reveals the importance of including PROs in clinical trial study designs. Our study also shows greater concordance between PROs and ClinROs at the end of the treatment period (Day 25) compared to baseline, which is consistent with reports from previous studies examining PRO and ClinRO relationships (2). Overall, these results help to further elucidate the relationship between ClinROs and PROs for suicidality on the SIBAT, which may contribute to the effective incorporation of PROs for suicidality into clinical trials of MDD in the future.

W32. ESKETAMINE NASAL SPRAY VERSUS PSYCHOACTIVE COMPARATOR FOR RAPID REDUCTION OF DEPRESSIVE SYMPTOMS IN ADOLESCENT PATIENTS WITH MAJOR DEPRESSIVE DISORDER AT IMMINENT SUICIDE RISK

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Abstract: Background: Increasing rates of major depressive disorder (MDD) and suicidal behavior in adolescents pose a major public health concern; as of 2020, suicide was the second leading cause of death among adolescents in the US. Esketamine nasal spray is approved for use in conjunction with an oral antidepressant for the treatment of depressive symptoms in adults with MDD with acute suicidal ideation or behavior. The current study evaluated the efficacy and safety of esketamine nasal spray in conjunction with comprehensive standard-of-care (SOC) treatment in acutely ill adolescents with MDD who were at imminent risk for suicide. This study is the first pharmacological treatment trial conducted in this under-studied and vulnerable patient population.

Methods: This double-blind (DB), double-dummy, multicenter, global phase 2b study randomized (1:1:1:2 ratio) adolescents (12 to <18 years old) to esketamine nasal spray (28, 56, or 84 mg) or psychoactive comparator (oral midazolam) twice-weekly for 4 weeks. All participants were treated in the context of comprehensive SOC treatment, including initial hospitalization, an oral antidepressant, and psychological therapy. The primary efficacy endpoint is change from baseline to 24 hours post-initial dose (day 2) in Children's Depression Rating Scale-Revised (CDRS-R) total score. Other endpoints include improvement in depressive symptoms based on change in CDRS-R and Montgomery-Asberg Depression Rating Scale (MADRS) total score and change in severity of suicidality based on Clinical Global Impression of Severity of Suicidality-Revised (CGI-SS-R) from the Suicide Ideation and Behavior Assessment Tool (SIBAT), which are being assessed throughout 25 days of the DB treatment phase.

Results: The full analysis population includes 82 adolescents in the combined esketamine plus SOC groups (28 mg, n=28; 56 mg, n=31; 84 mg, n=23) and 63 in the midazolam plus SOC group. Mean age of all participants is 14.9 years, the majority (78%) female. At baseline, mean CDRS-R and MADRS total scores are 76.3 and 39.8, respectively, with 94% of participants moderately-to-extremely suicidal per CGI-SS-R, and 80% of participants having a lifetime suicide attempt, 54% within the past month. Analyses of efficacy and safety data are ongoing and will be presented.

Conclusion: Findings from this first-in-kind study will inform on an acutely ill, highly vulnerable population and on whether esketamine nasal spray may hold a therapeutic role when given in addition to comprehensive SOC, for rapid improvement in depressive symptoms, including measures of suicidal ideation, among depressed adolescents at imminent risk for suicide.

W33. DEVELOPMENT OF MACHINE LEARNING MODEL FOR ESTIMATING PHQ-9 SCORES FROM CLINICAL NOTES

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Abstract: Background: The Patient Health Questionnaire-9 (PHQ-9) is a validated patient-reported measure for assessing depressive symptoms and symptom severity over the past two weeks. The PHQ-9 is widely used in both mental health and primary care settings because it is brief and easy to score (1). Consistent capture of the PHQ-9 over time is important for monitoring changes in depressive symptoms, understanding response to treatment, and tracking outcomes such as remission and recurrence (2). Yet, documentation of the PHQ-9 is inconsistent in real-world data (RWD) sources such as electronic medical records (EMRs). This limits the potential role of these data sources for supporting large, heterogeneous research studies on depression treatment and outcomes. This effort aimed to apply machine learning methods to estimate PHQ-9 scores using routinely-recorded data from unstructured and semi-structured clinical notes.

Methods: A machine learning model was developed to generate estimated PHQ-9 (ePHQ-9) scores for specific clinical encounters using clinical notes from visits with mental health professionals. Data were drawn from the OM1 PremiOM Major Depressive Disorder (MDD) Dataset, a RWD source containing data on over 490,000 MDD patients receiving treatment from mental health professionals across the U.S. Patients with both recorded PHQ-9 scores and clinical notes were identified and randomly assigned to a training cohort (32,802 patients contributing 96,891 encounters) to train an ensemble model when both notes and questionnaire data are available or a validation cohort (15,792 patients contributing 46,333 encounters). Notes were transformed via medical language processing, and the resulting features were reviewed and approved by a subject matter expert. To assess model performance, the area under the receiver-operating-characteristic curve (AUC) was calculated using a binarized version of the outcome, and continuous ePHQ-9 scores were evaluated using Spearman R and Pearson R values.

Results: The model had an AUC of 0.81 when evaluating performance using the binarized version of the outcome in the validation cohort and a Spearman R value of 0.62 and a Pearson R value of 0.61 when evaluating performance using the continuous ePHQ-9 scores. Of note, model features included items similar to PHQ-9 questions (e.g., fatigue) as well as other concepts (e.g., medication usage, condition-specific scores). When applied to the larger MDD Dataset, the model resulted in the generation of new ePHQ-9 scores for 2,215,662 (2.7x enrichment over 814,166 recorded PHQ-9's) encounters for 208,692 (1.2x enrichment over 174,897 patients with a PHQ-9) distinct patients.

Conclusion: A machine learning model can estimate PHQ-9 scores using information routinely recorded in clinical notes from psychiatrists. At the individual patient level, use of

the model could provide a more complete view of a patient's depressive symptom severity and response to treatment over time. At the population level, application of the model to RWD sources increases the number of patients and encounters available for research on depression treatment and outcomes.

W34. SLEEP DISTURBANCES ARE HIGHLY PREDICTIVE OF MAJOR DEPRESSIVE DISORDER RECURRENCE

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Abstract: Background: The association of sleep disturbances and major depressive disorder (MDD) has been well documented and is recognized as part of the natural evolution of MDD.1 The role of hypersomnolence in MDD is unknown.2 We examined data collected over 3 years evaluating symptoms and impact of sleep disturbances in the progression of each study participant.

Methods: In this longitudinal study, 2 interview waves were conducted between 2002 and 2015. The initial interviews (wave 1 [W1]) were carried out with 12,218 individuals aged ≥18 years from the general US population in 8 states. At follow-up 3 years later (wave 2 [W2]), 10,931 of the initial participants agreed to be interviewed again, and predictors of recurrence were determined for those who participated in both interview waves using logistic regression (adjusted for age, sex, race, and body mass index). MDD diagnosis and definitions of hypersomnolence and insomnia were made according to Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria. Individuals in complete or partial (not meeting DSM-5 criteria for MDD but experiencing more than minimal symptoms) remission of an MDD episode at W1 but with a full episode at W2 and those in complete remission at W1 but in partial remission at W2 were classified as recurrent MDD.

Results: The 1-month prevalence of MDD was 5.1% (95% CI, 4.7%¬–5.5%) in W1 and 4.2% (95% CI, 3.8%–4.6%) in W2, and the 12-month prevalence was 9.5% (95% CI, 9.0%–10.0%) in W1 and 12.1% (95% CI, 11.5%–12.7%) in W2. Overall, 41.8% of the individuals with a diagnosis of MDD in W1 still reported depressive symptoms in W2. The 1-year incidence of MDD at W2 was 1.1% (95% CI, 0.9%–1.3 %). Over the course of the study, 2.6% of participants experienced recurrence of depression (95% CI, 2.3%–2.9%). Participant characteristics in W1 that predicted recurrent MDD in W2 included the presence of insomnia symptoms without excessive daytime sleepiness (EDS) (relative risk [RR] 2.2; 95% CI, 1.5–3.2) and with EDS (RR 3.8; 95% CI, 2.7–5.3), as well as being dissatisfied with one's sleep (RR 3.4; 95% CI, 2.6–4.6). Among hypersomnolence symptoms, an unrefreshing prolonged main sleep period (>9 hours of sleep) was highly predictive of MDD recurrence (RR 5.5; 95% CI, 3.2–9.5). More specifically, of participants with recurrent MDD at W2 (n=284), 9.8% experienced EDS alone (vs 16.9% of participants with no MDD in W1; n=10,091), 20.4% (vs 12.7%) experienced insomnia symptoms alone, and 30.7% (vs 11.3%) experienced insomnia with EDS. An unrefreshing prolonged main sleep period in W1 was reported by 7.7% of individuals with recurrent MDD (vs 1.9%). Global sleep dissatisfaction in W1 was observed in 37.8% of the recurrent group (vs 13.7%).

Conclusion: Depression affects a sizeable part of the general population in the United States, with a 1-year prevalence of MDD of 9.5%. Sleep disturbances appear early in the care pathway and are highly predictive of recurrent MDD.

W35. A RANDOMIZED, PLACEBO-CONTROLLED, EXPLORATORY, DOUBLE-BLIND STUDY TO ASSESS THE SAFETY AND EFFICACY OF INTRAVENOUS PCN-101 IN TREATMENT-RESISTANT DEPRESSION

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Abstract: Background: Perception Neuroscience, is developing the R-isomer of ketamine (PCN-101, R-ketamine, arketamine) for the treatment of Treatment Resistant Depression (TRD). Evidence from nonclinical depression model studies of subanesthetic doses in rodents, and both nonclinical and preliminary clinical studies suggest that R-ketamine may have a more favorable safety profile with a decreased incidence of adverse events (AEs) (e.g., dissociative, cognitive impairment, and psychotomimetic effects) compared with S-ketamine. Based on nonclinical studies, R-ketamine may also have less abuse potential than S- ketamine.

Objective: To determine the safety and efficacy of 2 doses (30 mg and 60 mg) of intravenous (IV) PCN-101 compared with placebo in subjects with TRD

Design: This double-blind, randomized, placebo-controlled, multicenter study comprised 3 phases: screening (up to 2 weeks), in-patient treatment (Day -1 to Day 2), and post-treatment follow-up (7 and 14 days after infusion). The study consisted of 3 arms: placebo, PCN-101 30 mg, and PCN- 101 60 mg, all given as an i.v. infusion over 40 minutes. A planned total of 93 adult subjects with TRD were randomly allocated in equal cohorts of 31 subjects/arm to the 3 arms of the study in a blinded manner. The primary endpoint was a change on the MADRS from pre dose to 24 hours post dose.

Results: The study enrolled a total of 102 subjects across the three arms. At the primary endpoint, subjects in the placebo and 30 mg groups had a change of 13.7 points change, while subjects randomized to the 60 mg dose had a 15.3 point change, with a adjusted mean difference between placebo and 60 mg of -1.6 (p=0.49). The study did not meet statistical significance at the primary endpoint. A pre specified post-hoc analyses showed that there were regional differences, with patients in the US (n=27) demonstrating a clinically meaningful difference of -4.77 (p=0.32) at 24 hrs, -9.2 (p=0.15) points on day 8, and -13.12 (p=0.03) from placebo on day 15. Subjects on 60 mg also demonstrated greater sustained response, lasting for 15 days, compared to subjects on 30 mg or placebo.

PCN-101 was generally well-tolerated with rates of sedation and dissociation comparable to placebo. Mean PBO corrected blood pressure changes were less than 5 mm Hg.

Conclusion: Single dose of R-ketamine was well tolerated, with sedation, and dissociation seen at rates similar to placebo. R-ketamine in a single dose demonstrated a trend towards efficacy at the 60 mg dose.

W36. BREXPIPRAZOLE: A SYSTEMATIC REVIEW ON CURRENT STUDIES IN MAJOR DEPRESSIVE DISORDER

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Abstract: Background: Brexpiprazole, a third-generation antipsychotic, exerts actions as a partial agonist of 5HT1A, D2 and D3. Since its initial Food and Drug Administration (FDA) approvals in 2015, the medication has become increasingly utilized as an adjunctive treatment for major depressive disorder (MDD). At present, only a single review has assessed the use of brexpiprazole in MDD. While that review reported the agent as both tolerable and effective treatment for depression, it relied on an assessment of only six clinical studies. Current review of the literature also reveals other studies, both contemporaneous with the catchment period of the review, and subsequent to its creation. Given the limitations of the past published review, further available studies, and with increasing use in the treatment of MDD, we report a systematic review assessing utility of brexpiprazole in MDD.

Methods: A comprehensive search of published studies on "brexpiprazole" OR "Rexulti" was conducted on PubMed, CINAHL Complete, APA PsycNet, APA PsycInfo, Cochrane Library, and Ovid Medline through December 25, 2022. All peer reviewed articles in English were collected (n=2179). A total of 567 studies were screened for titles and abstracts after removing duplicates. All human trials using brexpiprazole in MDD were screened for the inclusion criteria. Full-text analysis of extracted studies was conducted adhering to Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.

Results: The initial search yielded 2,179 articles of which 1590 were found to be duplicates. The remaining 567 studies were manually reviewed of which 14 publications, comprising 20 different clinical studies, were included for final analysis. These were published between 2010 and 2021 with a total sample across all studies of 12,447 participants. The participant mean age range was 26.6-74.1 years. Gender distribution ranged from 19-68% male. Among the studies that reported the racial composition, the range was 55-98% Caucasians, 1-36% blacks, and other races, comprising 0-7% of the participants. The following is a summary of study designs for all 20 studies: (a) 7 open-label studies; (b) 13 studies with comparator arms - 2 studies compared brexpiprazole with placebo, 1 study compared switch from adjunct ADT to brexpiprazole, 7 studies compared brexpiprazole to placebo plus ADT, 1 study compared with Seroquel+ADT/placebo+ADT, 1 study with placebo+ADT+Seroquel, and 1 study placebo+ketamine. The study duration varied from 4-52 weeks with extension and cross-over transpiring in some study designs. Ten studies included participants exclusively from the United States and the rest included Canada, multiple European nations, South Korea, and Mexico. The dose of brexpiprazole ranged from 0.5 mg to 3 mg daily with step or different dose arms employed in several studies. All studies were funded by Otsuka-Lundbeck. Among these, a uniform reduction in the mean score of the scale was seen in most studies. The following is a summary of all 20 studies: (a) 14 studies indicate improvement in depression; (b) 4 studies did not assess the efficacy and only commented on tolerability; (c) one study reported no efficacy in depression remission; (d) one study was terminated early and data are not analyzable.

Conclusion: Our review revealed significant differences between brexpiprazole and both placebo as well as multiple alternative medication management strategies. The effect size of this agent was reported to be substantial as were its usefulness in several specific MDD

symptoms. Of note, many of the studies employed this agent among treatment refractory individuals, buttressing notions of its efficacy.

W37. AN OPEN LABEL STUDY OF THE SAFETY AND EFFICACY OF PSILOCYBIN IN VETERANS WITH SEVERE TREATMENT-RESISTANT DEPRESSION

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Abstract: Background: Rapid acting treatments are needed for people with treatment-resistant depression (TRD). Recent studies showed rapid decrease in depressive symptoms when psilocybin is coupled with psychological support in the general population. This open-label trial aims to assess the effectiveness of 25 mg of psilocybin in U.S. Military Veterans with severe TRD.

Methods: This study will enroll 15 Veterans with TRD who will receive a single 25mg dose of psilocybin. TRD is defined as a major depressive disorder that failed to respond to ≥5 treatments during the current episode or has a current episode that persisted >2 years. The primary outcomes at 3 weeks post-dosing are treatment response, defined as ≥50% reduction in the Montgomery-Asberg Depression Rating Scale (MADRS) total score, and remission, defined as MADRS of ≤10. A frequencies analysis was performed to determine the number of participants who met remission and/or response criteria. Secondary outcomes include response and remission at 12 weeks post-dosing and safety assessments.

Results: Initial results on 12 participants (10M/2F; age: 45[11.15]) indicate that 58% (n=7) met response criteria and 50% (n=6) met remission criteria 3 weeks post-dosing. The mean MADRS score decreased from 35 (SD=7.46) at baseline to 15 (SD=13.14) at 3 weeks post-dosing. With preliminary data available, scores at 3 weeks appear to be maintained at 12 weeks post-dosing. All 15 participants will be dosed by February 2023.

Conclusion: Preliminary results from this pilot study suggest that psilocybin reduces depression in Veterans with severe TRD. The full sample including primary and 12-week outcomes, secondary measures, and safety data will be reported on.

This is the first study on psilocybin that is conducted within the Veterans Affairs (VA) system for Veterans with severe treatment-resistant depression. Results from this study provides preliminary evidence that psilocybin-assisted therapy may be beneficial to Veterans. Further research is needed to fully assess the utility and safety of this treatment for Veterans with severe TRD.

W38. IMPACT OF AXS-05 (DEXTROMETHORPHAN-BUPROPION) ON PATIENT-REPORTED INSOMNIA SYMPTOMS: RESULTS FROM THE GEMINI TRIAL

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Abstract: Background: Insomnia is frequently reported among individuals with major depressive disorder (MDD) and some antidepressants may worsen insomnia. AXS-05 [dextromethorphan-bupropion (Auvelity® extended-release tablet)] is a novel, oral, NMDA receptor antagonist with multimodal activity approved by U.S FDA for the treatment of MDD in adults. The dextromethorphan component of AXS-05 is an antagonist of the NMDA receptor (an ionotropic glutamate receptor) and a sigma-1 receptor agonist. The bupropion component of AXS-05 is an aminoketone and CYP450 2D6 inhibitor, which serves primarily to increase the bioavailability of dextromethorphan.

Objective: To assess the impact of AXS-05 compared to placebo on patient-reported insomnia symptoms.

Methods: GEMINI (N=327) was a randomized, double-blind, placebo-controlled, 6-week, U.S trial, which randomized (1:1) adults with MDD to AXS-05 (dextromethorphan 45 mg-bupropion 105 mg) or placebo, twice daily for 6 weeks (Iosifescu DV, et al. J Clin Psychiatry. 2022;83:21m14345).

A post-hoc analysis was conducted to determine the impact of AXS-05 on patient-reported insomnia symptoms as assessed by the Quick Inventory of Depressive Symptomatology (Self-Report) (QIDS-SR-16) as compared to placebo. The three insomnia-related items on the QIDS (falling asleep, sleeping during the night, waking up too early) were combined into a single score ranging from 0-9.

Results: No insomnia (QIDS insomnia score ≤ 1), mild insomnia (QIDS insomnia score 2-5), and moderate-severe insomnia (QIDS insomnia score > 5) were reported in 4.7%, 42.1%, and 52.7% of patients, respectively. Baseline QIDS insomnia scores were 5.9 and 5.3 in the AXS-05 and placebo groups, respectively.

Rates of response, defined as at least a 50% reduction in QIDS insomnia scores from baseline, were statistically higher for AXS-05 starting at Week 3 and every timepoint thereafter. At Week 6, 40% (50/125) of subjects randomized to AXS-05 had achieved response on the QIDS insomnia subscale compared to 26% (39/150) of those randomized to placebo (p=0.013). At Week 6, the LS mean change from baseline in the QIDS insomnia subscale score was similar between AXS-05 and placebo, 1.93 vs. 1.59 (p=0.22). The most commonly reported adverse reactions (≥5% and more than twice the rate of placebo) in the GEMINI trial were: dizziness, headache, diarrhea, somnolence, dry mouth, sexual dysfunction, and hyperhidrosis

Conclusion: In the GEMINI study, improvements in insomnia response rates were seen with AXS-05 compared to placebo. These data provide additional evidence of the efficacy of AXS-05 on patient centric outcomes in MDD.

Sponsorship: This research was supported by Axsome Therapeutics.

W39. THE SAFETY AND EFFICACY OF COMP360 PSILOCYBIN THERAPY IN TREATMENT-RESISTANT DEPRESSION: RESULTS: FROM A LONG-TERM OBSERVATIONAL FOLLOW-UP STUDY

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Abstract Title: The safety and efficacy of COMP360 psilocybin therapy in treatment-resistant depression: results from a long-term observational follow-up study

Background: The largest clinical trial of psilocybin to date demonstrated the acute safety and efficacy of investigational drug COMP360 (COMPASS Pathways' proprietary synthetic psilocybin formulation) 25mg in participants with treatment-resistant depression (TRD), administered alongside psychological support. Here, we report findings from a long-term follow-up study post-COMP360 psilocybin therapy.

Methods: An observational follow-up study (COMP 004) recruited completers from a 12 week, double-blind, monotherapy study where 233 participants received a single dose of COMP360 25mg, 10mg or 1mg (COMP 001). COMP 004 followed participants out to 52 weeks post-treatment. Time to first depressive event was assessed across participants entering COMP 004 from COMP 001. Depressive events included starting a new antidepressant treatment; hospitalization due to depression/suicidality; completed, attempted or prevented suicide; increased suicidality; Montgomery-Åsberg Depression Rating Scale (MADRS) total score worsening; or discontinuation due to a depression-related adverse event (AE)/lack of efficacy.

Results: 58 completers from COMP 001 entered COMP 004 (25 mg n=22, 10 mg n=19, 1mg n=17). 50.0% of participants were female. Age ranged between 20-69 years, with a mean of 40.5 years. 3 (5.2%) participants had prior psilocybin experience (25mg arm (n=1); 10mg arm (n=2).

The median time to depressive event was 189 days for the 25mg arm, 43 days for the 10mg arm, and 21 days for the 1mg arm. A larger proportion of participants in the 1mg arm than in the 25mg arm started a new antidepressant drug by Week 52 (76.5% vs 54.5%) and initiated earlier, prior to entry into COMP 004 (58.8% vs 27.3%). Initial MADRS responders to COMP360 25mg showed durability of response up to approximately 6 months, with a subset of the 25mg responders demonstrating sustained response to Week 28 (13.6%). In those not starting new antidepressant treatment, differences favoring 25mg over 1mg were seen until Week 28 in response rates (18.2% vs 5.9%) and remission (13.6% vs 0%).

27 (46.6%) participants experienced a treatment-emergent AE that was ongoing or started after entry into COMP 004. One participant in the 25mg (n=1 event) and two participants in the 1mg (n=3 events) groups, experienced treatment-emergent serious AEs after entry into COMP 004, deemed unrelated to COMP360.

Conclusion: Following COMP360 25mg, participants took longer to experience a depressive event, compared with those in the 10mg and 1mg arms. Selection bias may have limited this study as the efficacy profile of participants entering the long-term study was not representative of the lead-in participant population. Any conclusion should also be tempered by the modest recruitment number which was attributable to later study initiation relative to the lead-in studies, optional participation, and COVID-19. Larger long-term studies are required to confirm the generalizability of these findings and provide clarity on the longer-term effects of COMP360.

W40. EFFICACY OF SPRAVATO TO AUVELITY CROSS-TITRATION IN MDD

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Abstract: Background: Spravato, a selective N-methyl-D-aspartate (NMDA) receptor antagonist, was approved in 2019 for treatment resistant depression, and enabled some patients with depression to find improvement in symptoms within hours of administration1. For some patients, however, dissociative side effects may be intolerable. For others, being driven to and from the office for treatment creates a barrier to care. Auvelity was approved by the FDA in 2022 and is an orally acting antidepressant agent that works in part due to NMDA receptor antagonism2. This oral formulation obviates the need for supervised administration, and therefore aids use in this population. This study aims to obtain pilot data regarding efficacy and safety of cross tapering subjects from Spravato to Auvelity. The proposed study would set the stage for further research with real world implications for the millions of people who suffer from depression.

Methods: The study proposed is a small, single site, proof of concept, open label study of 30 patients who have responded (MADRS decrease by at least 50%) to esketamine. These subjects will have been maintained and stabilized on esketamine together with standard of care that may include oral antidepressants, augmenting medications, and psychotherapy, prior to entering the study.

After enrollment and screening that would include informed consent, demographics, baseline Montgomery-Asberg Depression Rating Scale (MADRS), physical exam, and Mini International Neuropsychiatric Interview (MINI), subjects will be randomized to receive Auvelity or treatment as usual (Spravato and augmenting antidepressants). Those randomized to the experimental arm will discontinue Spravato and be started on Auvelity (45 mg of dextromethorphan hydrobromide, 105mg bupropion hydrochloride) once per day in the morning, and after three days of treatment, their dose will be increased (as tolerated) to 45mg dextromethorphan and 105mg bupropion twice a day at least 8 hours apart. Those on strong CYP2D6 inhibitors (eg. Fluoxetine) would remain on one tablet of 45mg Dextromethorphan, 105mg bupropion, and not increased to the higher dose. Follow ups with subjects will be performed weekly, including MADRS scale administration, and a psychiatric medication visit. It will be at these visits that augmenting medications may be prescribed, and if the subjects are found to be relapsing, will be transitioned out of the study if appropriate and reinitiated on Spravato. Primary endpoint will be 6 weeks after randomization to treatment as usual or Auvelity arms. The primary outcome variable is the total change and mean change post-Spravato score six weeks after randomization. Predictor variables of interest include age, sex, number of failed antidepressant trials, SUD history.

Data Analytic Plan: MADRS scores from baseline will be analyzed using a repeated measures analysis of variance (ANOVA). Mean values of MADRS change from baseline will be calculated in control and experimental groups and analyzed versus scores post index period, every week through 6 weeks post randomization. Significance will be set at $P < 0.05$.

Hypothesis and Conclusion: I hypothesize that the experimental group will not have significantly different MADRS scores from baseline, or from the MADRS scores of those in the control group; those with treatment resistant depression, who have responded to the NMDA receptor antagonist, Spravato, will continue to have a response with an oral medication with NMDA receptor antagonist activity.

These fast-acting antidepressants are being used with increasing frequency in the community, and this study proposed seeks to find out more regarding how these therapies fit into the treatment landscape.

W41. 50% IMPROVEMENT: SHOULD TREATMENT RESPONSE GO BEYOND SYMPTOM IMPROVEMENT WHEN EVALUATING THE TREATMENT OF DEPRESSION?

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Abstract: Background: The emphasis on symptom resolution in depression treatment research is at variance with the recommendations of official treatment guidelines and the results of surveys of depressed patients' views of the most important treatment goals. In the present study, we examined the interrelationship between response rates on various outcome domains and whether response on each domain was associated with patients' global rating of improvement (PGI) reported upon treatment completion. We also examined whether the PGI was associated with the number of domains on which the patients had achieved responder status and which domains were independent predictors of PGI response.

Methods: 844 patients with DSM-IV major depressive disorder completed the Remission from Depression Questionnaire (RDQ), a self-report measure that assesses 6 constructs considered by patients to be relevant to assessing treatment outcome. The patients completed the RDQ at admission and discharge from the treatment program. For each domain, response was defined as a 50% or greater reduction in scores. At discharge, the patients rated the PGI.

Results: The patients significantly improved from admission to discharge on each of the 6 domains assessed on the RDQ. The responders on each domain reported significantly greater improvement on the global rating of improvement at discharge. PGI ratings increased as a function of the number of domains the patient was a responder. Responder status in one domain mostly co-occurred with responder status in another domain. Because of the concordance of response rates on the 6 domains we further examined which domains independently predicted PGI response by conducting a logistic regression analysis. In a logistic regression analysis, responses on all domains, except nondepressive symptoms, were independently associated with PGI response. Because treatment studies of depression typically define response in terms of depressive symptoms, we repeated the logistic regression analysis entering the depression symptom domain first. The depression symptoms domain accounted for 15% of the variance of PGI response. The remaining variables accounted for another 10% of the variance. When we reversed this analysis and entered the nonsymptom domains first, they accounted for 22% of the variance of PGI response, and the symptom domains accounted for an additional 3% of the variance.

Conclusion: The results of the present study are consistent with multiple patient surveys which have suggested that focusing on symptom reduction is too narrow of an approach when measuring outcome in the treatment of depression. Expanding the assessment of outcome beyond symptoms and viewing nonsymptomatic outcome domains as critical composites of primary endpoints would be more consistent with a patient-centered approach towards the treatment of depression.

W42. EFFICACY AND SAFETY OF ATICAPRANT, A KAPPA OPIOID RECEPTOR ANTAGONIST, ADJUNCTIVE TO ORAL SSRI/SNRI ANTIDEPRESSANT IN

MAJOR DEPRESSIVE DISORDER: RESULTS OF A PHASE 2A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY

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Abstract: Background: Aticaprant is a small molecule, high-affinity, selective kappa opioid receptor (KOR) antagonist. KOR antagonism has demonstrated meaningful effects in animal models of depression and anhedonia that may translate to therapeutic benefit in humans.

Methods: This was a multicenter, double-blind (DB), placebo-controlled, randomized study of adults (18-64 years old) with a DSM-5 diagnosis of major depressive disorder (MDD) and anhedonia (defined by Snaith-Hamilton Pleasure Scale [SHAPS; range 0 - 56] ≥ 20) at baseline.

Eligible participants had inadequate response to antidepressant treatment at screening (i.e., Montgomery Åsberg Depression Rating Scale [MADRS] ≥25 after 6 continuous weeks to ≤ 12 months of SSRI/SNRI). Patients who had failed ≥3 antidepressants treatments, including the current SSRI/SNRI, during the current depressive episode were excluded.

The study consisted of a 5-week screening phase and an 11-week DB treatment phase, the latter consisting of 3 periods: 1) a placebo lead-in period (up to 3 weeks); 2) a 6-week DB treatment period; and, 3) for patients who completed DB treatment, a withdrawal period during which they received placebo for the remaining time of the treatment phase.

Patients were randomly assigned (1:1) to receive either aticaprant 10 mg or to continue placebo, each once daily during the DB treatment period. Patients were maintained on their SSRI/SNRI, without change, throughout the study.

Results: Of 184 patients enrolled, 169 were included in the safety analyses and 166 were included in the full ITT (fITT) analyses, 121 (73%) of whom were lead-in placebo non-responders (i.e., <30% reduction in MADRS total score from lead-in baseline) (enriched eITT population [eITT]) and 45 (27%) were lead-in placebo responders. The mean (SD) age (fITT) was 42.6 (12.7) years, 72.3% were female, and mean (SD) MADRS at baseline was 25.3 (7.86). All but 1 of the patients had anhedonia at baseline.

Improvement (LS mean [SE] difference vs. placebo) in MADRS total score at week 6 for aticaprant was significant compared to placebo in the eITT analysis set (-2.1 [1.25] with 1-sided 80% CI upper limit of -1.09; p=0.044, observed effect size 0.23). The treatment effect was larger in the fITT analysis set (-3.1 [1.05] with 1-sided 80% CI upper limit of -2.21; p=0.002, observed effect size=0.36).

Among patients with high anhedonia at treatment baseline (defined by SHAPS ≥38), larger differences between aticaprant and placebo at week 6 were observed (effect size: 0.38 eITT, 0.51 fITT) than in those with low anhedonia level (treatment baseline SHAPS ≥20 and <38) (effect size: 0.11 eITT, 0.29 fITT).

Study drugs were well tolerated: Few patients (1 [1.2%] in each treatment group) had adverse events that led to discontinuation of study drug. The most common adverse events reported for aticaprant and placebo, each combined with SSRI/SNRI, were headache (11.8%/7.1%, respectively), diarrhea (8.2%/2.4%), pruritus (5.9%/0%), and nasopharyngitis (5.9%, 2.4%). One serious adverse event (acute cholecystitis in the placebo group) and no deaths were reported.

Conclusion: In this first clinical study of aticaprant for patients with MDD and anhedonia, inadequately treated with SSRI/SNRI antidepressants, adjunctive treatment with aticaprant led to significantly greater reduction in depressive symptoms severity on the MADRS compared to placebo. The safety profile of aticaprant was favorable. These results support further investigation in larger trials.

W43. EFFICACY AND SAFETY OF ESMETHADONE (REL-1017) IN PATIENTS WITH MAJOR DEPRESSIVE DISORDER AND INADEQUATE RESPONSE TO STANDARD ANTIDEPRESSANTS: A PHASE 3 RANDOMIZED CONTROLLED TRIAL

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Abstract: Background: Esmethadone (REL-1017) is an N-methyl-D-aspartate receptor uncompetitive antagonist and antidepressant candidate with promising safety, tolerability, and efficacy results from Phase 1 and 2 trials.

Methods: A Phase 3, randomized, double-blind, placebo-controlled trial was conducted to assess the efficacy and safety of oral once-daily adjunctive REL-1017 in patients with major depressive disorder (MDD) and inadequate response to standard antidepressants. Patients were aged 18 to 65 years and experiencing a major depressive episode despite ongoing treatment with a standard antidepressant. Patients were randomly assigned to receive 75 mg REL-1017 (loading dose) or placebo on Day 1, followed by 25 mg REL-1017 or placebo from Day 2 to Day 28. The primary efficacy endpoint was change in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score from baseline to Day 28. The full analysis set (FAS) comprised all randomized and dosed patients. The per-protocol set (PPS) comprised patients completing the 28-day treatment without major protocol deviations that impacted efficacy assessments.

Results: In the PPS (N=198: 101 REL-1017; 97 placebo), the change in MADRS total score from baseline was 15.6 for REL-1017 and 12.5 for placebo, with a mean difference (MD) of 3.1 (p=0.051; effect size=0.29). Application of a mixed-effect model with repeated measures (MMRM) produced consistent results (least square MD=2.94; p=0.0565; effect size=0.28). In the FAS (N=227: 113 REL-1017; 114 placebo), there was a trend toward significance for the primary endpoint (MD=2.3; p=0.1537; effect size=0.21) and a statistically significant

difference in response rate (patients with ≥50% decrease in MADRS score compared to baseline: 39.8% REL-1017 versus 27.2% placebo; p=0.0438; odds ratio=1.77).

In the PPS, prespecified subgroup analyses showed statistically significant effects in females (N=146; MD=3.8; p=0.0417; effect size=0.36) and in patients >50 years of age (N=88; MD=6.3; p=0.0043; effect size=0.64).

Adverse events (AEs) were mild or moderate and transient. There were no treatment-related serious AEs. There were no indications of withdrawal or opioid abuse. Seven patients experienced AEs leading to discontinuation of the study drug (5 placebo and 2 REL-1017). Among the 29 patients in the FAS excluded from the PPS (17 placebo and 12 REL-1017), 19 (13 placebo and 6 REL-1017) did not complete treatment, and 11 (5 placebo and 6 REL-1017) had major protocol deviations (1 patient did not complete treatment and had a major protocol deviation).

Conclusion: The efficacy results of this trial support pursuing regulatory approval and confirm the favorable tolerability and safety results from Phase 1 and 2 studies. Efficacy results were more favorable in the PPS analysis compared to the FAS analysis. This difference was not caused by AEs impacting trial adherence. We hypothesize that the FAS may have included a higher number of inappropriately diagnosed patients (eg, "professional patients" and subjects with transient reactive depression, perhaps related to the stress of the COVID-19 pandemic) who were less motivated to complete treatment and comply with assessments, thereby explaining the more favorable results seen in the PPS compared to the FAS. PPS analyses may be better suited for evaluating drug efficacy compared to FAS in MDD trials assessing drugs with a favorable side effect profile.

W44. THE IMPACT OF SUBANESTHETIC DOSE OF INTRAVENOUS KETAMINE ON WORKING MEMORY IN INDIVIDUALS WITH TREATMENT-RESISTANT DEPRESSION

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Abstract: Introduction: Individuals with unipolar and bipolar treatment-resistant depression (TRD) frequently present with cognitive deficits that persist during and between mood episodes. These cognitive deficits, including problems in working memory, contribute to a decline in psychosocial abilities and quality of life. Working memory, a cognitive function associated with the temporary storage and manipulation of information, can be measured with an n-back task. This intellectual functioning is crucial for work, school, driving, and problem-solving skills. There is a lack of effective pharmacological interventions to treat cognitive dysfunction in patients with TRD. Ketamine, a high-affinity antagonist of the N-methyl-D-aspartate type glutamate receptor, has been studied for its rapid-acting antidepressant effects. Preliminary evidence suggests ketamine could improve cognition in patients with TRD through its synaptogenic effect on the prefrontal cortex.
Aims: To investigate the effect of ketamine on working memory performance (reaction time and accuracy on the n-back task) in patients with unipolar and bipolar TRD.

Methods: This posthoc analysis combined two cross-over double-blind, randomized, placebo-controlled trials performed at the National Institute of Mental Health. Twenty subjects (14

female, age mean 42.35 and SD = 11.10), 13 with bipolar disorder and 7 with major depressive disorder, received a single intravenous infusion of subanesthetic ketamine (0.5 mg/kg) or saline placebo over 40 minutes approximately two weeks apart. Patients with bipolar disorder had ongoing treatment with either lithium or valproate. Patients with major depressive disorder were unmedicated. The subjects performed an n-back task during magnetoencephalography scanning at baseline (1-3 days before the first infusion), within 4-9 hours after each infusion, and approximately 11 days after each infusion (interim). We used a mixed model regression to compare the effects of the drug on n-back performance after each infusion. All models included a random intercept per person and a fixed drug effect. Study, age, and gender were also included as covariates in the models. Only 7 subjects performed the interim n-back task; therefore, only descriptive statistics were provided for these time points.

Results: There were no statistically significant differences comparing ketamine and placebo regarding reaction time [(0-back: $p = 0.25$), (1-back: $p = 0.84$), (2-back $p = 0.95$)] or accuracy [(0-back: $p = 0.35$), (1-back: $p = 0.64$), (2-back: $p = 0.22$)] 4-9 hours after infusions. Descriptive statistics for 0-, 1-, and 2-back interim accuracy and reaction time also did not indicate a meaningful effect of ketamine.

Conclusion: A single infusion of ketamine was not associated with improvements in working memory performance measured by the n-back task compared to placebo. Additionally, interim performance on the task did not indicate longer-term improvements with ketamine. Further studies are needed in order to investigate the cognitive impact of ketamine in TRD with larger sample sizes, different cognitive tests, other aspects of cognition, assessments at different time points, and repeated ketamine infusions. Moreover, further studies should investigate magnetoencephalography prefrontal cortex changes following ketamine infusion in patients with TRD.

W45. EFFECTS OF NLS-12 (OXAFURAMINE) ON MEMORY IN THE NOVEL OBJECT RECOGNITION TEST IN MICE

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Abstract: Introduction: The novel object recognition (NOR) test has been used in numerous studies to evaluate long-term episodic memory in rodents. Donepezil, one of the most frequently used compounds for treatment of dementia due to Alzheimer's disease has been shown to improve long-term episodic memory in rats or mice. The aim of this study was to examine whether NLS-12 (oxafuramine; International Application No. PCT/EP2022/069200; Applicant NLS Pharmaceutics), a norepinephrine and dopamine reuptake inhibitor and muscarinic M4 receptor antagonist, improved long-term episodic memory in mice. Donepezil was used as positive control drug.

Methods: C57BL/6 male mice: 8 groups (N = 16 mice/group) were subjected to the effect of NLS-12 (1, 4, 8 mg/kg) and compared to those of vehicle and of donepezil (2 mg/kg). Long-term episodic memory was tested in the NOR test, using a 3-days interval between the acquisition session (called sample trial) and the retention session (called choice trial). This method allows to detect an improvement of memory in the natural forgetting condition. The

control group did not recognize the familiar object. Donepezil (2 mg/kg) improved the recognition of the familiar object, showing that experimental conditions were suitable to detect an improvement of memory. Donepezil also decreased the exploration time 30 min post-treatment, but not 3 days post treatment.

Results: NLS-12 dose-dependently improved the recognition of the familiar object, i.e. improved memory. This effect was significant at 8 mg/kg and was not significantly different to that of donepezil. The recognition of the familiar object was not modified by NLS-12 at 1 mg/kg and was improved in a non-significant manner by NLS-12 at 4 mg/kg. NLS-12 did not significantly modify the exploration time at 30 min post-treatment –contrary to donepezil– and at 3 days post treatment.

Conclusion: The results of this pre-clinical study suggest that NLS-12 induced a long-term memory improvement which was significant and of the same extent to that induced by donepezil. At doses tested, NLS-12 did not reduce exploratory behavior, contrary to donepezil, suggesting that NLS-12 may induce less side effects than donepezil.

W46. EFFECTS OF NLS-11 (BENEDIN) ON MEMORY IN THE NOVEL OBJECT RECOGNITION TEST IN MICE

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Abstract: Introduction: The novel object recognition (NOR) test has been used in numerous studies to evaluate long-term episodic memory in rodents. Donepezil, one of the most used compound for treatment of dementia due to Alzheimer's Disease (AD) has been shown to improve long-term episodic memory in rats or mice. The aim of this study was to examine whether NLS-11 (benedin; International Application No. PCT/EP2022/069188; Applicant NLS Pharmaceutics), a norepinephrine and dopamine reuptake inhibitor and muscarinic M1, M2, M3 receptor antagonist improved long-term episodic memory in mice. Donepezil was used as positive control drug.

Methods: 57BL/6 male mice, 8 groups (N = 16 mice/group), were subjected to the effect of NLS-11 (0.1, 0.5, 1 mg/kg) and compared to those of vehicle and of donepezil (2 mg/kg). Long-term episodic memory was tested in the NOR test, using a 3-days interval between the acquisition session (called sample trial) and the retention session (called choice trial). This method allows to detect an improvement of memory in the natural forgetting condition. The control group did not recognize the familiar object. Donepezil (2 mg/kg) improved the recognition of the familiar object, showing that experimental conditions were suitable to detect an improvement of memory. Donepezil also decreased the exploration time 30 min post-treatment, but not 3 days post treatment.

Results: NLS-11 improved the recognition of the familiar object, i.e. improved memory. This effect was significant at 0.5 mg/kg and was not significantly different to that of donepezil. It was not significant at 0.1 and 1 mg/kg. NLS-11 did not significantly modify the exploration time at 30 min post-treatment – contrary to donepezil – and at 3 days post treatment.

Conclusion: The results of this pre-clinical study suggest that NLS-11 induced a long term memory improvement which was significant and of the same extent to that induced by

donepezil. At doses tested, NLS-11 did not reduce exploratory behavior, contrary to donepezil, suggesting that NLS-11 may induce less side effects than donepezil.

W47. EFFECTS OF SOLRIAMFETOL ON COGNITIVE FUNCTION IN PARTICIPANTS WITH COGNITIVE IMPAIRMENT ASSOCIATED WITH EXCESSIVE DAYTIME SLEEPINESS IN OBSTRUCTIVE SLEEP APNEA: RESULTS OF THE SHARP STUDY

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Abstract Purpose: The SHARP study evaluated whether solriamfetol improves cognitive function in patients with impaired cognition concomitant with excessive daytime sleepiness (EDS) associated with obstructive sleep apnea (OSA).

Background:OSA is a common disorder characterized by repeated abnormal breathing events resulting in disrupted sleep and EDS. Positive Airway Pressure (PAP) reduces hypoxia and mitigates sleep disruption, but EDS often persists. Cognitive impairment is a burdensome symptom in many patients with EDS associated with OSA, which leads to occupational and social dysfunction and degrades quality of life. Solriamfetol (Sunosi®) is approved to improve wakefulness in adults with EDS associated with OSA. In nonclinical pharmacology studies, solriamfetol inhibited dopamine/norepinephrine reuptake and activated trace amine-associated receptor 1 (TAAR1).

Design/Methods: SHARP was a randomized, double-blind, placebo-controlled, crossover trial in 59 patients with EDS associated with OSA and demonstrated cognitive impairment. All patients received solriamfetol for 2 weeks (75mg for 3 days followed by 150mg/day), and placebo for 2 weeks, with treatment periods separated by a 1-week washout. The primary endpoint was change from baseline on the Digit Symbol Substitution Test equivalent of the Repeatable Battery for the Assessment of Neuropsychological Status (DSST-RBANS). Secondary endpoints included change from baseline on the British Columbia Cognitive Complaints Inventory (BC-CCI) and the Epworth Sleepiness Scale (ESS).

Results: The study completion rate was 96.7%. Solriamfetol treatment improved performance on the DSST-RBANS compared to placebo (6.49 vs. 4.75, p=0.009), with a Cohen's d effect size of d=0.36. Solriamfetol treatment also yielded improvements on the BC-CCI (-4.70 vs -3.11, p=0.002; d=0.43) and the ESS (-4.41 vs -2.31, p=0.004; d=0.50). The most common adverse events with solriamfetol treatment (incidence 3%) were nausea (6.9%) and anxiety (3.4%).

Conclusion: Solriamfetol (150mg/day) improved both objective and subjective measures of cognitive function in patients with EDS associated with OSA and impaired cognition. These data support the safety and efficacy of solriamfetol in improving cognitive symptoms of EDS associated with OSA.

Support: Axsome Therapeutics and Jazz Pharmaceuticals

W48. TWO RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIALS OF ADJUNCTIVE TRORILUZOLE, A NOVEL GLUTAMATE MODULATING AGENT, IN OBSESSIVE COMPULSIVE DISORDER

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Abstract: Objectives: Describe the design, scientific rationale, and demographic characteristics of the studies.

Design: Following up on a clinical signal seen in a Phase 2 proof of concept study, two identical Phase 3 studies will randomize 700 international participants for 10 weeks in a double-blind, placebo-controlled design. Subjects must have a diagnosis of OCD for ≥ 1 year with inadequate response to an ongoing standard of care medication as defined by a Yale-Brown Obsessive Compulsive Score (Y-BOCS) ≥ 22 at Screening and Baseline. The primary endpoint is the change from Baseline to Week 10 in the Y-BOCS.

Results: Demographic analysis of the subjects randomized as of January 11th, 2023 revealed that the majority of subjects randomized are women (67%). Subjects between the ages of 18-39 years comprise 57% of those randomized. Subjects reported baseline Y-BOCS ranges of 22-23, 24-27, 28-31, and 32-40 (12%, 43%, 30%, 15%). The majority of subjects reported between 2-10 OCD history years (54%), while 22% and 19% reported between 11-20 and 21+ OCD history years, respectively. The studies began enrollment in December 2020 and are currently ongoing.

Conclusion: The studies (NCT04641143 and NCT04693351) will investigate the efficacy and safety of troriluzole for patients with OCD. The majority of reported Baseline Y-BOCS fall within the 24-27 range indicating severe range symptoms with the highest scores in the 40-59 age group. Thus, as subject age increases, the relative proportion of individuals reporting more severe Y-BOCS scores also appears to increase.

W49. AN OPEN-LABEL TRIAL ASSESSING SHORT- AND LONG-TERM TOLERABILITY AND EFFICACY OF ZYN002 (CANNABIDIOL) ADMINISTERED AS A TRANSDERMAL GEL TO CHILDREN AND ADOLESCENTS WITH 22Q11.2 DELETION SYNDROME (INSPIRE)

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Abstract: Background: 22q11.2 deletion syndrome (22q), caused by a microdeletion of region 11.2 of chromosome 22, is the most common recurrent contiguous gene deletion syndrome. 22q is associated with developmental anomalies including heart defects, palate and pharyngeal defects and immunodeficiency. Behavioral problems, autism spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD), and mood disorders occur frequently in patients with 22q. ZYN002 is a pharmaceutically produced cannabidiol transdermal gel in development for treatment of the behavioral symptoms in 22q and Fragile X syndrome.

INSPIRE was an open-label, phase 2 trial to evaluate the safety/tolerability and efficacy of ZYN002, in children and adolescents ages 4 to <18 years, in the treatment of behavioral and anxiety-related symptoms in 22q.

Methods: Males and females with 22q having a Clinical Global Impression-Severity (CGI-S) score ≥4 and a Pediatric Anxiety Rating Score-Revised (PARS-R) score ≥10 were enrolled. Patients received 250 mg/day or 500 mg/day of ZYN002 (weight-based) added to current therapy for 14 weeks (Period 1). Patients with <25% improvement from baseline in the Aberrant Behavior Checklist-Community (ABC-C) Irritability subscale at week 6 could have their dose increased to either 500 mg/day or 750 mg/day. Patients with ≥35% improvement in the ABC-C irritability subscale at week 14 could continue treatment for an additional 24 weeks (Period 2). Safety assessments included adverse events, vital signs, laboratories, and electrocardiograms (ECGs). Primary efficacy assessments included change from baseline on the PARS-R, Anxiety, Depression and Mood Scale (ADAMS), ABC-C and the CGI-Improvement (CGI-I).

Results: Twenty patients, 60% males, with a mean age of 9.9 years were enrolled. Seventeen patients completed Period 1 and 13 patients entered Period 2. Statistically significant improvements were seen in the PARS-R, ADAMS and ABC-C scales at Week 14. Mean change and percent improvement from baseline were PARS-R: Total Score -6.2, 40.6%, p=0.0005; ADAMS: Total Score -18.4, 45.3%, p=0.0005; General Anxiety -5.4, 43.6%, p=0.0005; Depressed Mood -4.3, 50.3%, p=0.0033; Social Avoidance -4.4, 41.3%, p=0.0084; Obsessive/Compulsive Behavior -1.9, 64%, p=0.0037; Manic/Hyperactive Behavior -3.1, 38.2%, p=0.0032; and ABC-C: Social Withdrawal -6.4, 27.6%, p=0.011; Inappropriate Speech -1.8, 18.3%, p=0.0166; Stereotypic Behavior -2.3, 52.1%, p=0.0155; Irritability -8.4, 36.3%, p=0.0055; Hyperactivity -7.6, 16.5%, p=0.0091. Twelve of 16 patients (75%) were rated as "improved", "much improved" or "very much improved" at week 14, with 62.5% being "much improved" or "very much improved" on the CGI-I. The improvements in all endpoints at Week 14 were sustained in patients who completed Period 2. Over 38 weeks, 3 patients reported treatment related adverse events which were all mild application site adverse events which were transient and resolved with continued dosing. One patient discontinued treatment due to adverse events not related to ZYN002. Four non-treatment-related serious adverse events were reported in 3 patients. No clinically significant changes in vital signs, ECGs or laboratories were reported.

Conclusion: INSPIRE provides initial evidence suggesting a positive risk–benefit profile for ZYN002 in improving behavioral and anxiety-related symptoms in children and adolescents with 22q when added on top of stable standard of care. Further studies are warranted.

W50. LONG-TERM SAFETY AND SUSTAINED EFFICACY OF ZYN002 CANNABIDIOL TRANSDERMAL GEL IN THE TREATMENT OF BEHAVIORAL SYMPTOMS IN CHILDREN AND ADOLESCENTS WITH FRAGILE X SYNDROME (ZYN2-CL-017)

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Abstract: Background: ZYN002 is a pharmaceutically produced transdermal cannabidiol gel in development for the treatment of behavioral symptoms in Fragile X syndrome (FXS).

ZYN2-CL-017 is an ongoing, open-label extension (OLE) trial. CONNECT-FX was a randomized, double-blind trial assessing safety and efficacy of ZYN002 in children and adolescents. Patients with complete, 100% FMR1 gene methylation treated with ZYN002 had significant improvements as compared to placebo on multiple endpoints. FAB-C (ZYN2-CL-009) was the initial Phase 2, open-label trial.
OBJECTIVES: To assess the long-term safety and efficacy of ZYN002 in patients with FXS.

Methods: Interim analyses were conducted with data through 23-January-2023. Safety data for all patients, up to 45 months since entry into the study, and efficacy data through 24 months for patients with 100% FMR1 gene methylation who completed CONNECT-FX are reported. Patients screened for CONNECT-FX were eligible for entry, including patients ineligible for randomization, and patients who were randomized to 12-weeks of ZYN002 (250 mg or 500 mg daily [weight-based]) or placebo. Patients from FAB-C also entered the trial. Safety assessments included adverse events, vital signs, laboratories, and electrocardiograms (ECGs). The primary efficacy endpoint was change in the Social Avoidance (SA) subscale of the Aberrant Behavior Checklist–Community FXS (ABC–CFXS).

Results: 240 patients were enrolled; 197 who completed CONNECT-FX, 33 ineligible for randomization from CONNECT-FX and 10 from FAB-C. 110 patients received ZYN002 prior to entry. Mean age was 9.7 years (range 3 to 17 years at entry); 76.3% were male. 176 patients and 101 patients completed at least 12 and 24 months of treatment respectively (median 20 months). Treatment-related adverse events were reported in 13.3% of patients. The most common treatment-related event and only event reported by ≥ 5% of patients was application site pain (6.7%), which was short-lasting and reported as mild in 15 and moderate in 1 patient. Eight patients experienced 11 non-treatment related serious adverse events. Seven patients discontinued due to an adverse event. No clinically significant changes in vital signs or ECGs were reported. There was no evidence of ZYN002-related changes in liver function or any other laboratory tests. At the end of CONNECT-FX, completely methylated ZYN002 treated patients had a median improvement of 40% in SA verses 20% in placebo treated patients (p=0.027); 62% of ZYN002 treated patients and 41% of placebo treated patients reported a clinically meaningful improvement in SA (≥ 3 points) for at least 2 consecutive visits. Placebo treated patients who began ZYN002 in the OLE demonstrated a similar response profile to patients originally treated with ZYN002 in regard to improvement in SA; the effect was maintained through 24 months in both groups. 81% of these patients reported clinically meaningful improvement in SA for at least 2 consecutive visits by 9 months.

Conclusion: ZYN002 was well tolerated over a median of 20 months. In patients with complete FMR1 gene methylation, ZYN002 led to sustained improvement in Social Avoidance, a key behavioral symptom of FXS, following initial improvement seen after 12 weeks of double-blind therapy. The results from this OLE trial continue to support the effectiveness of ZYN002 in patients with complete FMR1 gene methylation.

W51. PSYCHOPHARMACOLOGY AND TRANSCRANIAL MAGNETIC STIMULATION IN VETERANS RECEIVING TMS FOR MDD

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Abstract: Introduction: TMS is a neuromodulation intervention for the treatment of MDD. One area which requires further study is the interplay between psychopharmacology and TMS. Most patients receiving TMS concurrently take psychiatric medications, yet there is a paucity of literature examining this relationship. The current study was conducted to examine the concurrence of psychopharmacology in Veterans receiving TMS for MDD.

Methods: A retrospective cohort analysis was conducted on Veterans receiving TMS treatment for MDD at the Tampa VA from 2013-2021. Interim analyses were conducted on the first 75 patients to provide descriptive information including patient characteristics, symptomatology, and data on concurrent pharmacological regimens. The cohort was then divided into groups based on med regimen at the time of initiating TMS, including those taking agents known to: increase cortical excitability; decrease cortical excitability; those on regimens with both groups of medications; and those without either group. The association between medication groups and improvement in depression with TMS was analyzed.

Results: 75 Veterans were included in this interim analysis and were mostly male (74.67%) and Caucasian (78.67%); mean age= 51.59 yrs. All patients had MDD. Co-occurring psychiatric disorders were common, most frequently: GAD (54.67%), PTSD (33.33%), and panic disorder (24.00%). There was a high degree of illness burden including rates of prior MH hospitalizations (41.33%) and past suicide attempts (29.33%). Mean past psychiatric medication trials was 5.77. Most patients received 10Hz TMS protocols applied to the left DLPFC, and this sub cohort was further analyzed to examine psychopharmacological prescribing patterns and outcomes of interest. Med regimens varied widely and most classes of medications commonly used for the treatment of mood disorders were represented. Mean psychiatric medications at the time of initiating TMS treatments were 2.59 with a range of 0-7. 9.09% of patients were on agents which increase cortical excitability; 37.88% on agents which decrease cortical excitability; an additional 12.12% on both groups of meds, and 40.91% without meds from either group. Chi-square and ANOVA were conducted to examine improvements in depressive symptoms in relation to pharmacological groupings. When analyzing patients with QIDS-SR assessments, 42.55% achieved treatment response (>=50% reduction on QIDS-SR); subgroup analyses showed differences in response rates based on pharmacological group with individuals on meds known to increase cortical excitability having the highest response rates (60.00%), compared to individuals on meds that decrease cortical excitability (46.67%), those on neither groups of meds (40.91%), and those on both groups of medications (20.00%). However, these results were not statistically significant, likely due to the underpowered nature of this interim analysis. Mean improvement in QIDS-SR scores was 7.43; no significant between group differences were observed, again likely secondary to the small sample size in this interim report.

Conclusion: Most patients receiving TMS for MDD are concurrently treated with psychopharmacological agents, yet the relationship between pharmacology and TMS remains understudied. Early results suggest that concurrent pharmacological prescribing patterns vary widely and often include medications known to influence cortical excitability. As TMS involves cortical stimulation, the impact of these medications on TMS remains a question of critical importance. Further study is warranted to examine pharmacological impacts on TMS including response to treatment and impacts on durability of response.

W52. EFFICACY AND ENGAGEMENT WITH A DIGITAL THERAPEUTIC IN PATIENTS WITH EXPERIENTIAL NEGATIVE SYMPTOMS OF SCHIZOPHRENIA

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Abstract: Introduction: Negative symptom severity is a robust predictor of real-world functioning in schizophrenia and is a key driver of the burden associated with the disorder. No FDA-approved pharmacological treatment for schizophrenia adequately addresses experiential negative symptoms (ENS). Digital treatments for schizophrenia may be a feasible resource for evidence-based care given ubiquitous smartphone ownership. The use, approval, and development of digital therapeutics have been steadily increasing in recent years, though few have been evaluated in schizophrenia. An exploratory study was conducted to evaluate an abbreviated version of a digital therapeutic for ENS to inform further development prior to additional efficacy and safety testing.

Methods: This study was a multi-center, exploratory, 7-week, single-arm study of a beta version of a digital therapeutic (study app) in adults with ENS of schizophrenia. Eligible participants were 18 years of age and older with a diagnosis of schizophrenia and self-reported negative symptoms (score of ≤30 on the Motivation and Pleasure Scale-Self Report) on a stable dose (≥12 weeks) of antipsychotic medication. Participants had on-demand access to the study app. Study app engagement was measured throughout the study. ENS were assessed at baseline with the Clinical Assessment Interview for Negative Symptoms Motivation and Pleasure Scale (CAINS-MAP).

Results: Enrolled were 50 adults, of which 43 (86%) completed the study. Participants were majority male (80%), non-white (70%), and without college education (64%). They were between 22 and 64 years of age (mean [SD] = 48.1 [12.4]), with the majority (80.5%) ≥30 and ≤59 years. Participants opened the study app on 77% of the 49 study days (mean [SD] = 37.8 [15.4]) and engaged in a mean (SD) of 42 (19.6) sessions ≥ 60 seconds. A significant reduction (p=0.004) in ENS was evident in the 7 weeks from baseline CAINS-MAP (mean [SD] = 20.2 [8.6]) to end of study (16.8 [7.8]; n=43). There was no association between baseline ENS and the number of sessions completed. There were 3 adverse events, none considered serious, during the study that were not related to study app use.

Conclusion: In this exploratory study of participants with ENS of schizophrenia, we observed high levels of study app use and a significant reduction CAINS-MAP scores. The CAINS measures ENS broadly, with the CAINS-MAP related to social, independent, and vocational functional capacity. Severity of ENS assessed with CAINS-MAP at baseline did not correlate with intensity of engagement with this study app. The positive results of this study, including signal of clinical efficacy alongside benign safety profile, provide confidence in advancing this asset into late-phase clinical development. These findings highlight the potential of digital therapeutics to treat even severe mental disorders. Limitations of the study include the small sample size, single arm, and exploratory nature of the study.

W53. MDMA-ASSISTED PSYCHOTHERAPY FOR BORDERLINE PERSONALITY DISORDER

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Abstract: Borderline Personality Disorder (BPD) is a complex mental health disorder associated with an elevated risk of suicide and extreme functional impairment. At present, there are limited treatment options for BPD. Available options are associated with large variability in outcomes and high dropout rates. As such, there is a pressing need for new BPD treatments that can improve outcomes. This research report will present a recently published review (Traynor, Roberts, Ross, Zeifman, and Choi-Kain, 2022) that outlines the promise for research on 3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy for BPD (MDMA-AP). The paper authors (Roberts, Ross, and Zeifman) have also developed a protocol for the first-ever clinical trial to investigate the safety, feasibility, and preliminary effects of MDMA-AP for comorbid BPD and posttraumatic stress disorder, which will be briefly presented as a hopeful next step forward in this area of novel intervention. Taken together, this research report will provide a theory-driven overview of the potential for psychedelic-assisted psychotherapy in BPD, highlighting initial treatment targets, promising initial findings, and considerations for designing clinical trials.

Traynor, J. M., Roberts, D. E., Ross, S., Zeifman, R., and Choi-Kain, L. (2022). MDMA-Assisted Psychotherapy for Borderline Personality Disorder. Focus, 20(4), 358-367.

W54. PSILOCYBIN FOR THE TREATMENT OF OBSESSIVE COMPULSIVE DISORDER

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Abstract: Our research aimed to explore the potential of psilocybin as a treatment for obsessive-compulsive disorder (OCD), a chronic condition with a lifetime prevalence of 2 to 3% that often does not respond well to existing treatments. To determine the acute efficacy, safety and tolerability of two different doses of psilocybin, we studied 15 patients with symptomatic OCD in two study phases.

In Phase 1, a four-week randomized controlled trial (RCT) assigned patients to either: a) low dose (100 µg/kg) psilocybin, b) high dose (300 µg/kg) psilocybin, or c) lorazepam (1 mg). Five subjects per group took the assigned study drug a total of four times, separated by a week. During the four-week Phase 2, all participants received high doses of psilocybin.

Symptom severity was assessed using the Yale-Brown Obsessive Compulsive Scale (YBOCS) before and after the trial and at 6 months follow-up. No severe drug-related adverse events (SAEs) occured during or following administration. Moreover, no psychotic symptoms emerged, and no increase in acute suicidality occurred.

Results showed a greater reduction in symptoms with psilocybin compared to lorazepam, with 73% of patients classified as responders and 40% achieving remission by the end of the 8=-week trial. We are exploring the relationship between the main outcome and altered states of consciousness (ASC) and mystical experience (ME) as predictors of symptom response using the 5D-ASC and a Mystical Experiences scale.

These findings suggest the promise of psilocybin for the acute and durable treatment of OCD, and support the merit of a larger clinical trial. Moreover, in the context of supervised clinical

research, psilocybin was safe and well-tolerated, and reduced OCD symptoms to a greater extent than the active control lorazepam.

W55. DOES PHARMACOGENOMIC TESTING AFFECT CLINICAL MANAGEMENT FOR POOR AND ULTRARAPID METABOLIZERS OF CYTOCHROME P-450 2D6 AND 2C19 IN MINORITY POPULATIONS? – A RETROSPECTIVE REVIEW

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Abstract: Background: Pharmacogenomic testing in the clinical practice of psychiatry is controversial but continues to be used. There is a relative lack of research done in minority populations.1 Our study collected real-world data on pharmacogenomic testing in minority patients, focusing on poor and ultrarapid metabolizers of cytochrome P-450 CYP2D6 and CYP2C19, to see if testing was helpful for clinical decision making.

Methods: A retrospective review of patients who received pharmacogenomic testing between 1/1/2003 and 11/2/2022 at Mayo Clinic. We selected poor and ultrarapid metabolizers of CYP2D6 and CYP2C19 who self-identified as Hispanics, Asian and Pacific Islanders, African Americans, or Native Americans. Reason for testing, diagnosis, medication trials before and after testing were recorded. A positive outcome was defined as test results able to explain past reactions to medications or if results changed medication management.

Results: 36,602 patients (31,699 or 86.6% Caucasian) received pharmacogenomic testing. 1525 (4.2%) and 502 (1.4%) patients were identified as poor metabolizers for CYP2D6 and CYP2C19, respectively. 324 (0.9%) and 1014 (2.8%) patients were identified as ultrarapid metabolizers for CYP2D6 and CYP2C19, respectively. The prevalence for CYP2D6 poor metabolizers in Hispanic, Black, and Asian patients were 2.7%, 2.7%, and 0.8%; it was 2.3%, 1.0% and 0.5% for CYP2D6 ultrarapid metabolizers. For CYP2C19 poor metabolizers, it was 0.8%, 2.7%, and 6.8%, and for CYP2C19 ultrarapid metabolizers, 1.1%, 3.4% and 0.7%, respectively. Among the 185 poor and ultrarapid metabolizers of minority races, 43 (23.2%) received testing for research purposes, 63 (34.1%) for guidance on psychotropic medications, 68 (36.8%) for other medications, and 11 (6.0%) had no reasons documented. Among the 63 patients who tested for psychotropic medication guidance, 58 were referred by their clinician (25 by psychiatrists, 27 by general practitioners, 4 by other specialists, and 2 by pharmacists), of which 52.4% had a positive outcome. When ordered by psychiatrists, 68% had a positive outcome. Reasons for negative outcomes include inaccurate diagnosis, patients' preference to not take or change medications, and no actionable pharmacogenomic recommendations for current medications.

Conclusion: Among the minority patients pursuing testing for psychotropic medication guidance who were poor and ultrarapid metabolizers of CYP2D6 or CYP2C19, half had resulting medication changes or a potential explanation for previous response to medications. In these cases, pharmacogenomic testing was clinically useful. The prevalence of poor and ultrarapid metabolizers in some minority races in our study was lower compared to other studies.2 Limitations of this study include retrospective study, small sample size, lack of data on symptom improvement, and not having a comparison group with intermediate and normal metabolizers. More studies are needed to understand the clinical utility of pharmacogenomic

testing in diverse populations with psychiatric disorders, and whether any health disparities might exist.

W56. CLOZAPINE THERAPEUTIC DRUG MONITORING: INVESTIGATING TOLERABILITY AND REDEFINING THRESHOLDS FOR SAFETY

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Abstract: Background: One third of schizophrenia patients do not respond to standard antipsychotic medication and are classed as "treatment resistant schizophrenia" (TRS). Clozapine is the only evidence-based treatment for TRS, yet clozapine is underutilized, in part, because clinicians fear serious side effects. Laboratory alerts caution that total serum clozapine and norclozapine levels above 1200ng/mL put patients at risk of adverse effects. In response to high levels, clinicians often decrease dose or discontinue treatment altogether overvaluing the risks compared to the treatment benefits for patients. The Glasgow antipsychotic side effects scale for clozapine (GASS-C) is a psychometric instrument used by clinicians to measure clozapine-related side effects. The current study aimed to evaluate within-subject and between-subject changes in clozapine levels and GASS-C severity.

Methods: The GASS was administered to treatment-resistant schizophrenia outpatients who were prescribed clozapine. All patients were followed at monthly intervals over three visits (n=152). We applied 1200 ng/mL as the upper limit for clozapine values. Our sample included patients with clozapine levels crossing the threshold across three follow up visits (n=20) (mean age, 41.0 ± 10.9). We completed a secondary sensitivity analysis between patients with consistently below threshold values (n=106) (mean age, 42.0 ± 12.6) versus patients with consistently above threshold values (n=26) (mean age, 51.0 ± 16.2). We completed baseline descriptive analyses and mixed logistic regression models to assess changes in clozapine levels and side effect severity.

Results: Amongst all the patients whose levels crossed the threshold across the three visits, no changes in side effects were reported in 66.67%, improvement of side effects was reported in 22.2%, and a worsening of side effects was reported in 11.1%. Results indicate no significant association (p=0.8463) between changes in clozapine levels and side effects.

At each visit when a level was below 1200ng/mL, 50% reported no side effects and 50% reported moderate side effects. When levels were above 1200ng/mL, 42.9% reported no side effects and 57.1% reported moderate side effects.

The sensitivity analysis mixed logistic regression model found higher clozapine levels were associated with increased odds of side effect severity (Odds ratio [OR]=1.72, 95% Confidence Interval[CI]=0.48-6.22, p=0.408) within subjects. Higher clozapine levels were associated with increased odds of side effects severity between high and low subjects (Adjusted OR=1.48, 95%CI= 0.253-8.686, p=0.662).

Conclusion: In patients whose total serum clozapine levels cross the safety threshold of 1200ng/mL, no significant differences in side effects are reported. Though reports of increased side effects was associated with higher levels, the results were not significant. Future studies are needed to confirm these results in larger cohorts to inform guidelines for clozapine safety

thresholds and optimize clinicians' use of clozapine to improve the outcomes for patients with TRS clozapine.

W57. INCREMENTAL BURDEN OF DEMENTIA AMONG PATIENTS WITH PARKINSON'S DISEASE PSYCHOSIS: ANALYSIS OF MEDICARE BENEFICIARIES

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Abstract: Objectives: There is limited research examining incremental health care resource utilization (HCRU) burden of coexisting dementia (PDP+D) among patients with Parkinson's disease psychosis (PDP). A database analysis of Medicare patients with PDP vs. PDP+D was conducted to address this gap in literature.

Methods: A retrospective cohort analysis of PDP patients using Parts A, B, and D claims from the 100% Medicare sample from January 1, 2013, to December 31, 2019, was conducted. Patients with incident dementia post PDP diagnosis (PDP+D) vs. PDP patients without incident dementia (PDP-only) during 01/01/14 to 12/31/18, formed the patient sample. Patients with a pre-index diagnosis of dementia, psychosis, secondary parkinsonism, delirium, other psychotic disorders, alcohol/drug-induced psychosis, schizophrenia, paranoia, or personality disorder were excluded from study sample. PDP+D vs. PDP-only patients were propensity score matched (PSM) 1:1 using 31 variables (age, sex, race, region and 27 Elixhauser comorbidity characteristics) as covariates. HCRU outcomes included: all-cause and psych-related inpatient hospitalization rates, and all-cause and psych-related hospitalizations by type of stay (i.e., short-term [ST-stay], skilled nursing facility [SNF-stay] and long-term [LT-stay]) rates, all-cause and psychiatric-ER visit rates after 1-year follow-up. HCRU differences between groups were evaluated using chi-square and t-tests. Logistic regressions controlled for demographic characteristics, comorbidities, coexisting dementia, and coexisting insomnia were conducted to compare PDP+D vs. PDP-only.

Results: From the eligible patient sample with PDP+D (n=14,194) vs. PDP-only (n=2,449), 1: 1 matched sample (n=1855 in each) were selected. Mean age (72 years), gender (50% males), and comorbidity profile were similar in both groups, after matching. Approximately, 49.7% (n=922) with PDP+D reported ≥1 all-cause inpatient hospitalizations vs. 36.0% (n=667) with PDP-only ($p<0.05$). Specifically, all-cause ST-stay, SNF-stay, and LT-stay among PDP+D vs. PDP-only patients were: 45.2% (n=839) vs. 35.7% (n=662), 28.3% (n=525) vs. 15.7% (n=291), and 8.5% (n=158) vs. 6.0% (n=113) ($p<0.05$), respectively. Similarly, 19.3% (n=358) with PDP+D vs. 12.2% (n=227) with PDP-only had ≥1 psych-related hospitalization ($p<0.05$). Psych-related ST-stay, SNF-stay, and LT-stay among PDP+D vs. PDP-only patients were: 12.3% (n=228) vs. 9.0% (n=167), 7.5% (n=140) vs. 3.4% (n=64), and 2.3% (n=43) vs. 1.2% (n=23) ($p<0.05$), respectively. Patients with ≥1 all-cause and psychiatric ER visit were: 72.6% (n=1,346) for PDP+D vs. 60.5% (n=1,123) for PDP-only and 13.3% (n=246) for PDP+D vs.11.3% (n=210) for PDP-only ($p<0.05$), respectively.

Conclusion: In this analysis of Medicare claims, patients with PDP+D have 10% and 12% higher all-cause hospitalization and ER visit rates vs. patients with PDP-only. PDP+D also resulted in higher psych-related hospitalizations and ER visits compared to PDP-only.

W58. A POST-HOC EXPLORATORY ANALYSIS OF THE PREVALENCE OF ANXIETY SYMPTOMS IN ACUTELY EXACERBATED SCHIZOPHRENIC PATIENTS AT BASELINE IN CLINICAL TRIALS

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[1]Signant Health

Abstract: A post-hoc exploratory analysis of the prevalence of anxiety symptoms in acutely exacerbated schizophrenic patients at baseline in clinical trials

Introduction: Anecdotal clinical experience suggests anxiety symptoms are frequently noted in schizophrenic patients suffering from acute psychotic exacerbation. We have previously reported an association between the severity of anxiety symptoms at the baseline evaluation and the strength of signal (Kott et al, in press) in a successful phase 2 clinical trial. It has also been reported that the severity of anxiety symptoms correlated with the overall symptom severity (Naidu et al, 2014). In the current analysis we explored the prevalence and severity of anxiety symptoms at the time of randomization into acute schizophrenia clinical trials and the relationship between the severity of anxiety symptoms and the PANSS total score.

Methods: Baseline data were obtained from 7,292 subjects participating in 20 clinical trials in acute schizophrenia. Descriptive statistics were used to summarize the severity of anxiety symptoms using PANSS item G2. Given the small number of cases in the extremes of the G2 scoring range, we have mapped the item on a new 4-point categorical anxiety score as follows: original G2 score of 1 and 2 as a score of 0, score of 3 as a 1, score of 4 as a 2, and scores 5-7 as a 3. The relationship between PANSS anxiety adjusted total score (PANSS without the anxiety score) and the newly created anxiety score was tested at baseline by means of linear regression.

Results: Anxiety symptoms were reported in 6,214 (85.2%) subjects at baseline. Of the whole sample 4,218 (57.8%) subjects had anxiety in clinically meaningful severity (score 4 or above). Based on the regression model at baseline, compared to those subjects who had no anxiety, no difference in PANSS anxiety adjusted score was identified in those subjects with only mild anxiety. A significant difference of 1.2(CI=0.4-2.1) and 3.2(CI=2.4-4.1) was identified for the moderate and severe anxiety groups, respectively.

Discussion: Our post-hoc analysis of trials in acute schizophrenia identified anxiety symptoms present in over 85% of subjects at baseline. Over 55% of subjects suffered from clinically meaningful levels of anxiety. The regression model at baseline found only a weak contribution of anxiety to PANSS total score. The results of our analyses are consistent with the notion that anxiety symptoms are prominent in acutely exacerbated schizophrenic patients at baseline in clinical trials. We suggest further exploration of clinical trial performance correlates post-baseline in high and low anxiety phenotypes of acute exacerbation of schizophrenia.

W59. DEVELOPMENT OF A POPULATION PHARMACOKINETIC MODEL TO DESCRIBE THE PHARMACOKINETICS OF ARIPIPRAZOLE 2-MONTH READY-TO-USE, A NOVEL LONG-ACTING INJECTABLE FORMULATION OF ARIPIPRAZOLE FOR ADMINISTRATION ONCE EVERY 2 MONTHS

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Abstract: Background: Compared with oral antipsychotics, long-acting injectable (LAI) antipsychotic formulations are associated with greater treatment adherence and a reduced risk of hospitalization or relapse (1). Aripiprazole 2-month ready-to-use (Ari 2MRTU) 960 mg is a novel LAI formulation of aripiprazole monohydrate for gluteal intramuscular administration once every 2 months. Ari 2MRTU 960 will offer an extended dosing interval versus aripiprazole once-monthly 400 mg (AOM 400). As part of the development of Ari 2MRTU 960, population pharmacokinetic (popPK) modelling was undertaken to characterize the pharmacokinetics (PK) of this formulation. The final popPK model is described here.

Methods: A previously developed and validated popPK model for characterizing aripiprazole plasma concentrations following administration of oral or AOM 400 (gluteal or deltoid intramuscular injection) formulations was expanded to include the novel Ari 2MRTU formulation (2). Overall, 8,899 aripiprazole PK samples from 1,191 adults (schizophrenia, schizoaffective disorder, or bipolar I disorder [BP-I], n=1,139; healthy individuals, n=52) from ten Phase 1 and 3 trials were included in the final combined analysis dataset; of these, 240 patients with schizophrenia or BP-I received Ari 2MRTU across three trials. All fixed-effects parameters from the prior model remained fixed throughout the model development, as did random-effects parameters for the first-order absorption rate constant of the oral and AOM routes, apart from CL/F and Vc/F, which were re-estimated. Covariate effects from the original model were retained, with additional potential effects related to the absorption and relative bioavailability of the Ari 2MRTU formulation formally tested using a modified stepwise approach. Data were analyzed using non-linear mixed effects modeling software (NONMEM v7.4.2).

Results: A 3-compartment model with linear elimination and different absorption models for each formulation best described the data. Absorption of the Ari 2MRTU formulation was modeled by a parallel zero-order and lagged first-order process that accounted for an identified double peak in plasma concentrations of aripiprazole post-administration of Ari 2MRTU. All disposition parameters were shared between the formulations except Vc/F (oral and AOM formulations, 93.4 L; Ari 2MRTU formulation, 2035 L); the different Vc/F value for the Ari 2MRTU formulation was attributed to the terminal half-life being absorption driven. Sex was a significant covariate on the absorption of the Ari 2MRTU formulation (90.7% higher absorption rate constant and 56.0% lower fraction of first-order absorption in males versus females); however, simulated Cavg,ss values were identical in both sexes, indicating no clinically relevant effect. As expected, simulated aripiprazole concentrations were higher in poor versus extensive metabolizers of CYP2D6; the effect of CYP2D6 metabolizer status was thus retained as a covariate from the prior model.

Conclusion: The final popPK model was considered fit for purpose, adequately describing aripiprazole PK following administration of Ari 2MRTU 960. The model also established estimates for key popPK parameters and identified sources of variability in drug exposure. The model will be used to perform simulations to support dosing of Ari 2MRTU 960 across multiple realistic clinical scenarios.

W60. THE PHARMACODYNAMIC EFFECTS OF TAAR1 AGONIST ULOTARONT ON METABOLIC BIOMARKERS OF GLUCOSE, C-PEPTIDE AND INSULIN FOLLOWING A MEAL IN PATIENTS WITH SCHIZOPHRENIA

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Abstract: Background: Obesity, dyslipidemia, hypertension, and hyperglycemia are highly prevalent in schizophrenia and the current class of antipsychotic drugs may contribute to additional adverse metabolic effects. While each antipsychotic drug has its own benefit/risk profile, the adverse metabolic effects associated with many drugs in the current class have been shown to be associated with increased morbidity and mortality risks, and increased public health costs, that inform treatment decisions. Ulotaront is a trace amine-associated receptor 1 (TAAR1) and serotonin 5-HT1A agonist currently in Phase 3 clinical trials for the treatment of schizophrenia. Recent preclinical evidence has identified TAAR1 as a novel regulator of metabolic control and a promising target for the potential treatment of obesity and type 2 diabetes. Here we evaluated the effects of ulotaront on liquid metabolic biomarkers which were collected in Phase 1 clinical pharmacology studies.

Methods: Metabolic effects of ulotaront were examined in response to a meal following a 8-12 hour fast. In a study to determine the effect of ulotaront on QTc interval, subjects with a diagnosis of schizophrenia (N=60) were randomized, in a 3-way crossover design with a 5-day washout period between drugs, to receive single doses of ulotaront (150 mg), moxifloxacin (400 mg), and placebo. Separately, in a standard drug-drug interaction study, utilizing metformin-HCL (850 mg) as a substrate for the organic cation transporter (OCT)-2, subjects with a diagnosis of schizophrenia (N=25) were randomized in a single-blind, 2-way crossover design to receive metformin and single doses of either ulotaront (100 mg) or placebo. In both studies plasma samples were analyzed for C-peptide, insulin, and glucose; and for plasma concentrations of ulotaront.

Results: Following administration of a meal, ulotaront lowered insulin and C-peptide levels compared to placebo, indicating an effect of ulotaront on glycemic control in response to feeding, with large effect sizes (0.8–1.0) on insulin and C-peptide levels. An integrated population PK/PD model jointly described insulin, C-peptide, and glucose change, in response to a meal, as a function of ulotaront plasma concentrations.

Discussion: The effects of ulotaront on metabolic markers, derived from plasma samples collected in the course of clinical pharmacology studies, suggest that the beneficial effects observed in animal models may translate to humans. Phase 1 clinical studies are currently ongoing to test the direct effects of ulotaront on metabolic parameters in patients with schizophrenia. The healthcare burden of diabetes, dyslipidemia, and weight gain associated with the treatment of schizophrenia utilizing the currently available antipsychotic drugs would be reduced if a novel pharmacological class of compounds were available that demonstrated benefit on these metabolic parameters.

Supported by funding from Sunovion Pharmaceuticals Inc. and Otsuka Pharmaceutical Development and Commercialization Inc.

W61. LONG-TERM SAFETY AND SYMPTOM TRAJECTORY WITH ARIPIPRAZOLE LAUROXIL IN FEMALE PATIENTS WITH SCHIZOPHRENIA: A POST HOC SUBGROUP ANALYSIS

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Abstract: Introduction: Females are often underrepresented in clinical trials of antipsychotic treatment of schizophrenia. Symptom trajectory and safety outcomes in female patients who received aripiprazole lauroxil (AL) in successive long-term phase 3 safety trials (EXT-1 and EXT-2) are reported.

Methods: Adults with schizophrenia who completed a 12-week AL study or enrolled de novo were eligible to receive open-label AL (441 mg or 882 mg every 4 weeks) for up to 52 weeks in EXT-1 (NCT01626456), with the option of continuing into EXT-2 (NCT01895452) for up to 128 additional weeks. Symptom trajectory was evaluated using Positive and Negative Syndrome Scale (PANSS) total scores; body mass index (BMI), prolactin-related adverse events (AEs), and injection site reactions (ISRs) were also assessed.

Results: A total of 203/478 (42.5%) patients in EXT-1 were female (EXT-2, 135/291 [46.4%]). Mean (SD) overall PANSS total score at baseline was 61.5 (14.4). Mean PANSS total scores decreased over EXT-1 and remained stable through EXT-2. When assessed by age (≤40 vs >40 years) and illness severity (Clinical Global Impressions-Severity score ≤3 vs ≥4), patterns of change in females were similar to those in the overall population. Mean BMI was stable in EXT-1; variability increased with decreasing sample size during EXT-2. Rates of ISRs were comparable with those in the overall population. Few prolactin-related AEs were reported; all were mild or moderate in severity.

Conclusion: Long-term treatment with AL was safe and effective in females with schizophrenia. Symptom trajectory and safety outcomes in females by age and illness severity were consistent with the overall study population results.

W62. SITE-INDEPENDENT REPLICATION OF CLINICAL METRICS IN A STUDY OF KARXT IN SUBJECTS WITH AN ACUTE EXACERBATION OF PSYCHOSIS IN SCHIZOPHRENIA

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Abstract: In a previously reported phase II study of schizophrenic subjects experiencing an acute exacerbation of psychosis (EMERGENT-1), site-based PANSS scores revealed highly significant differences between subjects assigned to the study drug (KarXT) versus placebo-assigned subjects after 5-weeks of treatment on the primary total PANSS measure ($p<0.0001$) as well as all other related clinical metrics (positive and negative symptom scores and the Marder negative symptom factor). KarXT (xanomeline-trospium) is an oral, investigational M1/M4-preferring muscarinic agonist in development for the treatment of psychiatric and neurological conditions. Site-independent raters who were blinded to site location, visit number, or possible treatment emergent adverse events (TEAEs) provided PANSS scores after listening to audio-recorded site-based PANSS interviews. The site-independent scores affirmed the statistically significant KarXT vs. placebo differences in EMERGENT-1.

EMERGENT-2 was a new phase 3 study of KarXT in schizophrenic subjects experiencing an acute exacerbation of psychosis. Once again, KarXT yielded statistically significant improvement versus placebo on both the site-based total PANSS scores and the paired site-

independent scores ($p<0.0001$ and <0.001 respectively). The site-independent scores affirmed the site-based findings on the positive and negative symptom subscales and the Marder negative symptom factor as well. Further, using a criterion of >30% improvement from baseline for total PANSS score treatment response, both site-based and site-independent ratings yielded significant differences favoring KarXT over placebo ($P<0.002$). The total predictive value for independent ratings matching the site-based treatment response scores was 87.6%.

In this study, as in other analyses of paired ratings in both schizophrenia and depression studies, we found that site-independent raters tend to score the most severe symptoms less severely than live, site-based raters and score the least severe symptoms as slightly more symptomatic. This tendency yields a slight blunting effect on signal detection that might have implications if remote ratings are employed as the primary measure in a clinical trial.

Overall, the results of this new study (EMERGENT-2) have re-affirmed our initial report in EMERGENT-1 that blinded, site-independent PANSS scores replicated the site-based PANSS scores and showed that KarXT offers statistically significant benefit over placebo in acutely psychotic subjects with schizophrenia. The paired score findings demonstrate the utility of the paired ratings methodology for quality assurance surveillance. As in EMERGENT-1, the site-independent findings dispel concerns about functional unblinding by site-based raters given that the paired scoring replication was achieved by site-independent raters who were blinded to potential TEAEs.

W63. REVIEW OF THE TAAR1 AGONIST ULOTARONT: PART II - SUMMARY OF INITIAL CLINICAL EFFICACY/SAFETY RESULTS

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Abstract: Background: Ulotaront is a trace amine-associated receptor 1 (TAAR1) agonist with serotonin 5-HT1A agonist activity whose efficacy in schizophrenia is distinguished from the antipsychotic class by its lack of D2 and 5-HT2A receptor blockade. Ulotaront has received FDA Breakthrough Therapy Designation for treatment of schizophrenia, and WHO, based on the INN naming convention, has specified "-taront" as the stem for this new drug class. Here we summarize ongoing clinical research characterising the efficacy and safety profile of ulotaront as a member of the novel TAAR1 agonist class.

Methods: Summarized are results from a double-blind, placebo-controlled study to evaluate the efficacy of ulotaront in an acute exacerbation of schizophrenia, and a 6-month, open-label follow-up study. Also summarized are post-hoc analyses comparing the effect of ulotaront vs. lurasidone on negative symptoms (based on a Marder PANSS negative symptom factor [MPNS] enrichment strategy); and analyses comparing key safety and adverse event (AE) domains for ulotaront vs. atypical antipsychotics (APs), including an Empirical Bayes Geometric Mean (EBGM) analysis of the FDA Adverse Event Reporting System (FAERS) database.

Results: In the double-blind study, ulotaront was associated with significant ($p<0.001$) endpoint improvement in the PANSS total score (effect size [ES]: 0.45), the CGI-Severity score (ES: 0.52) and the Brief Negative Symptom Scale total score (ES: 0.48). In a post-hoc enrichment analysis, ulotaront demonstrated moderate-to-large treatment effects on negative symptoms with an endpoint MPNS factor score effect size of 0.84 (vs. 0.33 on the atypical

antipsychotic lurasidone). The incidence of any AE was lower on ulotaront vs. placebo (45.8% vs. 50.4%). Results of EBGM analyses of the FAERS database bh found treatment with ulotaront to be associated with markedly lower risk of both antipsychotic class-related AEs (EPS, akathisia, somnolence, nausea/vomiting), and adverse safety events frequently associated with APs (weight gain, increase in metabolic labs, prolactinemia). The follow-up study further confirmed the tolerability of ulotaront, with a 6-month completion rate of 67%, which compares favourably to benchmark 6-month completion rates in the CATIE study. Furthermore, 6 months of treatment was associated with a mean change from open-label baseline of -22.6 in PANSS total score and -1.0 in CGI-Severity score.

Discussion: The emerging profile of ulotaront, based on initial clinical trials, is characterized by statistically significant improvement in positive and negative symptoms of schizophrenia. The safety and tolerability profile of ulotaront is markedly different with respect to class-related AEs that are characteristic of both first- and second-generation antipsychotics. The benefit-risk profile of ulotaront, as a member of a novel TAAR1 agonist class, is distinguished from antipsychotics by lack of D2 and 5-HT2A receptor blockade.

W64. EFFECTS OF MENSTRUAL CYCLE ON SYMPTOMS IN INDIVIDUALS WITH SCHIZOPHRENIA ON AND OFF MEDICATION

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Abstract: Background: The relationship of symptoms of schizophrenia to fluctuations in gonadal hormones during the menstrual cycle has been of interest. However, available data have been limited, and published literature is mixed as to whether symptoms are exacerbated by menstrual cycle phase. Estradiol and progesterone levels fluctuate over the course of the normal menstrual cycle as a product of complex neuroendocrine interactions. The perimenstrual phase, when estradiol levels are low may be particularly relevant to this question since there is ample preclinical evidence suggesting that estradiol interacts with multiple aspects of dopamine function and may be protective in schizophrenia. Here we investigate if medication may affect menstrual cycle phase effects on symptoms in individuals with schizophrenia.

Methods: Medical records were examined to determine menstrual cycles for females with schizophrenia spectrum illness (n=46; mean age 30 years +/- 6.7 1SD) who were inpatients at the National Institute of Mental Health Clinical Center. Menstrual cycle days -15 to +10 were examined (day +1=first day of menses). Four phases of the menstrual cycle were operationally defined and analyzed [mid-luteal (day -9 to -5), perimenstrual (day -3 to +2), mid-follicular (day +4 to +7), and periovulatory (day -15 to -12)]. The Positive and Negative Syndrome Scale (PANSS) was collected at least weekly (total, positive, negative, disorganized, excited, and depressed symptom scores were analyzed). The effect of menstrual cycle phase on symptoms was tested using mixed linear models where menstrual cycle phase was a fixed factor and subject was a random factor. A subset of participants (n=12) participated in a study in which they were treated with antipsychotic medication during one month-long arm and placebo in the other month-long arm. Medication status was added to the models as well as the interaction

between medication and phase for this subset. Participants >45 years old or on birth control, menstrual cycles <21 days, or <3 PANSS measurements were excluded from analyses. The periovulatory phase was compared to the other phases in the analyses.

Results: While total PANSS scores during the perimenstrual phase compared to the periovulatory phase tended to be higher, they did not reach our statistical threshold (p=0.10). Negative symptoms were worse in the perimenstrual phase (p=0.02). In addition, in the smaller subset of participants accounting for medication status, total PANSS scores were higher during the perimenstrual phase than during the periovulatory phase (p=0.03). Unexpectedly, there was no interaction between medication status and phase identified except for depressed scores (mid-follicular phase p=0.03).

Conclusion: Our preliminary results suggest that the perimenstrual phase, when estradiol levels are lower than earlier in the luteal phase, may be associated with worsening PANSS scores (in particular negative symptoms) in menstruating individuals with schizophrenia. These results align with previous studies showing estradiol's potential protective role in schizophrenia. There were not robust effects of medication on menstrual cycle related changes in PANSS scores (except for depressed scores) which may be related to sample size. One possibility is that symptoms in only a subset of patients is affected by estradiol levels related, though further investigation is required to test this hypothesis.

W65. TITLE: LOOKING INTO "LONG COVID": THE POTENTIAL FOR A COMMON BIOLOGIC MECHANISM RELATING PERSISTENT CENTRAL and AUTONOMIC SYMPTOMS AFTER COVID-19 INFECTION, AND PRIOR EXPOSURE TO TRAUMATIC STRESS

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Abstract: Symptoms that persist for weeks, months, or years after infection with COVID-19 are reported by a significant proportion (10% or more) of those who experience an infection [1]. Many of these persistent symptoms are similar to those experienced after a traumatic stressor or a traumatic brain injury (TBI), where increased central and peripheral adrenergic signaling has been linked to symptom expression [2]. In an ongoing clinical study, we are working to test the hypothesis that one mechanism by which COVID-19 infection results in persistent symptoms is the activation of persistent increases in central and peripheral adrenergic signaling, a mechanism that overlaps and can interact with the effects of traumatic stress and traumatic brain injury.

Here, we present initial results from the self-report and neurocognitive-testing data from the first N=326 participants (N=214 with a history of COVID-19 infection, N=132 with self-identified "Long COVID"). We present 3 main initial findings from this work. First, we find that autonomic symptom burden is significantly elevated in the group with a history of COVID-19 infection compared to the group without a history of COVID-19 infection (p<1e-8), and that these peripherally driven somatic symptoms are strongly associated with and a strong statistical mediator of self-reported impairment in neurocognitive functioning (R=-.64 p< 1e-16), consistent with the potential for a co-regulated common mechanistic pathway underlying both peripheral and centrally generated symptoms.

Second, we have found that both history of COVID-19 infection and cumulative lifetime trauma burden are associated with higher autonomic symptom burden. Consistent with our specific hypothesis that a prior history of traumatic stress would increase the risk of persistent symptoms after COVID-19, in a multivariable linear regression model to explore the relative contributions of COVID-19 infection and history of traumatic stress to autonomic symptom burden, we found a statistically significant interaction term between these two factors (p=.03).

Finally, drawing from 6 independent self-administered online neurocognitive tests, we found that tests that depended on processing speed (e.g. the Fast Choices test) showed a significantly different relationship to self-reported neurocognitive functioning for those with versus without a history of COVID-19 infection: for those without a known history of COVID-19 infection, objective performance was not significantly related to self-reported cognitive functioning (R=.01, p=.93), while for those with a history of COVID-19 infection, objective test performance was significantly and positively associated with positive self-ported cognitive functioning (R-0.31, p=.0001). These findings are consistent with self-reported cognitive symptoms in individuals with persistent symptoms after COVID-19 demonstrating a meaningful relationship to objective performance on neurocognitive testing, particularly in the domain of processing speed.

W66. THE NATIONAL PREGNANCY REGISTRY FOR PSYCHIATRIC MEDICATIONS: RISK OF MAJOR MALFORMATIONS FOLLOWING FETAL EXPOSURE TO ATYPICAL ANTIPSYCHOTICS

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Abstract: Purpose: Atypical antipsychotics are widely used to treat several psychiatric disorders in reproductive aged women. The National Pregnancy Registry for Psychiatric Medications (NPRPM) is a systematic prospective pharmacovigilance program used to collect reproductive safety data on atypical antipsychotics, as well as other classes of psychotropic medications, to inform the care of women of reproductive age with psychiatric disorders.

Methodology: Data are prospectively collected from women, aged 18-45 years, with histories of psychiatric disorders. During pregnancy, two phone interviews are conducted, and a third interview is completed at 3 months postpartum. Enrollment and longitudinal follow-up of participants is ongoing. In this analysis, the exposed group is composed of women who reported use of an atypical antipsychotic during the first trimester of pregnancy. The comparison group is comprised of women who did not have an exposure to an atypical antipsychotic at any point during pregnancy but were prenatally exposed to other psychotropics. Information regarding the presence of major malformations is abstracted from medical records. Identified cases of potential major malformations are adjudicated by a dysmorphologist blinded to psychiatric diagnoses and drug exposure.

Results: As of July 25th, 2022, 2676 women were enrolled in the NPRPM, including 1031 in the exposure group and 1551 in the comparison group. Medical records were obtained for 78%

of participants. A total of 1997 participants (787 exposed to an atypical in the first trimester, 1210 unexposed to an atypical during pregnancy) completed the postpartum interview and were eligible for analysis. Of 810 infants in the exposure group, 22 confirmed major malformations were identified. In the control group of 1234 infants, 19 malformations were identified. No consistent pattern of malformation was seen in either group. The absolute risk of major malformations was 2.72% in the exposure group and 1.54% in the comparison group. The unadjusted odds ratio was OR = 1.79 (95% CI: 0.96 – 3.32).

Importance: The NPRPM provides a systematic approach to obtain prospective reproductive safety information which informs the care of women who may use atypical antipsychotics to sustain psychiatric well-being. Current data suggest that atypical antipsychotics are unlikely to have a major teratogenic effect. Future analyses will aim to better estimate risk with more generalizable cohort characteristics and larger sample sizes.

W67. DIFFERENTIAL TRAJECTORIES OF DEPRESSIVE SYMPTOM RESPONSE TO IV KETAMINE - EXAMINING SLEEP, CORE EMOTIONAL AND ATYPICAL SYMPTOMS CHANGES IN A LARGE, REAL WORLD SAMPLE OF DEPRESSED ADULTS

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Abstract: Background: Three distinct antidepressant treatment response patterns have been identified among patients seeking intravenous (IV) ketamine treatment in community-based settings (O'Brien et al 2021; O'Brien et al 2022). These response trajectories were based on total scores from a validated depression scale (QIDS-SR-16). Previous studies have demonstrated several specific symptom factors of depression and shown that medications have differential impacts to these symptom factors. In the current study, we aimed to better understand IV ketamine's specific or general impact on depressive symptomatology over the course of acute treatment.

Methods: Using the QIDS-SR checklist and Chekroud et al.'s (2017) scaling method, we constructed scores of sleep (insomnia), core emotional, and atypical symptoms for 344 depressed treatment seeking patients (mean baseline QIDS-SR = 17.03; SD = 4.71) receiving a course of IV ketamine (0.5-1 mg/kg, generally over 40 min) at a community-based clinic. Patients were assessed over 6 clinic visits (over 3-6 weeks) prior to each treatment infusion. Longitudinal clustering analysis was conducted to identify patient subgroups (classes), each characterized with unique joint trajectories of those depressive symptoms during IV ketamine treatment. Specifically, we utilized non-parametric unsupervised machine learning techniques to determine an optimal number of classes and class membership.

Results: We found three classes of patients sharing similar joint trajectories of depressive symptoms: (1) a class with severe baseline depression and modest improvement (SM; n = 101; 36%), (2) a class with severe baseline depression and rapid improvement (SR; n = 121; 35%), and (3) a class with moderate baseline depression and gradual improvement (MG; n = 122). In all 3 classes, patients improved more in core emotional symptoms during the ketamine

treatment compared to sleep and atypical symptoms, with the greatest improvement following the first infusion.

Discussion: Utilizing a nonparametric statistical method to address the heterogeneity of depressive symptoms, we reanalyzed a prior dataset of patients seeking IV ketamine treatment and identified 3 similar trajectories of antidepressant response. Consistent with our previous trajectory analysis of this group's total scores, over 1/3 of patients demonstrated rapid and robust improvements in sleep, core emotional and atypical symptoms. Future research should examine further whether endophenotypes and biological markers of depression may be associated with more or less benefit from IV ketamine treatment to better guide treatment planning.

W68. REDUCING CANNABIS OVERUSE WITH PRAZOSIN: INTERIM RESULTS FROM RECOUP, A PILOT FEASIBILITY STUDY

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Abstract: Purpose: Cannabis use disorder (CUD) remains an area of growing and unmet therapeutic need, and despite trials of over two dozen medications no FDA approved treatments are available. Individuals with posttraumatic stress disorder (PTSD) often report use of cannabis to ameliorate sleep and trauma-related nightmares. However, several risks associated with cannabis use in those with PTSD have been described, including tolerance and withdrawal, contributing to escalation of cannabis use. Prazosin, a drug which blocks norepinephrine (NE) at the alpha-1 adrenoceptor, has been shown to reduce trauma nightmares and sleep disturbances in PTSD. We have clinically observed that some patients with PTSD who wanted to but were unable to reduce cannabis use are finally able to do so while treated with prazosin. Cannabis withdrawal can produce insomnia and frightening dreams that have been associated with increased central nervous system NE release, and medications that increase synaptic NE worsen cannabis withdrawal symptoms. These distressing withdrawal symptoms may help explain difficulty with cannabis reduction or cessation. By reducing NE outflow alpha-2 agonists reduced cannabis withdrawal symptoms in an inpatient setting but were poorly tolerated and ineffective in outpatients. In contrast, prazosin has been well tolerated in outpatient clinical studies for PTSD-related nightmares and for alcohol use disorder. Therefore, we initiated a pilot study to examine the feasibility of using open label prazosin for CUD in those with and without PTSD in an outpatient setting.

Methods: Participants were included between ages 18 to 80, who use cannabis 4 or more days a week, were without active or recent other substance use disorder and no active substance use other than cannabis, alcohol, or tobacco, and were medically and psychiatrically stable. Cannabis use was measured by clinician administered timeline follow back and confirmed with urine and blood analysis. Participants were assessed by self-reports for symptoms of cannabis use and withdrawal, PTSD, major depressive disorder, and insomnia. Participants were titrated on prazosin up to a maximum of 25 mg/day or as tolerated over 6 weeks, maintained for an additional 6 weeks, and followed up 4 weeks after study treatment discontinuation. Changes in outcome measures from baseline to end of treatment were modeled with all available data. Outcomes are provided as mean ± std dev as applicable.

Results: Ten participants (8 males; age 33.9 ± 12.4 years) started prazosin; 6 completed the treatment phase (12 weeks), 2 withdrew during treatment phase (1 due to inability to tolerate the lowest prazosin dose), and 2 were lost to follow up during the course of the study. Immediately prior to prazosin initiation, mean days of cannabis use per week was 5.4 ± 1.8 and mean daily sessions of cannabis use 3.7 ± 4.4. Compared to baseline, by week 12 cannabis use was insignificantly decreased ($p=0.067$), cannabis withdrawal symptoms decreased by 29% ($p<0.05$), cannabis use disorder symptoms decreased by 19% ($p<0.05$), PTSD symptoms decreased by 31% ($p<0.05$), depression symptoms decreased by 20% ($p<0.05$), and insomnia symptoms decreased by 29% ($p<0.05$). Participants reported less emotional lability, feelings of stress, and reliance on cannabis to reduce those experiences. The last dose of prazosin taken by participants was 11.8 ± 10.1 mg/day. No serious adverse experiences were reported, and study related adverse experiences were largely consistent with known effects of prazosin.

Importance: Participant retention has been consistent with prior cannabis and substance use disorder trials. Prazosin is well tolerated and shows promise for CUD and may warrant continued investigation.

W69. ANC-501: A NOVEL V1B RECEPTOR ANTAGONIST FOR THE TREATMENT OF MDD

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Abstract Depression is ranked as the leading cause of disability worldwide by the World Health Organization (WHO). Major depressive disorder (MDD) is a psychiatric disorder that is characterized by the occurrence of one or more major depressive episodes, along with an absence of any history of manic, mixed, or hypomanic episodes. In addition to the high mortality rate due to suicide, depressed patients are more likely to develop coronary artery disease and type 2 diabetes among many other related health conditions.

Even after an adequate duration of treatment, the most commonly used treatments today (e.g., SSRIs and SNRIs) only result in approximately 35% to 45% of patients achieving clinical remission. Approximately 30% of patients are resistant to a series of treatments according to the STAR*D study, there is little data-driven guidance on next steps to treatment MDD patients in the event of a first-line failure. Thus, there is a clear need for new, efficacious, well-tolerated agents and personalized approaches for both the treatment of depressive episodes and the prevention of recurrent episodes of depression.

Stress mediated by the hypothalamus-pituitary-adrenal (HPA) axis has been hypothesized to be a pivotal factor in the pathophysiology of depression. Specifically, both corticotropin-releasing factor and arginine vasopressin, both of which are produced in the paraventricular nucleus of the hypothalamus, are considered primary factors in the regulation of HPA axis activity. Receptor subtypes for these neuropeptides, which may be involved in the regulation of HPA axis activity, have attracted much attention as potential targets for the treatment of depression and anxiety. With chronic stress in the context of the Covid pandemic likely contributing to the dramatic increase in MDD worldwide, correcting disruption in this pathway may be particularly important new way to treat those patients with clearly disrupted HPA axis function.

ANC-501 (formerly TS-121) is an investigational new drug with antagonistic activity of the vasopressin receptor 1b (V1b receptor), which plays a role in the modulation of stress and mood. Based on nonclinical and early clinical studies, ANC-501 appears to be a promising candidate for clinical development with a novel mode of action that may benefit MDD patients. ANC-501 is being developed as an adjunctive therapy for MDD patients who have responded inadequately to standard anti-depressants and clear disruptions in their HPA axis. A phase 2 study of ANC-501 will initiate in 2022. Preliminary evidence in an ongoing open-label trial suggests that ANC-501 shows evidence of activity on both MADRS and HAM-A scales in patients with Moderate to Severe MDD along with elevations in Cortisol. If this preliminary evidence is confirmed, ANC-501 would be the first MDD treatment specifically developed for patients with measurable disruptions in the stress response axis.

W70. EFFECT OF A SUBCUTANEOUS WEEKLY AND MONTHLY BUPRENORPHINE (CAM2038) EXTENDED-RELEASE DOSE ON OPIOID USE DISORDER (OUD) TREATMENT OUTCOMES

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Abstract: Background: The safety and effectiveness of buprenorphine (BPN) in sublingual (SL), and injectable and implantable, extended-release (XR) formulations for OUD treatment has been established. Guidelines encourage individualized dosing for treatment with the lowest effective dose. Adjustable dosing options enable individualized treatment to address evolving patient needs over the course of the disease. CAM2038 is an XR injectable BPN developed in a weekly and monthly formulation with multiple doses.

Methods: Post-hoc analysis of a 48-week, open-label, multi-national Phase 3 study evaluating long-term safety, tolerability and efficacy of CAM2038 in adults with OUD was conducted, and included individuals receiving SL BPN at baseline and new to treatment. Weekly or monthly doses were utilized with adjustments and visit frequency based on symptoms/tolerability. The mean percentage of urine drug samples (UDS) negative for illicit opioids was evaluated for each dose received. Missing values were not imputed.

Results: Of 190 participants receiving SL BPN at enrolment, 50 (26.3%) converted to, and remained on, CAM2038(weekly); 63 (33.2%) converted to CAM2038(weekly) and subsequently transitioned to CAM2038(monthly); and 77 (40.5%) converted to CAM2038(monthly). Of the 37 new-to-treatment participants, 25 (67.6%) commenced and remained on CAM2038(weekly), while 12 (32.4%) transitioned from CAM2038(weekly) to CAM2038(monthly). The majority of participants received 24 and 32mg (weekly) CAM2038 (mean [SD]: 25.2mg [7.1]), and 96 and 128mg (monthly) CAM2038 (mean [SD]: 107.3mg [32.2]), corresponding to 16 to 24mg SL BPN. Mean percentage UDS negative for illicit opioids were similar across CAM2038(weekly) 16mg, 24mg, and 32mg (range 66.6-72.0%) and all monthly doses (range 82.2-88.6%). CAM2038 was well-tolerated, with a safety profile consistent with the known profile of SL BPN, except for mild to moderate injection site reactions.

Conclusion: Treatment with CAM2038 individualized to lowest effective dose based on clinical response resulted in similar treatment outcomes independent of dose, and participants responded to all doses of CAM2038. Treatment outcomes were similar for CAM2038 (weekly) and (monthly) formulations at comparable doses. CAM2038 was well-tolerated systemically and locally. As these are post-hoc analyses, and, in some cases the sample size is limited, more research is needed to evaluate the impact of CAM2038 dose on treatment outcomes.

W71. TREATMENT PATTERNS, ACUTE CARE HEALTHCARE RESOURCE USE AND COSTS OF PATIENTS WITH TREATMENT RESISTANT DEPRESSION COMPLETING INDUCTION PHASE OF ESKETAMINE IN COMMERCIAL AND MEDICARE ADVANTAGE PLANS

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Abstract: Background: This study aimed to understand treatment patterns, acute care use and cost patterns among adults with treatment resistant depression (TRD) who complete induction treatment with esketamine nasal spray in the United States.

Methods: Adults with ≥1 esketamine claim (index date) on or after 03/05/2019 were selected from Optum's de-identified Clinformatics® Data Mart Database (01/2016-06/2022). Before the index date, patients had evidence of TRD and ≥12 months of continuous insurance eligibility (baseline period). Patients with ≥8 esketamine treatment sessions (per label, completed induction treatment) were included in the main cohort. A subgroup analysis was conducted among patients who also had ≥1 baseline mental-health (MH)-related inpatient (IP) admission or emergency department (ED) visit to observe trends among more severe patients. Treatment patterns were described during the follow-up period (spanned index date until earliest of end of insurance eligibility or data); acute care (i.e., IP and ED) costs (USD 2021) and resource use were reported during the baseline and follow-up period per-patient-per-month (PPPM).

Results: Of the 322 patients in the main cohort (mean age: 48.7 years, 62.1% female, 79.5% white), 111 were part of the subgroup (mean age: 46.4 years, 69.4% female, 76.6% white). Mean length of follow-up was 15.1 months in the main cohort and 16.1 months in the subgroup. During the follow-up period, mean [median] time from index date to 8th ESK session was 73.2 [40.5] days in the main cohort and 78.8 [40.0] days in the subgroup (per label, 28 days). Further, 75.2% in the main cohort and 73.9% in the subgroup completed ≥12 ESK sessions. During follow-up period, in the main cohort and subgroup, patients had a mean [median] of 2.1 [2.0] and 2.2 [2.0] unique antidepressant claims, and 76.4% and 82.9% received psychotherapy.

In the main cohort, mean PPPM all-cause IP and ED costs decreased from baseline to follow-up period (IP costs: baseline: $603, follow-up: $591; ED costs: baseline: $235, follow-up: $178). Similar reductions occurred for mean PPPM MH-related acute care costs (IP costs: baseline: $560, follow-up: $510; ED costs: baseline: $88, follow-up: $66). In the subgroup, mean PPPM all-cause IP and ED costs also decreased (IP costs: baseline: $1,717, follow-up: $1,098; ED costs: baseline: $606, follow-up: $326), driven by mean PPPM MH-related acute

care medical costs (IP costs: baseline: $1,623, follow-up: $1,009; ED costs: baseline: $256, follow-up: $130).

Mean PPPM all-cause acute care use remained stable from the baseline to follow-up period in the main cohort (IP days: baseline: 0.22, follow-up: 0.21; ED visits: baseline: 0.13, follow-up: 0.15) and reduced in the subgroup (IP days: baseline: 0.64, follow-up: 0.46; ED visits: baseline: 0.26, follow-up: 0.24). Trends in mean MH-related acute care use were similar.

Conclusion: Patients generally took longer than label recommendation to complete esketamine induction treatment, and most went on to have ≥12 ESK sessions. Completion of induction treatment correlated with reductions in mean all-cause and MH-related IP and ED costs. Larger reductions were seen in the subgroup with ≥1 MH-related IP admission or ED visit prior to esketamine initiation.

W72. REAL-WORLD OUTCOMES, CHARACTERISTICS AND ABILITY TO WORK OF PATIENTS WITH TREATMENT-RESISTANT DEPRESSION IN THE UNITED STATES

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Abstract: Background: One in three adults with major depressive disorder (MDD) fail to respond to two or more antidepressants of adequate dose and duration, and may have treatment-resistant depression (TRD). TRD negatively impacts patients' quality of life (QoL) and ability to work. There is limited real-world data on outcomes and characteristics of patients with TRD. **Objectives**: To assess real-world outcomes, characteristics and ability to work for patients with TRD.

Methods: Data were drawn from the Adelphi TRD Disease Specific Programme™, a large cross-sectional survey with retrospective data collection of physicians and their patients, conducted in the United States between July 2022 - February 2023. A geographically representative sample of physicians was identified from publicly available lists of healthcare professionals. Physicians completed a patient record form for their six consecutive patients with TRD, collecting data on demographics, symptoms and depression treatment history. Patients voluntarily completed a patient self-completion (PSC) questionnaire, providing data on their condition, experience and QoL using validated patient-reported outcome tools. Analyses were descriptive-only. Although ethics committee approval was not required this survey did undergo Institutional Review Board review.

Results: Overall, 102 physicians, comprising 82 psychiatrists and 20 primary care physicians, provided data for 605 patients with TRD of whom 137 completed a PSC questionnaire. Physicians reported that patients with TRD were female (61%), mean age of 45.1 years (standard deviation [SD] 13.8), had a mean time since MDD diagnosis of 6.9 years (SD 6.8), TRD diagnosis of 3.2 years (SD 4.6), and mean body mass index was 27.3 (SD 4.9). Additionally, 52% were working full-time, 36% were either working part-time/on long-term sick-leave/unemployed/retired (44% was due to their depression, which was 16% of all patients

with TRD), 5% required help with daily needs, 42% were considered moderately-extremely ill via the Clinical Global Impression severity scale. Patients recorded mean Patient Health Questionnaire-9 scores of 8.5 (SD 6.5), 38% met criteria for moderate-to-severe depression, and reported being bothered in the previous two weeks with problems related to: interest/pleasure in doing things (80%), feeling down (79%), sleep (73%), fatigue (72%), concentration (59%), feeling bad about themselves (58%), appetite (47%), speech (39%) and self-harm/suicide (35%). According to the Work Productivity and Activity Impairment Questionnaire, in the prior seven days, patients experienced overall impairment (25%, SD 29), absenteeism (6%, SD 12), presenteeism (22%, SD 26) and activity impairment (33%, SD 29).

Conclusion: These survey data show that TRD has serious impacts on a patient's QoL and ability to work, with high overall work impairment and presenteeism reported. Despite the average patient with TRD being of working age, only half are in full-time employment, with a sixth unable to work full-time due to depression. Prominent issues with engagement, sleep, fatigue, communication, self-worth and suicidal ideation highlight major inadequacies among current TRD treatment options. Therefore, interventions that could more effectively address the livelihood-limiting aspects of TRD may prove greatly beneficial for patients and their employers.

W73. A CASE SERIES PROVIDING CLINICAL EVIDENCE THAT METHYLONE PRODUCES RAPID IMPROVEMENTS IN DEPRESSION

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Abstract: Background: Methylone (3,4-methylenedioxy-N-methylcathinone; also known as MDMC, βk-MDMA, and M1), is a rapid-acting entactogen (RAE) and phenethylamine compound with chemical and pharmacological properties similar to 3,4-methylenedioxymethamphetamine (MDMA). A study comparing the acute effects of methylone and MDMA in healthy participants reported that while the subjective pharmacological effects of the two drugs were categorically similar, methylone demonstrated significant clinical, physiological, and pharmacological differences, including "softer" empathogenic and psychostimulant effects that may have potential for accelerated adoption across a broad range of medical settings and clinical applications. A recently published case series reported on methylone's potential as a treatment for stress- and trauma-related concerns, describing outcomes from 21 complex patients with Posttraumatic Stress Disorder (PTSD) as a primary diagnosis. Objective: Here, we present a case series of clinical data from 7 patients (4 female, mean age = 42 years) treated with oral methylone for Major Depressive Disorder (MDD) in a psychiatric clinic by a trained and experienced clinical psychologist. **Methods**: Summarized clinical data were used to examine patient characteristics and outcomes. Dosing

with methylone was highly variable and individualistic based on patient response for both the number of doses given during a single dose-session and the number of dose-sessions.
Results: Methylone was well tolerated in that no significant adverse events were reported. All patients achieved "very much improved" (n=3) or "much improved" (n=3) ratings on the Clinician Global Impressions-Improvement (CGI-I) scale. **Conclusion**: Methylone appears to produce rapid, and durable clinical benefits. There is an urgent need for rapid-acting, and meaningful interventions for MDD, especially for those patients not gaining clinical benefit from available treatments, such as SSRIs, and that can address some of the limitations and barriers to other rapid-acting interventions. These promising findings warrant further study to characterize the role and safety of methylone as a potential pharmacotherapy for MDD and other stress-related concerns.

W74. A PHASE 3 OPEN-LABEL SAFETY TRIAL OF FASEDIENOL (PH94B) NASAL SPRAY IN THE TREATMENT OF ANXIETY IN ADULTS WITH SOCIAL ANXIETY DISORDER (SAD)

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Abstract: Background: Social anxiety disorder (SAD) is characterized by intense and persistent fear of embarrassment or humiliation in social or performance situations that markedly impacts occupational functioning and social life. Fasedienol (PH94B; 3β-androsta-4,16-dien-3-ol) is a synthetic neuroactive steroid from the androstane family of pherines. When administered intranasally, fasedienol activates receptors in peripheral nasal chemosensory neurons connected to subsets of neurons in the olfactory bulbs that in turn connect to neurons in the limbic amygdala involved in the pathophysiology of SAD and potentially other anxiety and mood disorders. Fasedienol regulates the olfactory-amygdala circuits of fear and anxiety without direct GABA-A receptor activation or binding to neuronal receptors. In a phase 2 study (NCT01217788), fasedienol was well tolerated and significantly reduced anxiety during public speaking and social interaction challenges vs placebo. We report the long-term safety, tolerability, and exploratory efficacy of fasedienol in adults with SAD.
Methods: This phase 3, open-label study (NCT05030350) assessed the safety and tolerability of fasedienol in anxiety-provoking situations in daily life. Fasedienol was administered intranasally at 3.2 µg/dose (eg, 1.6 µg in each nostril) up to 4 times/day for up to 12 months. Adults aged 18-65 years with SAD enrolled after completing the PALISADE-1 (NCT04754802) or PALISADE-2 (NCT05011396) acute SAD studies or enrolled de novo. Patients had a HAMD-17 score <18 and a Liebowitz Social Anxiety Scale (LSAS) score >50 at baseline to be eligible. Patients with other Axis I disorders, history of nasal pathology/surgery/trauma, or other conditions compromising intranasal drug delivery; alcohol use disorder; benzodiazepine (BZD) or beta-blocker use within 30 days; BZD use of >1 month duration at Visit 1; or suicidal risk were excluded. Monthly safety and tolerability assessments included treatment-emergent adverse events (TEAEs), clinical laboratories, vital signs, physical exam, and 12-lead electrocardiograms; the LSAS, Clinical Global Impressions of Severity and Improvement (CGI-S, CGI-I), and Patient Global Impressions of Change (PGI-C) assessed efficacy monthly. Efficacy results were calculated based on observed cases.

Results: The study was closed early for reasons unrelated to clinical results or safety findings. 481 patients received ≥1 dose of fasedienol; 273 (56.8%) had ≥1 TEAE, of which only 9 (1.9%) were severe. TEAEs occurring in ≥5% of patients were headache (17.0%) and COVID-19 infection (11.4%). Serious TEAEs occurred in 6 (1.2%); none were considered fasedienol-related. TEAEs led to discontinuation in 14 (2.9%). One death occurred, considered unrelated to study drug, and no relevant laboratory or clinical findings were observed. Mean baseline LSAS total score (93.4) changed by 16.2 points at month 1 and by 24.1 points at month 3. CGI-S scores indicated 50.3% were severely/extremely ill at baseline; 21.8% and 12.4% remained in those categories at months 1 and 3, respectively. CGI-I and PGI-C response (ie, "much" or "very much" improved) was achieved by 28.6% and 26.8%, respectively, at month 1, improving to 42.7% and 43.6%, respectively, at month 3.

Discussion: Long-term, open-label treatment data from ~500 patients suggest that repeated, as-needed administration of fasedienol 3.2 µg was safe and well tolerated and provided improved overall symptom control in adults with SAD.

W75. BRII-296 DEMONSTRATES A FAVORABLE SAFETY PROFILE FOR SEDATION - RESULTS FROM A PHASE 1 STUDY OF SAFETY, AND PHARMACOKINETICS OF BRII-296, AN EXTENDED-RELEASE INJECTABLE FORMULATION OF BREXANOLONE IN HEALTHY ADULT SUBJECTS

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Abstract BRII-296 Demonstrates a Favorable Safety Profile for Sedation - Results from a Phase 1 Study of Safety, and Pharmacokinetics of BRII-296, An Extended-Release Injectable Formulation of Brexanolone in Healthy Adult Subjects
Ji Ma, Leela Vrishabhendra, David Margolis, Chetana Trivedi, Kamlesh Patel, Heather Snyder, Oyeniyi Oyesina, Aiyang Tao, Claudia Prilliman, Aleksandar Skuban, Lianhong Xu

Objective: Postpartum depression (PPD) is the most common psychological condition impacting mothers after giving birth. Mothers are especially vulnerable to sedative effects from pharmacotherapy due to existing potential for sleepiness/fatigue as a symptom of PPD, and from sleep deprivation associated with the care of infants. Intravenous brexanolone, approved for PPD, is associated with sedation and loss of consciousness (LOC). BRII-296 is an extended-release IM injectable of brexanolone in development for treatment of PPD. The BRII-296 formulation and route of administration are designed to provide a pharmacokinetic exposure profile that provides an extended continuous drug release, steady plasma levels, and slow taper elimination, to yield a potential low risk for sedation and LOC. This study evaluates the pharmacokinetic and safety profile of BRII-296. The safety analysis includes the Stanford Sleepiness Scale (SSS) used in conjunction with AE reporting to assess changes in sedation.

Design: Phase 1 open-label, single ascending dose escalation, safety, tolerability, and pharmacokinetic study of BRII-296 at dose levels ranging from 30 to 600 mg, given to 116 subjects over 16 cohorts. The SSS was used to measure self-reported assessment of sedation and was administered 1 hour post-dose and every 6 hours daily (during waking hours).

Results: IM administration of BRII-296 was generally well-tolerated in healthy adult subjects at dose levels up to 600 mg. Local injection site reactions were the most common adverse event (AE) and were treated prophylactically. No serious AEs were reported, and no clinically significant systemic AEs were observed.

Median SSS scores across all cohorts and doses were 1.0 – 1.5 (alert or wide awake to high functioning), within the normal range of alertness. Two sedation-related AEs for drowsiness, both mild, were reported from the 116 subjects treated in the study. SSS scores of 6 (sleepiness) were recorded with these AEs. Neither AE progressed in severity, and both resolved completely without further incident or need for treatment. There were no treatment related AEs reported for sedation-related dizziness, vertigo, sedation-related presyncope, syncope or LOC.

Conclusion: PK and safety profile in male and female healthy volunteers support further assessment of BRII-296 in PPD patients. No excessive sedation or loss of consciousness was observed. SSS median scores were normal across all cohorts with two isolated reports of sleepiness. Results highlight the potential for BRII-296 as a better tolerated treatment option for PPD. Mothers with PPD vulnerable to sedative effects from pharmacotherapy can benefit from a treatment with a potential for a lower risk for excessive sedation. Results support further Phase 2 investigation into this novel treatment for PPD.

W76. CLINICAL CORRELATES OF LITHIUM USE IN PATIENTS WITH BIPOLAR DISORDER

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Abstract Introduction: Despite lithium being considered a first-line mood stabilizer for bipolar disorder (BD), less than 10% of newly diagnosed patients with BD in the US receive lithium and the predictors of lithium treatment duration and response remain unclear. We describe the clinical and sociodemographic characteristics of patients with BD who have used lithium treatment, monotherapy or not; and explore the predictors of treatment duration and response.

Methods: This cross-sectional study included adult participants with BD from the Mayo Clinic Bipolar Biobank. We tested univariable associations with either Student's T or X2 test and multivariable associations through regression models including variables with a p-value ≤.10 in the univariable stage.

Results: We analyzed a total of 721 patients with BD. The mean age was 39.61 ± 14.70, 256 (35.7%) were males, and 489 (72.3%) were white. In the univariate analysis, lithium users were older (41.05 ± 14.54 vs. 37.76 ± 14.71, p=.003), more likely to be male (39.1% vs. 31.2%, p=.035), white (78.6% vs. 64.2%, p<.001), to have BD-I (69.4% vs. 48.1%, p<.001), and a positive psychosis history (43.8% vs. 29.3%, p<.001). We found a lower proportion of lithium monotherapy in white patients (68.3% vs. 81.1%, p=.021) and in those with an evening

chronotype (16.9% vs. 28.7%, p=.044), a higher total Alda score in those with monotherapy (3.18 ± 2.67 vs. 2.00 ± 2.22, p<.001), a lower substance use disorder comorbidity sum (0.89 ± 1.05 vs. 1.17 ± 1.07, p=.035), and a lower BMI (28.51 ± 6.27 vs. 30.34 ± 7.51, p=.047). After adjustment for gender, race, age of diagnosis of BD, suicide attempt, and psychosis history, age was associated with a positive increase in the odds of being a lithium user [OR: 1.020 (1.006, 1.035), p=.005] and a diagnosis of BD-II (compared to BD-1) was associated with lower odds of lithium usage [OR: 0.442 (0.285, 0.682), p<.001]. In the multivariable analysis for longer (>2 years) treatment with lithium, adjusted for gender, race, and BMI, age was associated with a positive increase in the odds of longer (>2 years) treatment duration [OR: 1.021 (1.005, 1.037), p=.009], and a longer lithium treatment duration was associated with lower odds of having a current depressive [OR: 0.500 (0.302, 0.820), p=.006] or manic episode [OR: 0.499 (0.255, 0.955), p=.038] (compared to being euthymic). In the multivariable analysis using the Alda score Criterion A as a measure of treatment response, adjusted for age, gender, age of BD diagnosis, onset age of 1st mania, depression, and hypomania, suicide attempt, history of psychosis, evening chronotype, and comorbidity sums of anxiety and substance use disorders, having a current manic episode (compared to being euthymic) was associated with higher treatment response [β: 4.139 (0.439, 7.840), p=.039], and having current rapid cycling with lower treatment response [β: -3.638 (-7.114, -0.161), p=.041]. In the multivariable analysis, no significant associations were found using the total Alda score as the outcome measure. Limitations include a cross-sectional design that precludes the exploration of causality and the possibility of confounding by indication.

Conclusion: Older age and BD-I diagnosis were associated with higher odds of lithium treatment; age and being euthymic were associated with longer lithium treatment duration; and a current manic episode and absence of rapid cycling with a higher treatment response. A lower proportion of patients with a history of lithium monotherapy among those with an evening chronotype is puzzling.

W77. THE POTENTIAL ROLE OF THE M1/M4 MUSCARINIC RECEPTOR AGONIST KARXT IN THE TREATMENT OF COGNITIVE IMPAIRMENT IN PATIENTS WITH SCHIZOPHRENIA

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Abstract Background: The central cholinergic system plays a key role in cognition and has been the target of numerous drug development efforts, including cognitive impairment in Alzheimer's disease (AD) and in schizophrenia (CIAS). Acetylcholinesterase inhibitors are indicated for the treatment of cognitive impairment in AD and further development efforts have focused on directly targeting muscarinic receptors, including M1, M4, or dual M1/M4 muscarinic receptor agonists. In preclinical models, activation of M1 muscarinic receptors enhances synaptic plasticity in both prefrontal and hippocampal circuits, whereas M4 receptor activators have potential antipsychotic effects and may impact attention and memory circuits. KarXT is an M1 /M4 preferring central muscarinic receptor agonist based on xanomeline, which has previously been shown to improve cognition in patients with AD and schizophrenia. Here, we present phase 2 and phase 3 data on the impact of KarXT on cognition from the EMERGENT program in patients with schizophrenia experiencing acute psychosis.

Methods: The phase 2 EMERGENT-1 (NCT03697252) and phase 3 EMERGENT-2 (NCT04659161) studies consisted of a randomized, double-blind, placebo-controlled, 5-week inpatient trial in patients with schizophrenia experiencing acute psychosis. The effect of KarXT on cognition was assessed using either the Cogstate computerized battery or the CANTAB computerized battery. Both batteries included assessments of core cognitive functions with demonstrated impairments in patients with schizophrenia including: working memory, attention, executive function, verbal learning/memory, and processing speed. Change from baseline to week 5 in those on KarXT vs placebo was assessed both in all individuals with valid computerized battery data at each timeline, as well as in those performing >1 standard deviation below normative standards at baseline (high impairment) and those with higher performance (low impairment). Separate analysis of covariance models assessed treatment effects for all completers and the high and low impairment subgroups. Linear regression was used to assess the relationship between cognitive performance and Positive and Negative Syndrome Scale (PANSS) scores.

Results: As previously reported, there was a nonsignificant treatment effect for KarXT (n=60) vs placebo (n=65) in the phase 2 EMERGENT-1 study, with greater improvement with KarXT (P=0.16, d=0.20). Significant treatment effects were observed in the high impairment group, despite the smaller sample size (KarXT, n=23 vs placebo, n=37; P=0.03, d=0.50). Additional data from the phase 3 EMERGENT studies will be presented.

Discussion: The dual M1/M4 muscarinic receptor agonist KarXT and its active component, xanomeline, are associated with improvements in cognitive function in at least some subsets of patients with CIAS or AD. These findings suggest that drugs targeting M1/M4 muscarinic receptors may have procognitive effects. Further development of KarXT and other similarly acting therapeutic agents is warranted.

W78. A PHASE 2 RANDOMIZED CONTROLLED ADJUNCTIVE TREATMENT TRIAL WITH CLE-100 ESKETAMINE TABLET FOR PATIENTS WITH MAJOR DEPRESSIVE DISORDER AND INADEQUATE RESPONSE TO ANTIDEPRESSANTS DURING THE COVID-19 PANDEMIC

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Abstract: Introduction: CLE-100 is an oral esketamine tablet formulated with abuse-deterrent technology for daily use at home as an adjunctive treatment for Major Depressive Disorder (MDD) patients with an inadequate response to antidepressants (AD). CLE-100 is a NMDAR antagonist metabolized to active metabolites with AD activity. This Phase 2 US trial assessed home-dosing of CLE-100 40mg vs. placebo and enrolled subjects from August 2020 to August 2022. This coincided with an acute phase of the COVID-19 pandemic, followed by a post-acute phase beginning in 2022, when most of the population had been vaccinated, masking and isolation diminished, and the US government declared to move forward without

shutting down schools and businesses. We did a post-hoc analysis to test the hypothesis that recruitment during these two phases would yield differences in CLE-100 vs. placebo responses.
Methods: The study was a randomized, double-blind, placebo-controlled, parallel-arm trial in moderate to severe MDD subjects [Montgomery-Asberg Depression Rating Scale (MADRS) score ≥ 24] with inadequate response to ≥ 2 ADs. Subjects were randomized (1:1) to 4 weeks of daily CLE-100 40mg or placebo added to their current AD. The primary endpoint (PEP) was change in MADRS score from baseline at Week 4. A mixed model repeated measures (MMRM) analysis was used to estimate the difference in the estimated Least Square Means (LSM) at week 4 between the CLE-100 and the placebo groups. To evaluate the cohort effect of the acute (2020-2021) vs. post-acute (2022) phases of the pandemic on the PEP, a post-hoc analysis was performed by adding it to the MMRM model.

Results: The study randomized 130 subjects across 32 US sites; 125 subjects were included in the primary analysis. The mean (SD) age was 44.3 (13.3) with 72.3% females. Mean baseline MADRS was 32.9 (4.9). The LSM [SE] difference of CLE-100 from placebo for change in MADRS at Week 4 in the overall cohort was not statistically significant (−1.26 [1.69], 95% CI: [-4.93 to 1.58] P = 0.46; Cohen's d effect size of 0.14). The post-hoc cohort analysis was performed with 60 subjects in the 2020-2021 cohort and 65 subjects in the 2022 cohort. No meaningful differences were found in baseline characteristics between the two cohorts. No statistically significant difference was seen on the PEP between CLE-100 vs. placebo in the 2020-2021 cohort (2.92 [SE 2.40], 95% CI: [-1.85 to 7.68]; P = 0.227) while in the 2022 cohort CLE-100 was statistically superior to placebo (PEP difference −5.28 [2.34], 95% CI: [-9.91 to -0.65]; P = 0.026; Cohen's d = 0.62). There were no deaths or serious adverse events, or discontinuations due to adverse events in the CLE-100 group. The most common treatment-emergent adverse events (TEAE) occurring more frequently than placebo were dizziness (13.9% vs. 1.8%), headache (12.5% vs. 8.8%), and somnolence (11.1% vs. 1.8%). TEAEs of dissociation occurred in 2.8% of CLE-100 vs. 1.8% of placebo subjects. Drug abuse, dependence, or withdrawal were not observed.

Conclusions: The trial did not meet its PEP in the overall cohort. CLE-100 was well-tolerated and its safety profile was compatible with at-home dosing. We observed a strong cohort effect related to subjects randomized during the acute (2020-2021) vs. post-acute (2022) phases of the pandemic, with CLE-100 statistically significantly better than placebo in the post-acute pandemic cohort. We hypothesize that these temporal differences were due to the disruptive impact of the pandemic which may have, among other factors, produced an enrollment bias along with possible adjustment reactions that diverge in the pattern of placebo-drug responses. Additional studies of CLE-100 are warranted to confirm the positive results observed in the post-acute pandemic phase.

Thursday, June 1, 2023

Poster Session II with Lunch

T1. CENTANAFADINE (CTN) SUSTAINED RELEASE (SR) IN THE TREATMENT OF ADULT ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: SECONDARY OUTCOMES FROM A PHASE 2A STUDY

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Abstract: Background: Centanafadine (CTN) is a norepinephrine/dopamine/serotonin reuptake inhibitor being investigated for the treatment of attention-deficit/hyperactivity disorder (ADHD). In a phase 2a study in adult males with ADHD (ClinicalTrials.gov NCT01939353), CTN sustained release (CTN-SR) treatment significantly improved ADHD Rating Scale-IV (ADHD-RS-IV) total and subscale scores vs placebo between baseline 2 (i.e., end of single-blind placebo run-in) and week 4 ($P<0.001$ for each) and was well tolerated. Additional efficacy outcomes from this phase 2a study are reported here.

Methods: This flexible-dose (CTN-SR 200–500 mg/d), single-blind, exploratory study enrolled males who were age 18–55 years inclusive and who met Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria for ADHD derived from the Mini International Neuropsychiatric Interview–Plus. Eligible patients had a baseline ADHD-RS-IV total score of ≥28 and a Clinical Global Impression severity-of-illness score of ≥4. The study had a screening period, a 1-week placebo run-in, and a 4-week CTN-SR treatment phase. Presented here are previously unreported secondary outcomes of ADHD-RS-IV change from baseline 2 (i.e., end of single-blind placebo run-in) and ADHD-RS-IV ≥30% and ≥50% score reductions (response) over time at weeks 1, 2, 3, and 6 (week 6 [follow-up] visit, 2 weeks after the last treatment dose). Analyses were based on observed results using descriptive statistics.

Results: All 45 patients enrolled at baseline 1 received placebo; 4 discontinued, leaving 41 patients (baseline 2) who received ≥1 dose of study medication. Of these 41 patients, 37 completed the 4-week drug treatment phase. Mean (SD) age was 38.24 (11.88) years; 34 patients (91.9%) were White, 2 (5.4%) Black, and 1 (2.7%) Asian. At baseline, mean (SD) ADHD-RS-IV total, Inattentive subscale, and Hyperactive/Impulsive subscale scores were 38.7 (6.19), 22.81 (2.55), and 15.89 (4.8), respectively. Mean (SD) ADHD-RS-IV total scores decreased (improved) by 11.14 (8.64), 16.14 (11.08), and 20.86 (11.11) at weeks 1, 2, and 3 and by 11.53 (8.78) at week 6 (follow -up). Correspondingly, Inattentive subscale scores decreased by 6.32 (4.99), 9.76 (6.4), and 12.16 (6.61) at weeks 1, 2, and 3 and by 6.36 (5.7) at week 6, and Hyperactive/Impulsive subscale scores decreased by 4.81 (4.74), 6.38 (5.94), and 8.7 (5.81) at weeks 1, 2, and 3 and by 5.17 (4.33) at week 6. ADHD-RS-IV ≥30% response was observed in 13 (35.14%), 23 (62.16%), and 28 (75.68%) patients at weeks 1, 2, and 3 and in 12 (33.33%) patients at week 6. ADHD-RS-IV ≥50% response was observed in 6 (16.22%), 16 (43.24%), and 23 (62.16%) patients at weeks 1, 2, and 3 and in 8 (22.22%) patients at week 6. The pattern of Inattentive and Hyperactive/Impulsive subscale ≥30% and ≥50% response was similar to that observed with ADHD-RS-IV total score response.

Discussion: These secondary outcome analyses from the phase 2a study of CTN-SR in the treatment of adult ADHD support published primary outcome results showing CTN-SR provided statistically significant improvements in ADHD-RS-IV total and both Inattentive and Hyperactive/Impulsivity subscale scores from baseline 2 to week 4. CTN-SR treatment improved total ADHD symptoms rapidly (improvements observed within first 2 weeks) and was well tolerated. The present findings support the usefulness of CTN-SR in providing rapid treatment benefit to adults with ADHD with different clinical presentations.

Funding: Otsuka.

T2. UNDERSTANDING PATIENT PROFILES IN TREATMENT MODALITIES FOR TREATMENT RESISTANT DEPRESSION IN COMMERCIAL AND MEDICARE ADVANTAGE PLANS

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Abstract Background: Administration of esketamine (ESK) nasal spray, an innovative therapy for treatment resistant depression (TRD), is subject to organizational and reimbursement barriers. Socio-economic and clinical characteristics of patients initiated on ESK or other therapies can help understand access to new and conventional treatment modalities in TRD.

Methods: Commercially and Medicare Advantage insured adults with evidence of TRD were selected from Optum's de-identified Clinformatics® Data Mart Database (01/2016-06/2022). Based on therapy initiated on or after 03/05/2019 (ESK approval date for TRD), patients were classified into mutually-exclusive cohorts: ESK, electroconvulsive therapy (ECT), transcranial magnetic stimulation (TMS), and antipsychotic augmentation (AP). Patient profiles were described 12 months before index therapy initiation (baseline period) and ESK use was described in the follow-up period spanning the ESK initiation date to earliest of continuous insurance eligibility or data end.

Results: Cohorts included 500 patients (ESK), 399 patients (ECT), 1,230 patients (TMS), and 40,889 patients (AP). Mean age was lower in ESK (48.7 years) and TMS (50.4 years) relative to ECT (59.5 years) and AP (61.3 years) cohorts. Consistently, proportion in Medicare Advantage plans was lower in ESK (29.4%) and TMS (32.1%) relative to ECT (56.1%) and AP (64.8%) cohorts. Proportion of females was similar in ESK (63.4%), ECT (64.9%), and TMS (66.6%) cohorts relative to AP cohort (72.6%). Proportions of Black or Hispanic adults were similar in ESK (14.8%), ECT (12.3%), TMS (11.5%), and AP (18.0%) cohorts. Higher proportion had education above high school in ESK (83.2%), ECT (84.0%), and TMS (87.6%) relative to AP (69.6%) cohort. Additionally, most had household income ≥$75K in ESK (58.8%), ECT (55.6%), and TMS (58.3%) relative to AP (35.8%) cohort. During baseline period, higher proportion used psychotherapy in ESK (75.2%), ECT (66.7%), and TMS (76.2%) relative to AP (36.3%) cohort. Mean time from evidence of TRD to index therapy initiation was longest in ESK (15.0 months) followed by TMS (12.9 months), ECT (11.8 months), and AP (8.5 months) cohorts.

During the mean of 13.5 months of follow-up, ESK cohort had a mean of 16.1 ESK treatment sessions. 64.4% completed ≥8 ESK treatment sessions (induction phase); mean time to

complete induction was 73 days (per label, 28 days). 59.4% continued treatment post induction and 48.4% completed ≥4 ESK maintenance sessions.

Conclusion: Use of advanced therapies including ESK, ECT, and TMS was correlated with higher education and income; further, use of ESK and TMS was correlated with younger age and commercial insurance. Completing ESK induction took almost three times longer than per label and large proportion did not transition to ESK maintenance suggesting access and reimbursement related barriers with ESK.

T3. QELBREE® (VILOXAZINE EXTENDED-RELEASE CAPSULES): FINAL RESULTS OF THE LONG-TERM, PHASE 3, OPEN-LABEL EXTENSION TRIAL IN ADULTS WITH ADHD

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Abstract: Background: Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder that begins in childhood and typically (in up to 90% of children) persists into adulthood, with fluctuating periods of exacerbation and remission (1). Despite the prevalence of ADHD, fewer clinical treatment studies are available in adults compared to pediatric populations. Initially approved for pediatric ADHD (≥6 years), viloxazine extended-release (ER) is just the second nonstimulant medication to receive FDA-approval to treat adult ADHD; approval was based on the results of a 6-week, double-blind (DB), multicenter, flexible dose, pivotal, Phase 3 clinical trial (2).

Objective: Report the long-term safety and efficacy of viloxazine ER in the open-label extension (OLE) of the pivotal Phase 3 clinical trial in adult ADHD.

Methods: Upon completing the DB trial, consenting subjects initially received viloxazine ER 200 mg/day for 1-2 weeks, with further adjustments (based on clinical response and tolerability) within the range of 200-600 mg/day. Following Week 12, based on response, investigators could supplement the optimized viloxazine ER dose with a stimulant at their discretion. The OLE trial enrollment was temporarily closed at the outset of the COVID pandemic, resulting in subjects being unable to immediately transition into the OLE trial following DB completion. Subjects who remained eligible were offered delayed entry into the trial when it reopened (~ 4 months later). Safety and efficacy measures were assessed relative to DB Baseline (or OLE re-entry Baseline) at OLE Weeks 2, 4 and every ~8 weeks thereafter. The trial was planned for 3 years or until commercial availability of viloxazine ER.

Results: In the OLE trial, 133 immediate and 26 delayed-rollover subjects received viloxazine ER for a mean±SD of 265±254.9 days. Overall, 81, 50, 30 and 9 subjects remained in the trial for ≥ 6, 12, 18, and 24 months respectively. Nine subjects used adjunctive stimulant medication during the trial. The primary reasons for early discontinuation were withdrawal of consent (25.6%), loss to follow up (17.7%), or adverse event (17.6%). Adverse events were generally similar to those seen in DB, most common: insomnia (13.8%), nausea (13.8%), headache (10.7%), and fatigue (10.1%). Most TEAEs were mild or moderate in severity and did not result in study discontinuation. Two subjects reported serious adverse events (considered by investigators unrelated to study treatment). There were no meaningful changes observed in

clinical laboratory measures. Changes in vital signs and ECG parameters did not indicate any safety concerns. No AEs for suicidal behavior were reported. Overall ADHD symptoms, as well as executive function rating scale scores showed continued improvement over DB Baseline (or OLE trial re-entry Baseline). The mean±SD AISRS total score was 37.9±6.34 (n=159) at Baseline and 14.5 ±10.18 (n = 51) at Week 52, and the mean±SD BRIEF-A 'GEC' T-score was 70.4±10.94 (n=156) at Baseline and was 54.7±14.84 (n = 50) at Week 52.

Conclusion: The safety and tolerability of long-term administration of viloxazine ER were consistent with that seen in shorter term trials. Overall ADHD symptoms and executive function showed consistent improvement compared to Baseline measures. The onset of the COVID-19 pandemic and temporary trial enrollment closure impacted trial participation. Future studies should investigate which patients would best benefit from treatment.

T4. POLYGENIC RISK-BASED DRUG-REPOSITIONING FOR ALCOHOL USE DISORDER IN THE NATIONAL HEALTH AND RESILIENCE IN VETERANS STUDY COHORT

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Abstract Background: Alcohol use disorder (AUD) often co-occurs with other mental health problems, increasing the likelihood of adverse health outcomes. Therefore, elucidating mechanisms underlying comorbid diagnoses is crucial, particularly for high-risk groups such as military veterans. Here, we evaluated the association of polygenic risk with AUD comorbidities in a nationally representative cohort of US veterans. Then, we performed a drug repositioning analysis to identify existing drugs that may be repurposed for treating AUD and its comorbid diagnoses.

Methods: We investigated polygenic risk scores (PRS) with respect to alcohol-related phenotypes and AUD comorbidity phenotypes in the National Health and Resilience in Veterans (NHRVS) cohort (n=3,317) which is a nationally representative sample of U.S. veterans (1). We used genome-wide association statistics from the Million Veterans Program for AUD, Alcohol Use Disorders Identification Test-Consumption (AUDIT-C), problematic alcohol use, maximum habitual alcohol intake, major depressive disorder (MDD), posttraumatic stress disorder (PTSD), generalized anxiety disorder (GAD), and opioid use disorder (OUD) to derive PRSs and test them in relation to co-occurring mental disorders and suicidality in AUD. Next, PRS associations were subsequently tested for enrichments with respect to molecular pathways with PRSet. Then, molecular pathways were used as input in a repurposing analysis performed with the Gene2drug tool to identify currently available drugs that act in such pathways.

Results: The analyzed sample included 3,317 U.S. military veterans, 86.6% were males with a mean age of 68.17 years. AUD-PRS was significantly associated with lifetime PTSD (R2=0.69%, p=0.008), past-month PTSD (R2=0.64%, p=0.03), and current GAD symptoms (R2=0.52%, p=0.01). AUD-related PRS associations were enriched for molecular pathways implicated in cell morphogenesis, cell projection organization, and neurodevelopment. Drug repurposing analyses revealed interaction of the pathways mapped to AUD-PRS with adiphenine, an inhibitor of nicotinic receptors, and clozapine, an antipsychotic.

Discussion: Our findings indicate that AUD-PRS is associated with psychiatric conditions, such as PTSD and anxiety in military veterans. This association is somehow different from previous investigations conducted in general-population samples that have shown that PRS related to measures of alcohol consumption (e.g., AUDIT-C) tend to be more associated with non-pathological behavioral traits than mental illness. This difference may be related to the characteristics of the cohort investigated, which is a sample representative of a population at high risk of adverse mental health outcomes. Accordingly, it is plausible that veterans with AUD and comorbid mental disorders require a treatment different from those patients without an increased risk for mental disorders. The candidate drugs represent potential treatments for veterans with AUD with other mental health comorbidities, and their study in other AUD high-risk groups is encouraged. Genetic-informed drug repositioning approaches could integrate an individual's genetic risk to inform personalized interventions.

Conclusion: Our findings showed that AUD is associated with PTSD and anxiety-related comorbidities in military Veterans. Adiphenine and clozapine are candidate pharmacological treatments for AUD with other mental health comorbidities.

T5. THE POSSIBILITY OF AFFECTING RISKY SEXUAL BEHAVIORS THROUGH PHARMACOLOGICAL METHODS: A SECONDARY ANALYSIS OF THE ADAPT-2 TRIAL

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Abstract: Background: Recently, the Accelerated Development of Addictive Treatment for Methamphetamine Disorder (ADAPT-2) trial concluded that combination extended-release injectable naltrexone and extended-release oral bupropion offered a possible intervention to treating methamphetamine use disorder (1). While the ADAPT-2 trial highlighted the potential of pharmacological methods to curb methamphetamine use, it is unknown if the treatment affected sexual risk behaviors in the population studied. Studies in the past have compared risky sexual behaviors in MSM who use methamphetamine before and after single medication regimens, and have yielded mixed results (2, 3, 4). The primary aim of this secondary analysis of the ADAPT-2 trial was to determine if the combination of naltrexone-bupropion affected sexual behaviors in all participants of the study across time points as well as if there were differences among subgroups.

Methods: The data for this secondary analysis came from the ADAPT-2 trial, a 12-week randomized, double-blind trial conducted at eight sites from May 2017-June 2019. Sexual risk behaviors were collected at baseline, week 6, and week 12. Participants were asked about sexual behavior over the previous 30 days. Participants were asked to report the number, gender, and HIV status (HIV positive, HIV negative, status unknown) of partners who they engaged in oral, anal, or vaginal intercourse with along with number of times in the past 30 days that they had intercourse while high on meth. The participants also reported the frequency of condomless sex with HIV positive or unknown partners as well as with HIV negative partners.

Results: Across all demographics, combination naltrexone-bupropion had no effect on number of sexual encounters, number of partners, or number of chemsex encounters. Interestingly, when looking across all groups, the number of condomless encounters was significantly higher

in the treatment group (p=0.016). The number of condomless encounters was 4.50 (SE=0.36) (95% CI 2.22-9.13) in the Nal-Bup group and 1.12 (SE=0.60) (95% CI 0.35-3.62) in the placebo group. When looking at MSM/W (gay and bisexual men) as well as MSW (heterosexual men), the results for number of encounters, number of partners, and number of chemsex episodes were in-line with the all-group analysis and were not statistically significant. However, no significant difference was found between the number of condomless encounters. For the female and HIV positive subgroup analysis, a negative binomial distribution without zero-inflation for all outcomes was used and found that there was no significant difference for any outcome across both stages.

Conclusions: The results from the secondary analysis of the ADAPT-2 trial suggest that combination naltrexone-bupropion did not have a statistically significant effect on sexual risk behaviors, which highlights the need for follow up investigation. The preliminary findings in this abstract may be used to inform public health interventions for meth use, risky sexual behaviors, and pharmacological methods of interventions, especially since heterosexual and non-heterosexual men, as well as women, were included in the analysis when past studies have mainly focused on MSM. However, when comparing the responders in the original study, the difference, while statistically significant, was small. Thus, future analysis of the ADAPT-2 trial would benefit from comparing behavioral change in responders rather than treatment group compared to placebo. In doing so, it is possible to determine the benefit of pharmacotherapy on complex behaviors which lead to negative health outcomes and ways to mitigate them.

T6. BENZODIAZEPINE PRESCRIPTIONS AND RISK OF PSYCHIATRIC DISORDERS IN PATIENTS WITH ANXIETY DISORDERS: A REAL-WORLD MULTICENTER RETROSPECTIVE COHORT STUDY

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Abstract: Background: While the role of benzodiazepines (BZDs) has been well established for anxiety and related disorders, there are significant concerns about BZD dependence, withdrawal, and tolerance. There is a lot of ambiguity regarding the potential long-term effects of BZDs on other mental health disorders. Considering BZD's effects on the central nervous system, the risk of subsequent mood disorders, such as depression and bipolar disorder, is unclear.

Method: We used TriNetX Analytics, an analytic tool built with a real-time electronic medical record network, to conduct a retrospective cohort study investigating the incidence and risk ratio of depressive disorders, bipolar disorders, and substance use disorders in patients with anxiety disorders. We recruited patients from September 08, 2017, to September 08, 2022. The study cohort was defined as patients between the ages of 18 and 65 with anxiety disorders prescribed with at least one BZD; the control cohort was defined as patients between the ages of 18 and 65 with anxiety disorders with no BZD prescription during the five-year timeframe examined. Index event was defined as the time subjects were diagnosed with anxiety; identified outcomes included depressive disorders, bipolar disorders and substance use disorders within 5 years after the index event. Patients in the two cohorts were matched by gender, age, race, ethnicity, and common medical conditions at a 1:1 ratio by propensity scoring and then

underwent Kaplan–Meier analysis and association analysis. Hazard ratios (HRs) and 95% Confidence intervals (CIs) of the incidences were calculated between propensity score–matched study versus control cohorts.

Results: 626,754 patients were identified and matched for analysis for each group. In the study cohort, 8.7% developed depressive disorders, 0.7% bipolar disorders, and 4.2% substance use disorders. In the control cohort, 2.9% developed depressive disorders, 0.2% bipolar disorders, and 1.9% substance use disorders. Patients in the study cohort were more likely to be female (67.6% vs. 66.7%, $p < 0.001$), non-Hispanic (65.8% vs. 62.5%, $p < 0.001$), and white (72.8% vs. 69.1%, $p < 0.001$). Kaplan–Meier analysis showed the survival probability at the end of the time window was 90.3% for the control cohort and 79.0% for the study cohort (HR [95% CI] = 2.99 [2.95-3.05]; $P < 0.001$) in depressive disorders; 99.5% for the control cohort and 98.4% for the study cohort (HR [95% CI] = 3.73 [3.50-3.97]; $P < 0.001$) in bipolar disorders; 94.1% for the control cohort and 89.5% for the study cohort (HR [95% CI] = 2.20 [2.16-2.25]; $P < 0.001$) in substance use disorders. Patients with anxiety disorders prescribed with BZDs were at a higher risk of depressive disorders (Risk Ratio [RR] [95% CI] = 2.95[2.90-3.00]), bipolar disorders (RR [95% CI] = 3.81 [3.58-4.06]), substance use disorders (RR [95% CI] = 2.22 [2.17-2.27]) during the five years following the diagnosis and prescription.

Conclusion: Patients with an anxiety disorder who were prescribed BZDs are at higher risk of mood disorders and substance use disorders than a matched cohort not prescribed BZDs. Given this notable association, clinicians should be cautious while prescribing BZDs and inform the patient about the risks associated with their utilization. While the initial results are extremely promising, further studies are warranted to shed light on a potential causality between BZDs and depressive disorders, which would be quite extraordinary.

T7. FACING CHANGES IN CANNABIS USE DURING THE COVID-19 PANDEMIC

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Abstract The Covid-19 pandemic started in March 2020 and has caused an increased demand for physical as well as mental health care. In the beginning of the pandemic, the focus was given to the physical concerns and effects of Covid-19 ranging from severe illness with sepsis, shock and respiratory failure to milder symptoms including fatigue, lethargy, fevers and cold like symptoms. It did not take long until the psychiatric consequences became more evident and are expected to persist way past the pandemic.

Social isolation and lack of support are known contributors to the development of depression and anxiety disorders requiring mental health treatment. An estimated 45% of the adult U.S. population have reported that the Covid-19 pandemic has negatively affected their physical and mental health.

At the same time, marijuana has been gaining popularity. About 48.2 million people used the substance at least once in 2019, which is about 18% of the U.S. population. Throughout the pandemic, the use of cannabis and cannabis-products has further increased in the U.S. but also worldwide.

While many developments were put on hold during the pandemic, many states have proceeded towards legalization of marijuana for recreational use, others have medical marijuana programs

allowing the use for debilitating medical or psychiatric conditions including AIDS/HIV, Multiple Sclerosis, Amyotrophic Lateral Sclerosis, Alzheimer's but also depression, anxiety, and Post-traumatic Stress-Disorder. 37 states allow now some form of medical cannabis while only 3 states don't have any marijuana programs in place.

The current trend of legalization of marijuana and easy access causes people to have a false perception of marijuana as a natural and safe drug. Even amongst medical professionals, the opinions on safety, benefit and harm differ significantly.

Marijuana is a substance that contains more than 421 compounds and 60 pharmacologically active cannabinoids. The two best-described cannabinoids are THC and CBD. Most of the other compounds are not yet understood, their mental and physical effects are unknown.

Current available studies are limited by small sample sizes and short-term follow-ups but raise concerns regarding marijuana's toxicity. Health risks associated with the use of marijuana range from physical diseases COPD, cancer, hormonal changes to psychiatric disorders mania, psychosis, ADHD- like symptoms and impaired cognition.

This oral presentation will provide an overview on the current available data of marijuana use and associated risks and benefits during the Covid-19 pandemic. Utilized sources were PubMed, Cochrane, Ovid, Medline, Psych Info, EMBASE.

T8. CANNABIS USE IN PREGNANT FEMALES: IMPORTANCE FOR A NEED OF BIOMARKER FOR PERINATAL CANNABIS USE

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Abstract: Background: The use of marijuana and/or cannabidiol (CBD) during pregnancy is increasing with growing legislative acceptance in the US whether recreationally or to self-medicate for conditions such as morning sickness or anxiety. The active compound of marijuana, Δ9-tetrahydrocannabinol (Δ9-THC), and its metabolites cross the placenta, and are detected in breastmilk, viable exposure pathways for fetuses and infants.
Previous studies relying on self-disclosure of marijuana use in pregnant women suggest under reporting, confirming the importance of biomarker measurement for exposure assessment. Existing literature does not examine the patterns of marijuana use across the perinatal period, which is crucial for identifying windows of vulnerability for health effects in offspring. As such, a need of biomarker for cannabis use during pregnancy and post-natal period is critical given the long-term effects of prenatal and early life cannabis exposure in offspring.

Specific Aims: To quantify urinary concentrations of cannabis and its metabolites in banked samples from mothers from a contemporary birth cohort in New York City (NYC).

Method: This proposal leveraged banked urine samples of 74 mothers in an existing birth cohort of NYU Children's Health and Environment Study in NYC. Pregnant women, 18 years and older and <18 weeks pregnant were recruited at three NYU-affiliated hospitals in NYC. The pregnant women reported cannabis use perinatally. Urine samples were collected serially over the course of pregnancy. Three urine samples were utilized, one in early pregnancy, one after mid gestation, and one postnatal sample at 12 months. All urine samples from women were analyzed for several metabolites of cannabinoids using ultra-high-performance liquid chromatography coupled with tandem mass spectrometry. Cannabis metabolites that were

examined included 11-nor-9-carboxy-Δ9-tetrahydrocannabinol (COOH-THC), Δ9-THC, CBD, cannabinol, and 11-hydroxy-THC to determine the active or recent use from intermittent use from their half-life.

Results: Of the 74 mothers, the mean maternal age was 32 (±5) years, of which 41% (n=30) were nulliparous and 93% (n=68) were married or lived with a partner. Majority of these women were Hispanic (63%) and Non-Hispanic White (30%). Of the total sample, 54% (n=39) had a college degree. Out of these 74 mothers, only 3% (n=2) mothers self-disclosed marijuana use before and during pregnancy, while 22% (n=16) mothers tested positive for urinary cannabinoids. The mean maternal age of these 16 mothers was 31 years. Among these 16 women, 50% (n=8) were Hispanic, 37% (n=6) were Non-Hispanic White. 75% (n=12) of these 16 women had a college degree and 87% (n=14) were married or living with a partner. Cannabis use was equally seen between nulliparous (n=8) and parous (n=8) women in these 16 women. No statistical significance was seen with race, marital status, and education in them. An intermittent cannabis use pattern was observed in 12 women during perinatal period indicated from the longer half-life of the metabolite, COOH-THC. While a recent cannabis use during perinatal period was determined through presence of urinary metabolites with shorter half-life, Δ9-THC (n=10), CBD (n=4), cannabinol (n=2), and 11-hydroxy-THC (n=15). Ten women showed postnatal detection at 12 months visit while eight tested positive in early pregnancy.

Conclusion: As the New York State legislature considers legalization of recreational marijuana use, a need of biomarker is critical to identify the cannabis use in female given an active and passive exposure risk in offspring.

Funding: The project was funded by NYU-Center for the Investigation of Environmental Hazards and AACAP Pilot Research Award.

T9. EXPLORE-EXPLOIT DYNAMICS AND STRESS AMONG HEALTHCARE WORKERS DURING THE COVID-19 PANDEMIC

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Abstract: Background: The ability to flexibly adapt to a changing environment is critical for resilience in the face of an uncertain and challenging world. During the COVID-19 pandemic, health care workers (HCWs) have been required to make decisions in a rapidly changing environment. For instance, facing tremendous uncertainty about outcomes and resource availability, HCWs have had to decide when and how long to continue to use, or exploit, a given approach to treatment and when to explore alternative approaches. Exploiting too long can lead to diminishing results and missed opportunities for better treatments, while exploring too soon or too often can mean forgoing a successful option. The balance between exploration and exploitation is disrupted in a range of neuropsychiatric disorders. Further, both acute and chronic stress have been shown to increase exploitative behavior, possibly by making the environment seem excessively harsh.

Methods: We conducted a prospective cohort study to measure the relationship between prolonged stress, mental health and exploration-exploitation tradeoffs in a population-based study of HCWs during the COVID-19 pandemic. 42 HCWs our of 123 initially recruited

completed all three parts of the study. Questionnaires were administered to assess mental health symptoms and behaviors. Additionally, we measured hair cortisol as a biomarker of prolonged stress with liquid chromatography-tandem mass spectrometry. To measure behavior, we administered a classic sequential dynamic decision making task: a multi-arm bandit. In this task, participants choose between options of unknown and varying reward, mirroring many of the decisions that are made in life. Participants switch between exploiting choices and exploring for potentially better options. We analyzed behavior on this task with validated computational models that identify states of exploration and exploitation, and examined how individuals incorporated reward information into their choices while those states persisted. We hypothesized that HCWs propensity to overexploit and their degree of depressive symptoms would predict their hair cortisol levels, our objective measure of prolonged stress. Pearson's correlations and generalized linear models were performed to assess associations. Reported p-values are FDR-corrected.

Results: We found that subjective symptoms on their own had little utility for explaining physiological stress (cortisol). In contrast, we found that explore-exploit behavior successfully predicted cortisol levels, and that depressive symptoms shaped this relationship. As cortisol levels and depressive symptoms increased, health care workers tended to overexploit options ($r = -0.36$, $p = 0.046$) and learn less from rewards ($r = -0.467$, $p = 0.022$). By leveraging the power of our computational model, we uncovered a putative mechanism for this effect: a decrease in reward sensitivity during exploration (beta $= 0.46$, $p = 0.022$) that was amplified by depressive symptoms (beta $= -0.42$, $p = 0.022$).

Conclusion: We provide striking experimental evidence for a link between stress and cognitive flexibility in the context of a global catastrophe. It also provides novel, mechanistic insight into how prolonged stress and depression may cause inflexible decision-making: through constraining the ability to take in new information. Lastly, our results add to the important ongoing debate over the connection (or lack thereof) between behavior and subjective symptoms or symptoms and physiological measures. We found that we needed both computationally defined behavior and symptom reports to best explain variation in hair cortisol levels, underscoring the importance of considering all three dimensions.

T10. ERG AS A POTENTIAL BIOMARKER OF SSRI-RESPONSIVE PTSD: A PILOT STUDY

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Abstract: Background: Although serotonin selective reuptake inhibitors (SSRIs) are the only FDA approved medications for PTSD, evidence supporting their use in Veterans with PTSD remains conflicting and limited. A potential explanation for these inconsistencies comes from findings of heterogeneity in PTSD pathophysiology, with some individuals exhibiting alterations in noradrenergic regulation, while others show more evidence of serotonergic signaling changes underlying symptom expression. While biomarkers of noradrenergic dysregulation in PTSD may predict treatment benefit from the noradrenergic medication prazosin(1), we have no similar clinically accessible biomarkers to detect altered serotonin regulation or predict treatment response to SSRIs.

As the only part of the CNS directly visible on physical exam, the retina offers a unique and underutilized window into neural signaling, with histological and physiological evidence of direct inputs from serotonergic brain centers to retina. Electrical retinal signals can be measured noninvasively with electroretinogram (ERG), allowing assessment of brain serotonergic signals via retinal signals. Furthermore, ERG biomarkers may predict treatment response to SNRIs in MDD, with higher baseline b-wave amplitudes (a component of the ERG waveform) seen in antidepressant responders compared to non-responders, and normalization of b-wave amplitudes with treatment(2). While evidence supports development of an ERG biomarker to predict response to serotonergic agents, its use has yet to be investigated in PTSD.

Purpose: While a portable handheld ERG device improves feasibility outside of eye clinics compared to traditional ERG setups, its clinical application in outpatient mental health requires validation. Here we present initial work validating this handheld ERG device, and describe an ongoing pilot study of the relationship of baseline ERG to PTSD symptom profiles and ERG response to SSRIs.

We hypothesize a statistically significant negative correlation between baseline and post-SSRI change in ERG signals, consistent with high baseline b-wave amplitudes representing clinically meaningful altered serotonergic functioning that is normalized by an SSRI (higher baseline amplitudes will correlate with larger decreases in amplitudes).

Methods: ERG waveform in 27 veterans with PTSD will be characterized before and after a single dose of an SSRI (sertraline), and the relationship between baseline and change in ERG following treatment determined. This number of participants assumes a (conservative) ERG recording success rate of 90% for a sample size of 24 participants with high quality recordings for analysis, providing a power of 80% to detect an effect size of 0.6 based on previous data(2). ERG recordings were performed according to ISCEV (International Society for Clinical Electrophysiology of Vision) guidelines.

Results: ERGs were performed on 4 healthy volunteers using methods identical to those that will be used on study participants. Dark adapted 0.01 ERG recordings demonstrated b-wave amplitudes falling within one standard deviation of those previously reported in healthy individuals(2).

Conclusion: Recordings using a handheld ERG device are comparable to data from traditional ERG reported in the literature(2). These results, along with previously published studies, make the ERG a promising, novel, and feasible biomarker for application to mental health disorders. The planned work will characterize retinal signals in patients with PTSD and how they change in response to SSRIs, a first step toward developing a biomarker with the potential to target gaps in our knowledge of PTSD pathophysiology, clinical assessment, and treatment.

T11. CLINICAL/DEMOGRAPHIC AND BIOLOGICAL CORRELATES OF COGNITIVE IMPAIRMENT IN PATIENTS WITH BIPOLAR DISORDER

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Abstract: Aims: Deficits in various domains of cognitive functioning have been identified in patients with bipolar disorder (BD). Our goal in the present study was to examine the associations of cognitive functioning with clinical/demographic factors (i.e., BMI, childhood trauma, number of mood episodes, number of prior psychiatric hospitalizations, psychosis history, number of weeks since most recent mood episode), and biological markers (i.e., serum levels of C-Reactive Protein [CRP], Interleukin [IL]-6 and Tumor Necrosis Factor [TNF]-α) in patients with BD.

Methods: As part of an ongoing longitudinal study, 83 BD patients (mean age: 40.8 ± 14.7; 60% women; 81% White) were recruited from Boston, MA and surrounding areas. Participants were assessed by The Structured Clinical Interview for DSM-5 to confirm eligibility. Depressive and manic symptoms were respectively assessed by the Hamilton Depression Rating Scale and the Young Mania Rating Scale. Cognitive functioning was assessed by six domains of MATRICS consensus cognitive battery (MCCB) and California Verbal Learning Test (CVLT). All scores were age and sex adjusted using MCCB normative data. Multiple linear regression analyses were performed to determine the associations between biological and clinical factors, and MCCB composite score controlling for medications, current depressive, and current manic symptoms. A composite inflammation index of CRP, IL-6 and TNF-α was formed to minimize type I error. This decision was supported by the results of principal component analysis (PCA).

Results: Most BD patients (79.5%) were diagnosed with bipolar I disorder and the remainder were bipolar II disorder. Approximately 48% had a history of psychosis. Global cognitive functioning (MCCB Composite) was negatively correlated with BMI (β=-.42, p<.001), childhood trauma (β=-.37, p=.003) and number of prior psychiatric hospitalizations (β=-.28, p=.01). Total number of prior mood episodes, history of psychosis, and weeks since most recent episode were not significantly associated with global cognition. Global cognition was also negatively correlated with the inflammation composite (β=-.29, p=.01). To further explore the role of each inflammatory marker, individual regression analyses were performed. Global cognition was negatively correlated with peripheral levels of CRP (β=-.27, p=.02) and IL-6 (β=-.30, p=.008), but not TNF-α. In the model including covariates above and each of the significant predictors (i.e., BMI, childhood trauma, hospitalization number, inflammation composite), the association remained significant for childhood trauma (β=-.25, p=.02) and trend-level results were noted for BMI (β=-.24, p=.08) and number of prior psychiatric hospitalizations (β=-.18, p=.09).

Conclusion: Prior severe mood episodes, early life experiences, elevated body weight and inflammation may play a role in cognitive impairment associated with bipolar disorder. This information provides insight into identifying risk factors that may contribute to the development and progression of cognitive deficits in bipolar disorder and therefore point to mechanistic treatments targets aimed at optimizing outcomes in BD.

T12. CSF AND PERIPHERAL INFLAMMATORY BIOMARKERS AFTER COVID-19 INFECTION IN A PREGNANT POPULATION

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Abstract: Background: In light of growing evidence of long-term sequelae after COVID-19 infection (termed
post-covid conditions, long COVID or Post-Acute Sequelae of COVID [PASC]), there is an urgent need to investigate the potential long-term neuropsychiatric effects of SARS-CoV-2 infection. It has been estimated that between 10 and 30% of individuals who are infected with the virus, including those with mild disease, could experience post-covid sequelae. The central nervous system (CNS) is potentially susceptible to long-term changes from systemic inflammation that may occur during infection. While some evidence suggests that pregnant women may be more vulnerable to the acute effects of SARS-CoV-2 infection than the general population, the risk for potential long-term sequelae is unknown. This research aims to examine cerebrospinal fluid (CSF) and peripheral cytokine levels in pregnant individuals at delivery in relation to SARS-CoV-2 infection and vaccination status during pregnancy, to assess any potential long-term differences in inflammation.

Methods: Participants were recruited from a prospective NIH-funded pregnancy cohort, Generation CSF, in the Mount Sinai Health System. CSF and plasma samples were drawn from 105 participants during labor and delivery (CSF n=83, plasma n=93). A panel of fourteen cytokines was analyzed using a high sensitivity assay. In addition, SARS-CoV-2 infection and vaccination status were collected through self-report and medical records. Cytokine levels in CSF and Plasma were compared between Infected vs. Non-Infected and Vaccinated vs. Non-Vaccinated groups in univariate analyses using Independent sample t-tests.

Results: In univariate uncorrected analyses, we found significant differences in plasma IL-1β, IL-13, IL-10, IL-23, and IL-8 levels by infection status ($p=0.027$, $p<0.001$, $p<0.001$, $p=0.048$, $p=0.028$); CSF cytokine levels did not significantly differ by COVID-19 infection status. Plasma GMCSF, IFNγ, IL1β, IL4, IL-10, IL12p70, IL-17A, IL-23, TNFα levels and CSF IL1β, IL2, IL12p70, IL13 and TNFα levels were significantly higher (all $p<0.05$) in those vaccinated compared to not vaccinated during pregnancy.

Conclusions: This preliminary univariate uncorrected data analysis found potential differences in central and peripheral cytokines by SARS-CoV-2 infection and vaccination in a pregnant population. This project is ongoing (Generation C-SF, target N=600, R01MH127315) and further analyses in a larger sample are currently in progress. Multiple linear regressions will be performed to further explore associations controlling for confounders and relevant covariates.

T13. PROPENSITY WEIGHTING METHOD TO ASSESS THE TREATMENT EFFECT IN CLINICAL TRIALS FOR MAJOR DEPRESSIVE DISORDERS ACCOUNTING FOR HETEROGENEOUS PLACEBO EFFECT USING AN ARTIFICIAL INTELLIGENCE APPROACH

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Abstract: Background: The treatment effect in clinical trials for major depressive disorders (RCT) can be viewed as the resultant of treatment specific and non-specific effects. The baseline individual propensity to respond to any treatment can be considered as a major non-specific confounding factor. Larger is the baseline propensity lower is the chance to detect any treatment specific effect. The individual baseline propensity to respond to placebo is associated

with individual expectation, it varies from individuals to individuals and is not controlled by the currently deployed randomization process. Furthermore, the statistical methodologies for analyzing RCTs doesn't account for potential unbalance in subjects allocation to treatments due to unbalance in the distribution in the individual propensity to respond to placebo. Hence, the groups to be compared may be imbalanced, and thus incomparable due to baseline differences.

Methods: Propensity weighting was proposed as a novel methodology of causal inference to reduce baseline imbalances between arms1. This technique is based on the calculation of propensity, which is the individuals' probability of showing a placebo effect given observations of individual items of HAMD-17 evaluated between two pre-randomization time points (screening and baseline). The predicted probability was estimated using artificial intelligence (AI) methodologies based on the artificial neural network (ANN) approach².

Results: A case study is presented using a randomized, double-blind, placebo-controlled, three-arms, parallel-group, 8 weeks, fixed-dose study to evaluate the efficacy of paroxetine CR at 12.5 and 25 mg/day. An ANN model was developed to predict the placebo response at week 8 using the individual HAMD-17 items change from screening to baseline of subjects in the placebo arm. This model performed well in terms of predictive performance estimated by the area of 0.81 under the receiver operating characteristic curve. This model was used to predict individual propensity probability to respond to placebo in each subject included in the three arms.

The inverse of the estimated probability was used as a weight in the mixed-effects model for repeated measures applied to assess the treatment effect (SAS PROC MIXED). The comparison of the results with and without propensity weight indicated that the weighted analysis provided an estimate of treatment effect and effect size about twice larger than the conventional non-weighted analysis.

Conclusion: The propensity weighting method provides an unbiased strategy to account for the potential confounding factor of heterogeneous and uncontrolled placebo effect making the patients' data comparable across treatment arms. The major advantage of this methodology with respect to the historical approaches aimed to 'control' the placebo effect using different enrichment strategies is that all subjects randomized in the study are included in the analysis.

T14. PREFERENCES FOR CHARACTERISTICS OF ORAL ANTIPSYCHOTIC TREATMENTS: SURVEY RESULTS OF PATIENTS LIVING WITH SCHIZOPHRENIA OR BIPOLAR I DISORDER

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Abstract: Background: Antipsychotic treatments are effective in managing symptoms in patients with schizophrenia (SZ) or bipolar I disorder (BD-I); however, they are associated with various side effects, including weight gain and sexual dysfunction. This study assessed

patients' preferences for characteristics associated with oral antipsychotics. Further, this study explored potential tradeoffs that patients may make between efficacy and tolerability.

Methods: A cross-sectional online survey was designed to collect preference data using a discrete choice experiment (DCE). The DCE consisted of a series of choices between pairs of hypothetical oral antipsychotic treatments based on 5 characteristics: treatment efficacy (ie, symptom improvement), weight gain over 6 months, sexual dysfunction, sedation, and akathisia. The DCE was pretested to ensure its comprehension and understanding among people with SZ (n=15) or BD-I (n=15). The final survey was administered to US adults with a self-reported diagnosis of SZ or BD-I.

Results: A total of 144 respondents with SZ (mean age 41 years, 50% female, 69% White) and 152 respondents with BD-I (mean age 40 years, 70% female, 78% White) completed the survey. Most respondents with SZ or BD-I experienced side effects included in the DCE: weight gain (85%, 83%), sedation (82%, 93%), sexual dysfunction (75%, 76%), and akathisia (71%, 72%), respectively. Symptom improvement was the most important treatment attribute for respondents with SZ or BD-I. Weight gain and sexual dysfunction were the 2 side effects that respondents most wanted to avoid. Respondents preferred treatments associated with 0, 4, or 7 lb of weight gain over 6 months significantly more than treatments associated with 11 lb of weight gain. Respondents were willing to accept an increase in weight of 7 to 9 lb over 6 months for the smallest improvement in symptoms (1 incremental step of improvement in disease severity). For the largest improvement in symptom severity (2 incremental steps of improvement in disease severity), respondents were willing to accept weight gain of more than 11 lb over 6 months. With respect to sedation, respondents were willing to accept higher than 25% risk of sedation for any level of symptom improvement.

Discussion: In this survey, treatment efficacy was the most important attribute of oral antipsychotics among the respondents with SZ or BD-I; weight gain and sexual dysfunction were the 2 side effects patients most wanted to avoid. Respondents with SZ or BD-I were willing to accept some weight gain as a side effect for better efficacy. As oral antipsychotics have different efficacy and tolerability profiles, it is important to understand the features that patients most value in a treatment and how they balance benefits and risks when choosing among options.

T15. EFFICACY OF LUMATEPERONE IN POOLED SHORT-TERM LATE-PHASE CLINICAL TRIALS FOR THE TREATMENT OF MAJOR DEPRESSIVE EPISODES ASSOCIATED WITH BIPOLAR II DISORDER

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Abstract: Background: Bipolar II disorder has limited treatment options and is associated with significant functional impairment and mood instability. Lumateperone is an FDA-approved antipsychotic to treat adults with schizophrenia and depressive episodes associated with bipolar I or bipolar II disorder as monotherapy and as adjunctive therapy with lithium or valproate. A robust late phase clinical trial program established the safety and efficacy of lumateperone 42 mg in patients with a major depressive episode (MDE) associated with bipolar I or bipolar II disorder. This analysis evaluated the efficacy of lumateperone 42 mg across

pooled short-term studies in patients with depressive episodes associated with bipolar II disorder.

Methods: Trials enrolled adults (18-75 years) with a clinical diagnosis of bipolar I or bipolar II disorder who were experiencing an MDE (Montgomery-Åsberg Depression Rating Scale [MADRS] Total score ≥20 and Clinical Global Impression Scale-Bipolar Version-Severity [CGI-BP-S] score ≥4 at screening and baseline). Patients in each trial were stratified by their bipolar I or bipolar II disorder diagnosis. Lumateperone 42 mg was administered once daily in the evening.

This post hoc analysis pooled efficacy data for the intent-to-treat (ITT) population and subgroup of patients with bipolar II disorder from 3 short-term, 6-week, placebo-controlled studies. Study 401 (NCT02600494) and Study 404 (NCT03249376) investigated lumateperone 42-mg monotherapy and Study 402 (NCT02600507) assessed lumateperone 42 mg adjunctive to lithium or valproate.

Assessments included change from baseline in MADRS Total score, CGI-BP-S Total score, CGI-BP-S subscores (Depression, Overall Bipolar Illness, and Mania), and Quality of Life Enjoyment and Satisfaction Questionnaire-Short Form (Q-LES-Q-SF) percent score.

Results: The pooled ITT population comprised 1,067 patients with bipolar I or bipolar II disorder (placebo, 539; lumateperone, 528). Lumateperone 42 mg significantly improved symptoms of depression in the ITT population compared with placebo, as measured by the change from baseline to Day 43 in MADRS Total score (least squares mean difference vs placebo [LSMD], −2.5; 95% confidence interval [CI] −3.8, −1.2; P<.001). In the 174 patients (16.3%) with bipolar II disorder (placebo, 87; lumateperone, 87) lumateperone also significantly improved MADRS Total score from baseline to Day 43 compared with placebo (LSMD, −4.0; 95% CI −7.2, −0.7; P<.05), with significant improvements beginning at Day 22 (P<.05). In patients with bipolar II disorder lumateperone significantly improved illness severity at Day 43 compared with placebo as measured by CGI-BP-S Total score (LSMD, −1.0; 95% CI −1.8, −0.2; P<.05), CGI-BP-S Depression subscore (LSMD, −0.5; 95% CI −0.9, −0.1; P<.05), and CGI-BP-S Overall Bipolar Illness subscore (LSMD, −0.5; 95% CI −0.9, −0.1; P<.05); change from baseline to Day 43 in CGI-BP-S Mania subscore was minimal with lumateperone treatment compared with placebo (LSMD, −0.0; 95% CI −0.2, 0.1; P=.61). Lumateperone 42 mg also significantly improved quality of life in the bipolar II disorder subgroup, as measured by Q-LES-Q-SF percent score compared with placebo at Day 43 (LSMD, 6.3; 95% CI 1.1, 11.4; P<.05).

Conclusion: In adults with bipolar II disorder experiencing an MDE, short-term treatment with lumateperone 42 mg as monotherapy or as adjunctive therapy significantly improved symptoms of depression, disease severity, and quality of life.

T16. LUMATEPERONE IN THE TREATMENT OF MAJOR DEPRESSIVE EPISODES ASSOCIATED WITH BIPOLAR I OR BIPOLAR II DISORDER: EVALUATION OF EXTRAPYRAMIDAL AND MOTOR SYMPTOMS IN LATE-PHASE CLINICAL TRIALS

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Abstract: Background: Atypical antipsychotics with high dopamine D2 receptor occupancy (65%-80%) are associated with an increased risk of extrapyramidal symptoms (EPS). Lumateperone is an FDA-approved antipsychotic to treat schizophrenia and depressive episodes associated with bipolar I or bipolar II disorder as monotherapy and as adjunctive therapy with lithium or valproate. Lumateperone has a low D2 receptor occupancy (~39%) at the recommended 42-mg dose. This analysis evaluated EPS across short- and long-term studies of lumateperone in patients with bipolar depression.

Methods: All trials enrolled adults (18-75 years) with bipolar I or bipolar II disorder experiencing a major depressive episode (Montgomery-Åsberg Depression Rating Scale Total score ≥20 and Clinical Global Impression Scale-Bipolar Version-Severity score ≥4). Lumateperone 42 mg was administered once daily in the evening.

This analysis included 3 groups: (1) data pooled from 2 short-term, 6-week, placebo-controlled studies of lumateperone 42-mg monotherapy (Study 401 [NCT02600494]; Study 404 [NCT03249376]); (2) a 6-month open-label extension period (OLE) of Study 401 that evaluated long-term effects of lumateperone 42-mg monotherapy; (3) a Phase 3 placebo-controlled study (Study 402, NCT02600507) that investigated lumateperone 42-mg therapy adjunctive with lithium or valproate.

Incidence and severity of EPS-related treatment-emergent adverse events (TEAEs) and changes in the clinician-rated Abnormal Involuntary Movement Scale (AIMS), Barnes Akathisia Rating Scale (BARS), and Simpson Angus Scale (SAS) were reported.

Results: The short-term safety population comprised 746 patients in pooled monotherapy trials (placebo, 374; lumateperone, 372) and 352 patients in the adjunctive study (adjunctive placebo, 175; adjunctive lumateperone, 177). In the short-term studies, the only EPS-related TEAEs reported were 1 patient (0.3%) with mild dyskinesia on lumateperone monotherapy, 1 patient (0.6%) with mild akathisia on adjunctive lumateperone, and 1 patient (0.3%) with severe akathisia on placebo in the monotherapy trials. Benztropine and propranolol use was rare (<1% in any group). Mean changes from baseline in AIMS, BARS, and SAS scores were similar across short-term trial groups. In patients without baseline parkinsonism (SAS ≤3), SAS-confirmed incidences of parkinsonism (SAS >3) were rare in monotherapy (placebo, 1/347 [0.3%]; lumateperone, 2/327 [0.6%]) and adjunctive therapy (placebo, 1/168 [0.6%]; lumateperone, 2/168 [1.2%]). In patients without baseline akathisia (BARS ≤2), BARS-confirmed akathisia (BARS >2) was also rare for monotherapy (placebo, 2/353 [0.6%]; lumateperone, 0/334 [0%]) and adjunctive therapy (placebo, 2/170 [1.2%]; lumateperone, 2/168 [1.2%]).

The long-term OLE safety population comprised 127 patients. There was a low incidence of EPS-related TEAEs, with 2 patients (1.6%) experiencing akathisia of mild and moderate severity. Rates of concomitant benztropine (1.6%) and propranolol (0%) use were low. There were no notable changes (no increases) in AIMS, BARS, or SAS scores during 6 months of treatment and no SAS-confirmed incidences of parkinsonism (SAS >3, 0/122 [0%]). BARS-confirmed akathisia (BARS >2) occurred in 3 of 122 patients (2.5%) without baseline akathisia (BARS ≤2).

Conclusion: In patients with bipolar depression, lumateperone 42-mg monotherapy or adjunctive therapy had a favorable EPS profile in both acute and long-term treatment.

T17. OLDER AGE OF FIRST PSYCHIATRIC HOSPITALIZATION AND LOWER RATES OF DEPRESSION SPECTRUM, ATTENTION DEFICIT AND HYPERACTIVITY COMORBID DISORDERS AND NICOTINE USE ARE ASSOCIATED WITH ABRUPT ONSET MANIA: A COMMUNITY-BASED COHORT STUDY

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Abstract: Background: The Kraepelin dichotomy of dementia praecox and manic-depressive illness, in part, is related to time from initial symptom presentation to full episode severity. The insidious vs abrupt onset of schizophrenia and mania respectively has been less distinct in recent investigations. Our community based epidemiological cohort reported similar prodrome duration for bipolar disorder (BD) (7.39 ± 6 years) and schizophrenia (8.2 ± 6 years). This secondary post-hoc analysis was conducted to identify clinical correlates of abrupt onset mania, often referred to classic BD type-I or Cade's illness.

Methods: Using the Rochester Epidemiology Project data, we identified retrospectively a cohort of BD-I adult patients born after 1985 in Olmsted County, MN. We examined prodrome duration and defined shorted and longer durations before first episode mania using the median 33.3 percentile of prodrome (11.4 months). Then, we compared sociodemographic and clinical correlates between the two groups by bivariate methods and multivariable logistic regression modeling to examine clinical predictors independently associated with either prodromes.

Results: 74 patients with BD-I (mean age 21.3±3.6 years, 39% female, 24% non-White) were identified. Compared to BD patients with a longer prodrome phase, those with shorter prodrome had an older age of first hospitalization (16.5±4.5 vs. 19.1±0.5, p=0.041). In addition, those with shorter prodrome had lower Mood total Sum scores (1.96±2.2 vs. 3.46±1.89, p=0.005), nicotine use (9.5% vs. 32.4%, p=0.05), and lower prevalence of previous psychiatric diagnosis such as: ADHD (4.1% vs. 27%, p=0.008), anxiety disorders (9.5% vs. 32.4%, p=0.05), depressive disorder spectrum (12.2% vs. 51.4%, p<0.001) and adjustment disorders (5.4% vs. 31.1%, p=0.006). Binary logistic regression analysis identified depressive disorder spectrum (OR=0.25, 95% CI 0.07-0.89, p=0.032) and ADHD (OR=0.22, 95% CI 0.05-0.98, p=0.047) differentiated short vs. long prodrome.

Conclusion: BD patients with abrupt onset mania displayed an older age of first hospitalization, lower rates of nicotine use and lower prevalence of ADHD and depressive disorder spectrum. Importantly, ADHD and higher rates of depressive spectrum disorders before first episode mania can result in a longer prodromal phase and earlier age of first psychiatric hospitalization. Their clinical recognition could guide early intervention strategies and tailor adequate management of this prodrome phase.

T18. "TELEPSYCHIATRY FOR BIPOLAR DISORDER: A SYSTEMATIC REVIEW OF THE LITERATURE"

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Abstract Introduction: Bipolar (BP) disorder is a highly morbid disorder that is often misdiagnosed or undiagnosed and affects a large number of adults and children. Due to the COVID-19 public health emergency stay at home orders, most outpatient mental health care was provided via telepsychiatry, and the many benefits of virtual care ensure that this will continue as an ongoing practice. The main aim of this review was to investigate what is currently known about the use of telepsychiatry services in the diagnosis and treatment of BP disorder across the lifespan.

Methods: A systematic literature review assessing the use of telepsychiatry in BP disorder was conducted in PubMed, PsychINFO, and Medline.

Results: Six articles were included in the final review. All included articles assessed populations aged 17 years or older. The literature indicates that BP disorder was addressed in telepsychiatry services at a similar rate as in-person services, reliable diagnoses can be made using remote interviews, satisfaction rates are comparable to in-person services, telepsychiatry services are able to reach and impact patients with BP disorder, are sustainable, and patient outcomes can improve using a telepsychiatry intervention.

Conclusion: Given the morbidity of BP disorder, the research addressing the telepsychiatry diagnosis and treatment of BP disorder is sparse, with only emerging evidence of its reliability, effectiveness, and acceptance. There is no research assessing the safety and efficacy of telepsychiatry in pediatric populations with BP disorder. Giver the morbidity associated with BP disorder at any age, further research is needed to determine how to safely and effectively incorporate telepsychiatry into clinical care for BP adult and pediatric patients.

T19. SAFETY AND EFFICACY OF SYNTHETIC PSILOCYBIN IN BIPOLAR TYPE II DEPRESSION: AN OPEN LABEL TRIAL

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Abstract Treatment options are limited for patients with bipolar depression. With accelerating interest in the use of psychedelics in difficult to treat mood disorders and early evidence of efficacy along with safety, the question is raised as to whether some patients with cyclical mood disorders may also benefit. Given the limited treatment options for patients with bipolar type II depression, novel therapies are urgently needed.

Methods: Fifteen adults (9 female, 6 male)(mean age 38.4 SD=11.6) with bipolar type II depression who had failed at least two medications in the current episode, without rapid cycling by history, and no history of mania or psychoses were recruited to be dosed with a single 25 mg dose of a proprietary synthetic psilocybin (COMP360) after withdrawal from psychotropic medication for two weeks prior to dosing. All subjects had three preparatory psychotherapy sessions prior to dosing and three integration sessions post dosing. Subjects were followed for 12 weeks post dose. The primary outcome measure was the Montgomery Asberg Depression Rating Scale at three weeks post dose. Response was defined as a MADRS score reduction of >50% since baseline and remission as a score of <10. Safety was captured by the Young Mania

Rating Scale (YMRS), to observe for any manic or hypomanic activation and the Columbia Suicide Severity Rating Scale (CSSRS) to assess any increased suicidality. Each were performed at each visit.

Results: At the 3 week primary outcome measure 12/15 (80%) participants met response criteria and 11/15 (73.3%) showed remission. At week 12 (end of study) 80% of participants were both remitters and responders. The effect of treatment in the overall mixed-effects model of repeated measures was significant at $p<0.0001$. One participant discontinued the study at week 6 due to a return of depression. There were no unexpected adverse events. Across 12 weeks, 13 of 14 (92.9%) remaining subjects showed a decrease or no change in YMRS scores. YMRS scores at all visits were below the threshold for hypomanic criteria. Across 12 weeks, 13 of 14 (92.9%) remaining subjects showed a decrease or no change in suicidal ideation severity or intensity. No subjects developed hypomania or mood instability as confirmed by no increase in scores on the YMRS or the CSSRS from baseline. There was a suggestive treatment effect of decreasing manic symptoms ($p=0.058$). Most participants were able to stay off psychotropic medications other than resuming mood stabilizers prophylactically after week 3. Two subjects with some mild increase in depressive symptoms after week 3 resumed antidepressant medication with positive effect.

Conclusion: In this small, open-label pilot study, most subjects reported significant improvement in chronic depressive symptoms with durability lasting for the three months they were followed post dosing. There was no evidence for inducing mania, agitation or insomnia in this vulnerable population. While this is too small a population to provide clear evidence, this study supports further investigation in the use of psychedelics in bipolar type II depression.

T20. A VALIDATED RATING SCALE TO ACCURATELY DETERMINE THE TREATMENT EFFECTS IN CHILDHOOD ONSET FLUENCY DISORDER (STUTTERING)--THE MLGSS.

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Abstract: Childhood Onset Fluency Disorder (COFD), commonly known as Stuttering, is a neuropsychiatric condition that affects over one percent of our population yet no FDA approved treatments exist. Speech therapy yields limited results in improving the symptoms of stuttering with high relapse rates and poor patient adherence (non-natural flow of speech.) Emerging data reveal that stuttering is related to disturbances in basal ganglia function under the influence of dopamine activity. Several trials in the past have shown antipsychotic agents (typical and atypical--Dopamine 2) to be effective in reducing the severity of stuttering. However, no such agent has ever been developed through formal FDA registration trials for this indication. Past trials of pagoclone (GABA-A) and Ecopipam (D1 antagonist), formal Phase II trials, did not achieve statistical superiority over placebo in adults who stutter. These studies were challenged by the high variability of the stuttering condition and poor reliability of the scales utilized. The primary endpoint utilized, the SSI-4 (Stuttering Severity Instrument-4), is a scale that captures a point in time via a ten minute speech sample, which is repeated throughout the trial. Stuttering severity commonly worsens in stressful, novel situations and the SSI-4 is hampered by the subject's accommodation to the clinic/research setting and is thus subject to expectation bias and placebo response. In addition, stuttering is a quite variable condition with fluctuations

common throughout the day or among days. Patient rated scales thus better reflect the longitudinal course of stuttering and directly reflect the patient's own perception of their condition. A commonly used scale in stuttering assessment, the OASES, (secondary endpoint in the Ecopipam trials) although subject rated, is not reliable to measure treatment effects over time given its lengthy nature (100 questions for the adult version--subject rater fatigue.) A more compact subjective measure, the SSS, also a secondary endpoint in the above trials, yielded more reliable results than the above scales but it too is limited by several factors including that the items are unstructured and not standardized as to the time (e.g. "today's session" vs. "last week.")

To overcome our unmet medical need in developing viable treatments for our stuttering community, Maguire, Leal and Garibaldi created the MLGSS (Maguire, Garibaldi, Leal Stuttering Scale), a 10 item, subject rated assessment of their own stuttering and its impact over the prior week. The MLGSS has now been validated as a reliable measure to assess clinically meaningful change in stuttering. Twenty adult subjects who stutter participated in the validation trial (16 biologic/identified male/4 biologic/identified female--in line with the general population ratio.) The scale yielded excellent face and content validity and good to excellent test to retest reliability (ICC for total score 0.83 and ICC for the global item 0.90.) The scale also exhibits high construct with all items highly correlated to the total score. A further validation study of the ability of the MLGSS to measure treatment effects over time is currently being conducted in the Orpheus study which is a trial of gemlapodenct (NOE-105), a PDE-10A inhibitor, in a double-blind placebo-controlled, multicenter Phase II trial for the treatment in COFD (stuttering.)

T21. REPLICATING AND EXTENDING THE RELIABILITY, CRITERION VALIDITY, AND TREATMENT SENSITIVITY OF THE PANSS10 AND PANSS20 FOR PEDIATRIC TRIALS

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Abstract: Background: Pediatric studies of schizophrenia have relied on the 30-item Positive and Negative Syndrome Scale (PANSS) as a primary outcome measure. There have been many efforts to create shorter versions of it to reduce costs and burden while keeping good reliability and validity. The present aim is to conduct a confirmatory investigation of the reliability and validity of 10 and 20 item abbreviated versions developed in another pediatric sample that reflect the five-factor structure underlying the PANSS, adding more detailed examination of patient-level score reproducibility.

Methods: We applied the same psychometric and treatment sensitivity analyses as in Findling et al., (2023) to an international placebo-controlled adolescent schizophrenia paliperidone randomized clinical trial, accessed via the YODA secure data environment. Analyses included confirmatory factor analyses, graded response models, omega reliability coefficients, tests of convergent criterion validity, sensitivity to change, and Bland-Altman plots to evaluate score reproducibility.

Results: Using the paliperidone RCT dataset, the 10-item or 20-item vs. 30-item versions had similar average interitem correlations (.11 to .15), ωTotal reliabilities of .78 to .89 with reliability >.80 across patient presentations from mild residual symptoms to severe pathology,

correlations of .92 and .98 with the 30-item total, partial eta-squared values for time, treatment, and time x treatment, and similar correlations with CGI-severity and CGAS ratings. Patient scores differed by 0.04 points on average on the 10- and 0.01 for the 20-item version versus the 30-item, all not significant.

Conclusion: The 10- and 20-item PANSS short forms replicated strong reliability and validity in a large international RCT. Besides replication and generalization to an international sample, findings extend prior work by being the first to apply modern reliability models (omega) for multi-factor composites, also using Bland-Altman methods to evaluate patient-level score reproducibility. Scores based on the 10- or 20-item version reproduce traditional scores with high fidelity, offering substantial savings in terms of time, cost, and burden, especially when used for tracking progress or outcomes.

T22. ADMINISTRATING AND TRAINING ON THE PLACEBO-CONTROL REMINDER SCRIPT: A DEEPER DIVE INTO THE TOOL'S PSYCHOMETRIC PROPERTIES

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Abstract: Introduction: Placebo and nocebo responses continue to hinder potential treatment effects (Haflioadottir et al., 2021). The Placebo-Control Reminder Script (PCRS; Cohen et al., 2020) is the only empirically-validated tool found to significantly mitigate these phenomenon by reviewing factors causing placebo responses (Evans et al., 2021). The PCRS is read by the site rater to each participant throughout the study and assesses participants' comprehension. The PCRS has been sponsor licensed in over 25 clinical trials. Assessing this tool's face and content validity is essential for further substantiating its instrument properties (American Educational Research Association, 2014). PCRS raters were surveyed about their training and the effectiveness of the PCRS's content, structure, phrasing, length, and administration process to mitigate placebo and nocebo responses. This gold standard method for obtaining these validities (Beck and Robert, 2001; Parrott, 1991) also addresses sponsors' questions regarding the tool's operational integration into trials.

Methods: The PCRS User Survey assessed face and content validity, with four placebo/nocebo content experts confirming this goal. The survey contained four demographic questions, ten 5-point Likert items regarding raters' views about training and face/content validity principles, and three open-ended questions. Sponsors who licensed the PCRS since 2017 agreed to (a) send us the email addresses of the PCRS raters to be emailed a link to the SurveyMonkey questionnaire, or (b) send the survey link by the sponsor. Raters were informed of why they were receiving the survey, how their email addresses were obtained, the voluntariness and anonymity of survey completion, and the 5-minute duration of completion.

Results: The survey was completed by 169 raters (39% male and 61% female), with a majority (68%) working in the industry for at least 6 years and thus having ample experience to comment on the PCRS. A majority (56%) administered the tool for at least 2 years, and most used the PCRS in depression (78%) and schizophrenia (45%) trials. Rater response rate could not be specifically calculated because three sponsors sent the survey directly to raters without

providing us their email addresses, but we estimate the total survey response to be 70%. Using a chi-square test, significantly more raters reported the PCRS has appropriate wording, phrasing, content, and length aimed to reduce the placebo effect, successfully assesses participants' PCRS understanding, is a better strategy than others used in the industry to reduce the placebo and nocebo effect, and would not revise anything in the PCRS (all factors yielded $p<.001$). A Pearson coefficient indicated a significant positive relationship between years administering the PCRS and its ease of use ($r=.27$; $p=.001$), phrasing/wording ($r=.17$; $p=.03$), and length ($r=.20$; $p=.008$) which all complemented the tool's intent. Significantly more raters confirmed the PCRS training was sufficient to administer the tool and that the PCRS integrated well into study procedures (all were $p<.001$).

Discussion: A survey of experienced trial raters provided significant evidence for the PCRS's face and content validity, noting that the instrument's language is suitable to address its aim and the content effectively represents what it purports to mitigate. Raters who administered the PCRS longer had greater understanding of the tool's principles than those with less years using it. Sponsors can be assured the scale does not hinder study processes.

T23. RISK OF DRUG OVERDOSE FOLLOWING SIMULTANEOUS BENZODIAZEPINE AND SSRI TREATMENT IN YOUNG ADULTS

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Abstract: Background: Benzodiazepines (BZD) and selective serotonin reuptake inhibitor (SSRI) antidepressants are sometimes prescribed concurrently for treating anxiety or depressive disorders. However, the literature on the safety of simultaneous BZD and SSRI prescribing is limited, with BZDs carrying a risk of drug overdose when taken with other central nervous system depressants. We aimed to examine the risk of drug overdose following simultaneous BZD and SSRI treatment compared to SSRI treatment alone in young adults with depression or anxiety.

Methods: The study utilized two nationwide administrative claims databases covering privately (MarketScan, 1/1/2009 to 12/31/2018) and publicly (Medicaid TAF, 1/1/2015-12/31/2016) insured young adults aged 18-29 years. We included young adults with depression or anxiety diagnoses newly initiating prescription SSRI treatment without prior BZD or SSRI prescriptions in the previous year. Young adults initiating a BZD on the same day as SSRI initiation were considered simultaneous initiators ('BZD+SSRI'). Individuals without a BZD fill were considered to have initiated an SSRI alone (SSRI-only). Medically treated drug overdose events were identified from emergency department (ED) and inpatient encounters during 6 months following treatment initiation defined through ICD codes. Crude and adjusted cumulative incidence and hazard ratios (HR) were estimated. Propensity score inverse probability of treatment weighting was applied for adjusted estimates.

Results: The study cohort included 468,896 privately insured young adults (12% initiating BZD+SSRI treatment) and 86,845 publicly insured young adults (7% initiating BZD+SSRI). Crude incidence of drug overdose was 0.96% (BZD+SSRI) vs. 0.73% (SSRI-only) in the privately insured cohort and 1.57% (BZD+SSRI) vs. 1.23% (SSRI-only) in publicly insured cohort. After propensity-score adjustment, young adults initiating BZD+SSRI treatment had an increased risk of drug overdose compared to initiators of SSRI-only treatment: privately insured cohort, adjusted HR=1.99 (95%CI:1.77-2.25), publicly insured cohort, HR=1.92 (1.42-

2.59). In a sub-analysis separately evaluating intentional (50-58% of overdose events) and unintentional drug overdoses, the association between BZD+SSRI vs. SSRI-only treatment and drug overdose was greater for intentional drug overdoses (privately insured, HR=1.75, 1.25-2.45; publicly insured, HR=2.21, 1.46-3.34) than for unintentional drug overdoses (HR=1.19, 0.80-1.79; HR=1.42, 0.87-2.31, respectively).

Conclusions: In young adults with depression or anxiety, we observed an association of drug overdose with simultaneous BZD+SSRI treatment vs. SSRI-only treatment. This association was seen in both publicly and privately insured individuals. Residual confounding by illness severity may be present. Still, the observed association warrants further investigation as it may represent an important safety consideration for simultaneous BZD+SSRI prescribing.

T24. USING THE KETOGENIC DIET AS AN INTERVENTION TO TREAT CHRONIC MENTAL DISORDERS

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Abstract: Purpose: To identify the clinical impact of using the ketogenic diet to treat chronic psychiatric disorders.

Content: Nutritional interventions are a unique and promising non-pharmacological approach to chronic mental illness. A significant body of evidence supports the efficacy of the ketogenic diet (KD) in treating neurologic disorders such as epilepsy, Alzheimer's disease, autism spectrum disorder, and multiple sclerosis. The ketogenic diet has been an evidence-based treatment for children and adults with epilepsy for over 100 years. It does not appear a coincidence that we commonly use anticonvulsant medications, such as topiramate, lamotrigine, valproate, carbamazepine, clonazepam, and others, to treat psychiatric disorders. While we do not fully understand what causes brain dysregulation associated with chronic mental disorders, key pathophysiological underpinnings have been identified that are associated with brain dysfunction. The KD is hypothesized to target inflammation, oxidative stress, glucose hypometabolism, and neurotransmitter imbalance. While most treatments of chronic mental disorders have focused on monoaminergic function, aiming at symptomatic control, the KD is thought to affect and improve the brain's metabolic function. It has been postulated that mitochondrial dysfunction is responsible for impairments in neuroplasticity and synaptogenesis that contribute to mental illness.

Methods: Using the Johns Hopkins Nursing Evidence-Based Practice Model as a guideline, this literature review focused on the research query, "What is the clinical impact of using the ketogenic diet when treating patients with chronic mental illness?"

Findings: A total of 13 articles met the inclusion criteria for this literature review. The articles ranged from 2013- 2021. The following themes were identified from the analysis of these articles: (1) the potential impact of the KD on psychiatric disorders due to the association of underlying metabolic pathophysiology of neurological disorders and psychiatric disorders (2) addressing other causes of brain dysregulation such as inflammation, oxidative stress, hypometabolism of glucose and neurotransmitter imbalances (specifically GABA and glutamate) (3) recognition that current mainstream treatments that solely target the monoaminergic system are limited in treating chronic psychiatric disorders

Results: A growing body of evidence suggests that ketogenic diets effectively manage epilepsy, autism spectrum disorder, multiple sclerosis, and Alzheimer's disease. As mental illnesses share common underlying metabolic diseases with these diseases, it is not surprising that emerging clinical evidence suggests that ketosis may play a role in treating mental illnesses. Furthermore, early clinical evidence supports the KD in treating schizophrenia, bipolar disorder, major depressive disorder, attention deficit hyperactivity disorder, and binge eating disorder. The lack of randomized, controlled clinical trials is the challenge in making a definitive judgement regarding the efficacy of the ketogenic diet in the treatment of psychiatric diseases.

Importance: In 2020, an estimated 14.2 million adults aged 18 or older in the United States with serious mental illness. This number represented 5.6% of all U.S. adults. Unfortunately, traditional psychiatric treatment approaches that target the monoaminergic system have been insufficient. Thus, the field of psychiatry must embrace the concept of brain metabolism, which when addressed, can improve mitochondrial function, neuroplasticity, and synaptogenesis leading to better outcomes for patients with chronic mental illness.

T25. EXCESSIVE DAYTIME SLEEPINESS IN A REAL-WORLD STUDY OF PARTICIPANTS WITH OBSTRUCTIVE SLEEP APNEA WITH OR WITHOUT COMORBID DEPRESSION

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Abstract: Background: Obstructive sleep apnea (OSA) is a sleep disorder that is often comorbid with psychiatric disorders. Excessive daytime sleepiness (EDS) is common in both psychiatric disorders and OSA. In patients with OSA, EDS can persist despite use of positive airway pressure (PAP) therapy. This study aimed to describe EDS and its relationship with PAP use in participants with and without depression.

Methods: US adult residents with OSA completed a survey in Evidation Health's Achievement app assessing sleepiness (Epworth Sleepiness Scale [ESS]) and PAP usage. ESS score >10 defined EDS. A linear model assessed relationships between PAP use and ESS score.

Results: 2289 participants completed the survey. Anxiety and depression were the most common comorbidities and were more common in participants with EDS (49% and 49%) than those without EDS (41% and 37%). Overall, EDS was more common among participants with comorbid depression (49%) than those without (38%), even among highly adherent PAP users (46% vs 30%). In a linear model, each 1 h/night of PAP use was associated with lower ESS scores in participants without depression (n=928; estimate [SE], −0.42 [0.09]; $P<0.05$), but not in those with depression (n=661; estimate [SE], −0.15 [0.10]; $P>0.05$).

Conclusions: In this real-world population of participants with OSA, those with EDS were more likely to have comorbid anxiety or depression. EDS was more common in participants with comorbid depression than those without, even with PAP use. PAP use was associated with lower ESS scores in participants without comorbid depression, but not in those with comorbid depression.

Support: Axsome Therapeutics and Jazz Pharmaceuticals

T26. EFFICACY, SAFETY AND TOLERABILITY OF BREXPIPRAZOLE FOR THE TREATMENT OF AGITATION IN ALZHEIMER'S DEMENTIA: A 12-WEEK, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL, AND A 12-WEEK EXTENSION TRIAL

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Abstract: Background: Agitation is common in Alzheimer's dementia, and is one of the most challenging aspects of care. There are currently no FDA-approved pharmacological treatments for agitation associated with Alzheimer's dementia. Two prior trials suggested that brexpiprazole 2 mg/day is efficacious and well tolerated in patients with agitation in Alzheimer's dementia. This poster presents data from two further 12-week trials of brexpiprazole – a third double-blind, placebo-controlled trial (results previously reported), and a 12-week active-treatment extension trial.

Methods: The third placebo-controlled trial was a 12-week, multicenter, randomized, double-blind, parallel-arm trial (NCT03548584). Eligible patients were aged 55–90 years, in a care facility or community-based setting, had a diagnosis of probable Alzheimer's disease, and met criteria for agitation (International Psychogeriatric Association [IPA] criteria). Patients were randomized 2:1 to brexpiprazole (further randomized 1:2 to fixed-dose 2 mg/day or 3 mg/day) or placebo. Stable background medications for Alzheimer's disease were permitted. Efficacy was assessed by the change from baseline to Week 12 in Cohen–Mansfield Agitation Inventory (CMAI) Total score and in Clinical Global Impression − Severity of illness (CGI-S) score as related to agitation. Safety was assessed using standard variables, including treatment-emergent adverse events (TEAEs), vital signs, laboratory evaluations, body weight, and cognition. The 12-week, single-arm extension trial (NCT03594123) enrolled eligible patients who completed treatment with brexpiprazole or placebo in the above placebo-controlled trial. In the extension trial, patients received brexpiprazole 2 or 3 mg/day; patients previously randomized to brexpiprazole continued on their previous dose, and patients previously randomized to placebo were initiated on brexpiprazole. Dosing was blinded, and dose adjustments were permitted. The primary objective was to assess long-term safety and tolerability, with a particular focus on known safety issues for antipsychotics. Efficacy was evaluated by change in CMAI Total score, and in CGI-S score as related to agitation.

Results: In the third 12-week placebo-controlled trial, a total of 345 patients were randomized. The mean change from baseline to Week 12 in CMAI Total score was greater with brexpiprazole versus placebo (p=0.0026), and similarly for CGI-S score as related to agitation (p=0.0078). The incidence of TEAEs was 40.7% in the brexpiprazole group, and 31.0% in the placebo group. Aside from headache, no other TEAE had an incidence ≥5% in the brexpiprazole group (2 or 3 mg/day), or in either brexpiprazole dose group. There was one death (a patient randomized to brexpiprazole 3 mg/day), which was considered unrelated to brexpiprazole. The 12-week extension trial enrolled 259 patients (prior brexpiprazole, n=163;

prior placebo, n=96). A total of 5% of patients discontinued due to AEs. The overall incidence of TEAEs was 25.9% (prior brexpiprazole, 25.2%; prior placebo, 27.1%). TEAEs with an incidence ≥2% were headache (3.5%) and fall (2.3%). There were no deaths. In exploratory efficacy analyses, CMAI Total score and CGI-S score as related to agitation improved throughout the trial – in the prior brexpiprazole subgroup, and in the prior placebo subgroup.

Conclusion: Data suggest that brexpiprazole 2 or 3 mg/day is efficacious on symptoms of agitation in Alzheimer's dementia, with continued improvement for up to 24 weeks (as measured by CMAI Total score, and CGI-S score as related to agitation). In both trials, brexpiprazole was well tolerated, which is of particular importance in this vulnerable patient population.

T27. EFFECTS OF BREXPIPRAZOLE ACROSS AGITATION BEHAVIORS IN ALZHEIMER'S DEMENTIA: COHEN–MANSFIELD AGITATION INVENTORY FACTOR SCORES FROM TWO PHASE III FIXED-DOSE TRIALS

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Abstract: Background: Agitation is a prevalent clinical manifestation of Alzheimer's dementia, for which brexpiprazole has been investigated as a potential treatment. In the brexpiprazole clinical trials of agitation in Alzheimer's dementia (AAD), the Cohen–Mansfield Agitation Inventory (CMAI) was used to evaluate changes in patients' agitation. The CMAI evaluates the frequency of 29 agitated behaviors, 22 of which can be grouped into three factors: 1. Aggressive behaviors (12 items); 2. Physically non-aggressive behaviors (6 items); 3. Verbally agitated behaviors (4 items). CMAI factors provide a framework to enable improved understanding and reporting of agitation behaviors in dementia. This poster presents CMAI factor data for brexpiprazole (2 or 3 mg/day) and placebo, from two fixed-dose trials.

Methods: The two fixed-dose trials were Phase III, 12-week, randomized, double-blind, placebo-controlled, parallel-arm trials of brexpiprazole versus placebo in patients with AAD (NCT01862640, NCT03548584). The first fixed-dose trial investigated doses of brexpiprazole 1 and 2 mg/day and the second investigated doses of 2 and 3 mg/day. The primary endpoint was the change in CMAI Total score from baseline to Week 12. Secondary efficacy endpoints included change in CMAI Factor 1, 2, and 3 scores. In post hoc analyses of the first fixed-dose trial, efficacy outcomes were also evaluated in a subgroup of patients who met criteria for baseline agitation and aggressive behavior (defined using CMAI Factor 1), which were pre-specified inclusion criteria for the second fixed-dose trial.

Results: In the first fixed-dose trial, 140 patients were randomized to brexpiprazole 2 mg/day, and 136 patients were randomized to placebo. Brexpiprazole 2 mg/day separated from placebo on the primary endpoint (p=0.040; reported elsewhere). There were numerically greater least squares mean changes from baseline to Week 12 in CMAI Factor 1, 2, and 3 scores with brexpiprazole 2 mg/day versus placebo (treatment differences -0.97 [p=0.15], -1.18 [p=0.09], and -1.26 [p=0.0153], respectively). In the subgroup of patients who met criteria for baseline agitation and aggressive behavior, corresponding treatment differences versus placebo at Week 12 were -1.37 (p=0.0688), -1.68 (p=0.0208), and -1.64 (p=0.0034), respectively. In the second

fixed-dose trial, 228 patients (all of whom met inclusion criteria for baseline agitation and aggressive behavior) were randomized to brexpiprazole 2 or 3 mg/day, and 117 patients were randomized to placebo. Brexpiprazole 2 or 3 mg/day separated from placebo on the primary endpoint (p=0.0026; reported elsewhere). CMAI Factor 1, 2, and 3 scores showed greater least squares mean changes from baseline to Week 12 with brexpiprazole 2 or 3 mg/day versus placebo (treatment differences -1.95 [p=0.0040], -1.41 [p=0.0296], and -1.24 [p=0.0113], respectively).

Conclusion: In two trials of patients with AAD, fixed-dose brexpiprazole 2 or 3 mg/day was associated with numerically greater improvements than placebo across the three distinct CMAI factors of Aggressive behaviors, Physically non-aggressive behaviors, and Verbally agitated behaviors.

T28. EQUITABLE PRICING OF A NOVEL ANTI-ALZHEIMER'S THERAPEUTIC: YOUR VIEWPOINT DETERMINES YOUR VIEW

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Abstract Purpose: The January 6, 2023 expedited FDA approval of lecanemab (Leqembi™), a novel disease-modifying treatment for MCI-early-Alzheimer's, generated debate and controversy over its initial pricing. We analyzed the top seven global pricing models, including comparisons with other indications. It seems quite possible that payers may be paying substantially more for essentially equal benefit(s) in one disease versus another.

Content: Our analysis of pricing models indicated that value-based pricing is the most popular paradigm. Measurement of outcomes and costs are essential ingredients for value-based pricing. In 2023 the five top-selling medicines for multiple sclerosis cost more than $64,000/yr. and the five top-selling medicines for cancer average more than $165,000/yr. While the Institute for Clinical and Economic Review (ICER) preliminarily affixed a "cost-effective" range of $8,500/yr. to $20,600/yr. for lecanemab, their analyses were based on preliminary and incomplete data. In contrast, Eisai's analysts reported that their medicine equated with a societal value of $37,000/yr. (1). There are alternative quantitative models and metrics that translate into substantially different valuations.

Methods: The clinical evaluation of anti-Alzheimer's medicines, as well as the usual regulatory review(s) of data, almost always include critically important statistical analyses of standardized validated scales, for both cognition and global function. More recently, with respect to potentially disease-modifying treatments, such as aducanumab (Aduhelm™) and lecanemab (Leqembi™), biomarker results such as PET-scans demonstrating amyloid removal have gained acceptance as well. Key aspects of the global function assessments include Activities of Daily Living (ADLs) and Instrumental Activities of Daily Living (IADLs). We believe that from both a patient's and caregiver's perspective, the value associated with one's sustained ability to perform IADLs and ADLs is of paramount importance and value.

Results: The International Consortium for Health Outcomes Measurement (ICHOM) notes that patient-centered outcome measures represent the ultimate measure of quality and they are always multidimensional. While the approval of aducanumab was, primarily, based mostly on biomarker (i.e., PET-scan) results, it was initially priced at $56,000/yr. and then reduced to $28,200/yr. In contrast, the lecanemab data were positive for cognition, global function and

PET-scans as well. It has been initially priced at $26,500/yr. One conceptual lens for valuation calculation is quality-adjusted life-years (QALYs). On a global perspective, amongst the industrialized nations, there are 2023 valuations ranging from $32,618/yr. as the lower end in Australia, to $98,158/yr. as the upper end in the United Kingdom. Here in the United States, there is an almost equally broad range of valuations based on services that may need to be provided by a Home Health Aide; for example, in Mercedes, Texas $36,408/yr. versus those same services being provided in Atherton, California $85,800/yr. (2).

Importance: It's quite possible that pricing-related valuations for anti-Alzheimer's medicines would be increased if their benefits could be more readily compared to medicines for other indications. Moreover, just as medicines may have different valuations in different countries, here in the US, the cost-benefit analysis of an anti-Alzheimer's medicine looks quite different based on the cost-of-living in one state versus another.

T29. A PREDICTION MODEL TO IDENTIFY CANDIDATES FOR ATYPICAL ANTIPSYCHOTIC ADJUNCTIVE TREATMENT OF MAJOR DEPRESSIVE DISORDER

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Abstract Introduction: Current guidelines recommend that patients with major depressive disorder (MDD) with partial or no response to antidepressant therapy should switch antidepressant therapies or augment with another medication. Augmentation with atypical antipsychotics (AAs) can be an effective treatment option in MDD yet is utilized infrequently or often delayed. This study aimed to develop and validate a claims-based prediction model to identify potential candidates of AA adjunctive therapy.

Methods: Adults (≥18 years) with ≥1 MDD diagnosis claim were selected from IBM® MarketScan® Research Databases (Commercial, Medicare, Medicaid). Patients were included in model development if they received AA adjunctive therapy as a second line of therapy (LOT) or later. A random subsample of an equal number of patients with at least one LOT who did not initiate AA adjunctive therapy within ≥36 months following their first MDD diagnosis were also included as a control group. The index date for the model was the end of the first LOT following initial MDD diagnosis. Patient demographics and clinical characteristics were assessed in the 6 months prior to index (baseline). Least absolute shrinkage and selection operator (LASSO) logistic regression models selected potential predictors (patient characteristics) of adjunctive AA use; the magnitude of selected predictors was assessed using odds ratios (OR) and p-values. Predictors with an OR <1.25 were excluded from the final parsimonious model. Model performance was assessed using area under the curve (AUC). The parsimonious prediction model was used to identify potential candidates for AA adjunctive therapy among patients with: MDD, at least one LOT, and unconfirmed receipt of AA adjunctive therapy within <36 months of follow-up (i.e., at-risk cohort).

Results: A total of 26,256 patients received AA adjunctive therapy in their second LOT or later. Patients with a first LOT duration of <30 days had 3.84 times higher odds of initiating AA augmentation versus patients with first LOT duration of ≥30 days (p<0.001). Additional

significant predictors of initiating AA adjunctive treatment were history of drug abuse (OR=1.83), severe/moderate MDD versus mild MDD close to the index date (OR=1.62), a psychiatric diagnostic evaluation (OR=1.62), anxiety disorders (OR=1.43), age of 18–34 years versus 35+ years (OR=1.39), post-traumatic stress disorder (OR=1.34), and baseline use of anticonvulsants (OR=1.30) or benzodiazepines (OR=1.25). The AUC of the final model was 0.75, indicating good discrimination. When applied to the at-risk cohort, the proportion of patients predicted as suitable candidates for AA adjunctive therapy after first LOT was 32%.

Conclusion: This prediction model identified several patient and clinical factors associated with adjunctive AA use. This evidence can help clinicians ensure timely receipt of therapy for patients who are likely candidates for AA adjunctive use.

T30. A PHASE 1 SAD AND MAD TRIAL OF EVX-101, A NOVEL GASTRO-RETENTIVE PROLONGED-RELEASE 5-HTP/ LOW-DOSE CARBIDOPA TABLET, IN HEALTHY SUBJECTS TAKING ESCITALOPRAM

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Abstract:Background: Inadequate response to antidepressant treatment (ADT) is a significant issue for many patients. Enhancing extracellular serotonin (5-HT) levels beyond that produced by serotonin-reuptake inhibitor ADTs may more effectively treat depression. EVX-101 is a novel gastro-retentive sustained-release tablet formulation of 5-hydroxytryptophan (5-HTP, 250 mg) plus low-dose carbidopa (CD, 0.3125-2.5 mg) under study as an adjunctive depression treatment. CD inhibits the enzyme that converts 5-HTP (the natural precursor of 5-HT) to 5-HT, resulting in more 5-HTP available for absorption. Coadministration of 5-HTP with very low-dose CD, magnitudes lower than used with L-DOPA in Parkinson's, enhances 5-HTP bioavailability many-fold when delivered in close spatial and temporal juxtaposition to the upper intestine (site of 5-HTP absorption). When added to existing ADT, EVX-101 amplifies brain 5-HT synthesis which may augment ADT response in inadequately treated patients.

Objective: Evaluate safety, tolerability, and PK of single-ascending (SAD) and multiple-ascending (MAD) BID (q12h) EVX-101 doses administered to healthy subjects taking escitalopram (ESCIT). Secondarily, to assess the effect of adjunctive EVX-101 on cortisol, a pharmacodynamic biomarker of acute elevations in brain extracellular 5-HT.

Methods: Double-blind, placebo (PBO)-controlled 2-part trial in which subjects randomly received EVX-101 or PBO (ratio 8:2 Part 1 SAD, 7:3 Part 2 MAD). ESCIT was dosed both pre-randomization (10 mg/day[d] x 7d then 20mg/d for 14d) and throughout randomized treatment (20 mg/d). In Parts 1 and 2 the 5-HTP total daily dose (TDD) was fixed at 500 mg (250 mg BID). Plasma 5-HTP levels were increased by escalating CD TDD. In Part 1, 2 cohorts (CD TDD 0.625 mg and 1.25 mg) were dosed BID for 1 day with PK profiling for 48h. In Part 2, 1 cohort was up-titrated weekly based on tolerability: CD TDD by week = 0.625 mg (DL1) → 1.25 mg (DL2) → 2.50 mg (DL3) →5.0 mg (DL4). PK profiling occurred on Day 1 and at steady state (SS) at each DL (Days 6, 13, 20, 27). Safety/tolerability was assessed via AEs, VS, ECGs, labs, PE, C-SSRS, and Hunter Criteria for Serotonin Toxicity.

Results: 34 randomized subjects received at least 1 dose of EVX-101 or PBO (SAD n=16; MAD n=18). No safety signals of concern were apparent, and no serious or severe AEs were reported. In Part 1 the max tolerated TDD (5-HTP/CD) was 500 mg/0.625 mg. Escalation stopped after the 500 mg/1.25 mg TDD due to dose-limiting GI-related AEs, primarily nausea/vomiting. Mean 5-HTP Cmax0-12 and AUC0-12 at that dose were 88.7 ng/mL and 445 ng.h/mL. GI AEs were also most frequent in Part 2; however, up-titration appeared to improve tolerability, allowing escalation to DL4 in over half (61%) of all subjects despite much higher SS 5-HTP levels upon repeated dosing (Rac≈3-5, DL1 D1 vs D6). At DL4 mean SS max 5-HTP levels (Cmax0-12=565 ng/mL) were ≈ 3 times higher than at DL1 (Cmax0-12=175 ng/mL). Serum cortisol levels generally increased in a dose-dependent manner in EVX-101 subjects, suggesting target engagement.

Conclusion: Escalating doses of adjunctive EVX-101 over 4 weeks appeared safe in healthy subjects treated with ESCIT. Tolerability of GI AEs, due to EVX-101's serotonergic mechanism, appeared to be improved by titration. Sustained target plasma 5-HTP levels were achieved at all DLs (mean Cavg 0-24 ≈100-300 ng/mL). Adjunctive EVX-101 showed evidence of target engagement, i.e., elevation of extracellular 5-HT beyond the ADT effect.

T31. A PROSPECTIVE, MULTI-CENTER, RANDOMIZED, CONTROLLED, BLINDED TRIAL OF VAGUS NERVE STIMULATION FOR DIFFICULT TO TREAT DEPRESSION: THE RECOVER TRIAL BASELINE DATA

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Abstract Background: Numerous studies demonstrate therapeutic Vagus Nerve Stimulation (VNS) efficacy in treatment-resistant major depression (TRD). The US FDA approved VNS for TRD in 2005. In 2007, the US Centers for Medicare and Medicaid Services (CMS) issued a "non-coverage decision", which limited access to VNS for TRD. In 2019, CMS requested a "coverage with evidence trial" to study VNS efficacy in Medicare TRD patients. Entitled the RECOVER Trial, this large, multi-center (71 US sites), randomized, double-blind, sham-controlled trial assesses VNS efficacy over 12 months.

Methods: RECOVER inclusion criteria: ≥18 years old, Major Depressive Disorder (MDD) or Major Depressive Episode (MDE) current in uni/bipolar disorder, chronic (≥2 years) or recurrent (≥4 MDEs), failure of four, medical-record verified antidepressant (AD) treatments in current MDE, and a score of ≥ 22 on the Montgomery Åsberg Depression Rating Scale (MADRS). Exclusion criteria: substance use disorder (past year), lifetime psychosis, acute suicidal ideation/intention, and severe personality disorders. All subjects are implanted and randomized to active treatment (device on) or sham (device off) for 12 months. RECOVER employs offsite blinded raters; the primary outcome is months in response (active –vs- sham; 50% reduction from MADRS baseline). RECOVER secondary outcomes, include: MDD remission, and changes in quality of life, overall function/disability, and suicidal ideation.

Results: The RECOVER trial is a group of highly refractory TRD patients. To date there are 480 patients enrolled, with a mean age of 54.0 years, mean baseline MADRS 34.6, mean MDE onset age is 20.9 (20.4 years lifetime MDE). Average failed lifetime ADs is 14.1, with many receiving aggressive AD treatments: ECT (41.9%), TMS (46.7%), and ketamine (21.3%). Many report psychiatric hospitalizations (64.0%) and suicide attempts (43.8%). To date, 239 patients (including withdrawals) have completed the trial's first year.

Conclusions: RECOVER is the largest double-blind, prospective, randomized, device-based, sham-controlled TRD trial ever conducted. This study is enrolling severe TRD patients not studied in most MDD clinical trials. It will provide clearer understanding of VNS responsivity (e.g., onset of response and baseline outcome predictors).

T32. EXAMINING SITE RATER BASELINE INFLATION IN DEPRESSION TRIALS: A COMPARISON OF INDEPENDENT RATER SCREENING HAM-D VERSUS SITE BASELINE RATERS MADRS SCORES CONVERSIONS

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Abstract: Introduction: The phenomenon of "baseline inflation" where Site Raters (SRs) artificially inflate subject's illness severity to enhance recruitment, is a risk to antidepressant trial differentiation1, yet can be difficult to study given different screening and baseline scales are often used. To control for this, vendors offer blinded Independent Rater (IR) services for Major Depressive Disorder (MDD) trials, yet their impact on trial differentiation is mixed2 and no research on variables that may impact IR efficacy has been conducted. We compared the Hamilton Depression Rating (HAM-D) scoring between blinded IRs at screening with equivalent Montgomery-Åsberg Depression Rating Scale (MADRS) scores by SRs at baseline across MDD studies utilizing the Cronos approach to improve clinical trial data quality.

Methods: Screening and baseline depression severity scores were obtained via the structured interview guides for the HAM-D (SIGH-D-17) and MADRS (SIGMA). MADRS scores were converted to HAM-D scores for each IR screening and SR baseline pair using published score conversions between the HAM-D-17 and MADRS scales.3 We reviewed the distribution of IR screening HAM-D scores against study inclusion criteria (HAM-D total score ≥18 or ≥20). Time between screening and baseline visits and the magnitude of the difference in HAM-D were correlated using the Pearson correlation coefficient. The difference between converted screening and baseline HAM-D scores and the effect of study were evaluated using repeated measures factorial 2x4 ANOVA.

Results: Total HAM-D scores were compared between screening and baseline for a sample of 1357 MDD clinical trial participants across four clinical trials utilizing multiple IR vendors. The median time between the visits was five days (IQR = three days, Min = one day, Max =45 days). HAM-D IR scores at screening were normally distributed, (M = 27.19 , SD = 4.22, Min = 14, Max = 42). There was a significant reduction in the HAM-D total score between screening (M = 27.19 , SD = 4.22) and baseline (M = 25.52, SD = 4.32), [$F(1, 1353) = 41.39$, $p < .001$]. The difference in mapped HAM-D scores between screening and baseline didn't correlate significantly with the time between the two visits ($r = .021$, $p = .449$). There was no significant interaction between the HAM-D score change from screening to baseline and by study [$F(3,1353) = 1.43$, $p = .23$].

Conclusion: Our findings suggest that IR effectiveness to mitigate baseline inflation may be influenced by the use of concurrent data quality control efforts. The screening HAM-D score distribution was normal, suggesting the use of blinded IRs prevents scores skewing toward the study inclusion cutoffs (a trend expected if the raters were unblinded). Additionally, the use of IRs at screening to determine trial eligibility corresponded to a relative SR "baseline deflation" of 1.67 points when used in conjunction with additional data quality controls. This value trends toward the minimal change (1 point or less) demonstrated to predict drug-placebo separation and contrasts with the rise of 2 or more points between visits known to increase placebo response4. The effect was robust across multiple studies and was not related to the time between visits. Limitations include the use of score conversions between semi-structured and structured depression rating scales. Future work will compare changes from screening to baseline between IRs and SRs on the same scale, and across SRs at both screening and baseline.

T33. DOES LAMOTRIGINE AFFECT THE ANTIDEPRESSANT EFFECT OF KETAMINE/ESKETAMINE IN PATIENTS WITH TREATMENT-REFRACTORY DEPRESSION? A CASE-SERIES OF 12 PATIENTS

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Abstract: Background: Racemic ketamine and FDA approved Esketamine are increasingly used for treatment-resistant depression (TRD).(1) Ketamine, an N-methyl-D-aspartate (NMDA) receptor antagonist, may lead to increased release of synaptic glutamate. This has been proposed as one of the mechanisms for ketamine's efficacy.(2) Lamotrigine is a mood stabilizing agent that acts by inhibiting voltage-sensitive sodium channels and reducing the glutamatergic neurotransmission, thus, theoretically may reduce ketamine/esketamine' efficacy. Some preliminary studies and animal data suggest a synergistic effect of ketamine and lamotrigine. However, the animal data do not easily extrapolate to humans, especially in TRD. Herein, we report the response to serial ketamine/esketamine treatment in patients with TRD who were on concomitant lamotrigine therapy.

Methods: We included consecutive patients with TRD on lamotrigine who received serial intravenous (IV) racemic ketamine or intranasal (IN) esketamine treatments for TRD. Patients received up to 6 IV ketamine (0.5 mg/kg over 40−100 minutes) or up to 8 IN esketamine (56- or 84-mg) treatments. Change in depressive symptoms was assessed using the 16-item Quick Inventory of Depressive Symptomatology self-report (QIDS-SR) before and 24 hours after treatment. Treatment response was defined as ≥ 50% change in QIDS-SR score, and remission as QIDS-SR score ≤ 5.

Results: A total of 12 patients (median age = 43.5, 83% female, MDD=10, bipolar depression=2) were included. Patients were followed up for up to 6-8 treatment sessions. 10 patients received IV ketamine treatment, 1 patient was initiated on IN esketamine, and one patient switched from IV ketamine to IN esketamine after third infusion. Eight patients (75%) responded to the repeated dose regimen, of which 5 (42%) attained the remission criteria. Four patients discontinued due to lack of adequate response. Patients tolerated ketamine and esketamine well.

Conclusion: This case series does not suggest that concomitant lamotrigine therapy attenuate the antidepressant effect of repeated ketamine/esketamine treatments. Our findings are limited by study design. These findings need to be investigated in large observational studies or randomized controlled trials.

T34. EFFECT OF ADJUNCTIVE CARIPRAZINE ON SYMPTOMS OF ANHEDONIA IN PATIENTS WITH MAJOR DEPRESSIVE DISORDER

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Abstract: Background: Anhedonia, a multidimensional domain including the reduced ability to experience pleasure, is a core diagnostic symptom of major depressive disorder (MDD) and a common residual symptom. In patients with MDD, anhedonia has been associated with poor treatment outcomes, suicide and reduced functioning and quality of life. This post-hoc analysis of data from a phase 3 trial (NCT03738215) evaluated the efficacy of adjunctive cariprazine (CAR) treatment on anhedonia symptoms in patients with MDD.

Methods: Patients with MDD and inadequate response to ongoing antidepressant therapy (ADT) were randomized to CAR 1.5 mg/d + ADT, CAR 3 mg/d + ADT, or placebo + ADT for 6 weeks of double-blind treatment. Post hoc analyses evaluated the change from baseline to Week 6 in Montgomery–Åsberg Depression Rating Scale (MADRS) total score, MADRS anhedonia subscale score (items: 1 [apparent sadness], 2 [reported sadness], 6 [concentration difficulties], 7 [lassitude], and 8 [inability to feel]), and MADRS anhedonia item 8 in the overall modified intent-to-treat (mITT) population and in subgroups of patients with baseline MADRS anhedonia item 8 score of ≥4 or baseline anhedonia subscale score of ≥18. Least square (LS) mean change from baseline to Week 6 was analyzed using a mixed-effects model for repeated measures.

Results: There were 751 patients in the mITT population (CAR + ADT: 1.5 mg/d=250, 3 mg/d=252; placebo + ADT=249). At baseline, 508 (67.6%) patients had MADRS anhedonia item 8 scores ≥4, and 584 (77.8%) had MADRS anhedonia subscale scores ≥18. In the overall mITT population, LS mean change from baseline to Week 6 in anhedonia subscale score was significantly greater for CAR 1.5 mg/d + ADT (-8.4) and CAR 3 mg/d + ADT (-7.9) than for placebo + ADT (-6.8; both P<.05). The LS mean change from baseline in MADRS individual item 8 was also significantly greater for CAR 1.5 mg/d + ADT (-1.7) vs placebo + ADT (-1.3; P=.0085). In both subgroups of patients with baseline anhedonia, CAR 1.5 mg/d + ADT was associated with significantly greater reduction in MADRS total score, MADRS anhedonia subscale score, and MADRS item 8 score compared with placebo + ADT (all P<.05). In the CAR 3 mg/d + ADT group, significantly greater reductions vs placebo + ADT were observed for MADRS total score and MADRS anhedonia subscale score in the subgroup of patients with baseline anhedonia subscale scores ≥18 (both P<.05).

Conclusion: Adjunctive treatment with CAR was associated with a reduction in symptoms of anhedonia relative to adjunctive placebo in patients with MDD and inadequate response to ADT alone. In subgroups of patients with moderate-to-severe anhedonia at baseline, CAR + ADT demonstrated greater improvements than placebo + ADT in overall depressive symptoms and symptoms of anhedonia. These results suggest that adjunctive CAR treatment may be

effective for improving symptoms of anhedonia in patients with MDD who have symptoms of anhedonia.

T35. SODIUM-GLUCOSE COTRANSPORTER-2 INHIBITORS IN MAJOR DEPRESSIVE DISORDER

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Abstract Psychiatry needs novel treatment strategies for mood disorders refractory to existing treatment algorithms. Abnormal brain bioenergetic metabolism may represent an alternative, therapeutically targetable neurobiological basis for mood disorders. A growing body of research points to endogenous ketones as candidate neuroprotective metabolites with the potential to correct mitochondrial dysfunction, enhance brain bioenergetic metabolism, and ultimately improve mood. Originally approved for the treatment of diabetes, sodium-glucose cotransporter-2 (SGLT2) inhibitors induce ketogenesis and have been associated with improvements in mood in population-based studies. We highlight the rationale for the hypothesis that ketogenesis induced by SGLT2 inhibitors may be an effective treatment for mood disorders. We also propose a six-week, pilot, single arm clinical trial of SGLT2 inhibitor empagliflozin in major depressive disorder, which tests whether potential antidepressant effects may be mediated by ketogenesis or changes in brain metabolism as studied via neuronally-derived exosomes.

T36. TREATMENT DISPARITIES FOR MAJOR DEPRESSIVE DISORDER

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Abstract: Background: In recent years, there has been an increasing awareness of health disparities in diagnosing and treating depression among the general population, with several studies highlighting the important role of social determinants of health as predictors of major depressive disorder (MDD) and its evolution.1-2 This study aims to show the impact of these social determinants on the treatment of MDD.

Methods: In this longitudinal study, 2 interview waves were conducted between 2002 and 2015 with participants from a program that evaluates sleep and mental disorders. The initial interviews (wave 1) were carried out with 12,218 participants aged ≥18 years from the general population in 8 US states. At follow-up 3 years later (wave 2), 10,931 of the initial participants agreed to be interviewed again. The analyses were carried out on those who participated in both interviews (N=10,931). Diagnosis of MDD was made according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition criteria. Logistic regression was used to compare participants with MDD who were not taking any antidepressant medication (untreated) with those receiving antidepressants for MDD (treated).

Results: Among the 10,931 participants who completed both interviews, 12-month prevalence of MDD was 9.5% (95% CI, 9.0%–10.0%); 26.3% of the participants with MDD were

untreated. Compared with treated participants, untreated participants were more likely to be male (odds ratio [OR], 3.1; 95% CI, 2.2–4.5; P<0.0001); aged 18–24 years (OR, 17.6; 95% CI, 6.7–46.5; P<0.0001); or Black (OR, 6.4; 95% CI, 2.9–14.2; P<0.0001). After adjusting for age, sex, and race, untreated participants were more likely to have less than a high school education (OR, 2.5; 95% CI, 1.0–6.2; P=0.046); be a shift or night worker (OR, 1.8; 95% CI, 1.1–2.9; P=0.011); have no health insurance (OR, 1.6; 95% CI, 1.1–2.5; P=0.021); have a household income <$50,000 per year (OR, 2.0; 95% CI, 1.3–3.2; P=0.002); or live in densely populated areas (>2 million inhabitants) (OR, 2.2; 95% CI, 1.1–4.2; P=0.019). Untreated participants were also less likely to have consulted a physician specifically for their depression compared with treated participants (30.6% vs 61.5%, respectively) or to receive mental health support from a nonmedical professional (29.8% vs 39.4%, respectively).

Conclusions: This study shows that treatment of MDD is strongly linked to key domains of social determinants of health and ethnodemographic factors in a population that is highly representative of clinical practice. These disparities negatively impact the treatment of MDD, with more than 25% of individuals diagnosed with MDD not receiving any antidepressant medication. Our findings underline the importance of reducing disparities through ongoing efforts to improve MDD screening and treatment, including addressing social determinants of health for groups experiencing disadvantages.

T37. HEALTHCARE RESOURCE UTILIZATION ASSOCIATED WITH SWITCHING VERSUS AUGMENTING ANTIDEPRESSANT MONOTHERAPY IN TREATMENT OF MAJOR DEPRESSIVE DISORDER

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Abstract: Introduction: Many patients with major depressive disorder (MDD) do not respond adequately to their first antidepressant therapy. These patients may discontinue their current monotherapy and switch to a new one or augment their existing therapy with adjunctive treatments, such as atypical antipsychotics (AAs). Understanding healthcare resource utilization (HRU) associated with these treatment options may inform on the most effective treatment strategy. The objective of this study was to compare all-cause and mental health (MH)-related HRU between patients who switch versus augment their antidepressant monotherapy.

Methods: This retrospective cohort study used claims data from the MerativeTM MarketScan® Commercial Database (1/1/2015-9/30/2020). The study population consisted of adults (patients ≥18 years of age) who initiated first-line antidepressant monotherapy within 60 days of their first observed MDD diagnosis, received ≥2 lines of therapy (LOT) after diagnosis (index date was start of second LOT), and had continuous commercial health insurance coverage for ≥6 months before MDD diagnosis and ≥3 months after the index date. Patients who switched were defined as those who discontinued their first-line antidepressant monotherapy and began a new monotherapy treatment as second LOT. Patients who augmented were defined as those who initiated an adjunctive MDD treatment while continuing their

previous antidepressant monotherapy as second LOT. Weighted analysis was performed using inverse probability of treatment weighting based on propensity scores. Rates of HRU per person-year were evaluated over the observation period, which spanned from the index date up to the earliest of: end of eligibility, end of data availability, one year post-index, or first diagnosis of bipolar disorder or schizophrenia. Rate ratios (RRs) were calculated from weighted Poisson regression models. P values were generated using robust variance estimators.

Results: A total of 195,097 patients with MDD met selection criteria; 111,419 (57%) switched their therapy in second LOT and 83,678 (43%) augmented their therapy in second LOT. Baseline characteristics were generally similar between weighted cohorts. All-cause and MH-related HRU rates were significantly lower in patients who augmented compared to those who switched. All-cause outpatient (OP) visit rates were 15.05 per person-year in patients who augmented versus 18.27 per person-year in those who switched (RR=0.82, P<.001). Similarly, MH-related OP visit rates were 6.81 per person-year in patients who augmented versus 7.43 per person-year in those who switched (RR=0.92, P<.001). Patients who augmented also had significantly lower rates of MH-related hospitalizations (RR=0.91; P=.004) and ER visits (RR=0.83; P<.001).

Conclusions: Patients with MDD whose antidepressant monotherapy was augmented in their second LOT had significantly less HRU compared to patients who switched treatments. These findings suggest that, in patients with MDD and an inadequate response to first-line antidepressant monotherapy, augmenting treatment may reduce resource use burden on the healthcare system compared to switching treatment.

T38. BARRIERS TO ESKETAMINE NASAL SPRAY TREATMENT AMONG ADULTS WITH TREATMENT RESISTANT DEPRESSION

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Abstract: Background:: Under a Risk Evaluation and Mitigation Strategy program, esketamine nasal spray CII (esketamine) requires self-administration at a certified treatment center with a two-hour clinical observation period. Dosage is two administrations per week for the four-week induction period1. Our objective was to examine distance and patient characteristics associated with not initiating esketamine treatment.

Methods: A retrospective observational cohort study was conducted using claims data from Clarivate linked to the Social Vulnerability Index2. Eligible adults met criteria for treatment-resistant depression (TRD); had no claims for bipolar disorder, schizophrenia, or MDD with suicidal ideation; were <65 years; and were benefits eligible 6 months prior to (Baseline) initiation. Cases had an esketamine claim between 10/11/2019 and 2/28/2022. Controls met TRD criteria with no esketamine use. Baseline was used to identify demographics, county of residence, comorbidities, and healthcare utilization. For cases, distance (geodesic miles) was derived from individuals' ZIP5 centroid to index esketamine treatment center. For controls, distance to closest treatment center was derived from a random sample with results projected to the entire TRD population.

Results: Of 714,225 eligible individuals, only 824 (0.1%) initiated esketamine. Cases resided significantly closer to an esketamine treatment center (8.9 vs. 20.3 miles, p<0.01). Compared to individuals residing within nine miles of a treatment center, the initiation rate decreased by 11.9%, 50.8%, 68.1%, 75.9%, and 92.8% for individuals residing 10-19, 20-29, 30-39, 40-49, and 50+ miles from a treatment center. Excluding three outliers, the maximum distance a case traveled for treatment was 69.5 miles. Overall, 49.7% (n=354,560) of controls lived more than 8.9 miles from the nearest treatment center, an estimate that increased to 91.2% for rural residents.

Compared to controls, cases were more likely male (36.8% vs. 24.3%), commercially insured (76.0% vs. 55.9%), younger (42.3 vs. 45.4 years), and to reside in counties with a higher proportion of Asian (8.6% vs. 4.3%) and Hispanic (16.4% vs. 12.4%) populations, in low socioeconomic vulnerability areas (23.2% vs. 18.4%), and in urban areas (73.3% vs. 60.9%) (all p<0.01). Cases had fewer comorbidities including hypertension (12.0% vs. 29.7%), low back pain (15.0% vs. 24.1%), obesity (15.0% vs. 24.1%), hyperlipidemia (12.1% vs. 23.5%), osteoarthritis (9.5% vs. 18.9%), among others (all p<0.01). Cases were more likely to have generalized anxiety disorder (47.9% vs. 29.0%), sleep-wake disorders (33.9% vs. 27.0%), and PTSD (21.5% vs. 10.7%), but less likely to have substance use disorder (13.0% vs. 19.5%) (all p<0.01). Cases were more likely to visit a psychiatrist (85.0% vs. 38.2%), while controls were more likely to visit a primary care physician (64.7% vs. 44.7%), have an inpatient admission (8.4% vs. 4.5%) or ED visit (20.6% vs. 11.2%), and to have at least one prescription filled (93.2% vs. 71.2%) (all p<0.01).

Conclusions: Findings suggest distance from treatment center is a potential barrier to treatment, with a nearly linear decline in treatment for each 10-mile increase in distance. Further, regardless of travel distance, numerous population subgroups are at increased risk of not initiating esketamine and further understanding of other barriers to care is needed. The exploration of alternative models of care is vital to eliminate the burden of the travel distance to the treatment center.

T39. PHASE 1 RESULTS AND PHASE 2 CLINICAL DEVELOPMENT OF RE104: A NOVEL SEROTONERGIC PSYCHEDELIC 4-OH-DIPT PRODRUG

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Abstract: Background: RE104, a unique 4-OH-DiPT prodrug, is a proprietary, novel serotonergic psychedelic compound in clinical stage development for the treatment of postpartum depression (PPD) and other mental health conditions. Preclinically, its receptor binding affinity is largely overlapping the well-characterized profile of psilocin (4-OH-DMT), but it exhibits more rapid metabolism in rodents and primates, with pharmacodynamic (PD) evidence of shorter duration hallucinogenic potential. Here we present the interim results from a prespecified analysis of cohorts 1-4 of the first-in-human (FIH) phase 1 study characterizing the safety, pharmacokinetics (PK) and PD of RE104, and an overview of the phase 2 trial in postpartum depression (PPD).

Method: The phase 1, FIH, double-blind, parallel group trial allowed up to 6 ascending dose cohorts of 8 psychedelic experienced healthy volunteers (randomized 6 active: 2 placebo). Predefined dose escalation in cohorts 1-4 ranged from 5.5 mg to 33 mg RE104, administered subcutaneously as a single injection. Maximum dose not to exceed 52.7 mg. A safety review committee (SRC) was responsible for determining dose escalation after each cohort. Adequate set and setting for psychedelic drug delivery included one preparatory session, followed by a dosing session, both conducted by a qualified and trained session monitor. Follow-up study visits occurred on days 2 and 10. Study objectives were safety and tolerability, PK, and PD (Drug Effect Questionnaire [DEQ] and Mystical Effect Questionnaire 30 [MEQ]). A "complete" mystical experience (CME) was defined as ≥60% max value in all 4 MEQ domains. DEQ ≤1 represented a subjective end of the psychoactive experience. The study was conducted at PARC Clinical Research in Australia.

Results: 32 subjects with a mean age of 37 years, 25% female, and 97% white were enrolled across 4 ascending cohort dose levels or placebo (n=6 at 5.5 mg, n=6 at 11 mg, n=6 at 22 mg, n=6 at 33 mg, n=8 placebo). Overall, treatment-emergent adverse events (TEAEs) occurred in 2/6 RE104-treated subjects at 5.5, 11, and 22 mg, in 6/6 at 33 mg, and in 3/8 on placebo. There were no serious or severe AEs and all subjects completed dosing. At 33 mg RE104, all 6 subjects experienced a treatment-related TEAE, most commonly mild-moderate nausea, abdominal pain, sinus tachycardia (maximum value recorded 109 bpm) and muscle twitches. There were no evident blood pressure effects, clinically significant vital sign changes, laboratory or ECG findings. The average time to peak DEQ score (8.5/10) was 1.1 hr and all subjects had DEQ ≤1 at 4 hr, with mean experience duration of 3.7 hr (range 2-4h). There was a dose related increase in frequency of CME, with 4/6 subjects treated with 33 mg RE104 reporting a CME. A 5th subject at 33 mg achieved ≥60% in 3/4 MEQ domains, and a total score of 59.3%. PK was well behaved without excessive variability and with dose proportionality.

The SRC recommended initiation of cohort 5 at 44 mg, and enrollment is ongoing. Final results of the Phase 1 study will inform RE104 dose for a 40-patient randomized, placebo-controlled, Phase 2 treatment trial in women with moderate to severe PPD, planned for initiation in 2H 2023.

Conclusions: A single dose of RE104 was found to be safe and generally well-tolerated at doses up to 33 mg, with corresponding evidence of robust PD effect lasting about ½ the published duration of experience relative to 25 mg psilocybin, with a similar AE profile. MEQ measures indicative of CME provide justification for selecting a dose of RE104 that could yield clinical efficacy in PPD treatment trials.

Acknowledgements: MWJ participated in his role as an advisor rather than his role as faculty at Johns Hopkins.

T40. ELEVATED ANXIETY IN PATIENTS WITH UNRESOLVED MAJOR DEPRESSIVE DISORDER

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Abstract: Background: The incremental economic burden of major depressive disorder (MDD) in US adults increased by 37% between 2010 and 2018 while percentages of patients treated was stable over the decade indicating high unmet need. Antidepressants are generally the first line of pharmacological treatment for MDD, they can fail to effectively alleviate depressive symptoms in some patients even when multiple antidepressants are used individually or in combination. Several severity indicators could account for the lack of response to pharmacotherapy, including comorbid hyperarousal/anxiety-related symptoms. However, few studies have explored the presence of elevated anxiety (EA) in patients with unresolved symptoms of MDD.
Objective: To provide real-world evidence on the presence of EA and changes in medical utilization/EA status in patients with unresolved symptoms of MDD by leveraging real-world data (RWD) generated from NeuroBlu™, an electronic health records database.

Methods: Using a retrospective cohort design with data from January 1, 2000 to December 31, 2020, this study assessed a cohort of patients with unresolved MDD symptoms as defined by the Clinical Global Impression – Severity (CGI-S) scale. The CGI-S utilizes a 7-point scale with higher scores indicating greater illness severity. Patients with CGI-S scores of ≥4 ("moderately ill") at the first-recorded MDD diagnosis and later between 90-120 days were included. The index date was defined as the first date of visit within 90 to 120 days following diagnosis where patients had a CGI-S score of ≥4, suggesting that their symptoms persisted for a minimum of 90 days following diagnosis. Patients were required to have a prescription order for ≥90 consecutive days of any antidepressant treatment(s) (ADT), and those with records of a diagnosis of bipolar disorder, any schizophrenia spectrum disorder, or prescription(s) of lithium were excluded. The follow-up period was defined between 16 and 365 days following the index date. Within the primary cohort, patients were separated into sub-cohorts of those with EA versus without EA at baseline. EA was identified if there were anxiety-related medical visits recording a comorbid diagnosis of generalized anxiety disorder (GAD) or prescription(s) of an anxiolytic drug. Survival analyses were conducted on the changes in anxiety-related healthcare resource utilization (HCRU) involving GAD-related medical visits and medical encounter for anxiolytics in patients with unresolved MDD during follow up.

Results: 3,342 patients were included in the primary cohort of patients with unresolved MDD symptoms (mean age 44.4 years; female, 70.6%; White, 60.7%). Majority of the cohort were identified as having EA at some point within the study period. In the identified patients 53.3% had EA at baseline. Survival analysis demonstrated that among patients who were identified as having EA at baseline, the probability of anxiety-related HCRU was 2-fold higher than patients who were identified as not having EA at baseline by the end of the follow-up period.

Conclusions: The study findings highlight EA as likely a co-occurring symptom of patients with unresolved MDD, potentially adding complexity to the management of unresolved MDD and increasing HCRU. Further research is needed to better understand the anxiety burden in patients with unresolved MDD.

T41. A RANDOMIZED PLACEBO-CONTROLLED MULTICENTER TRIAL OF MONOTHERAPY WITH TNX-601 ER* (TIANEPTINE HEMIOXALATE EXTENDED-RELEASE TABLETS) FOR TREATMENT OF MAJOR DEPRESSIVE DISORDER (MDD)

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Abstract: Background: About 21 million adults in the United States (US) experienced at least one major depressive episode in 2020. Virtually all antidepressants in the US market have mechanisms of action involving central monoaminergic (MA) systems, with the selective serotonin reuptake inhibitors (SSRIs) making up the most prescribed class. Yet, only about 50% of patients respond to initial SSRI treatment, and only 35-40% achieve remission. Moreover, common side effects of the MA antidepressants, e.g., sexual dysfunction, agitation, insomnia with daytime sedation, weight gain, and mild cognitive impairment, are poorly tolerated by many over extended treatment periods typically necessary.

Tianeptine is a unique non-MA antidepressant long available in Europe, Asia, and Latin America. Via indirect glutamatergic modulation, tianeptine has restorative properties on neuroplasticity and neurogenesis in hippocampus and is associated with a reduction in neuroinflammation, all key to addressing MDD. Its tolerability profile compares favorably to the MA antidepressants available in the US, without significant sexual side effects, adverse effects on sleep, or weight gain, and it uniquely provides anxiolysis without sedative effects, and is known for pro-cognitive effects. In this randomized, Phase 2 clinical trial, a novel once-daily formulation of a new salt, tianeptine hemioxalate, is being tested as a monotherapy for efficacy and safety in MDD.

Methods: In this multicenter, double-blind study, adults ages 18-65 meeting DSM-5 MDD will be randomized 1:1 to 6-weeks of TNX-601 ER 39.4 mg or Placebo each morning, enrolled across ~30 US sites. Eligible participants will be free or washed off antidepressant and other psychotropics prior to baseline. Primary efficacy endpoint is mean change from baseline at Week 6 on the Montgomery-Åsberg Depression Rating Scale (MADRS) total score. Screening (V1) MADRS must be ≥ 28, and Baseline (V2) ≥ 25, with $\leq 25\%$ variation between V1 and V2. Exclusion criteria include serious suicide risk, unstable medical illness, lifetime opioid or sedative-hypnotic use disorder, and past 12 months alcohol and other substance use disorders (mild alcohol and cannabis use disorder allowed at discretion of investigator), and lifetime bipolar disorders, psychotic disorders, current obsessive-compulsive disorder, PTSD, anorexia nervosa, or borderline or antisocial personality disorder. Secondary endpoints include Clinician Global Impression – Severity scale, Sheehan Disability Scale, and Hamilton Anxiety Rating Scale. A total of 300 patients with MDD will be recruited, and an interim analysis for potential sample size re-estimation will occur once 50% have completed or discontinued.

Results/Discussion: The advances in understanding of tianeptine's mechanism of action and the development of the TNX-601 ER formulation will be described. Details of the Phase 2 UPLIFT study design will be provided. It is estimated that about 25% of the total sample will have been recruited by the time of the meeting, and an update on enrollment will be reported. The proposed clinical development plan toward a US marketing NDA will be discussed.

Trial Registration: NCT05686408 Study to Evaluate TNX-601 ER Monotherapy Versus Placebo in Patients with Major Depressive Disorder (MDD) (UPLIFT)

*TNX-601 ER is an Investigational New Drug and has not been approved for any indication.

T42. DISTINCT FORMS OF REGRET LINKED TO RESILIENCE VERSUS SUSCEPTIBILITY TO STRESS ARE REGULATED BY DIFFERENT BRAIN REGIONS

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Abstract Stress-related disorders such as depression are debilitating illnesses in which individuals struggle with severe emotional dysregulation. Regret describes the phenomenon in which an individual recognizes that an alternative action could have led to a better outcome. It is widely accepted that regret contributes to disease burden. Yet, little is known about the neurobiology of what might make this process maladaptive and what aspects of regret, if any, carry positive utility that is worth preserving in order to restore healthy emotional processing and adaptive coping. Animal models used for the study of depression have made significant contributions to the field. However, animal models have been limited in their ability to capture the complexity of human emotion. To shed light on this translational gap, we combined the well-established chronic social defeat stress model in mice that effectively distinguishes between stress-susceptible (SUS) and stress-resilient (RES) animals with novel approaches in neuroeconomics that have only recently demonstrated the ability to extract the behavioral and neurophysiological correlates of regret in rodents. By characterizing mice exposed to chronic social defeat stress on a novel neuroeconomic decision-making paradigm, we demonstrate fundamentally distinct forms of regret between SUS versus RES phenotypes and establish a brain region-specific role for the biological marker CREB, a key regulator of gene expression implicated in chronic stress. We characterized SUS, RES, and non-stressed control (CON) mice longitudinally on our task, where mice have a limited time period each day to forage for their sole source of food. On each trial, a tone sounds whose pitch indicates how long of a delay mice will have to wait in a cued countdown should they choose to work for food. We found choice history influenced subsequent decisions but only in certain economic situations when mice make mistakes. From this rich economic dataset, fundamentally distinct types of scenarios can be operationalized that have been shown to have different behavioral and neural correlates of regret-like processes. We found SUS mice were uniquely sensitive to scenarios that capture risky decisions with poor outcomes to which neither RES nor CON mice were sensitive when they skipped a valuable option. Conversely, RES mice were more sensitive to change-of-mind decisions following snap-judgment mistakes. SUS mice lost sensitivity to these situations. We found that manipulating the function of CREB in two brain regions differentially perturbed these distinct forms of regret. These data reveal new insights into how adaptive versus maladaptive stress responses are related to distinct forms of counterfactual thinking regarding missed opportunities. We found that one type of regret is absent as a loss-of-function and conversely enhanced as a gain-of-function in mice uniquely vulnerable to stress. The study provides a novel framework for understanding pathological versus healthy forms of regret that may be at play in mood disorders and hinge on the framing of one's own mistakes. This work can guide not only the development of new diagnostic tools or interventions for depression but can also steer therapy toward unveiling distinct computations through a careful description of one's decision narrative.

T43. INCREASED PLACEBO RESPONSE ASSOCIATED WITH GREATER FREQUENCY OF STUDY VISITS IN MAJOR DEPRESSIVE DISORDER (MDD) CLINICAL TRIALS

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Abstract: Background: Previous research in major depressive disorder (MDD) trials has shown that more frequent study visits may increase placebo therapeutic effect, potentially diminishing effect size. In particular, this phenomenon may affect trials of emerging rapid acting antidepressants (ADTs), which often require more frequent trial visits, such as the recently completed Phase 3 WATERFALL study of zuranolone, an investigational positive allosteric modulator of GABAA receptors and a neuroactive steroid in clinical development as an oral, once-daily, 14-day treatment course for adults with MDD and postpartum depression. **Objective:** To assess the impact of the frequency of study visits on depressive symptoms for participants with MDD receiving placebo in recent ADT trials.

Methods: A systematic literature review identified 11 US Phase 2-4 placebo-controlled randomized monotherapy trials of approved ADTs in adults with MDD from 2012-2022 reporting HAMD-17 or MADRS scores. Weighted correlations between visit frequency and percent change from baseline (CFB) in HAMD-17 and MADRS scores for placebo were calculated. Weighted linear regressions predicted CFB HAMD-17 and MADRS scores and the difference in these scores between active treatment and placebo using visit frequency.

Results: The average visit frequency of included ADT trials was 0.8 visits/week compared to 2.5 visits/week during the treatment period of the WATERFALL study. Correlations demonstrated that as visit frequency increased, a greater percent CFB in HAMD-17 or MADRS for placebo (R^2=0.39, P=0.04) was observed. Regression analyses also indicated that with increasing visit frequency, HAMD-17 and MADRS CFB scores for placebo improved more than active treatment scores, thus decreasing differences between active treatment and placebo groups. Active treatment was estimated to not outperform placebo on HAMD-17 or MADRS for trials with visit frequency >2 visits/week.

Conclusions: More frequent MDD trial visits were associated with increased placebo response and decreased differences in depressive symptoms between treatment groups. The WATERFALL study had higher CFB placebo scores than most included ADT trials. Visit frequency in the WATERFALL study was considerably higher than most recent US MDD trials of approved ADTs, which may have contributed to the high placebo response seen. While results of the present analysis suggest that there may be an increased placebo effect in WATERFALL associated with higher visit frequency, zuranolone nevertheless achieved statistical significance vs placebo on its primary endpoint (CFB HAMD-17 LS mean difference = -1.7, P=0.01) at Day 15. The impact of visit frequency should be considered when interpreting effect size in MDD trials, particularly with the emergence of novel, rapid acting treatments, which often require more frequent trial visits to monitor treatment effect.

T44. ASSESSMENT OF WITHDRAWAL SYMPTOMS AFTER DISCONTINUATION OF AXS-05 (DEXTROMETHORPHAN-BUPROPION) TREATMENT: RESULTS FROM THE GEMINI TRIAL

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Abstract: Background: Traditional oral antidepressants that act primarily via the monoamine pathway can be associated with withdrawal effects upon discontinuation in up to 60% of patients (1). Antidepressant withdrawal symptoms can be wide ranging and include flu-like symptoms, insomnia, nausea, imbalance, sensory disturbances, and hyperarousal (anxiety/agitation) (2).

AXS-05 [dextromethorphan-bupropion (Auvelity® extended-release tablet)] is a novel, oral, NMDA receptor antagonist with multimodal activity approved by the U.S FDA for the treatment of major depressive disorder (MDD) in adults. The dextromethorphan component of AXS-05 is an antagonist of the NMDA receptor (an ionotropic glutamate receptor) and a sigma-1 receptor agonist. The bupropion component of AXS-05 is an aminoketone and CYP450 2D6 inhibitor, which serves primarily to increase the bioavailability of dextromethorphan.

Assessment of potential withdrawal symptoms upon discontinuation of AXS-05 in MDD have not been previously reported.

Objective: To evaluate potential withdrawal symptoms following discontinuation of AXS-05 compared to placebo in patients with MDD using the 20-item Physician Withdrawal Checklist (PWC-20).

Method: GEMINI (N=327) was a randomized, double-blind, placebo-controlled, 6-week, U.S trial, which randomized (1:1) adults with MDD to AXS-05 (dextromethorphan 45 mg-bupropion 105 mg) or placebo, twice daily for 6 weeks (Iosifescu DV, et al. J Clin Psychiatry. 2022;83:21m14345). The primary endpoint was change from baseline in the MADRS total score at Week 6. Study drug was discontinued without taper at the end of Week 6. The PWC-20 was evaluated at Week 7, when the subject had been off study drug for one week.

The PWC-20 (Rickels K, et al. J Clin Psychopharmacol. 2008;28:447-51) evaluates the presence and severity of 20 withdrawal symptoms including somatic symptoms (insomnia, diaphoresis, tremor-tremulousness, headaches, muscle aches/stiffness), mood symptoms (anxiety-nervousness, irritability, dysphoric mood-depression, restlessness-agitation, difficulty concentrating/remembering), cognitive symptoms (poor coordination, dizziness-lightheadedness, increased acuity for sound/smell/touch, depersonalization-derealization), fatigue symptoms (fatigue/lethargy/lack of energy, weakness, paresthesia), and gastrointestinal symptoms (loss of appetite, nausea/vomiting, diarrhea).

Results: No significant differences were observed between the AXS-05 and placebo groups for 18 of 20 symptoms evaluated by the PWC-20. Differences were observed for only nausea/vomiting (11.7% vs. 4.7% for AXS-05 and placebo subjects, respectively, p=0.031), and dizziness/lightheadedness (18.2% vs. 6.2% for AXS-05 and placebo, respectively, p=0.002). Among AXS-05 treated patients, nausea/vomiting and dizziness/lightheadedness were rated on the PWC as mild or moderate in 88% and 92% of subjects, respectively.

Conclusions: Following 6 weeks of treatment, discontinuation of AXS-05 without taper was well tolerated with similar rates compared to placebo for almost all PWC-20 symptoms.

Sponsorship: This research was supported by Axsome Therapeutics.

T45. CELLULAR IMMUNOMETABOLIC SIGNATURES ARE ASSOCIATED WITH ANHEDONIA IN DEPRESSION WITH HIGH INFLAMMATION

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Abstract Inflammation is implicated in the pathophysiology of major depression (MD) and its core feature anhedonia; yet the immune cell mechanisms and related metabolic programing that fuel inflammation to impact the brain and behavior are largely unknown. Using microarray, single cell RNA-Sequencing (scRNA-Seq), and Seahorse cellular bioenergetic assessments, we investigated transcriptomic and immunometabolic pathways within immune cells that underlie increased inflammation, and their relationship with anhedonia in MD outpatients. In unmedicated, medically-stable MD patients (n=62), we found relationships between anhedonia and a whole-blood gene expression pattern consistent with monocytic glycolysis, but only among patients with high inflammation (C-reactive protein [CRP]>3 mg/L; n=19). scRNA-Seq in PBMCs from six patients – three with high inflammation (CRP>3 mg/L) before and after anti-inflammatory challenge with infliximab and three with low inflammation (CRP □3mg/L) – further revealed that CD14+ and CD16+ monocytes were more abundant in MD patients with high inflammation, and 29% and 55% reduced after infliximab. Genes upregulated in patients with high compared to low inflammation enriched inflammatory (phagocytosis, complement, chemotaxis) and immunometabolic pathways (hypoxia-inducible factor [HIF]-1, aerobic glycolysis). Following infliximab, changes in the number of CD14+ monocytes predicted improvements in anhedonia ($r=1.0$, $p<0.001$). Real-time bioenergetic profiling of intact monocytes from four additional MD patients and one healthy control showed that monocytic glycolysis was associated with CRP levels ($r=0.85$, $p=0.06$) and greater anhedonia ($r=0.9$, $p=0.03$). Our results indicate that MD patients with increased inflammation have enrichment of circulating monocyte populations. These monocytes exhibited greater glycolysis and immunometabolic reprograming needed to sustain cellular activation, in association with symptoms of anhedonia. Together, these findings begin to elucidate the cellular and molecular pathways associated with high inflammation in MD, which may lead to novel monocyte-targeted immunomodulatory treatment of psychiatric illnesses with increased inflammation.

T46. NO INDICATION OF ABUSE POTENTIAL AND ABSENCE OF WITHDRAWAL SIGNS AND SYMPTOMS FROM ESMETHADONE (REL-1017): RESULTS FROM A PHASE 3 RANDOMIZED CONTROLLED TRIAL IN PATIENTS WITH MAJOR DEPRESSIVE DISORDER

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Abstract: Background: Esmethadone (REL-1017) is an N-methyl-D-aspartate receptor uncompetitive antagonist and antidepressant candidate with promising safety, tolerability, and efficacy results from Phase 1 and 2 trials. Given its structural similarity to methadone, the abuse and dependence potential of REL-1017 in patients with major depressive disorder (MDD) was assessed.

Methods: A Phase 3, randomized, double-blind, placebo-controlled trial was conducted in 18- to 65-year-old patients with MDD experiencing a major depressive episode despite ongoing treatment with a standard antidepressant. Patients received 75 mg REL-1017 (loading dose) or placebo once daily on Day 1 and 25 mg REL-1017 or placebo from Days 2 to 28. "Drug liking," "drug high," and "desire to take the drug again" were assessed with a 0-100 visual analogue scale (VAS). The Misuse, Abuse, and Diversion Drug Event Reporting System (MADDERS®) was used to assess potentially abuse-related events. Potential withdrawal was assessed for 14 days after treatment discontinuation (Days 28-42) using the Physician Withdrawal Checklist (PWC), Clinical Opiate Withdrawal Scale (COWS), and Subjective Opiate Withdrawal Scale (SOWS).

Results: Among 227 patients receiving any study drug (114 placebo, 113 REL-1017), adverse events (AEs) were mild or moderate and transient. There were 3 serious AEs, although none were treatment related. Placebo and REL-1017 groups showed no differences in VAS scores for "drug liking," "drug high," or "desire to take the drug again." There was no indication of abuse on the MADDERS®. Among patients who participated in the safety withdrawal assessment (97 placebo, 87 REL-1017), change from baseline on the PWC, COWS, and SOWS was slight, not clinically meaningful, and did not differ between groups.

Conclusions: No indications of abuse potential for REL-1017 were observed, and discontinuation resulted in no withdrawal signs or symptoms. These results confirmed the lack of meaningful abuse potential seen in earlier studies.

T47. RACIAL AND ETHNIC ISSUES IN CLINICAL PSYCHOPHARMACOLOGY: A THEMATIC REVIEW OF LITERATURE

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Abstract: Background: Race-ethnicity is considered an important but often underexamined factor in psychopharmacology and mental healthcare. Yet, there remain significant questions around exact differences in pharmacological response, inter- vs intra-ethnic variation, the existence of systemic discrimination in treatment provision, and how best to care for patients in an equitable manner.

Objectives: The aims of this thematic review are to elucidate some important high-yield findings on racial/ethnic issues to consider in psychopharmacological and psychiatric practice and identify key questions for further exploration in psychopharmacology when considering race and ethnicity

Methods: A focused thematic review of studies and reviews were completed. We searched PubMed and PsycInfo with a snowball search for relevant studies. Findings and issues of racial/ethnic differences in psychopharmacology are presented.

Results: We summarized our findings under three major themes, to illustrate the importance of considering race and ethnicity with respect to drug response, prescription and clinician or patient's attitude to care.

Conclusion: Key questions remain to navigate the best psychopharmacological treatment across races/ethnicities. Also, there is a need to clarify the utility of race/ethnicity as proxies for underlying demographic factors. In the interim, there is a need to consider identified differences in drug responses, care provision, and patient attitudes across different ethnicities

T48. BENZOFURAN DERIVATIVES INCREASE EXTRACELLULAR MONOAMINES AND HAVE MDMA-LIKE EFFECTS IN RATS

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Abstract: Background: MDMA is an experimental adjunct to psychotherapy for PTSD that represents a novel class of therapeutic. 5-MAPB (5-(2-methylaminopropyl) benzofuran) is a reportedly less stimulating analogue of MDMA that is used in underground contexts for both therapeutic and recreational purposes. We synthesized and characterized the enantiomers of 5-MAPB and the novel beta-keto derivative BK-5-MAPB (1-(1-benzofuran-5-yl)-2-(methylamino)propan-1-one).
Purpose: We sought to conduct preliminary evaluation of these four isomers as potential MDMA-like therapeutics.

Methods: Ability to release monoamines via DAT, SERT, and NET was quantified using rat synaptosomes and [3H]5-HT or [3H]MPP+ as substrate. MDMA-like interoceptive properties were assessed using a drug discrimination paradigm with rats trained to discriminate MDMA (1.5 mg/kg, I.P., 15 min) under a FR-20 schedule of food reinforcement. Cardiovascular effects of the S-enantiomers of 5-MAPB and BK-5-MAPB were further measured using telemetry in adult male Wistar rats at two dose levels (2.66 and 5.32 umol/kg, S.C.).

Results: The four isomers were substrate-type releasers at DAT, SERT, and NET. S-5-MAPB, R-5-MAPB, and S-BK-5-MAPB all displayed MDMA-like profiles, with greater potency at SERT than DAT (DAT/SERT ratios of 0.8, 0.15, and 0.6, respectively), while R-BK-5-MAPB had a typical stimulant profile (DAT/SERT ratio of 18). Consistent with this, all substances except R-BK-5-MAPB substituted for MDMA in the drug discrimination paradigm. S-BK-5-MAPB, which had relatively poor potency at NET (EC50 380 nM), appeared to have attenuated cardiovascular effects in comparison to S-5-MAPB (NET EC50 22 nM). While both dose-dependently increased heart rate and median blood pressure, effects of S-5-BK-MAPB were less than those of S-5-MAPB. 2.66 umol/kg S-BK-5-MAPB, a dose that fully substituted for MDMA, resembled vehicle in its effects. 5.32 umol/kg S-BK-5-MAPB was similar in magnitude to 2.66 umol/kg S-5-MAPB. 5.32 umol/kg S-5-MAPB produced changes that persisted beyond 4 hours post-dose.

Importance: Benzofuran derivatives may have MDMA-like therapeutic effects with fewer of MDMA's undesirable effects. 5-MAPB appears to have long lasting acute effects, potentially avoiding MDMA's requirement for redosing. S-BK-5-MAPB appears to have only subtle

cardiovascular effects, which may reduce need for safety monitoring during entactogen-assisted psychotherapy.

T49. EFFECTS OF NLS-8 (MELAFENOXATE) ON MEMORY IN A MODEL OF ALZHEIMER'S DISEASE, THE SCOPOLAMINE-INDUCED AMNESIA IN THE NOVEL OBJECT RECOGNITION TEST IN MICE

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Abstract: Background: Scopolamine produces cholinergic deficits similar to those observed in Alzheimer's disease and has been employed as a reference to develop dementia-related disorders in animals as well as humans. Accumulated evidence demonstrates a clear correlation between scopolamine administration and impairment of memory. For instance, a dose of scopolamine harms short-term and procedural recall classes in individuals. Evidence suggests that scopolamine triggers a marked reduction in the activity of neuronal networks within the hippocampus. Additionally, scopolamine impairs hippocampus-dependent acquisition and consolidation of information in rats. Donepezil, one of the most used compound for treatment of dementia due to Alzheimer's Disease (AD), has been shown to improve scopolamine-induced amnesia in rodents. The novel object recognition (NOR) test has been used in numerous studies to evaluate episodic memory in rodents. The aim of this study was to examine in mice whether NLS-8 (melafenoxate; International Application No. PCT/EP2022/069204; Applicant NLS Pharmaceutics), a melatonin ML1A receptor agonist also targeting on the relaxin-3/RXFP3 receptors involved in the neuromodulator system, improved scopolamine-induced amnesia. An improvement of scopolamine amnesia is indicative of a potential efficacy to improve cognitive symptoms in AD patients. Donepezil was used as positive control drug.
Methods: C57BL/6 male mice, 6 groups (N=16 mice/group), were subjected to two 12-min trials, 90-min apart, in the NOR test: a sample (acquisition) trial during which they were exposed to two identical objects, and a choice (retention) trial during which they were exposed to two different objects presented, the familiar object (presented at the sample trial), and the novel object. They received 30 min before the sample trial i.p. injections of vehicle (control group), of scopolamine, of scopolamine + donepezil (1 mg/kg) or of scopolamine + NLS-8 (50, 100 or 150 mg/kg). Scopolamine was injected at 1.2 mg/kg. Data recorded were two variables considered as indices of exploration, the exploration time of the two objects in the sample trial and in the choice trial, and two variables usually accepted as indices of memory, the difference of exploration time between the novel object and the familiar object and the discrimination index in the choice trial. The control group recognized the familiar object. Therefore, experimental conditions were suitable to detect an amnesia induced by scopolamine. Scopolamine induced amnesia and also increased exploration, i.e. induced hyperactivity, during the sample trial (30 min post-treatment), but not during the choice trial (2 h post-treatment).

Results: Donepezil improved scopolamine-induced amnesia but did not modify the increase in exploration, i.e. the hyperactivity, induced by scopolamine at 30 min post-treatment and did not induce visible sedation at 2 h post-treatment. NLS-8 improved (50 and 150 mg/kg) or induced a very close to significant improvement (100 mg/kg) of scopolamine-induced amnesia.

This effect was similar to that of donepezil. NLS-8 did not modify the increase in exploration induced by scopolamine at 30 min post-treatment and did not significantly alter the exploration at the choice trial, i.e. did not induce visible sedation at 30 min and at 2 h post-treatment

Conclusion: The results of this pre-clinical study show that NLS-8 improved amnesia induced by scopolamine suggesting that NLS-8 may improve memory and reduce cognitive symptoms of AD. These effects were significant at doses of 50 and 150 mg/kg and was close to significant at the dose of 100 mg/kg.

T50. EFFECTS OF NLS-4 (LAUFLUMIDE) AND MODAFINIL IN A RAT MODEL OF CHRONIC SEVERE FATIGUE

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Abstract: Background: The chronic fatigue syndrome (CFS) is a heterogeneous disorder characterized by easy fatigability, feverishness, diffuse pains, and depression. Many COVID-19 patients expressed long-term effects of coronavirus (long-COVID), with some characteristics typically found in CFS. To examine the efficacy of NLS-4 (lauflumide; International Application No. PCT/EP2022/069170; Applicant NLS Pharmaceutics), a dopamine reuptake inhibitor, NPY1 and relaxin-3/RXFP3 receptor agonist, in comparison with a positive control, modafinil, which has been shown to improve recovery from CFS in humans, to improve recovery from severe fatigue in rats.

Methods: Male 7-8 weeks old Sprague-Dawley rats were subjected to a fatigue procedure for seven consecutive days. Their locomotor activity in home cage was then recorded for 3 days following the end of the fatigue procedure. A Sham group was subjected to the same measurement of circadian activity but without the fatigue procedure. Rats were divided into different groups which received, before the start of the dark period, three daily administrations of NLS-4, modafinil or vehicle (Control and Sham groups).

Results: The fatigue procedure induced an impairment in the circadian activity, that is a decrease in motor activity during the dark period and an increase in motor activity during the period of light. Accordingly, the difference of distance travelled between the dark period and the light period was lower in the Control group than in the Sham group. This impairment was still present 3 days after the end of the fatigue procedure. Both modafinil and NLS-4 increased locomotor activity in a dose-dependent manner during the dark phase and, to a lesser extent, during the light phase. The increase in activity during the dark phase was significant at doses of 16, 32 and 64 mg/kg with NLS-4 and at doses 64 and 128 mg/kg with modafinil but the effect of NLS-4 was more sustainable than that of modafinil.

Conclusion: This study suggests that the impairment of circadian rhythm induced by a fatigue procedure was reduced by a similar magnitude with modafinil (64 mg/kg) and NLS-4 (16 mg/kg). Since modafinil has been shown to improve recovery from chronic fatigue in human, these results suggest that NLS-4 could improve recovery from CFS in human at doses four times lower than those used for modafinil.

T51. EFFECTS OF THE SELECTIVE AMPA MODULATOR NBI-1065845 ON THE PHARMACOKINETICS OF ETHINYL ESTRADIOL LEVONORGESTREL OR MIDAZOLAM IN HEALTHY ADULTS

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Abstract: Background: NBI-1065845 (TAK-653) is an investigational AMPA receptor positive allosteric modulator in phase 2 development for the treatment of major depressive disorder (NCT05203341). Here we report the results of a drug-drug interaction (DDI) study assessing the potential CYP3A induction effect of NBI 1065845 on the pharmacokinetics (PK) of an oral contraceptive ethinyl estradiol–levonorgestrel and midazolam.

Methods: This phase 1, open-label, parallel-arm study was conducted in healthy adults aged 18–55 years. The high dose of NBI-1065845 currently under evaluation in the ongoing SAVITRI study was selected for further evaluation in this DDI study. In treatment arm A, females received a combination oral contraceptive (ethinyl estradiol 30 μg and levonorgestrel 0.15 mg) on day 1, followed by NBI 1065845 alone on days 5–13. On day 14, NBI 1065845 was administered with ethinyl estradiol–levonorgestrel and then alone on days 15–17. In treatment arm B, females and males received midazolam 4 mg on day 1, followed by NBI 1065845 alone on days 5–13. On day 14, NBI 1065845 was administered with midazolam 4 mg and then alone on day 15. Blood samples were routinely collected, with serial PK assessments collected on days 1, 5 and 14. The primary PK endpoints were: area under the concentration-time curve (AUC) from time 0 to infinity (AUC0–∞), maximum plasma concentration (Cmax) of ethinyl estradiol and midazolam, and AUC from time 0 to last measurable concentration (AUC0–last) and Cmax for levonorgestrel, in the presence or absence of NBI 1065845. Safety endpoints included assessment of adverse events (AEs), laboratory tests, and vital signs.

Results: Treatment arm A comprised 17 females (mean age 41.5 years), of whom 16 completed the study (one participant discontinued due to an AE of COVID-19 considered unrelated to treatment). Treatment arm B comprised 14 males and 4 females (mean age 38.2 years), of whom 16 completed the study (one participant withdrew and one discontinued due to an AE of tonsillitis considered unrelated to treatment). Ethinyl estradiol, levonorgestrel, and midazolam were rapidly absorbed in the absence of NBI-1065845. Following multiple daily doses of NBI 1065845, the geometric mean ratios (GMRs) (90% CI) for Cmax were: ethinyl estradiol, 1.00 (0.87, 1.15); levonorgestrel, 0.99 (0.87, 1.13); and midazolam, 0.94 (0.79, 1.13). The GMRs (90% CI) for AUC0-∞ were 1.01 (0.88, 1.15) and 0.88 (0.78, 0.98) for ethinyl estradiol and midazolam, respectively. The GMR for AUC0-last was 0.87 (0.78, 0.96) for levonorgestrel. All AEs were mild or moderate in severity. Potentially clinically significant laboratory findings (NBI-1065845 alone, treatment arm B, n=2) were associated with AEs of moderately increased blood creatine phosphokinase and mildly decreased white blood cell count that were considered unrelated to treatment.

Discussion: No DDIs were observed between NBI-1065845 and ethinyl estradiol, levonorgestrel, or midazolam. The 13% decrease in AUC0–last for levonorgestrel and 12% decrease in AUC0–∞ for midazolam following NBI 1065845 coadministration did not meet the US Food and Drug Administration's definition of weak CYP3A induction (decrease of ≥20% to <50%), therefore NBI 1065845 coadministration with combined oral contraceptives

and other CYP3A substrates is supported. NBI 1065845 was generally well tolerated when administered with or without ethinyl estradiol, levonorgestrel, or midazolam.

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T52. PRECLINICAL PHARMACOLOGY OF SOLRIAMFETOL: POTENTIAL MECHANISMS FOR WAKE PROMOTION

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Abstract: Background: Solriamfetol is a wake-promoting agent (WPA) approved for the treatment of excessive daytime sleepiness associated with narcolepsy and obstructive sleep apnea. The wake-promoting mechanism of solriamfetol may result from dopamine and norepinephrine reuptake inhibition, but other mediators of cognition and arousal warrant exploration. Preclinical studies in rodents and non-human primates indicate that TAAR1 agonists may have wake promoting properties. We conducted preclinical pharmacology studies to identify additional targets activated by solriamfetol and compare them to those of WPAs and traditional stimulants.

Methods: In vitro binding and functional studies were conducted to measure the activity of solriamfetol and comparator WPAs. Electrophysiology studies were conducted in slice preparations from mouse ventral tegmental area (VTA). Locomotor activity studies were conducted in mice.

Results: In vitro studies showed agonist activity of solriamfetol at human, mouse, and rat TAAR1 receptors. TAAR1 EC50 values (10–16 μM) were within the clinically observed therapeutic plasma concentration range and overlapped with the observed DAT/NET inhibitory potencies of solriamfetol in vitro. Solriamfetol also exhibited agonist activity at serotonin 1A (5HT1A) receptors in vitro, with lower potency (EC50=25μM). Neither modafinil nor the DAT/NET inhibitor bupropion had TAAR1 agonist activity. Solriamfetol (1–10 μM) dose-dependently inhibited the firing frequency of dopaminergic VTA neurons in mouse brain slices, similar to known TAAR1 agonists. Unlike traditional stimulants, solriamfetol did not increase locomotor activity in naive mice, but inhibited locomotor activity in DAT knockout mice.

Conclusions: Preclinical studies have identified agonist activity at the TAAR1 receptor and lower potency agonist activity at 5-HT1A receptors for solriamfetol, in addition to its activity as a DAT/NET inhibitor. TAAR1 agonists are modulators of monoamine transmission with potential wake-promoting effects seen in preclinical studies, so TAAR1 activity may represent an additional mechanism underlying the effects of solriamfetol.

Support: Axsome Therapeutics and Jazz Pharmaceuticals

T53. PHARMACOLOGICAL PROFILE AND RELATIONSHIP BETWEEN PDE10A ENZYME OCCUPANCY AND PRECLINICAL EFFICACY FOR MK-8189, A NOVEL PDE10A INHIBITOR

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Abstract: Background: Phosphodiesterase 10A (PDE10A) is a member of the cyclic nucleotide phosphodiesterase family that functions to metabolically inactivate both cAMP and cGMP. PDE10A is expressed in the brain with high levels in medium spiny neurons of the striatum. Evidence from preclinical studies suggests that PDE10A inhibition may be a therapeutic target for schizophrenia. Here we present the preclinical pharmacological profile of MK-8189, a novel PDE10A inhibitor. We characterize the relationship between PDE10A enzyme occupancy (EO) and efficacy in preclinical behavioral models to establish EO targets for clinical studies with MK-8189.

Methods: In vitro functional activity of MK-8189 against PDE10A and other PDE families was evaluated using a fluorescence polarization assay. The ability of MK-8189 to inhibit PDE10A in vivo was determined by measuring changes of cGMP and phosphorylation of the AMPA receptor subunit GluR1 (Ser845) in the striatum of rats. A PDE10A selective radioligand, [3H]MK-8193, was used to determine PDE10A EO of MK-8189 in the rat striatum. In vivo PET EO studies of MK-8189 were also carried out in rhesus monkey using [11C]MK-8193. MK-8189 was tested in 3 assays (attenuation of psychomotor activity, conditioned avoidance responding, and pre-pulse inhibition) predictive of antipsychotic effects in the clinic.

Results: MK-8189 is a potent, competitive inhibitor of the human PDE10A enzyme (Ki = 0.029 nM) with greater than 500,000-fold selectivity over other PDE families. MK-8189 has a promising in vitro safety profile against ion channels (Iks, Cav1.2 and Nav1.5 > 30 μM, and hERG Ikr IC50 = 33 μM). Transporter studies indicate high potential for CNS penetration, with MK-8189 having high passive permeability and not being a substrate of human and monkey P-gp (B-A / A-B ratio of < 2). Administration of MK-8189 (0.3 – 3 mg/kg, p.o.) dose-dependently increased cGMP in the striatum of rats, and MK-8189 also produced a dose-dependent increase in GluR1 phosphorylation. Ex vivo EO studies revealed that a MK-8189 plasma concentration of 52 nM yielded ~50% EO of PDE10A in the rat striatum. EO studies of MK-8189 in rhesus monkey determined that a plasma concentration of 200 nM yielded ~50% EO in the striatum. MK-8189 (0.25 – 0.75 mg/kg, p.o.) produced a dose-dependent decrease in the MK-801 (non-competitive NMDA receptor antagonist) locomotor response at plasma exposures that corresponded to ~25 – 50% PDE10A EO. In the conditioned avoidance responding assay, MK-8189 (0.125 – 0.5 mg/kg, p.o.) dose-dependently decreased avoidance, and the threshold for full efficacy was achieved between 0.375 and 0.50 mg/kg doses that correspond to EO of ~ 48% and 75%, respectively. MK-8189 significantly reversed an MK-801-induced deficit in pre-pulse inhibition. Doses ranging from 0.25 - 0.5 mg/kg produced statistically significant reversal of MK-801, similar to the magnitude observed with clinically relevant doses of antipsychotics. Plasma levels indicated that these effects were observed at PDE10A EO of ~47% and higher.

Conclusions: MK-8189 is a potent and selective PDE10A inhibitor with excellent pharmaceutical properties. MK-8189 inhibited PDE10A in vivo and produced robust activation of the striatum as measured by cAMP and pGluR1 signaling. A novel PDE10A PET tracer (MK-8193) was used to establish a drug plasma level/ PDE10A EO relationship in both rat and rhesus monkey. These data were used to determine the PDE10A occupancy range required to achieve efficacy in preclinical models of antipsychotic behaviors. These studies

suggested that a minimum level of ~30% PDE10A EO was required to produce an efficacy signal in some assays, however, full antipsychotic-like activity across assays required >50% PDE10A EO.

T54. WEIGHT LOSS FOLLOWING PDE10A INHIBITOR SCHIZOPHRENIA TREATMENT EXPLAINED BY ADIPOSE TISSUE PHYSIOLOGY CHANGES IN OBESE MICE

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Abstract: Background: MK-8189 is an investigational selective PDE10A inhibitor which shows promise for treating schizophrenia. In a Phase 2a clinical trial MK-8189 showed an improvement in positive symptoms in people with schizophrenia versus placebo. Interestingly, MK-8189 was also observed to reduce body weight, particularly in those who were overweight and obese, while a significant weight gain was observed for the standard-of-care risperidone. The weight reduction represents a potentially important advantage over currently available antipsychotics which can cause significant weight gain, undesirable for patient well-being and treatment compliance. Previous preclinical results suggest this effect of PDE10A inhibition may be due to conversion of energy-storing white adipose tissue (WAT) into energy-burning brown adipose tissue (BAT) (so called 'WAT beiging'). Here, we report results from an in vivo Magnetic Resonance Imaging (MRI) study performed to further understand the treatment-induced adipose tissue physiology changes to inform future clinical studies and potential novel indications.

Methods: C57BL6 mice receiving a high fat diet for 10 weeks starting at age 6 weeks were treated for 14 days with the PDE10A inhibitor THPP-6 (n=9, 30 mg/kg) or vehicle (50% tween 80/0.25% MC, Veh, n=11). MultiGradient Echo MRI was performed and a multipeak magnitude model used to quantify adipose tissue fat fraction (FF) maps, according to protocol utilized in patient imaging. Vascular volume fraction (VF) was defined as ratio of voxels identified as vessels in FF maps to total voxels in the region of interest. After imaging, animals were sacrificed, and brown and white adipose tissue samples collected for PCR analysis.

Results: Mice receiving THPP-6 showed greater weight loss than vehicle-treated animals (-7.1±0.2g vs -0.8±0.4g THPP-6 vs Veh, p<10^-9). Imaging showed lower fat fraction in brown adipose tissue in THPP-6 treated vs Veh animals (FF=0.607±0.014 vs 0.700±0.0.008 THPP-6 vs Veh, p=0.0001), consistent with brown fat activation, as well as decreased fat fraction (FF=0.860±0.003 vs 0.8715±0.0.0014 THPP-6 vs Veh, p=0.003) and increased vascular infiltration in inguinal WAT (VF=0.022±0.005 vs 0.0086±0.0.0010 THPP-6 vs Veh, p=0.003), consistent with conversion of white fat to brown fat deposits. Gene expression analysis showed significant upregulation (p=0.02) of Ucp1 and PGC1alpha in the inguinal WAT of THPP-6 vs Veh animals (p=0.03 and p=0.01 respectively), genes highly expressed in normal BAT, further supporting the beiging hypothesis. Additionally, upregulation of angiogenesis marker Vegf-A (p=0.02) in THPP-6 group provides validation for vascular changes observed in MRI after treatment. No difference in blood lipid profile (cholesterol, triglycerides, HDL and LDL) was observed between groups (p>0.12).

Discussion: This work provides a detailed understanding of the mechanism of action of PDE10A inhibitor treatment on body weight in an obese mouse model, confirming transition

of white into brown adipose tissue, increasing thermogenesis. These findings will be valuable to guide the use of MK-8189 in schizophrenia. We showed for the first time that MRI can be successfully used for characterization of adipose tissue physiology changes and the beiging transition in mice after investigational drug treatment. This imaging approach could be translated into clinical studies to validate the effect of MK-8189 on human adipose tissue physiology.

T55. BIOMARKER FOR PARKINSON'S DISEASE USING RESTING STATE EEG AND MACHINE LEARNING

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Abstract: Background: Parkinson's disease (PD) is a neurodegenerative brain disorder that causes movement disorders, as well as cognitive impairment in a subset of patients. However, brain-based physiological biomarkers that could be used to diagnose PD are lacking. Therefore, we developed an automated machine learning (ML) pipeline with the following novel features: (1) unbiased removal of electroencephalography (EEG) artifacts, (2) automated data pre-processing and ML, (3) relatively low sample size and low density channel numbers, (4) explainable ML approaches guided by statistical selection of conventional EEG features.
Objective: To develop an EEG-based automated ML algorithm for differentiating patients with PD from healthy subjects.

Methods: Data were collected at Rennes University Hospital (Rennes, France), recruiting patients with PD (n=25, mean age 59.8±7.3, 60% males), and healthy subjects (n=25, mean age 56.6±8.2, 52% males). Patients with PD had a mean Montreal Cognitive Assessment (MoCA) of 27.8±1.7 and were on medication for the management of tremor. EEG was recorded for 5-6 min during resting state (eyes closed), 44 out of 256 EEG channels were selected and a band pass filter 3-50 Hz was applied. EEG data were transformed from the time domain to the frequency domain. A previously validated support-vector machine pipeline automatically detected and removed artifacts. Power spectral density (PSD) analysis was performed, and PSD features were selected based on unbiased statistical ranking. These features were input into a logistic regression model using 5-fold cross-validation.

Results: We reached a mean area under the receiver operating characteristic curve (AUROC) of 0.78 for classifying subjects as PD or healthy

(accuracy 0.70, sensitivity 0.52, specificity 0.88, positive predictive value 0.88, negative predictive value 0.66). Performance metrics are computed as the average across all 5 validation folds.

Conclusion: We developed a fully automated EEG-ML algorithm for differentiating healthy subjects from patients with PD. The novelty in our findings includes the identification of brain-based candidate biomarkers for PD that could guide diagnosis and enhance treatment. Technical novelty includes the transparent ML approach as opposed to black box deep learning methods, and the automated removal of artifacts enabling reproducible, rigorous, and scalable results. Our future research will focus on applying our automated EEG/ML processes to

develop biomarkers to enhance safety, patient selection, and assessment of treatment efficacy of neurodegenerative disease in clinical trials.

Disclosures: Julia Trabulsi,Haba Fonseca-Sabune, Arnaud Fosso-Pouangué, and Cécile Low-Kam are employees of SynapseBio, Inc.

Acknowledgement: This study is part of a research collaboration with Dr. Mahmoud Hassan (MINDIG) and the Institute of Clinical Neurosciences of Rennes (INCR), Rennes, France

T56. COMPUTATIONAL LINGUISTIC ANALYSIS OF SPEECH TASKS INDEXES SYMPTOM SEVERITY AND CHANGE IN ARABIC-SPEAKING INDIVIDUALS WITH SCHIZOPHRENIA

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Abstract: Background: Emerging evidence suggests that natural language processing and computational speech analysis may improve objective symptom assessment to help diagnose and monitor psychiatric disease. However, limited research exists for this approach in non-Western languages. In this study, we examined the ability of computational speech analysis to index symptom severity and track symptom change in Arabic-speaking schizophrenia patients. **Methods:** Participants were outpatients diagnosed with schizophrenia from three clinical sites in the Middle East and North Africa: Algeria (n=14), Jordan (n=27), and Saudi Arabia (n=16). Participants completed monthly speech- and language-focused tasks and clinical symptom evaluations for seven months. Symptom severity was assessed with the Positive and Negative Syndrome Scale (PANSS). Speech tasks were open-ended narratives, picture description, paragraph reading and recall, and verbal fluency. Recordings of participant speech were transcribed and translated into Modern Standard Arabic (MSA) to standardize speech across spoken dialects. Participant speech recordings and accompanying MSA transcripts were then analyzed to extract speech and language features capturing linguistic (lexical, syntactic, morphological, semantic coherence, discourse) and paralinguistic (acoustic, timing) speech properties. Correlation analyses examining associations between speech features and PANSS symptom scores were performed using Spearman correlations pooling all visits, and significant correlations ($p < .05$, False Discovery Rate-corrected within each task) were validated by examining if findings remained significant ($p < .05$) using partial Spearman correlations adjusted for demographic variables (age, sex, education) and study site. Associations between longitudinal change in identified speech features and change in symptom severity were examined with partial Spearman correlations performed on change scores calculated from adjacent visits, with results considered statistically significant at $p < .05$, FDR-corrected within each task.

Results: There were 116 significant correlations between speech features and symptom severity across 36 unique features, which included mostly paralinguistic and to a lesser extent linguistic feature categories, with most significant associations present for more than one symptom domain (partial correlations = -0.19-0.17). Features with significant symptom associations present on more than one task included acoustic (intensity variance, minimum fundamental frequency, zero-crossing rate, shimmer, jitter, Mel-frequency cepstrum coefficients), timing (medium paused duration), and lexical (noun use) features. Longitudinal

change score analyses indicated 25 significant correlations between change in speech and change in symptom severity, across five unique acoustic features (partial correlations = -0.26-0.23). Correlations present on multiple tasks included decreasing variance in intensity associated with increasing symptom severity, and increasing shimmer associated with increasing symptom severity.

Discussion: Computational speech and analysis can identify features associated with symptom severity and symptom change in Arabic-speaking schizophrenia participants, suggesting the cross-linguistic utility of this approach. Identified speech features may serve as novel digital markers to facilitate screening and symptom monitoring in clinical trials.

T57. MAPPING THE FUTURE OF INTERVENTIONAL PSYCHIATRY FOR THE OBSESSIVE-COMPULSIVE RELATED DISORDERS: A SCOPING REVIEW

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Abstract Body dysmorphic disorder (BDD), hoarding disorder (HD), skin-picking disorder (SPD), and hair-pulling disorder (HPD) are obsessive-compulsive related disorders (OCRDs) which are characterized by compulsive behaviours leading to distress and impairment. Current treatments for these disorders are able to attain only partial or non-response, leaving a significant gap in care and outcomes for patients. Interventional psychiatric approaches using neuromodulation (e.g., repetitive transcranial magnetic stimulation (rTMS)) may directly target specific regions of the brain for treatment, and such approaches are quickly becoming part of the standard of care for other disorders such as major depressive disorder. This scoping review maps the current literature on interventional psychiatric approaches for BDD, HD, SPD, and HPD, and synthesizes key findings in this burgeoning field. Databases were searched up to June 27, 2022 for studies examining interventional psychiatric treatments for BDD, HD, SPD, and HPD, producing 910 results. Twenty were included; 16 were case reports, two were case series, and two were randomized controlled trials. Studies reported on electroconvulsive therapy (ECT) (n=7), deep brain stimulation (DBS) (n=1), and intermittent theta-burst rTMS (n=1) for BDD; rTMS (n=1) and transcranial direct current stimulation (n=1) for HD; gamma knife capsulotomy (n=1) and rTMS (n=1) for SPD; and rTMS (n=2) and ECT (n=1) for HPD. Four studies reported on DBS for other indications complicated by SPD or HPD. The current literature consists mainly of case reports which is a significant limitation toward generalizability. There was also considerable variety in the choice of anatomic target and protocol parameters for any given technique and disorder, and these details were also inconsistently reported. This variability likely reflects the current limited knowledge regarding the neurobiological basis for the OCRDs. Future studies should be randomized, controlled, adequately powered and blinded, ideally beginning with investigations of rTMS localized to various hypothesized anatomical targets for each disorder. This scoping review suggests a field that is nascent in both the quality and quantity of extant investigations, with very few mechanistic hypotheses that have been tested and elucidated leading to an inability to draw conclusions about any of the interventions. Presently, the mainstay of treatment remains disorder-specific psychotherapy with limited evidence for medications. With current treatments that are difficult to access, limited in evidence, or not efficacious, it is anticipated that interest in interventional psychiatry and the ability to target underlying brain mechanisms

will continue to grow, and this review will contribute to the development of these novel treatments and their potential to be applied to the oft-undertreated and debilitating OCRDs.

T58. EFFECT OF LEMBOREXANT ON SLEEP ONSET AND SLEEP MAINTENANCE IN PATIENTS WITH COMORBID INSOMNIA DISORDER AND MILD OBSTRUCTIVE SLEEP APNEA

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Abstract: Background: Insomnia and obstructive sleep apnea (OSA) are frequently comorbid sleep disorders. However, hypnotic drugs such as benzodiazepines may exacerbate pre-existing respiratory dysfunction (Hsu, 2021). This post-hoc analysis evaluated the effects of lemborexant (LEM), a competitive dual orexin receptor antagonist approved in multiple countries for the treatment of insomnia, in subjects with comorbid insomnia disorder and OSA (COMISA) of mild severity.

Methods: Study E2006-G000-304 (Study 304; NCT02783729) was a 1-month, randomized, double-blind, placebo (PBO)-controlled and active-comparator (zolpidem tartrate extended release 6.25 mg [ZOL]) study of LEM 5 mg (LEM5) and LEM 10 mg (LEM10) in subjects age ≥55 y (Rosenberg, 2019). This post-hoc analysis included subjects with both insomnia disorder and mild OSA (apnea hypopnea index [AHI] ≥5 and <15 events/h of sleep). Sleep onset (latency to persistent sleep [LPS]), sleep maintenance (sleep efficiency [SE] = total sleep time / time in bed), wake after sleep onset (WASO), and WASO in the second half of the night (WASO2H) were assessed at Nights 1/2 (NT1/2) and Nights 29/30 (NT29/30) using polysomnography.

Results: In this study, 40.8% of the population (n=410/1006) had mild OSA, with AHI mean (SD) 9.33 (2.9) events/h at screening; median age was 65 y, and 83.9% of subjects were female. Improvement (increase) in SE from baseline was larger and significantly different for both LEM5 and LEM10 versus PBO and ZOL on NT1/2 ($P<0.05$) and NT29/30 ($P<0.0001$). LPS, WASO, and WASO2H were significantly improved (decreased) ($P<0.005$) with LEM5 and LEM10 compared with PBO at both time points. Compared with ZOL, LEM10 produced significantly greater improvements for LPS, WASO, and WASO2H at NT1/2 and NT29/30 ($P<0.01$, all assessments) and with LEM5 on NT29/30 ($P<0.02$, all assessments). LEM was well tolerated, with no new safety signals.

Conclusion: These results demonstrate the effectiveness of LEM versus PBO and ZOL in an older patient population with insomnia disorder and mild OSA.

Support: Eisai Inc.

T59. TRAZODONE FOR TREATING INSOMNIA: ABUSE AND SAFETY RISKS

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Abstract: Background: Trazodone (TRAZ) is currently one of the most commonly prescribed medications for insomnia in the United States despite not having FDA approval for the disorder (Jaffer et al, 2017). TRAZ use has surpassed that of z-drugs and benzodiazepines (BZ) in part because of the perception that its lack of scheduling makes it a safer option. However, no formal assessment of potential abuse/dependence was conducted at the time of its approval (per prescribing information). The objective of this study was to collate information on patient's abuse/dependence of TRAZ and other safety risks by using publicly available data sources and published literature.

Methods: Nationally reported data from multiple databases were used to identify cases where TRAZ was the suspect drug. Adverse events (AEs) captured in the FDA Adverse Events Reporting System (FAERS) from January 1, 2015, through June 30, 2022 that were attributed to TRAZ or any of 3 most commonly prescribed BZ indicated for insomnia (temazepam, triazolam, estazolam) were identified for inclusion in this study. Additionally, instances of drugs that included TRAZ confiscated by law enforcement captured in the National Forensic Laboratory Information System (NFLIS) were evaluated. Incidences of potential TRAZ poisoning reported to the American Association of Poison Control Centers' National Poison Data System (AAPCC-NPDS) were also assessed. Published claims data analyses of comparative risk of falls with TRAZ, BZ, and zolpidem immediate release (IR) use reported in Medicare 100% Sample and MarketScan Commercial Claims were also included.

Results: Of the 11,228 TRAZ reports in FAERS, 6.4% and 1.1% were for drug abuse or drug dependence, respectively; 81.8% of the cases were considered serious, 35.4% associated with death, and 33.8% included initial or prolonged hospitalization. Of the 5120 BZ reports in FAERS, 12.6% and 3.6% were for drug abuse or drug dependence, respectively; 83.9% of the cases were considered serious, 36.0% associated with death, and 25.7% with initial or prolonged hospitalization. In 2020, among drug seizure cases reported to NFLIS, 612/1575874 included TRAZ, whereas 22,225/1446011 case mentions of TRAZ and 8445 single exposures to TRAZ were reported to the AAPCC-NPDS. Among Medicare beneficiaries age ≥65 years, the risk of falls over a 1-year period after initiating TRAZ was 9.5% vs 11.3% for BZ and 7.7% for zolpidem IR (Amari et al, 2022a). Among commercially insured enrollees age ≥18 years, the risk of falls over a 1-year period after initiating TRAZ was 4.6% compared with 3.7% for BZ and 2.5% for zolpidem IR (Amari et al, 2022b).

Conclusions: TRAZ has important and underappreciated risks, including the risk of abuse/dependence. Although the percentage of abuse/dependence-related AEs reported were lower than for BZ, there were findings of overdose, deaths, falls, and drug-related arrests which support that TRAZ should be used with caution. Together with the lack of efficacy data from large and well-controlled studies and its lack of FDA approval, the continued high rate of prescribing TRAZ for insomnia should be re-evaluated from a public health perspective.

Support: Eisai Inc.

T60. SKILLED NURSING FACILITY STAYS AND LONG-TERM CARE ADMISSIONS AVOIDED WITH PIMAVANSERIN OR OTHER ATYPICAL ANTIPSYCHOTICS: A COST-OFFSET ANALYSIS OF PATIENTS WITH PARKINSON'S DISEASE PSYCHOSIS

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Abstract: Background: Patients with Parkinson's disease psychosis (PDP) that are treated with pimavanserin (PIM) vs. other atypical antipsychotics (AAPs) may have fewer skilled nursing facility-stays (SNF-stays) and long-term care admissions (LTCA). Consequently, SNF-stay and LTCA associated rehabilitation and room/board costs may be avoided. A cost-offset analysis from a Medicare perspective was developed to compare cost savings due to avoided SNF-stays/LTCA among patients treated with PIM vs. (i) quetiapine-only (QUE), and (ii) other-AAPs (i.e., quetiapine, risperidone, olanzapine, aripiprazole).

Methods: A decision tree model was developed using the 2019 Medicare Patient-Driven Payment Model (PDPM) to estimate SNF-stay and LTCA associated per patient per year (PPPY) facility and rehabilitation costs among Medicare patients that initiated PIM vs. QUE or vs. other-AAPs. PDPM was implemented to replace the SNF/LTC per diem volume-based payment with a case-mix adjusted value-based payment that reflects patients' primary diagnosis and clinical status. Model inputs for annual SNF-stay and LTCA rates and costs, respectively, were derived from: (i) an analysis of Medicare beneficiaries with PDP (PD diagnosis-ICD-9 332.0/ICD-10 G20 with the concurrent occurrence of ≥1 psychosis or psychotic disorder claims with hallucination/delusions, psychosis, delusion disorder, visual disturbances, hallucinations) treated with PIM, QUE, or AAPs, and (ii) PDPM rehabilitation costs associated with the 5 PDPM case-mix adjusted components (i.e., physical therapy, occupational therapy, nursing, speech-language pathology, non-therapy ancillary), and an additional variable-per-diem (VDP) for room/board services. PPPY costs were estimated from SNF-stay and LTCA rates multiplied by total costs of stay per year and reported in 2022 USD. Probabilistic sensitivity analysis (PSA) was performed using 1000 monte carlo simulations to determine model robustness.

Results: Overall SNF-stay rates of 18.3%, 27.0%, and 27.2%, and LTCA rates of 20.7%, 28.7%, 29.2% were observed for patients on PIMA, QUE, and other-AAPs, respectively. Based on annual mean costs, PPPY SNF-stay costs for patients on PIM ($37,858) vs. QUE ($55,912) or vs. other-AAPs ($56,271), resulted in $18,054 and $18,413 PPPY cost savings, respectively. Similarly, PPPY LTCA costs for patients on PIM ($42,875) vs. QUE ($59,389) or vs. other-AAPs ($60,566) resulted in $16,514 and $17,691 PPPY cost-savings, respectively, due to fewer annual LTCA with PIM. PSA Results: suggested PIM would provide cost-savings compared to QUE or other-AAPs in >99% of iterations.

Conclusion: In this analysis, PIM demonstrated 32.3% and 27.8% lower PPPY SNF-stays and LTCA costs, respectively compared to QUE. Similarly, PIM also demonstrated a 32.7% and 29.2% lower PPPY SNF-stay and LTCA costs, respectively, vs. other-AAPs. Research examining additional medical cost-offsets (i.e., fewer falls/fractures) associated with SNF-stay/LTCA avoidance may be needed.

T61. DYSGLYCEMIA AND CLINICAL IMPROVEMENT IN PATIENTS WITH SCHIZOPHRENIA TREATED WITH ANTIPSYCHOTICS: A SYSTEMATIC REVIEW

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Abstract: Background: Antipsychotics are the cornerstone of treatment for schizophrenia; however, their use is associated with several metabolic consequences including weight gain, dyslipidemia, and dysglycemia. Previous research suggests that a 'metabolic threshold', which delineates a relationship between antipsychotic efficacy and metabolic burden, may exist with respect to both weight gain and dyslipidemia. Therefore, the aim of this exploratory review is to determine whether a similar relationship between dysglycemia and clinical improvement exists among patients with schizophrenia.

Methods: To accomplish this, we conducted a systematic search in MEDLINE, EMBASE, PsychINFO, CINAHL, CENTRAL, and Scopus from inception to June 2022. Longitudinal studies that directly examined the relationship between changes in glucose parameters and psychopathology among patients with schizophrenia treated with antipsychotics were included. Findings were synthesized qualitatively according to symptom domain, antipsychotic type, patient treatment status, study duration, and study quality.

Results: Our search identified 11 studies that compared changes in parameters of glucose metabolism and psychopathology over time. In most cases, we found that increased levels of glucose parameters following treatment were associated with clinical improvement. This provides evidence for a metabolic threshold for antipsychotics related to glucose homeostasis. However, independence from weight gain and alterations in lipid parameters remains to be conclusively shown. In addition, further research is needed to determine how factors such as illness duration, cumulative antipsychotic exposure, and treatment resistance may impact the relation.

Conclusions: This review supports a need for additional work aimed at exploring the validity of a glucose-psychopathology relation to improve our understanding of antipsychotic side effects in relation to mechanism of action. Subsequent findings can then be used to inform treatment planning, side effect management, and overall patient care.

T62. A COMPARISON OF ORAL ARIPIPRAZOLE WITH AN INGESTIBLE SENSOR WITH ORAL ATYPICAL ANTIPSYCHOTIC TREATMENT AND IMPACT ON PSYCHIATRIC HOSPITALIZATIONS IN ADULTS WITH SCHIZOPHRENIA IN A REAL-WORLD CARE SETTING

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Abstract: Background: To compare the risk of psychiatric hospitalization among adults with schizophrenia using aripiprazole with an ingestible sensor (AS), to those on oral atypical antipsychotic (OAA) treatment in the real world.

Methods: A real-world data (RWD) platform, NeuroBlu was used to develop a retrospective cohort of adults with schizophrenia, using US MindLinc electronic health data. This RWD cohort was compared to adults with schizophrenia from a completed single-arm phase IIIb trial using AS. Risk of psychiatric hospitalization was the primary clinical trial endpoint.

Inclusion criteria for the RWD cohort closely mirrored the AS trial, and the index date for the RWD cohort occurred 6 months post-initiation of an OAA. Propensity scores were used to match the AS and RWD cohorts on a 1:1 basis and to balance covariates across cohorts. Covariates were selected using stepwise regression and clinical judgement, and standardized mean differences (SMDs) were used for covariate balance diagnostics. Retrospective hospitalizations within 6 and 3 months pre-index were ascertained for both cohorts. The primary outcome was the number needed to treat (NNT) to prevent a hospitalization within 3 months post-index.

Results: Cohort matching with six variables (baseline CGI-S, duration of psychiatric hospitalizations, age, sex, race, and baseline OAA dose) produced 95 matched pairs out of 113 possible pairs. These covariates were well balanced (SMD < 0.1) across cohorts (mean/max SMD 0.041/0.08). There were 10 (10.5%) hospitalizations pre-index, and 0 hospitalizations post-index for the trial cohort. In the RWD cohort, there were 29 (30.5%) and 11 hospitalizations (11.6%) pre/post-index respectively. The post-index difference was statistically significant ($p<0.05$) and the NNT for AS was 9 (95% CI 6-20).

CONCLUSION: The results of this analysis are consistent with findings from the AS trial; it might suggest that treatment with AS for adults with schizophrenia indicates a reduction in psychiatric hospitalization.

Sponsor: Otsuka Pharmaceutical Development and Commercialization, Inc.

T63. PHARMACOKINETIC SIMULATIONS OF ARIPIPRAZOLE 2-MONTH READY-TO-USE LONG-ACTING INJECTABLE TO INFORM ADMINISTRATION IN ADULT PATIENTS WITH SCHIZOPHRENIA OR BIPOLAR-I DISORDER

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Abstract: Background: Ongoing symptom control in schizophrenia and bipolar I disorder relies on continued antipsychotic treatment, but suboptimal adherence occurs with oral formulations (1). Aripiprazole 2-month ready-to-use 960 mg (Ari 2MRTU 960) is a novel long-acting injectable (LAI) formulation of aripiprazole for gluteal intramuscular administration once every 2 months. Ari 2MRTU 960 was developed to extend exposure to aripiprazole concentrations within the established aripiprazole therapeutic window to 2 months, potentially reducing the treatment burden for patients and clinicians and improving adherence. A combined population pharmacokinetic model for oral aripiprazole, aripiprazole once-monthly 400 mg (AOM 400), and Ari 2MRTU 960 was developed (2). Use of this model to explore dosing with Ari 2MRTU 960 in various patient scenarios relevant to the US clinical context is reported herein.

Methods: Aripiprazole plasma concentration–time profiles were simulated for various Ari 2MRTU treatment initiation and maintenance scenarios. Simulations were performed using Pumas v2.0 in a population of 1,000 virtual patients.

Results: Across multiple simulated treatment initiation scenarios, in which 14 days of oral aripiprazole 10 or 20 mg/day was co-administered, Ari 2MRTU 960 resulted in aripiprazole concentrations that were comparable to AOM 400. This was the case for: initiation of Ari

2MRTU 960 after a switch from AOM 400; initiation of Ari 2MRTU 960 with prior stabilization on oral aripiprazole 10 or 20 mg/day; initiation of Ari 2MRTU 960 without prior oral aripiprazole stabilization; initiation of Ari 2MRTU 960 on Day 28 after administration of AOM 400 on Day 0 with prior stabilization on oral aripiprazole 20 mg/day; and initiation of Ari 2MRTU 960 on Day 28 after administration of AOM 400 on Day 0 without prior stabilization on oral aripiprazole. In maintenance scenarios, median trough concentrations were 191, 144, 110, and 80.1 ng/mL after an Ari 2MRTU 960 dosing delay of 2, 4, 6, and 8 weeks, respectively, increasing to 231, 217, 205, and 196 ng/mL, respectively, 56 days after the delayed dose was given (plus 14 days of oral aripiprazole 10 mg/day overlap in the last scenario). In CYP2D6 poor metabolizers, Ari 2MRTU 720 mg showed comparable steady-state aripiprazole concentrations versus AOM 300 mg, but less overall variability. Compared with Ari 2MRTU 960 without a CYP3A4 or CYP2D6 strong inhibitor, aripiprazole concentrations were similar with Ari 2MRTU 720 plus a CYP3A4 strong inhibitor and higher with Ari 2MRTU 720 with a CYP2D6 strong inhibitor.

Conclusion: Model simulations showed that aripiprazole plasma concentrations over the 2-month dosing interval with Ari 2MRTU 960 were comparable to those observed with AOM 400 administered once-monthly. These data will inform dosing of Ari 2MRTU 960 across the patient and clinical scenarios considered in these simulations, not all of which can be feasibly evaluated in a clinical trial.

T64. PREDICTED PANSS SCORE AFTER WEEKLY LYN-005, A LONG-ACTING ORAL FORMULATION OF RISPERIDONE, ADMINISTRATION

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Abstract: Background: LYN-005 is a once weekly, long-acting oral formulation of risperidone being developed to reduce the dosing frequency and improve treatment adherence in the management of schizophrenia and schizoaffective disorder. LYN-005 is a capsule containing a folded star-shaped dosage form, with polymeric arms connected to a flexible core. The capsule contains 15, 30 or 45 mg of risperidone (equivalent to 2, 4, and 6 mg immediate release (IR) risperidone, respectively), depending on the number of arms which contain active drug that are designed to release risperidone in a controlled manner over the entire week. Weekly administration of oral risperidone is proposed to provide more consistent plasma concentrations compared to daily dosing.

Methods: Modeling approaches have helped greatly in drug development by diminishing the need for large clinical studies. A population pharmacokinetic (PK) model for IR risperidone and LYN-005 was developed using PK data from a Lyndra clinical study. The active moiety of risperidone was considered responsible for its antipsychotic efficacy. The minimum (Css,min) and average (Css, avg) steady state concentrations of the active moiety were predicted from the developed population PK model. A published population pharmacodynamic (PD) model for risperidone was evaluated and linked to the population PK model to predict positive and negative syndrome scale (PANSS) scores for IR risperidone and LYN-005 at steady state. The relationship between steady state concentrations and PANSS score was explored via linear regression and locally weighted scatterplot smoothing curve fitting.

Results: Steady state for LYN-005 PK was noted by the 5th dose. Total PANSS scores reduction was similar between dose-equivalent IR risperidone and LYN-005 groups with higher variability noted in the IR groups. This variability was not clinically significant and was attributed to greater variability in the IR PK profile and the inherent variability in PANSS scores. The median Css,min for LYN-005 15, 30 and 45 mg doses were 8.14, 17.46 and 26.19 ng/mL respectively, all of which were higher than the literature reported effective concentration of 5.2 ng/mL. The maximum decrease in total PANSS scores from baseline was noted by week 5. A slight decrease in PANSS score was noted with an increase in Css,min. No trends were noted between Css,avg and PANSS score.

Conclusions: The simulations predicted that LYN-005 will have similar efficacy to IR risperidone as noted by the decrease in PANSS score at steady state. A slight decrease in PANSS score was noted with an increase in Css,min suggesting that efficacy may be driven by Css,min and not Css,avg.

T65. ARIPIPRAZOLE 2-MONTH READY-TO-USE: A NOVEL LONG-ACTING INJECTABLE ANTIPSYCHOTIC FORMULATION FOR ADMINISTRATION ONCE EVERY 2 MONTHS

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Abstract Schizophrenia and bipolar I disorder (BP-I) are chronic mental health conditions that require maintenance pharmacological treatment to ensure symptom control. Despite this, suboptimal adherence with daily oral antipsychotic treatment is common. Long-acting injectable (LAI) antipsychotics have been developed to increase adherence versus oral medication; currently available LAIs offer dosing intervals that range from 2 weeks to 6 months. Data have shown a beneficial effect of LAIs versus oral antipsychotics in terms of reducing the risk of hospitalization and relapse (1).

Aripiprazole exhibits partial agonist activity at dopamine D2 receptors and serotonin 5-HT1A receptors, full agonist activity at dopamine D3 receptors, and antagonist activity at serotonin 5-HT2A receptors (2). To date, aripiprazole has been available in a daily oral formulation and as an extended release once-monthly formulation for intramuscular (IM) injection (aripiprazole once-monthly 400 mg [AOM 400]). Aripiprazole 2-month ready-to-use (Ari 2MRTU) is a novel LAI formulation of aripiprazole monohydrate for gluteal IM administration once every 2 months, in development for the treatment of schizophrenia or BP-I. Ari 2MRTU has been developed to extend exposure to aripiprazole concentrations within the therapeutic window to 2 months. Ari 2MRTU has been shown to be generally well tolerated; investigator's assessment of the injection site reflected minimal reactions in adults with schizophrenia or BP-I.

Ari 2MRTU is planned for presentation as a prolonged-release suspension for injection in a single use pre-filled syringe; it will be provided in its final container, with no dilution or reconstitution required prior to administration. Each Ari 2MRTU pre-filled syringe will contain 960 mg of aripiprazole monohydrate (total volume 3.2 mL) for administration once every 2 months, providing a dose of aripiprazole that is comparable with a monthly dose of AOM 400. In case of any tolerability issues, a 720 mg dose of Ari 2MRTU (total volume 2.4 mL) for

administration once every 2 months will be available, providing a dose of aripiprazole that is comparable with a monthly dose of AOM 300 mg. The suspension is a white to off-white color, with a neutral pH (approximately 7.0); Ari 2MRTU should be stored at controlled room temperature.

Ari 2MRTU is to be injected slowly as a single IM injection in the gluteal muscle. For patients who have never taken aripiprazole, tolerability to aripiprazole must be established prior to initiating treatment with Ari 2MRTU. Overlapping treatment with oral aripiprazole is required for patients initiating Ari 2MRTU, unless they have been stabilized on AOM. The recommended maintenance dose of Ari 2MRTU is 960 mg. A maintenance dose of 720 mg dose should be considered in the event of adverse reactions with the 960 mg dose and is recommended in patients who are poor metabolizers of CYP2D6 or who are taking strong inhibitors of CYP2D6 or CYP3A4. Following an initial dose, Ari 2MRTU should be administered once every 2 months (56 days after the previous injection).

In conclusion, Ari 2MRTU is a novel LAI formulation of aripiprazole monohydrate for gluteal IM administration that comes in a ready-to-use syringe and does not require reconstitution. Increasing the dosing interval to 2 months has the potential to reduce the treatment burden for patients and clinicians.

T66. LATITUDE: LONG-ACTING ANTIPSYCHOTIC TREATMENTS IN COMMUNITY TELEPSYCHIATRY: KNOWLEDGE, ATTITUDES, AND PERCEIVED BARRIERS

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Abstract: Background: The South Carolina Department of Mental Health instituted a Community Telepsychiatry Program (CTP) to increase patient access to mental health practitioners. The need for in-person administration of long-acting injectable (LAI) antipsychotics may add barriers to their use in telepsychiatry, despite the known effectiveness of these agents for schizophrenia. The LATITUDE study assessed knowledge of, attitudes toward, and perceived barriers to using LAI antipsychotics via telepsychiatry.

Methods: LATITUDE used quantitative surveys of CTP providers and qualitative interviews with CTP providers, community mental health center (CMHC) clinicians, patient caregivers, and adults with schizophrenia to gather perceptions regarding LAI antipsychotic use within the telepsychiatry treatment paradigm.

Results: Eleven CTP providers, 10 CMHC clinicians, 3 caregivers, and 15 adults with schizophrenia participated in qualitative interviews between October 2021 and January 2022. Telepsychiatry services were perceived positively overall; barriers included patient hesitancy (59%) and provider perceptions that patients faced technical challenges in accessing telepsychiatry appointments (44%). A hybrid virtual and in-person treatment approach was endorsed by CTP providers (55%), who stated that improvements were needed in support services for administering LAI antipsychotics after virtual appointments. The main reported benefit of LAI antipsychotics was medication compliance (67%); barriers included fear of needles (49%) and treatment side effects (44%).

Conclusions: The LATITUDE study findings highlight both barriers and facilitators of telepsychiatry use. Considering the rapid and potentially long-term adoption of telepsychiatry and hybrid care, this information may prove helpful to understanding and implementing best practices that support LAI antipsychotic treatment within the context of community telepsychiatry.

T67. REVIEW OF THE TAAR1 AGONIST ULOTARONT: PART I - FROM DISCOVERY TO CLINIC

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Abstract: Background: Trace amine-associated receptors (TAARs) are a family of G-protein-coupled receptors (GPCRs). TAAR1 has emerged as a promising therapeutic target for several neuropsychiatric disorders due to its ability to modulate monoaminergic and glutamatergic neurotransmission. Ulotaront is the first therapeutic agent in this class to complete Phase 2 clinical trials. Here we provide a brief review of the discovery of ulotaront and the preclinical research suggesting its efficacy in schizophrenia, leading to the first clinical trial resulting in FDA designation of ulotaront as a Breakthrough Therapy.

Methods: Candidate compounds were screened using a high-throughput, mouse-behavior phenotyping platform (SmartCube®) in combination with in vitro anti-target screening designed to identify compounds exhibiting antipsychotic-like activity in the absence of dopamine (D2) and serotonin (5-HT2A) receptor activity.

Ulotaront was identified and subsequently studied in established preclinical models of schizophrenia and tested against several panels of known molecular targets. Follow-up studies, including in vitro and in vivo electrophysiology recordings, as well as PET imaging, were conducted to elucidate the underlying mechanism of action.

Results: The high-throughput, mouse-behavior phenotyping methodology identified ulotaront as a promising drug candidate. In vivo, ulotaront demonstrated efficacy in preclinical models of schizophrenia, including phencyclidine (PCP)-induced hyperactivity, prepulse inhibition of the acoustic startle response, and subchronic PCP-induced deficits in social interaction. Although not fully elucidated, the mechanism is thought to be largely mediated by agonism at TAAR1 and 5-HT1A receptors. This was further corroborated with whole cell patch clamp recordings, demonstrating inhibition of dorsal raphe nucleus (DRN) and ventral tegmental area (VTA) neuronal firing via 5-HT1A and TAAR1 receptors. Furthermore, ulotaront attenuated the ketamine-induced increase in striatal dopamine synthesis capacity, suggesting that it may modulate presynaptic dopamine dysfunction, hypothesized to contribute to the pathophysiology of schizophrenia. The results of a standard preclinical abuse liability battery suggest that ulotaront is not likely to pose a risk for abuse in humans and may even have potential therapeutic utility as a treatment of substance use disorders.

Conclusions: Findings from in vitro and in vivo studies have identified ulotaront as a TAAR1 agonist with robust antipsychotic-like activity in rodent models. Ulotaront's unique target profile led to its designation as a member of the new "-taront" class of TAAR1 agonists, distinct from the approved D2/5-HT2A class of antipsychotics. A companion poster will summarize the broad-spectrum efficacy, tolerability, and safety features of ulotaront based on initial clinical trials in patients with schizophrenia.

T68. OPIOID TREATMENT FOR PAIN AND COGNITIVE IMPAIRMENT: A CASE REPORT

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Abstract A 68-year-old male with a past medical history of dementia, incidental finding of hydrocephalus, and chronic opioid use, was brought in by ambulance from an assisted living facility for altered mental status. He was disoriented with tangential speech and psychiatric consult was called. He was diagnosed with dementia and anomia by his neurologist less than a year ago and reportedly has been worsening since. As per his health care proxy, the patient had long term use of Vicodin for hip pain management and prior to admission, had been misusing his prescription. During the interview, the patient was unable to provide any history due to cognitive impairment, despite being alert and ambulating. His speech was repetitive and nonsensical. Obtaining history involved contacting his health care proxy and pain management physician, as well as his primary care physician. A thorough search of his prescription history revealed continuous monthly prescriptions of Vicodin. Due to his mental status, he was ineligible for transfer to the detox unit and instead was treated on the medical floor with Suboxone. Considering his age and mental status, his worsening trajectory in less than a year was unusual. To investigate whether our patient's history of long-term opioid use could have contributed to his declining function, we reviewed literature on the effects of opioid use on neurocognitive function and it was supportive of such evidence in some, but not all studies. Prescribers should be aware of the potential complications and subsequent effects of higher dosage opioids on cognition and functioning levels, as well as possibly addiction or dependence. Risks and benefits of opioids for pain management and addiction treatment must be weighed, treatment duration should be kept shorter, and dosage as low as possible.

T69. PATIENT JOURNEY OF CIVILIAN ADULTS TREATED FOR POST-TRAUMATIC STRESS DISORDER – A CHART REVIEW STUDY

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Abstract: Background: The post-traumatic stress disorder (PTSD) patient journey from experiencing a traumatic event through onset of symptoms, diagnosis, and treatment is poorly understood due to scarce literature, heterogeneous manifestation, and limited approved treatments. This study aims to improve our understanding of the journey of civilian patients with PTSD receiving treatment in the United States.

Methods: In this retrospective study, psychiatrists who diagnosed and treated ≥1 civilian adult patient with PTSD were requested to provide patient-level information via a pre-specified case report form and were surveyed for psychiatrist-level information. Eligible patient charts included those of civilian adults diagnosed with PTSD in 2016-2020 who received ≥1 PTSD-related treatment (selective serotonin reuptake inhibitor [SSRI], serotonin-norepinephrine reuptake inhibitor [SNRI], atypical antipsychotics [AA]) and who had ≥1 medical visit in the 12 months prior to data collection (February-May 2022). Clinical and treatment characteristics

in the 6 months pre-PTSD diagnosis, on the date of diagnosis, and during the 24 months post-diagnosis were collected from patient medical charts. Psychiatrist characteristics and perspectives on current PTSD treatments were collected from the survey.

Results: The 273 psychiatrists surveyed (59.0% aged 35-54 years; 60.1% male) abstracted data for 687 patients with PTSD (average age 36.1; 60.4% female). On average, the traumatic event occurred 8.7 years pre-diagnosis (average age 27.5), with 55.5% experiencing multiple or continuous traumas, and symptom onset occurred 6.5 years pre-diagnosis (average age 29.8). Pre-diagnosis, 88.9% of patients had previously received a PTSD-related treatment. At diagnosis, 49.0% had psychiatrist-reported severe PTSD and commonly presented with intrusion symptoms (87.8%) and alterations in cognition/mood (78.9%); comorbidities included depressive disorder (41.2%), anxiety (38.7%), and insomnia (26.5%). Post diagnosis, patients were treated within an average of 1.9 months and often received an SSRI as the first-line treatment in monotherapy (52.8%) or combination therapy (24.9%). PTSD diagnosis led to a treatment change for 79.3% of patients, with inadequate symptom management being the most common reason reported (51.5%). Approximately 58.8% of patients received ≥2 distinct PTSD-related agents in the 24 months post diagnosis and only a third (34.4%) of adults with PTSD achieved remission (average time to remission: 13.6 months) as assessed and recorded by psychiatrists.

In the psychiatrist survey, the most common reason reported to document a PTSD diagnosis was to facilitate targeted PTSD symptom management (92.7%), patient acceptance of condition (58.2%), and access to PTSD-specific treatment (56.0%). Approximately 23.0% of psychiatrists were dissatisfied with approved PTSD treatments, with 88.3% at least somewhat likely to prescribe AAs for PTSD despite no currently approved options.

Conclusion: PTSD presents heterogeneously, with patients experiencing a variety of symptoms and comorbidities, contributing to a complex and lengthy journey from trauma to diagnosis (nearly 9 years), often with pre-treatment of symptoms. PTSD may be challenging to detect but early diagnosis may facilitate streamlined patient management to improve remission rates, especially considering limited treatment options.

T70. METHYLONE: DISTINCT PHARMACOLOGICAL AND MECHANISTIC EFFECTS COMPARED WITH MDMA

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Abstract Post-traumatic stress disorder (PTSD) is a debilitating psychiatric illness affecting 12 million adults in the United States in a given year. Available treatments are limited. Selective serotonin reuptake inhibitors (SSRIs) represent first-line pharmacological options. However, despite the established modest efficacy of SSRIs, these treatments are sub-optimal. The therapeutic response is slow – most patients do not show significant effects until at least 4 weeks (and often up to 8 weeks) of continuous treatment, and even when optimally delivered, 30-40% of patients do not respond at all. MDMA-assisted psychotherapy has shown promise in recent clinical trials and may soon become an available treatment for PTSD. But its outreach may be limited due to the cardiovascular side-effects and an inability to co-administer with SSRIs. Methylone is the beta-ketone analog of MDMA. However, methylone shows distinct

pharmacological and subjective effects. Initial clinical studies of methylone include two published Phase 1 studies and two retrospective clinical case series demonstrating that methylone is well-tolerated and may alleviate symptoms of PTSD and MDD. Unpublished data show methylone is active in a preclinical model of PTSD, and a recently published report shows robust, fast-acting, and long-lasting antidepressant-like activity in the Forced Swim Test (FST) as well as anxiolytic activity, measured by increased center time in the Open Field Test. An SSRI did not reduce methylone's activity, a notable distinction from MDMA. Here we explore methylone's underlying mechanism of action as it relates to efficacy and safety. In vitro studies were conducted using rat brain synaptosomes. We demonstrated that methylone blocked reuptake and facilitated release at monoamine transporters (i.e., SERT, NET, DAT). Results showed that methylone's relative affinities for the different transporters were distinct from MDMA. 68pecificallyy, methylone had less effect on serotonin and dopamine transporters. To determine whether these sites of action were specific, the agonist/antagonist activity of methylone (vs. MDMA) was measured using a high throughput beta-arrestin-based screen of 168 different G-protein coupled receptors (GPCRs). Methylone showed no agonist or antagonist activity at any GPCRs while MDMA showed activity at 7 GPCRs. Previous work has shown that MDMA is a 5HTR2B agonist, which may have cardiovascular safety implications. In contrast, we found that methylone showed no activity at this receptor. Finally, we examined the downstream gene expression changes induced by methylone and MDMA using RNAseq in brain areas relevant to PSTD and MDD. Rats were treated with methylone or MDMA and sacrificed 8 hours later. Drug-induced gene expression was compared between methylone and MDMA-treated groups, further highlighting the differences between these structurally similar drugs. Work is ongoing to understand what underlies methylone's lack of SSRI interaction observed in preclinical behavioral studies. Together, this work demonstrates that methylone shares important therapeutic features with MDMA but also has distinct pharmacological and mechanistic properties that may have significant therapeutic implications in the treatment of PTSD.

T71. RISK OF MAJOR MALFORMATIONS IN INFANTS AFTER FIRST-TRIMESTER EXPOSURE TO STIMULANTS: RESULTS FROM THE MASSACHUSETTS GENERAL HOSPITAL NATIONAL PREGNANCY REGISTRY FOR PSYCHIATRIC MEDICATIONS

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Abstract: Background: The prevalence of attention-deficit/hyperactivity disorder (ADHD) in adult women is 3-4%. ADHD is highly comorbid with other psychiatric disorders such as mood, anxiety, and substance use disorders. For reproductive-aged women, the treatment of ADHD with stimulant medications may be considered during pregnancy or breastfeeding, although historically, data are lacking to inform these decisions. The aim of this investigation was to determine the risk of major malformations in infants after first-trimester prescription stimulant exposure.

Methods: The Massachusetts General Hospital National Pregnancy Registry for Psychiatric Medications was established in 2008 to increase reproductive safety knowledge of psychiatric medications using rigorous, prospective data collection. The Registry systematically ascertains information from its participants including demographic information, medical and psychiatric

history, use of prescription medications, and other information relevant to fetal outcomes. Participants provide verbal informed consent and are interviewed twice during gestation and again at approximately 3 months postpartum. The primary outcome of interest is the presence of a major malformation identified within 6 months after birth. Redacted cases of major malformations are reviewed by a dysmorphologist blinded to medication exposure. Women taking a prescription stimulant during the first trimester of pregnancy (n=233) were compared with a comparison group of women who were taking other psychiatric medication(s) during pregnancy.

Results: N=1988 women who were eligible for this analysis, including n=173 exposed to mixed amphetamine salts, n=40 exposed to lisdexamfetamine, n=45 exposed to methylphenidate, and n=3 exposed to dexmethylphenidate; the comparison group included n=1755 women. Because of two twin gestations, a total of 235 infants were exposed to one or two stimulant medications. The odds ratio of a major malformation among infants after first-trimester exposure to any stimulant was 0.39 (95% CI 0.09-1.61) compared to controls. The odds ratio of a major malformation after exposure to mixed amphetamine salts or lisdexamfetamine was 0.48 (95% CI 0.11-1.96). There were no major malformations observed in the infants exposed to lisdexamfetamine, methylphenidate, or dexmethylphenidate. The prevalence of major malformations after first-trimester exposure to mixed amphetamine salts was 1.2%.

Conclusions: Although preliminary, this analysis from an ongoing pregnancy registry provides reassurance that these prescription stimulants do not appear to have major teratogenic effects.

T72. EFFICACY AND SAFETY OF ILOPERIDONE IN ACUTE AND MIXED MANIA ASSOCIATED WITH BIPOLAR I DISORDER: A DOUBLE-BLIND, PLACEBO-CONTROLLED, PHASE III STUDY

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Abstract: Background: This phase 3 trial evaluated the efficacy, safety, and tolerability of iloperidone in adult patients meeting DSM-5 criteria for bipolar I disorder with acute manic or mixed episodes.

Methods: A multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of iloperidone for 4weeks in the treatment of adult patients with acute manic or mixed episodes associated with bipolar I disorder. After a pre-randomization evaluation phase, patients were randomly assigned to iloperidone or placebo groups for a short-term double-blind treatment phase of 4 weeks. Most patients in the iloperidone group were titrated up to 24mg/day (12mg bid) within 4 days and then maintained at that dose for study duration. The primary measure of efficacy was change from baseline to endpoint (Day 28) in Young Mania Rating Scale (YMRS) total score. Secondary efficacy parameters included change from baseline in the Clinical Global Impressions Severity of Illness (CGI-S) score and Clinical Global Impressions of Change (CGI-C) score at Day 28. Post hoc analysis included change from baseline in YMRS single items Weeks 1-4.

Results: A total of 392 eligible patients were randomized and dosed with either iloperidone (n=198) or placebo (n=194). Results were assessed by comparing iloperidone to placebo using

the restricted maximum likelihood (REML)-based mixed-effects model for repeated measures (MMRM). Statistically significant benefit in the iloperidone group over placebo was observed as early as week 2 (p=0.0390) and progressively increased through week 4 (p=0.000008). Individual YMRS subscale items also showed increased improvements in the iloperidone group versus the placebo through week 4. The iloperidone treated group also achieved statistical significance at week 4 compared to placebo in CGI-S and CGI-C (p=0.0005 and p=0.0002, respectively).

Conclusions: Results of this study demonstrated that iloperidone at 24mg/day (12mg bid) was more effective than placebo in treatment of acute manic or mixed episodes associated with bipolar I disorder. Treatment was associated with acceptable tolerability and safety profiles that were consistent with those seen during the previous clinical studies in patients with schizophrenia and no new safety concerns were identified for this population.

T73. PREVALENCE OF MAJOR DEPRESSIVE DISORDER AND ACCESS TO PSYCHOTHERAPY SERVICES AMONG MAJOR DEPRESSIVE DISORDER PATIENTS IN THE UNITED STATES

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Abstract: Background: Major depressive disorder (MDD) is one of the most prevalent psychiatric disorders in the United States (US). Despite being a treatment modality for MDD, access to psychotherapy services among individuals with MDD is a concern. This study measured the annual state-level trends of MDD prevalence and access to psychotherapy among MDD patients in the US.

Method: This study used all-payer claims data (APCD) from January 1, 2014 to October 31, 2021. Patients ≥18 years old with an MDD diagnosis (ICD-9/10-CM) during the identification period (July 1, 2014 to October 31, 2020) were included. MDD patients with a diagnosis of bipolar disorder, schizophrenia, schizoaffective disorder, brief psychotic disorder, or pregnancy during the study period were excluded. MDD patients with psychotherapy had a claim for psychotherapy after their initial MDD diagnosis. County-level population estimates were obtained from the US Census Bureau to determine the annual number of residents in each state. Provider densities were calculated as the number of providers per 100,000 residents, while MDD prevalence was calculated as the number of MDD patients per 100,000 residents. Annual state-level heat maps were created as a visual representation of the national prevalence of MDD and distribution of psychotherapy providers among MDD patients.

Results: A total of 9,776,974 MDD patients and 332,706 MDD patients with psychotherapy met the study inclusion/exclusion criteria. The prevalence of MDD in the US nearly doubled between 2015 and 2020, rising from 548 to 1,055 per 100,000. However, there was only a slight increase in the number of psychotherapy providers among MDD patients from 2015 to 2020 (14.5 to 16.1 per 100,000). In 2020, Maine had the highest prevalence of MDD (2,943 per 100,000) while Hawaii (364 per 100,000) had the lowest. States in the Northeast, such as Vermont and Maine (21.9 and 16.1 per 100,000 in 2020), had the highest density of psychotherapy providers across all years whereas Texas (2.4 per 100,000 in 2020) had the lowest. Some states with a higher prevalence of MDD, such as Ohio and Michigan (2,261 and

1,959 per 100,000 in 2020), also had a much lower concentration of psychotherapy providers (8.4 and 8.0 per 100,000 in 2020) compared to, for example, Vermont and Maine (21.9 and 16.1 per 100,000 in 2020). While the number of psychotherapy providers and prevalence of MDD increased over time, the proportion of patients with MDD availing psychotherapy services remained relatively low (<5% in 2020).

Conclusions: The number of psychotherapy providers and prevalence of MDD varied by state and year. Although the number of psychotherapy providers and prevalence of MDD increased annually, states with the highest prevalence of MDD did not always have the highest number of psychotherapy providers. Appropriate future interventions are warranted to address the lack of access to psychotherapy services among adults with MDD in the US.

T74. RELATIONSHIP BETWEEN DOSE-DEPENDENT SUBJECT PSYCHEDELIC EFFECTS, THERAPEUTIC ALLIANCE, AND RESPONSE TO COMP360 PSILOCYBIN TREATMENT WITH PSYCHOLOGICAL SUPPORT

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Abstract: Background: Dose-dependent subjective psychedelic effects and psychological support from a trained therapist for psychological and physical safety are potentially important elements of treatment with psilocybin; however, their contributions to treatment response are unclear.

COMP360, an investigational drug, is a proprietary, synthetic psilocybin in development for treatment-resistant depression (TRD) that has FDA Breakthrough Therapy designation. A completed Phase IIb study showed that a single 25g dose significantly improved depression symptoms compared with a 1 mg dose1. This analysis explores the relationships between participant-reported psychedelic experience, emotional breakthrough, therapeutic alliance, and treatment outcome.

Methods: 233 participants received a single dose of COMP360 25mg (n=79), 10mg (n=75), or 1mg (n=79). Therapeutic alliance, psychedelic effects, and emotional breakthrough were assessed, respectively, with the Scale to Assess Therapeutic Relationship-Patient version (STAR-P) the day prior to dosing, 5-Dimensional Altered States of Consciousness (5D-ASC) questionnaire on the dosing day, and the Emotional Breakthrough Inventory (EBI) the next day.

The correlations of the 5D-ASC dimensions and EBI total score to the change from Baseline in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score at Week 3 were evaluated by the Pearson correlation method. Path analyses were conducted to investigate the relationship between the STAR-P total score, either the EBI total score or one of the 5D-ASC dimension scores, and MADRS total score at Week 3.

Results: Subjective psychedelic effects were dose related. There were moderate correlations between the EBI as well as 3 dimensions of the 5D-ASC and change from Baseline in MADRS total score at Week 3. At the 25mg, 10mg, and 1mg doses, Pearson correlation coefficients were -0.614, -0.363, and -0.424 for the EBI; -0.508, -0.485, and -0.477 for Oceanic

Boundlessness; -0.516, -0.431 and -0.410 for Visual Restructuralization; and -0.293, -0.224, and -0.358 for Auditory Alterations.

The EBI total score was the most reliable predictor of MADRS total score at Week 3, which was also predicted by Oceanic Boundlessness, Visual Restructuralization, and Auditory Alterations scores. In contrast, Anxious Ego Dissolution and Reduction of Vigilance dimension scores were not predictive of outcome. The effect of STAR-P score on MADRS total score was also not significant for any path.

Conclusions: Magnitude of emotional breakthrough and the quality of psychedelic effects were nominally significant predictors of improvement in depression symptom severity after COMP360 psilocybin therapy in the TRD study population. In contrast the effect of therapeutic alliance was not a significant predictor of outcome.

References: 1Goodwin GM, et al. Single-dose psilocybin for a treatment-resistant episode of major depression. N Engl J Med. 2022; 387(18): 1637-1648

T75. MAJOR DEPRESSIVE DISORDER DISEASE AND PATIENT CHARACTERISTICS ASSOCIATED WITH INADEQUATE TREATMENT EXPERIENCE: RESULTS FROM THE SUPPORT STUDY

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Abstract: Objectives: To quantify real-world treatment experiences, predictors of inadequate treatment experience, and treatment expectations of individuals living with major depressive disorder (MDD).

Background: MDD is the leading cause of disability and contributes to the largest share of overall disease burden with a lifetime prevalence of ~20.6%. Despite the availability of numerous therapies for MDD, considerable challenges exist, such as low remission rates, onset of action delays, and inadequate responses.

Methods: A web-based survey, developed in conjunction with the Depression and Bipolar Support Alliance, was conducted among US residents ≥18 years old, with self-reported MDD diagnosis and current and/or past use of MDD prescription medication(s). Patients were asked about their health condition, demographics, treatment experiences, and patient-doctor relationship. Logistic regression was used to identify predictors of inadequate MDD treatment experience based on a two-sided significance level of 0.05. Treatment experience was defined as perceived treatment efficacy, side effect burden, productivity, and likelihood to speak with a clinician on switching MDD medications. Key predictors assessed were patient-, disease- and treatment-related characteristics: race, sex, age, symptom severity, type of therapy, line of therapy, duration of current treatment, and presence of psychiatric and/or medical comorbidities. Backwards selection multivariable regression models were used. Data are reported as Odds Ratios (95% CI).

Results: A total of 385 patients (80% female; mean age 46.4 years) completed the survey between Dec 2021 and Jan 2022. Most were White (81%), had been diagnosed ≥5 years ago (79%), and were on prescription MDD treatments (predominately monoaminergic therapies)

(85%); nearly half (42%) were on 3L+ treatment. Per the QIDS-SR-16, only 6% were experiencing remission or no depression symptoms; among the 94% with active MDD symptoms, most were on MDD treatment for >5 years, where 87% reported a high level of adherence. Moderate and severe MDD symptoms were significantly associated with dissatisfaction with treatment efficacy (1.764 [0.95–3.26] and 3.538 [1.93–6.48], both P<0.001) and with productivity issues (3.183 [1.77–5.72] and 3.246 [1.75–6.00], both P<0.001) compared to those with no MDD symptoms. However, only those experiencing severe MDD symptoms were likely to discuss changing prescriptions with their clinicians (3.488 [1.52–8.01] P=0.003), whereas the moderate disease group was not (P=0.425). Respondents reporting their race as Asian, >2 races, or Hispanic were nearly 3 times as likely to experience dissatisfaction with treatment efficacy, higher side effect burden, and productivity issues compared to White or Black respondents (2.709 [1.27–5.78] P=0.010; 2.615 [1.22–5.62] P=0.014; 3.134 [1.25–7.86] P=0.015).

Discussion: Real world data gathered on treatment experience from individuals living with MDD in 2021 identified patient-, disease- and treatment-related characteristics associated with inadequate treatment. Specifically, respondents with moderate disease are dealing with debilitating depression, affecting productivity similar to those with severe disease, but are less likely to speak with a clinician to switch their current antidepressant. There is a substantial unmet need to support MDD patients in their treatment discussions for new MDD treatment options and for improved treatment outcomes.

T76. EFFICACY OF VILOXAZINE ER (QELBREE®) FOR ADHD IN ADULTS BASED ONPRIOR STIMULANT EXPOSURE

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Abstract: Introduction: Although many patients respond equally well to both stimulant and nonstimulant medications for ADHD, some patients respond preferentially to one class over another.1 Currently, most patients receive a stimulant as first-line therapy;2 however, nonstimulants present fewer obstacles for prescribers and patients and have low abuse/misuse potential. Still, when patients have suboptimal response to stimulants, physicians may be reticent to switch to a nonstimulant medication due to concerns that the nonstimulant response will be less robust or less preferable for patients. Viloxazine ER (viloxazine extended-release capsules; Qelbree®) is a nonstimulant, FDA-approved treatment for ADHD in children (≥6 years) and adults.3 This post-hoc analysis of adult Phase 3 trial data evaluates response to viloxazine ER (200-600 mg/day) based on whether or not patients reported a history of previous stimulant use.

Methods: For patients randomized to viloxazine in this Phase 3, double-blind, placebo-controlled trial, the change from baseline (CFB) in Adult ADHD Investigator Symptom Rating Scale (AISRS) score (primary trial outcome) was analyzed for prior stimulant users vs. nonusers using MMRM. Prior stimulant use was based on patient-reported medication history recorded upon enrollment. Subjects using stimulants at the time of study screening were required to undergo a ≥1-week washout period prior to randomization.

Results: Of 372 patients treated, 189 received viloxazine ER. Of the patients who received viloxazine ER, 40 reported prior stimulant use and 149 did not. Mean (SD) baseline AISRS scores for prior stimulant users and nonusers were 38.5 (7.40) and 38.3 (6.44), respectively. Response appeared similar in both patient groups. At Week 6/End of Study (EOS) the least squares (LS) mean (SE) CFB AISRS scores for prior stimulant users and nonusers were -15.8 (2.51) and -15.6 (1.08)]; treatment difference -0.2 (2.41); P=0.93. Though not significant, prior stimulant users showed a larger magnitude of improvement on the AISRS at early timepoints compared to those without prior stimulant use [Week 1, LS mean (SE) CFB AISRS Total scores: -9.2 (1.40) vs. -6.8 (0.70), respectively; treatment difference: -2.4 (1.56); P=0.12].

Conclusions: A history of prior stimulant use did not appear to influence the magnitude of ADHD symptom response to viloxazine ER in this preliminary analysis of Phase 3 trial data in adults. Rather, subjects with prior stimulant use showed numerically larger reductions in AISRS scores at early timepoints that were not significantly different from those without prior stimulant use. Additional analysis should be undertaken to evaluate patterns of response in the pediatric population.

T77. PHARMACEUTICAL PIPELINE OF BI 1358894: CLINICAL EVIDENCE FOR AN EMERGING DRUG FOR THE TREATMENT OF MENTAL HEALTH CONDITIONS

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Abstract: Introduction: Dysregulated emotional processing and strong negative emotions are core symptoms of borderline personality disorder (BPD), major depressive disorder (MDD), and posttraumatic stress disorder (PTSD) and are correlated with amygdala hyperreactivity. BI 1358894 may provide a novel mechanism of attenuating amygdala hyperreactivity to improve emotion regulation and reduce core symptoms in mental health conditions. Here we provide an overview of early BI 1358894 research in the treatment of conditions such as BPD, MDD, and PTSD, where emotional dysregulation and mood control play an important role.
Methods: Five Phase I studies of BI 1358894, in healthy male volunteers, were performed to determine the safety, tolerability, and pharmacokinetics (PK) of BI 1358894. The pharmacodynamic effects of BI 1358894 versus placebo were also assessed following the administration of cholecystokinin tetrapeptide (CCK-4) to induce anxiety/panic symptoms in healthy volunteers. A functional magnetic resonance imaging (fMRI) study of patients with MDD investigated the effects of BI 1358894 on cortico-limbic brain regions during faces and scenes tasks.

Results: Across the clinical studies, BI 1358894 ≤200 mg was generally well tolerated, with headache, dizziness, and fatigue reported as the most frequent adverse events. PK analysis of BI 1358894 indicated that exposure increased dose-dependently, but less than dose-proportionally, after single doses in the fed state and multiple doses in the fasted state. Positive food effect with increased exposure was observed with single doses of 50 mg and 100 mg. Compared with placebo, BI 1358894 reduced the physiological and psychological response to CCK-4 in healthy volunteers, as measured by the Panic Symptom Scale and the Emotional Faces Visual Analog scale, as well as by levels of stress biomarkers (adrenocorticotropic

hormone and serum cortisol), indicating target engagement and functional mechanistic effects. A fMRI study in people with MDD demonstrated that BI 1358894 attenuated activity in several cortico-limbic brain regions, including the amygdala bilaterally, during a task where participants viewed negative emotional faces and scenes.

Conclusion: BI 1358894 was well tolerated across the clinical Phase I studies; BI 1358894 attenuated amygdala hyperactivation in response to negative faces and scenes. These data support further investigation of this mechanism of action for patients with symptomatology associated with amygdala hyperreactivity. A Phase II study in BPD was recently clinically completed. Further Phase II studies are ongoing for MDD and PTSD.

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