ASCP
American Society of Clinical Psychopharmacology

ASCP 2021 ANNUAL MEETING ABSTRACT BOOK

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Tuesday, June 1, 2021

ASCP Lifetime Awardee

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

LIFETIME AWARDEE: ADVENTURES IN WONDERLAND: THE CIRCUITOUS ROUTE FROM STAGE AND SCREEN THROUGH DECADES IN ACADEMIA TO DIGITAL HEALTH STARTUP

Michael E. Thase, Perelman School of Medicine at the University of Pennsylvania

Overall Abstract: Like Alice, over the course of my professional life, I have found myself in the most unexpected places. This presentation will trace the seemingly illogical route by which a one-time drama student now finds herself in the challenging world of mobile startups. It will include considerable emphasis on the nearly forty years of intervening clinical research conducted at Western Psychiatric Institute and Clinic, tracing the journey from unprepared research assistant in a nascent department of psychiatry, through decades of designing and carrying out controlled studies of psychological interventions for depression and bipolar disorder, to IT developer, all in an effort to relieve the suffering of individuals with mood disorders. The presentation will conclude with a tribute to Donald Klein whose intellectual rigor, wisdom and counsel were absolutely central to the way in which I have navigated my adventure in the wonderland of clinical research.

ADVENTURES IN WONDERLAND: THE CIRCUITOUS ROUTE FROM STAGE AND SCREEN THROUGH DECADES IN ACADEMIA TO DIGITAL HEALTH STARTUP

Ellen Frank, University of Pittsburgh School of Medicine

Abstract: Like Alice, over the course of my professional life, I have found myself in the most unexpected places. This presentation will trace the seemingly illogical route by which a one-time drama student now finds herself in the challenging world of mobile startups. It will include considerable emphasis on the nearly forty years of intervening clinical research conducted at Western Psychiatric Institute and Clinic, tracing the journey from unprepared research assistant in a nascent department of psychiatry, through decades of designing and carrying out controlled studies of psychological interventions for depression and bipolar disorder, to IT developer, all in an effort to relieve the suffering of individuals with mood disorders. The presentation will conclude with a tribute to Donald Klein whose intellectual rigor, wisdom and counsel were absolutely central to the way in which I have navigated my adventure in the wonderland of clinical research.

Learning Objectives: NA

Literature References: NA

Pharmaceutical Pipeline

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

SEP-363856: A COMPOUND WITH A NON-D2 RECEPTOR MECHANISM OF ACTION FOR THE TREATMENT OF SCHIZOPHRENIA: UPDATE

Heather Dworak*[1]

[1]*Sunovion Pharmaceuticals, Inc.*

Abstract: SEP-363856, the first of a new class of CNS-active compounds, is a full agonist at trace amine-associated receptor 1 (TAAR1) and 5-HT1A receptors. SEP-363856 does not act on dopamine D2 or 5-HT2A receptors which are known to mediate the effects of currently approved first- and second-generation antipsychotics. SEP-363856 has been shown to reduce ketamine-induced increases in striatal dopamine synthesis capacity in mice, suggesting it can provide inhibitory modulation of the presynaptic dopamine dysfunction observed in patients with schizophrenia. Consistent with its mixed TAAR1/5-HT1A pharmacology, SEP-363856 has demonstrated antipsychotic-like activity in preclinical models of schizophrenia, including prepulse inhibition, and cocaine- and PCP-induced hyperactivity models. In a 4-week, double-blind, placebo-controlled study, SEP-363856 demonstrated significant efficacy in the short-term treatment of adults with an acute exacerbation of schizophrenia. The incidence of adverse events (AEs) was generally similar in the SEP-363856 and placebo groups, with a difference of 2.5% or less for each event. Groups were also similar with respect to the percentage of patients who reported extrapyramidal symptoms (3.3% vs. 3.2%) and findings on movement disorder scales. In addition, minimal effects on prolactin and other metabolic values were observed. These findings are consistent with the absence of D2-receptor binding for SEP-363856. These results were maintained in a subsequent open-label extension study (26 weeks) with continued improvement in various efficacy measures. Phase 3 studies are ongoing to confirm these results. Here, we provide an update on clinical research that further demonstrates the therapeutic characteristics of this compound.

Pharmacokinetic (PK) analyses across multiple Phase 1 and Phase 2 studies showed that SEP-363856 was well-absorbed and exhibited dose-proportionality in doses ranging from 10-100 mg. Moderate inter-individual variability was observed in concentration-time profiles. The estimated median time to maximal concentration (Tmax) was 2.8 hours and the median effective half-life was 7 hours, corresponding to an exposure accumulation ratio of 1.10 at steady-state with daily dosing. No clinically meaningful effects on SEP-363856 PK parameters were observed based on race, age, sex, or clinical status (healthy volunteer vs. patient with schizophrenia); body weight was the only meaningful covariate.

In secondary analyses of the completed Phase 2 studies SEP-363856 demonstrated significant and robust improvement relative to placebo in negative symptoms of schizophrenia as assessed by multiple measures, and continued improvement during 6-months of extension phase treatment. Notably, improvement in negative symptoms on SEP-363856 was observed in the Uncorrelated PANSS Matrix (UPSM) negative symptom factors, a measure of negative symptoms that has been shown to have minimal correlation with improvement in traditional PANSS subscales.

Lastly, we summarize the results of a disproportionality analysis used to identify and rank-order AE preferred terms associated with the 11 most recently approved antipsychotics from

the FDA Real-world Adverse Event Reporting (FAERS) database. We used the results of this analysis to evaluate the frequency and cumulative percentages of drug-associated AE signals in the currently available safety database of SEP-363856. SEP-363856 demonstrated markedly lower cumulative risk for antipsychotic class-related AEs in comparison with other atypical antipsychotic, providing confirmation of the non-D2 safety profile of the drug.

INJECTABLE WEEKLY AND MONTHLY BUPRENORPHINE IN THE OUTPATIENT TREATMENT OF FENTANYL USERS WITH OUD

Edward Nunes[1], Sandra Comer[1], Michelle Lofwall[2], Sharon Walsh[2], Stefan Peterson[3], Fredrik Tiberg[3], Natalie Budilovsky-Kelley*[4]

[1]NYSPI - Columbia University, [2]U.Kentucky, Lexington, [3]Camurus, [4]Braeburn

Abstract: Background: The introduction of the very high potency opioid analgesic fentanyl into the illicit heroin supply in the U.S. has compounded the opioid epidemic. Clinical reports suggest substantial proportions of patients seeking treatment for OUD in some regions test positive for fentanyl. Fentanyl and its high potency analogs now account for a majority of overdose deaths, and for the rise in overdose deaths. Few clinical studies conducted to date have tested patients for fentanyl, and data on the effectiveness of buprenorphine (BPN) among fentanyl users is limited.

Methods: This 24-week, randomized, double-blind, double-dummy, active-controlled study, evaluated treatment with weekly and monthly injectable extended-release BPN, CAM2038, compared to daily sublingual BPN/naloxone (SL BPN/NX) for initiation and maintenance treatment of patients with OUD at 35 centers throughout the US. Urine toxicology was evaluated using quantitative LC-MS/MS and GC-MS analytical techniques and included fentanyl and norfentanyl. Post-hoc analyses were conducted in the subgroup of participants with evidence of fentanyl use prior to randomization.

Results: Of the 428 randomized participants, 62 (29.1%) in the CAM2038 group and 49 (22.8%) in the SL BPN/NX group, demonstrated evidence of fentanyl use prior to randomization. Those with evidence of fentanyl use were primarily at sites in Ohio, Missouri, and Florida. Most participants in the fentanyl-positive group (83.8%) identified heroin as their primary opioid, compared to 66.2% in the fentanyl-negative group. There were no difference in intravenous route of use at baseline for both groups (54.1% vs 51.7% for fentanyl-positive and fentanyl-negative groups, respectively). At baseline, the fentanyl-positive group provided higher mean percentage of positive urine samples as compared to the fentanyl-negative group for cocaine (37.8% vs 20.2%) and benzodiazepines (21.6% vs 12.9%). Over the course of the study, mean percentage of opioid-negative urine toxicology results was ~10% higher for fentanyl-negative vs fentanyl-positive group. Within the fentanyl-positive group, mean opioid-negative urine toxicology results was higher for CAM2038 (29.6%) vs SL BPN/NX (20.0%), a difference of 9.6% (95% CI of -3.9%, 23.2%). For fentanyl-negative group, in both cohorts, opioid withdrawal (evaluated by COWS) and cravings (evaluated by Need-To-Use Visual Analog Scale [VAS]), were suppressed from day 1 and throughout the study, including during transitions from weekly to monthly injections, without significant group differences. For fentanyl-positive group, opioid withdrawal and cravings were suppressed in both cohorts, however, COWS and VAS scores were lower for CAM2038 vs SL BPN/NX.

Conclusions: In this sample of participants seeking treatment for OUD, the subgroup with exposure to fentanyl prior to randomization exhibited markers of greater severity of illness at baseline (more heroin use, more co-occurring non-opioid drug use) and fewer opioid negative urine results during treatment. Consistent with previous post-hoc analyses of subgroups reporting heroin or IV drug use at baseline, treatment with CAM2038 resulted in a greater percentage of urine samples negative for illicit opioids in participants with evidence of fentanyl use prior to randomization vs SL BPN/NX. CAM2038 may have an advantage over SL BPN/NX on illicit opioid use outcome among difficult-to-treat patient population, including those who test positive for fentanyl at treatment initiation. As these are post-hoc analyses from a randomized study, results should be interpreted with caution as further studies are needed to confirm the improved effectiveness of CAM2038 in these subgroups.

RANDOMIZED DOUBLE-BLIND, PLACEBO CONTROLLED STUDY TO EVALUATE NV-5138/SPN-820 (NV-5138), AN MTORC1 ACTIVATOR, BY QUANTITATIVE EEG (QEEG) IN HEALTHY VOLUNTEERS, SUPPORTS TARGET ENGAGEMENT AND TRANSLATIONAL STRATEGY

Leonardo Trejo[1], Larry Ereshefsky*[2], *Roman Rosipal*[1], *Adrienne Moore*[3], *Howard Hassman*[2], *Randall Owen*[4], *George Vlasuk*[4]

[1]*Pacific Development and Technology LLC,* [2]*APEX Innovative Sciences,* [3]*Q-Metrx, Inc,* [4]*Navitor Pharmaceuticals*

Abstract: Introduction: NV-5138, a direct mTORC1 activator demonstrates rapid and long-lasting 'antidepressant' effects comparable to ketamine in pre-clinical models. Ketamine and other antidepressants have been investigated for their effects on qEEG and this study was performed to understand the effects of NV-5138 in comparison with those agents as a possible valuable measurement of central pharmacological activity. qEEG may be useful to characterize the CNS impact of NV-5138 including confirmation of meaningful CNS target engagement and a dose to be carried forward to proof-of-concept.

Methods: 25 healthy male subjects were randomly assigned to a single dose of either placebo or 2400 mg NV-5138 on Day 1, and the same treatment on Day 3. Tolerability and PK were evaluated. Baseline (Day -1) and Days 1 and 3 time matched qEEGs (5 minutes each eyes closed (EC); eyes open (EO)) corresponding to 1 hour pre-dose and 1, 4, and 8 hours post-dose, were recorded. Spectral band amplitudes, frequency-derived measures, and magnitude squared coherence were assessed. Recording specs: Compumedics Grael 4k V2 EEG amplifiers, Curry 8E Software, 23 electrodes (International 10-20 system). Standard pre-processing of 2 second segments using a fast Fourier transformation and Irregular-Resampling Auto-Spectral Analysis (IRASA) to separate oscillatory and fractal components was performed (delta through gamma3 bands). Salient changes in end points for drug vs placebo on Days 1 and 3, were classified as small, medium or large, confirmed by MMRM. The pre-dose baseline time point was used as a covariate. The study was performed in accordance with all applicable requirements, including informed consent and IRB oversight.

Results: 56 subjects were screened, with a total of 25 randomized (13 placebo/12 drug). 24 subjects completed the study (1 participant withdrew consent on Day 1 (placebo). The two sequential doses of NV-5138 were well tolerated, with no incidents of death, no serious adverse events, or discontinuations due to adverse events. Dissociative effects were evaluated with the

CADSS, and there were no clinically meaningful abnormalities in laboratory or physical exam parameters. The strongest changes in qEEG parameters occurred in the NV-5138 group, on both days, 1-hour post-dose (approximately at the time of NV-5138 Tmax). These assessments revealed a decrease in low-frequency EEG bands (delta and theta) and an increase in high-frequency EEG bands (gamma), while alpha bands exhibited decreased amplitudes (or desynchronization) around Tmax. At later time points alpha 1, alpha 2 and beta 1 bands increased in amplitudes, with a resultant decrease in Theta/Beta ratio and increased Alpha Slow-wave Index, linked to increasing arousal and cognitive processing and effects on mood. Salient changes observed in the fractal part of the EEG spectrum included increases in amplitudes for high beta, gamma, gamma 1, gamma 2, and gamma 3 bands (greatest change). Increased inter- and intrahemispheric coherence occurred at several specific electrode pairs, and were more prominent in the high-beta through gamma bands. Changes in qEEG in the placebo group were minimal and not related to treatment. Consistent with the increased beta through gamma band amplitudes and coherences, NV-5138 might increase perceptual and cognitive processing.

Conclusion: NV-5138 was generally safe, well tolerated. NV-5138 actively modulated neural activity as measured by qEEG band amplitudes and coherences. The pattern of electrophysiology changes on drug was consistent with desired antidepressant effects. Limitations include small sample size and use of healthy male volunteers precluding conclusions in females or in patients with depression.

EFFECTS OF SINGLE-DOSE L-THEANINE ON MOTOR CORTEX EXCITABILITY IN HEALTHY SUBJECTS: A DOUBLE-BLINDED, RANDOMIZED ORDER, CROSS-OVER PAIRED-PULSE TMS STUDY

Shiwen Yuan*[1], *Joshua Brown[1], Michael Gold[1], Jee Won Kang[1], Eric Tirrell[1], Linda Carpenter[1]*

[1]Brown University, Butler Hospital

Abstract: Background: L-theanine (N5-ethyl-L-glutamine) is the primary psychoactive component uniquely in green tea. Epidemiological studies support that green tea consumption is an independent factor associated with lower prevalence of depression. Preclinical studies have demonstrated anti-depressant effect of L-theanine in rodents and provided evidences for its pharmacological properties of N- methyl-D-aspartate (NMDA) and gamma-aminobutyric acid (GABA) agonism. Yet these effects have not been proven in humans. We propose using pair-pulse transcranial magnetic stimulation (ppTMS) to probe how L-theanine may manipulate the glutamatergic and GABA systems in the frontal region by changing cortical excitability first in healthy subjects. ppTMS is a well-established technique to investigate frontal motor cortical excitability mediated by the inter-neuron NMDA and GABA receptors. Specific changes of ppTMS measures, including impaired short-term and long-term intracortical inhibition (SICI, mediated by GABA-A receptor; LICI, mediated by GABA-B receptor) and intracortical facilitation (ICF, mediated by NMDA receptor), have been demonstrated in MDD. Using this technique, we plan to investigate the neurobiological effects of L-theanine in healthy subjects first. Given the potential NMDA and GABA agonistic effects of L-theanine, we hypothesize that it increases intracortical inhibition and

facilitation through enhancement of NMDA- and GABA-receptor mediated neurotransmission, in healthy subjects (N=10 to complete study).

Methods: Double-blinded, Randomized-order, Cross-over placebo-controlled study in 10 healthy subjects. Dose of L-theanine or placebo is 400mg. At baseline, subjects will be randomized to L-theanine or placebo group, then receive ppTMS protocol before drug administration. The ppTMS protocol is repeated after 30min of administration. Then subjects will return to clinic after 1 week free of any medications and repeat the above protocol with the second drug condition. Wilcoxon signed-rank test will be used to compare the baseline-to-post-drug means of SICI, LICI and ICF measures. Two-sided P value < 0.05 is considered statistically significant.

Results: Compared to matching placebo, 400mg single dose L-theanine elicited significantly higher post-pre drug change (D) of ICF (Mean±SE DICFL-theanine=0.073±0.073 vs. DICFPlacebo=-0.341±0.176, p=0.016) and LICI (Mean±SE DLICIL-theanine=0.145±0.100 vs. DLICIPlacebo=-0.068±0.053, p=0.037) within each individual. No significant difference was found for DSICI. No adverse effects from L-theanine were observed.

Conclusion: The results suggest that a single dose of L-theanine may enhance NMDA-R mediated intracortical facilitation and attenuate GABA-B-R mediated intracortical inhibition in the human primary motor cortex.

POPULATION PHARMACOKINETIC MODELING AND SIMULATION TO GUIDE DOSE SELECTION FOR TV-46000, A NEW LONG ACTING FORMULATION OF RISPERIDONE FOR SUBCUTANEOUS INJECTION

Itay Perlstein[1], Avia Merenlender Wagner[2], Michael Lamson[3], Ofer Spiegelstein[2], Pippa Loupe[2], Roberto Gomeni[4], Anna Elgart[2], Itay Perlstein*[1]

[1]Magic Wand Research LLC, [2]Teva Pharmaceutical Industries, Ltd., [3]Nuventra Pharma Sciences, [4]Pharmacometrica

Abstract: Introduction: Patient adherence is a major challenge and an important factor for treatment success and relapse prevention of patients with schizophrenia. TV-46000 is a risperidone extended-release suspension for subcutaneous (sc) injection allowing multiple dose-exposure levels and flexible dosing regimens over an extended period of time. The objective was to determine potentially clinically effective dosing regimens of TV-46000 based on population PK (popPK) modeling and simulations of data obtained in a Phase 1 study in patients, to support further clinical development. To this end, a popPK model for the Total Active Moiety (TAM) comprised of risperidone + 9-OH risperidone (equipotent metabolite) concentrations, was developed to describe the population exposure following TV-46000 sc administration. Simulations of the TAM plasma levels for a range of TV-46000 doses and dose intervals were compared to published data of oral risperidone. Using published data, the dopamine D2 receptor occupancy (D2RO) values were derived from the simulated TAM plasma concentrations. PopPK modeling and simulations were then utilized to identify dosing regimens of TV-46000 that would provide 60-80% D2RO, considered as

the therapeutic window for optimal antipsychotic effect with minimal side effects (Eerdekens M, et al. Schizophrenia Research 2004;70:91-100).

Methods: The popPK model was generated by applying pharmacokinetic data from the phase 1 study in patients (n = 97) with a diagnosis of schizophrenia or schizoaffective disorder who received single doses of TV-46000 (between 50-225mg) or three consecutive monthly doses of 75mg and 150mg. TV-46000 pharmacokinetic profile was found to be best described by a double Weibull function of the in-vivo release rate and by a two-compartment disposition and elimination model. Simulations were performed to determine TV-46000 dose levels and intervals that maintained median TAM concentrations within the 60-80% D2RO over the dosing interval.

Results: The popPK model-based simulations indicated that TV-46000 is expected to successfully deliver therapeutic levels of the TAM over dosing intervals of one month (q1m) or two months (q2m). Four dose strengths of TV-46000 were identified for each dosing interval to deliver the required D2RO: 50mg, 75mg, 100mg and 125mg for the q1m dosing regimens, and 100mg, 150mg, 200mg and 250mg for the q2m dosing regimens.

Conclusion: PopPK modeling and simulations identified TV-46000 dosing regimens that would provide therapeutic exposure levels of TAM to treat patients with schizophrenia. These dosing regimens will be further assessed for safety and efficacy in a phase 3 program. The flexibility of the q1m and q2m sc dosing regimens has the potential to significantly improve patient compliance and acceptance of risperidone treatment, both of which are essential for the treatment of schizophrenia.

PHARMACOKINETICS, SAFETY, AND TOLERABILITY OF ULTRA-LONG ACTING SUSTAINED-RELEASE ORAL RISPERIDONE IN PATIENTS WITH SCHIZOPHRENIA OR SCHIZOAFFECTIVE DISORDER

David Walling*[1], *Cecilia Kruger*[2], *Jeff Miceli*[2], *Kristine Sykes*[2], *Nayana Nagaraj*[2], *Richard Scranton*[2]

[1]*CNS Network, LLC,* [2]*Lyndra Therapeutics Inc.*

Abstract: Background: Medication non-adherence, the most common risk factor for relapse in patients with schizophrenia, can be improved with the use of longer acting formulations of antipsychotic drugs. Lyndra Therapeutics is developing an ultra-long-acting oral formulation of risperidone (LYN-005) with the aim of reducing the dosing frequency to once weekly. LYN-005 is a capsule containing a folded star-shaped polymeric sustained-release formulation, designed to provide controlled drug release over the course of 1 week. In addition to improving adherence, weekly oral risperidone treatment may provide more consistent plasma drug levels than daily dosing and facilitate observed administration.
Methods: Multiple-dose, randomized, parallel group, placebo-controlled, study that enrolled 32 clinically stable patients with a primary diagnosis of schizophrenia or schizoaffective disorder. Patients received immediate-release (IR) risperidone tablets (2 mg or 4 mg, based on patient's current antipsychotic dose) for 13 days and then were randomized 3:1 to receive IR risperidone-matched placebo and LYN-005 (14 mg or 28 mg risperidone; 12 patients per group) or LYN-005 matched placebo and IR risperidone (2 mg or 4 mg; 4 patients per group)

for 3 weeks. LYN-005 was administered once weekly (total of 3 doses). IR risperidone was administered once daily. Treatment assignments were blinded; dose levels were not blinded. Primary endpoints were pharmacokinetics after LYN-005 capsules and after IR risperidone, and the incidence of adverse events (AEs). The secondary endpoint was pharmacokinetics after switching from IR risperidone to LYN-005. Pharmacokinetics analyses were done using a non compartmental model.

Results: Following LYN-005 administration, systemic exposure to risperidone active moiety (risperidone and 9-hydroxyrisperidone combined) increased with increasing dose. Exposure was observed throughout the dosing intervals with peak concentration generally observed within the first 3 days of dosing. Peak exposures from LYN-005 were lower than with IR risperidone. Inspection of predose concentrations suggested steady-state was attained prior to the third LYN-005 dose.

LYN-005 was well tolerated with ~85% of subjects completing all three dosages. No severe or SAEs were reported. In LYN-005 groups, AEs occurred in 18 (75%) patients: 10 in the 14-mg group and 8 in the 28 mg group. 8 patients had a moderate AE. The most common AEs were gastrointestinal disorders, which occurred in 13 (54%) patients, with a higher incidence in the 28-mg group than in the 14 mg group. Nine patients had abdominal pain, discomfort, and/or tenderness; 5 (21%) patients had nausea. Overall, the incidence of adverse events (AEs) was higher for LYN-005 compared to IR. However, These AEs were deemed mild and transitory with fewer AEs reported with subsequent LYN-005 dosing (58% after first dose vs 18% after the third dose).

In IR risperidone groups, AEs occurred in 2 (25%) patients: 1 patient had alanine aminotransferase and weight increases, and 1 patient had diarrhea and akathisia.

Discussion: A once-weekly oral risperidone dosage form provided sustained exposure to risperidone active moiety over 7 days while reducing the frequency and extent of peak drug exposure relative to IR risperidone. Both high and low doses of LYN-005 were well tolerated. Once weekly delivery of risperidone with this novel formulation has the potential to improve treatment adherence and quality of life of patients with schizophrenia or schizoaffective disorder.

REL-1017 (ESMETHADONE) IS SAFE, WELL-TOLERATED AND EXERTS RAPID, ROBUST AND SUSTAINED ANTIDEPRESSANT EFFECTS AS ADJUNCTIVE TREATMENT IN PATIENTS WITH MAJOR DEPRESSIVE DISORDER: A PHASE 2A DOUBLE BLIND RANDOMIZED TRIAL

Marco Pappagallo*[1], *Maurizio Fava[2], Stephen Stahl[3], Charles Inturrisi[4], Paolo Manfredi[4]*

[1]Albert Einstein College of Medicine, [2]Massachusetts General Hospital, [3]University of California San Diego, [4]Relmada Therapeutics

Abstract: Background: N-methyl-D-aspartate receptor (NMDAR) channel blockers are an emerging drug class with rapid antidepressant activity. REL-1017 (esmethadone; dextromethadone) has shown BDNF- and mToR-dependent antidepressive-like effects in all tested murine models. REL-1017 blocks NMDARs similarly to ketamine, but does not cause psychotomimetic effects typically associated with ketamine. Racemic methadone is a 50/50 mix of levomethadone and dextromethadone. Levomethadone is responsible for the opioid

effects, while dextromethadone (esmethadone) lacks significant respiratory depressant action and abuse liability and is inactive in animal models that test opioid effects and opioid withdrawal. This trial investigated for the first time the effects of REL-1017 as adjunctive treatment in patients with major depressive disorder (MDD) who failed 1 to 3 courses of standard antidepressant treatments (SAT) in the current major depressive episode (MDE).

Methods: This Phase 2, multicenter, randomized, double-blind, placebo-controlled 3-arm trial assessed the safety, tolerability, pharmacokinetics (PK) and efficacy of oral REL-1017 once daily as adjunctive therapy in patients with MDD. Patients were 18-65 year old adults with inadequate responses to 1-3 SATs in the current MDE. Patients were randomized in a 1:1:1 ratio to either placebo (n=22), or REL-1017 25 mg QD (n=19) or REL-1017 50 mg QD (n=21). Patients in the REL-1017 groups received a single oral loading dose of 75 mg (25 mg group) or 100 mg (50 mg group) on Day 1. On Days 2-7, inpatient treatment continued with placebo, 25 mg or 50 mg and patients then discharged on Day 9 with follow up visits on Days 14 and 21. Safety scales included the 4-Item Positive Symptom Rating Scale (4-PSRS) for psychotomimetic symptoms, Clinician-Administered Dissociative States Scale (CADSS) for dissociative symptoms, Clinical Opiate Withdrawal Scale (COWS) for withdrawal signs and symptoms and Columbia Suicide Severity Rating Scale (C-SSRS) for suicidality. The PK samples were collected on Days 1-9 and 14. Efficacy was assessed with the Montgomery-Asberg Depression Rating Scale (MADRS), Symptoms of Depression Questionnaire (SDQ) and Clinical Global Impression (CGI) scales at Days 2, 4, 7, and 14.

Results: All 62 randomized patients [$\bar{x}$ age = 49.2 years, $\bar{x}$ baseline Hamilton Depression Rating Scale-17 (HAM-D-17) score = 25.3, $\bar{x}$ baseline MADRS score = 34.0] were evaluated. Adverse event (AE) profiles were similar across placebo and REL-1017 groups: AEs were transient and mild or moderate and there were no serious AE. There were no dissociative or psychotomimetic effects and no opioid-like effects. There were no signs and symptoms of withdrawal after abrupt discontinuation. Statistically significant improvement on the MADRS appeared on Day 4 in both 25 mg and 50 mg REL-1017 dose groups and was sustained through Day 7 (last dose) and Day 14 (7 days after the last dose) with $p \leq 0.0308$ and effect sizes from 0.7 to 1.0. Similar improvements emerged from the CGI and SDQ scales.

Conclusion: Oral once daily treatment with 25 mg and 50 mg REL-1017 showed rapid, robust and sustained antidepressant effects and very favorable safety, tolerability, and PK profiles in patients with MDD and inadequate response to 1-3 antidepressants in the current MDE. If these results are confirmed in Phase 3 trials currently underway, REL-1017 may position itself as best in class among the emerging class of rapid acting NMDAR channel blocker antidepressants.

AN UPDATE AND BASELINE DATA FROM THE PHASE 2/3 GAIN TRIAL OF COR388 (ATUZAGINSTAT) A NOVEL BACTERIAL VIRULENCE FACTOR INHIBITOR FOR THE TREATMENT OF ALZHEIMER'S DISEASE

Michael Detke*[1], *Marwan Sabbagh[2], Ira Goodman[3], Mark Ryder[4], Shirin Kapur[1], Debasish Raha[1], Mai Nguyen[1], Florian Ermini[1], Ursula Haditsch[1], Joanna Bolger[1], Sonia Souza[1], Dave Hennings[1], Leslie Holsinger[1], Casey Lynch[1], Stephen Dominy[1]*

[1]Cortexyme, [2]Cleveland Clinic, [3]Global AES, [4]UCSF

Abstract: Introduction: The novel mechanism of action of atuzaginstat is based on the discovery of gingipains, toxic protease virulence factors from the bacterial pathogen Porphyromonas gingivalis (Pg), in >90% of Alzheimer's disease (AD) brains. Gingipain levels correlated with AD diagnosis and tau and ubiquitin pathology, and oral infection of mice with Pg results in brain colonization, increased Aβ1-42, detrimental effects on tau and loss of hippocampal neurons, effects which are blocked by atuzaginstat, an irreversible lysine-gingipain inhibitor. Pg is best known for its role in periodontal disease. Atuzaginstat was well tolerated in phase 1, including trends of efficacy on clinical scales, and significant improvement on a computerized speech assessment and two relevant biomarkers.

Methods: The Phase 2/3 GAIN trial, designed to be potentially pivotal, completed enrollment in November 2020. 642 subjects (aged 55-80; mild-moderate AD with MMSE 12-24) were randomized to one of two doses of atuzaginstat (40mg or 80mg BID) or placebo. The co-primary endpoints are mean change in ADAS-Cog 11 and ADCS-ADL from baseline to 48 weeks. Additional endpoints include change in CDR-SB, MMSE, NPI, Winterlight Speech Assessment, CSF and oral biomarkers, MRI and other measures.

Results: Baseline data show that the 642 randomized subjects are: 56.9% female, 64.3% ApoE4 positive, 49.5% mild (MMSE = 19-24) and 50.5% moderate (12-18). 73.2% of subjects received symptomatic AD co-medications. New baseline biomarker data from the full set of subjects in the study will be shared, including anti-Pg IgG, amyloid-β peptide ratio 42/40, and phospho tau. 233 GAIN trial patients are also participating in a dental sub-study, and while not selected for periodontal disease, approximately 90% have moderate - severe periodontitis.

Conclusions: Enrollment of the GAIN trial was completed in November 2020, and top-line efficacy data are expected December Q4 2021. An interim analysis in December 2020 indicated that the study should continue as planned without sample size adjustment. Subjects enrolled exhibit baseline characteristics consistent with AD and with Pg infection, indicating an appropriate population to test the efficacy and safety of atuzaginstat in mild-moderate AD. The high correlations of AD, periodontal disease, and Pg infections observed in GAIN replicates findings by others and supports a causal role of Pg in AD.

SPIRONOLACTONE AS A POTENTIAL PHARMACOTHERAPY FOR ALCOHOL USE DISORDER: PRELIMINARY EVIDENCE FROM RODENT AND HUMAN STUDIES

Mehdi Farokhnia*[1], *Vicky Chuong[1], Christopher Rentsch[2], Adriana Gregory-Flores[3], Brendan Tunstall[3], Adrienne McGinn[3], David Fiellin[4], George Koob[3], Amy Justice[2], Lorenzo Leggio[1], Leandro Vendruscolo[3]*

[1]Clinical Psychoneuroendocrinology and Neuropsychopharmacology Section, Translational Addiction Medicine Branch, NIDA and NIAAA, NIH, [2]VA Connecticut Healthcare System, US Department of Veterans Affairs, [3]Neurobiology of Addiction Section, NIDA, NIH, [4]Yale School of Medicine

Abstract: There is a critical need to increase the armamentarium of pharmacotherapies for alcohol use disorder (AUD). Recent evidence suggests that the aldosterone/mineralocorticoid receptor (MR) pathway contributes to the pathophysiology of AUD and that MR antagonism may reduce alcohol use. In this set of studies, we tested the hypothesis that spironolactone, an MR antagonist used in clinical practice for disorders related to the cardiovascular system, may

represent a potential novel treatment for AUD. Study 1 (preliminary data) tested the effects of intraperitoneal injections of spironolactone (0, 10, 25, and 50 mg/kg) on operant alcohol self-administration (0.1 mL, 10% w/v alcohol) in male Wistar rats made dependent on alcohol by chronic alcohol vapor exposure. As a control group, non-dependent rats exposed to air only were also used. Results showed that spironolactone reduced alcohol self-administration in both groups with a trend of increased effect in alcohol-dependent rats. Study 2 further tested this hypothesis in mice and expanded the work to both males and females. In this study, we tested the effects of subcutaneous injections of spironolactone (0, 25, 50, 100, and 200 mg/kg) on a binge drinking model (drinking-in-the-dark; 20% v/v alcohol + 0.1% saccharin + 3% glucose) in male and female C57BL6J mice. Results showed that spironolactone dose-dependently reduced alcohol binge-like drinking in both male and female mice, without influencing motor coordination, food intake, or water intake. Finally, in Study 3, we used a pharmacoepidemiological approach to query the clinical dataset of the United States Veteran Birth Cohort, in order to examine the potential bench-to-bed translational implication of our findings in rats and mice. According to a list of relevant covariates, 9,790 spironolactone-treated (for any indication among those for which spironolactone is approved by the Food and Drug Administration) individuals were propensity score matched to 31,579 untreated individuals and the difference-in-difference of alcohol consumption was analyzed. Spironolactone-treated individuals showed a greater reduction in AUD Identification Test - Consumption (AUDIT-C) scores from baseline to follow-up, compared to untreated individuals. Largest effects were observed among individuals with heavy alcohol consumption and daily spironolactone dose of ≥ 50 mg. Together, these data collected from rodent experiments and human pharmacoepidemiological studies provide converging evidence across three species suggesting that spironolactone may represent a novel pharmacotherapy for AUD.
* MF, VC, and CTR are co-first authors. ACJ, LL, and LFV are co-senior authors.

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Individual Research Reports: Connecting Clinical Trials to Everyday Practice: Novel Insights in Schizophrenia and Mood Disorders

12:00 p.m. - 1:15 p.m.

*INTERVENTIONS TO TREAT ANTIPSYCHOTIC-INDUCED DYSLIPIDEMIA IN SCHIZOPHRENIA PATIENTS: A SYSTEMATIC REVIEW AND META-ANALYSIS

Mahavir Agarwal*[1], *Pruntha Kanagasundaram[1], Jiwon Lee[1], Femin Prasad[1], Kenya Costa-Dookhan[2], Laurie Hamel[1], Gary Remington[1], Margaret Hahn[1]*

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Abstract: Introduction: Antipsychotic-induced dyslipidemia represents a common adverse effect faced by patients with schizophrenia that increases risk for developing further metabolic complications and cardiovascular disease. Despite its burden, antipsychotic-induced dyslipidemia is often left untreated, and the effectiveness of pharmacological interventions for mitigating dyslipidemia has not been well addressed. This review aims to assess the

effectiveness of pharmacological interventions in alleviating dyslipidemia in patients with schizophrenia.
Methods: Medline, PsychInfo, and EMBASE were searched for all relevant English articles from 1950 to November 2020. Randomized placebo-controlled trials were included. Differences in changes in triglycerides, HDL cholesterol, LDL cholesterol, and VLDL cholesterol levels between treatment and placebo groups were meta-analyzed as primary outcomes.

Results: Our review identified 48 randomized controlled trials that comprised a total of 3128 patients and investigated 29 pharmacological interventions. Overall, pharmacological interventions were effective in lowering LDL cholesterol, triglycerides, and total cholesterol levels while increasing the levels of HDL cholesterol. Within the intervention subgroups, approved lipid-lowering agents did not reduce lipid parameters other than total cholesterol level, while antipsychotic switching and antipsychotic add-on interventions improved multiple lipid parameters, including triglycerides, LDL cholesterol, HDL cholesterol and total cholesterol. Off label lipid lowering agents improved triglycerides and total cholesterol levels, with statistically significant changes seen with metformin.

Conclusion: Currently available lipid lowering agents may not work as well in patients with schizophrenia who are being treated with antipsychotics. Additionally, antipsychotic switching, antipsychotic add-ons, and certain off label interventions might be more effective in improving some but not all associated lipid parameters. Future studies should explore novel interventions for effectively managing antipsychotic-induced dyslipidemia.

Learning Objectives:

1. Understand how big a problem dyslipidemia is in severe mental illness.
2. Learn which pharmacological strategies are helpful in managing dyslipidemia in severe mental illness.

Literature References:

1. Correll CU, Robinson DG, Schooler NR, Brunette MF, Mueser KT, Rosenheck RA, Marcy P, Addington J, Estroff SE, Robinson J, Penn DL, Azrin S, Goldstein A, Severe J, Heinssen R, Kane JM. Cardiometabolic risk in patients with first-episode schizophrenia spectrum disorders baseline results from the RAISE-ETP study. JAMA Psychiatry. 2014.
2. Jiang WL, Cai DB, Yin F, Zhang L, Zhao XW, He J, Ng CH, Ungvari GS, Sim K, Hu ML, Zheng W, Xiang YT. Adjunctive metformin for antipsychotic-induced dyslipidemia: a meta-analysis of randomized, double-blind, placebo-controlled trials. Translational psychiatry. 2020;10:117.

*THE POINT OF FUTILITY: A UNIFYING CONCEPT TO DEFINE AND EDUCATE CLINICIANS ABOUT THE UPPER LIMIT OF THE ANTIPSYCHOTIC PLASMA LEVEL RANGE

Jonathan Meyer*[1]

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Abstract: Introduction: The 2020 ASCP/AGNP Consensus paper was a seminal work on the value of antipsychotic therapeutic drug monitoring (TDM). While acknowledging the

limitations of the literature, this paper provides a therapeutic reference range including an upper limit defined as a level above which adverse drug reactions (ADRs) are more likely or above which it is relatively unlikely that response will occur. Also provided is a second set of values (the laboratory alert level) that represent threshold levels above which the risk for ADRs is higher and which demands clinical assessment. The California Department of State Hospitals (Cal-DSH) system comprises 5 sites and 6600 patients, 90% of whom have schizophrenia spectrum disorders, with a disproportionate population of aggressive and treatment resistant individuals. Attempts to educate clinicians using these definitions of the upper limit have met resistance due to clinician difficulty in comprehending the need for two sets of values and their application. Importantly, the unintended consequence is that clozapine nonresponders without dose limiting ADRs were deprived of trials at plasma levels > 600 ng/ml despite literature supporting possible response (if tolerated) at plasma levels up to 1000 ng/ml. Educational Concept: The point of futility is a term developed within Cal-DSH over the past decade to educate clinicians about two important concepts with regard to an upper limit for antipsychotic plasma levels: (1) a small proportion of patients may never exhibit dose-limiting ADRs and will tolerate further titration; (2) ongoing titration beyond a certain plasma level (the point of futility) is fruitless as < 5% of schizophrenia patients will respond to these higher plasma levels. While ADRs may signal the end of many antipsychotic trials, the concept of a point of futility combines the essential concerns embedded in the ASCP/AGNP laboratory alert value (i.e. it is not inherently unsafe to proceed up to this point if tolerated), with a clearly delineated idea that, even when tolerated, pursuing response at higher plasma levels is an act of futility, with response rates for schizophrenia < 5% as best estimated from the literature. Utilizing the more exact descriptor of < 5% assists clinicians in the application of the point of futility, and provides the field of antipsychotic TDM a specific benchmark to utilize when defining the upper limit of an antipsychotic trial. From this definition, the point of futility will be provided for a range of antipsychotics where sufficient data exist to support an estimate: amisulpride, aripiprazole, chlorpromazine, clozapine, flupenthixol (cis isomer), fluphenazine, haloperidol, loxapine, olanzapine, paliperidone, perphenazine, risperidone (active moiety), thiothixene trifluoperazine, zuclopenthixol.

Learning Objectives:

1. To reinforce the concept that adverse effects may not limit antipsychotic titration, but clinicians need to be educated when further titration is futile with < 5% response rates in schizophrenia patients.
2. To provide evidence based estimates of the point of futility for a range of antipsychotics where sufficient data exist to support an estimate: amisulpride, aripiprazole, chlorpromazine, clozapine, flupenthixol (cis isomer), fluphenazine, haloperidol, loxapine, olanzapine, paliperidone, perphenazine, risperidone (active moiety), thiothixene trifluoperazine, zuclopenthixol.

Literature References:

1. Schoretsanitis G, Kane JM, Correll CU, Marder SR, Citrome L, Newcomer JW, Robinson DG, Goff DC, Kelly DL, Freudenreich O, Piacentino D, Paulzen M, Conca A, Zernig G, Haen E, Baumann P, Hiemke C, Gründer G. Blood levels to optimize antipsychotic treatment in clinical practice; a joint consensus statement of the American Society of Clinical Psychopharmacology (ASCP) and the Therapeutic Drug Monitoring (TDM) Task Force of the Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie (AGNP). J Clin Psychiatry. 2020;81:doi: 10.4088/JCP.4019cs13169.

2. Meyer JM. A rational approach to employing high plasma levels of antipsychotics for violence associated with schizophrenia: case vignettes. CNS Spectrums. 2014;19:432-438.

*DOES IT MATTER WHICH VERSION OF THE CGI IS USED IN SCHIZOPHRENIA CLINICAL TRIALS?

David Daniel*[1], *Alan Kott*[1]

[1]*Signant Health*

Abstract: Introduction: The original Clinical Global Impression (CGI) scale (Guy, 1976) provided a standardized instrument for clinicians to assess their overall impression of the severity and change in the symptom severity and functional impact of mental illness. The original CGI had relatively sparsely worded anchors. Subsequent iterations of the CGI have been designed with more extensive anchors and instructions for specific disorders and symptom domains.

In the current analysis of schizophrenic clinical trial subjects, we compared the scores of Guy's original CGI (1976) to the scores of symptom specific CGI's such as Haro et al's CGI-SCH (2007). The latter was designed with extended anchors and specifically to measure symptoms of schizophrenia. We assessed whether there were scoring differences, the direction of these differences, and whether these differed by visit type.

Methods: Out of a schizophrenia dataset, we extracted data from 30,848 visits where a symptom specific version of the CGI, as well as the general CGI, were completed by the investigator at the same visit. Separate analyses were performed for CGI-S, change from baseline in CGI-S, and for CGI-I. We operationally defined "different" as those assessments where the symptom specific and general CGIs differed by at least 1 point. We recorded the direction of difference, i.e., whether the symptom specific CGI was higher or lower compared to the generic one. To assess the effect of visit, we classified visits as entry (screening and baseline), first post-baseline, last, and other (consisting of visits between first post-baseline and last). Chi2 tests were used to explore the differences.

Results: Out of 30,848 CGI-S ratings, symptom specific CGI differed from the generic in 7,037 cases (23%). In 5,540 (79%) cases the specific CGI was higher that the generic one. No effect of visit was identified on the proportion of differences ($chi2 = 1.2$, $p = 0.763$). 3,477 out of 21,968 (16%) of CGI-S change from baseline data were different. Of those, in 2,607 (75%), the generic CGI-S change from baseline was higher compared to the specific CGI-S change from baseline, indicating either a larger worsening or lesser improvement compared to baseline. A significant effect of visit on the presence of differences was identified ($chi2 = 484$, $p < 0.001$) with higher proportions of differences identified in the later study visits. 3,331 out of 21,978(15%) of CGI-I ratings were different; of those, 2,332(70%) had the generic CGI-I score higher compared to the specific one. A significant effect of visit was identified ($chi2 = 270$, $p < 0.001$) with first post-baseline visit being affected in 6% of cases and last visit in 19% of cases.

Discussion: Our data indicate that symptom specific CGI differs from the generic one in approximately 20% of cases and that this proportion does not change over the course of the study. Our data as well indicate the differences in CGI-S and CGI-I grow over time; the

discrepancy of these findings can be explained by the different rates of changes in the specific and generic CGIs over the course of the study, with the specific CGI being more likely to change. Our preliminary results indicate that the symptom specific CGIs provide additional information compared to the generic CGI and should be used in schizophrenia clinical trials.

Learning Objectives:

1. Understand the nature of the different types of Clinical Global Impression (CGI) used in schizophrenia clinical trials.
2. Understand the impact of the type of CGI utilized.

Literature References:

1. Guy W. Clinical Global Impressions Scale. In: Guy W, ed. ECDEU Assessment Manual for Psychopharmacology. Rockville, MD: U.S. Department of Health, Education, and Welfare; 1976:218–222.
2. Haro JM, Ochoa S, Gervin M, Mavreas V, Jones P. Assessment of remission in schizophrenia with the CGI and CGI-SCH scales. Acta Psychiatr Scand. 2007;115(2):163–164

NEED FOR SPEED: PLATFORM TRIALS AND THE FUTURE OF CLINICAL DRUG DEVELOPMENT. EU-PEARL PROJECT TO DEVELOP A PLATFORM TRIAL MASTER PROTOCOL FOR MAJOR DEPRESSIVE DISORDER

Adam Savitz*[1], *Yanina Flossbach[2], Josep Ramos-Quroga[3], Carmine Pariente[4], Katherine Woo[5], Heidi De Smedt[1], Christian Otte[6], Stefan Gold[6]*

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Abstract: Clinical drug development is notoriously slow and risky. Psychiatry, including in Major Depressive Disorder (MDD), only a few medications with novel mechanisms of action have recently successfully moved through clinical trial phases and gaining approval by regulators. A least in part, this may due to the way clinical trials are run. With conventional clinical trial, each trial is set up uniquely where recruitment of participants is the major factor in the length of the studies. In addition, large percentages (often half) of the participants receive placebo. Further, patients often struggle to find the right trial for their needs.

Platform trials are one way to potentially overcome these problems and change the way we do clinical trials. Adaptive clinical trial platforms allow multiple compounds from different companies to test their candidate drugs simultaneously against a shared placebo group allowing compounds to be tested with fewer participants and in less time including potentially a reduced number of participants allocated to placebo. In an adaptive platform trial with a single master protocol, new treatment groups can be added at any time, and candidate drugs that prove ineffective can be dropped. Ongoing recruitment of participants through a readiness cohort allows for faster recruitment of patients.

The power of such approaches has been demonstrated during the SARS-CoV2 pandemic, when platform trials (such as the UK-based RECOVERY trial or the WHO-sponsored SOLIDARITY trial) rapidly produced urgently needed data on efficacy and safety of numerous treatment options.

In the EU Innovative Medicines Initiative (IMI) funded consortium "EU-PEARL", partners from academia and industry jointly develop platform trials for several diseases, including MDD. With a few exceptions, platform trials have not been performed in psychiatry for multiple reasons including the management of placebo response with a shared placebo. The goal of the MDD work package is to develop a master protocol for MDD platform trials focused on patients who do not respond to initial antidepressant treatment as well as the infrastructure to perform such trials. Topics that need to be resolved in the creation of the master protocol include: allocation ratio for placebo and active compounds, use of concurrent vs historical placebo controls, blinding of active medication, handling of compounds with different routes of administration, and inclusion of different MDD populations (such as partially responsive vs treatment resistant patients).

Learning Objectives:

1. Understanding the design of platform trials in psychiatry.
2. Understanding issues such as placebo response that needs to be considered when creating platform trials for MDD.

Literature References:

1. Gaynes BN, Lux L, Gartlehner G, Asher G, Forman-Hoffman V, Green J, Boland E, Weber RP, Randolph C, Bann C, Coker-Schwimmer E, Viswanathan M, Lohr KN. Defining treatment-resistant depression. Depress Anxiety. 37(2):134-145 (2020). doi: 10.1002/da.22968.
2. The Adaptive Platform Trials Coalition., Angus, D.C., Alexander, B.M. et al. Adaptive platform trials: definition, design, conduct and reporting considerations. Nat Rev Drug Discov 18, 797–807 (2019). doi.org/10.1038/s41573-019-0034-3

*CHARACTERISTICS OF REAL-WORLD COMMERCIALLY INSURED PATIENTS INITIATED ON ESKETAMINE NASAL SPRAY OR OTHER MAJOR DEPRESSIVE DISORDER THERAPIES IN THE UNITED STATES

Swapna Karkare*[3], *Maryia Zhdanava[1], Abigail Nash[2], Dominic Pilon[1], Laura Morrison[1], Aditi Shah[1], Patrick Lefebvre[1], Kruti Joshi[2]*

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Abstract: Objective: To describe characteristics of commercially insured patients initiating esketamine nasal spray or other major depressive disorder (MDD) therapies in the United States.

Methods: Adults (all-comers) with a claim for esketamine, electroconvulsive therapy (ECT), transcranial magnetic stimulation (TMS) or an antidepressant were selected from the IBM® MarketScan® Databases (01/2016-07/2020). Four mutually exclusive cohorts were created, depending on the treatment initiated on or after 03/05/2019 (esketamine's first indication approval date). Patients initiating esketamine (index date) were classified into the esketamine cohort. Patients newly initiating (i.e., no claims for the therapy in the 6-month pre-index [baseline] period) ECT, TMS, or an antidepressant with adjunctive aripiprazole (index date was therapy initiation date) were classified in respective cohorts prioritizing ECT, then TMS. All patients had continuous eligibility in the baseline period, over which patient characteristics were described.

Results: The esketamine cohort included 572 patients (mean age 45.3 years, 61.2% female), the ECT cohort included 1,229 patients (mean age 46.9 years, 60.3% female), the TMS cohort included 3,357 patients (mean age 43.5 years, 66.6% female), and the adjunctive aripiprazole cohort included 49,430 patients (mean age 41.0, 67.4% female). During baseline, in esketamine, ECT, TMS, and aripiprazole cohorts, 86.2%, 78.9%, 90.5%, and 57.6% had a claim with a diagnosis for MDD, 78.1%, 71.7%, 84.7%, and 38.4% had a claim with a diagnosis for moderate or severe MDD, and 7.0%, 30.3%, 6.4%, and 8.3% had a claim indicating suicidal ideation or behavior. The majority of patients in esketamine, ECT and TMS cohorts had a visit with a psychiatrist and received psychotherapy (esketamine, ECT, and TMS: 74.7%, 75.4%, 79.6% and 72.6%, 65.5%, 71.0%, respectively); among the aripiprazole cohort these proportions were 38.7% and 43.6%, respectively. In a subset of patients with outpatient care for MDD (esketamine: 85.7%, ECT: 72.3%, TMS: 90.1%, aripiprazole: 53.1%), 56.9%, 41.0%, 59.2%, and 34.4% in esketamine, ECT, TMS, and aripiprazole cohorts received care predominantly from mental health specialists. Among esketamine, ECT, TMS, and aripiprazole cohorts 60.8%, 57.0%, 54.9% and 37.8% received ≥2 unique antidepressants and 71.9%, 65.3%, 63.9%, and 48.7% received antidepressant augmentation therapy. Baseline mean monthly healthcare costs were $2,649, $4,798, $1,966, and $1,609 in esketamine, ECT, TMS, and aripiprazole cohorts. In esketamine and TMS cohorts, costs were driven by outpatient costs (esketamine: $1,216, ECT: $1,084, TMS: $851, aripiprazole: $555) and pharmacy costs (esketamine: $657, ECT: $532, TMS: $539, aripiprazole: $334) while in the ECT cohort, costs were driven by inpatient costs (esketamine: $599, ECT: $2,884, TMS: $427, aripiprazole: $570). Among esketamine, ECT, TMS, and aripiprazole cohorts, 54.8%, 72.7%, 47.3%, and 43.6% of costs were mental health-related.

Conclusions: Patients in real-world practice initiating esketamine, ECT, or TMS exhibited similar severity based on MDD diagnoses, specialized mental health care and pharmacotherapy use prior to therapy initiation, while the adjunctive aripiprazole cohort appeared less severe based on these characteristics. Higher total and inpatient costs were observed in the ECT relative to other cohorts possibly due to this therapy often starting during an inpatient stay.

Learning Objectives:

1. To understand the real-world characteristics of commercially insured patients (all-comers) initiated on esketamine nasal spray or other major depressive disorder therapies, irrespective of the presence of major depressive disorder or treatment-resistant depression.
2. To understand how esketamine fits into clinical practice.

Literature References:

1. Bahr, R., Lopez, A., & Rey, J. A. (2019). Intranasal esketamine (SpravatoTM) for use in treatment-resistant depression in conjunction with an oral antidepressant. Pharmacy and Therapeutics, 44(6), 340.
2. Karkare, S., Zhdanava, M., Nash, A., Pilon, D., Morrison, L., Shah, A., Lefebvre, P., & Joshi, K. (2020, September 10-13). Characteristics of commercially insured patients initiated on esketamine nasal spray in a real-world setting [Conference Presentation]. Psych Congress 2020 Virtual Experience.

Individual Research Reports: Novel Clinical and Translational Research in Stress-Related Psychiatric Disorders

12:00 p.m. - 1:15 p.m.

*A RANDOMIZED CONTROLLED TRIAL OF ELECTROCONVULSIVE THERAPY AND TRAUMATIC MEMORY REACTIVATION FOR THE TREATMENT OF POSTTRAUMATIC STRESS DISORDER

Victor Tang*[1], *Kathleen Trought[1], Kristina Gicas[1], Mari Kozak[1], Sheena Josselyn[2], Zafiris Daskalakis[3], Daniel Blumberger[4], Daphne Voineskos[1], Yuliya Knyahnytska[4], Yuan Chung[1], Young Zhou[1], Moshe Isserles[5], Albert Wong[4]*

[1]University of Toronto, [2]Neuroscience & Mental Health, The Hospital for Sick Children, University of Toronto, [3]UC San Diego Health, [4]Centre for Addiction and Mental Health, University of Toronto, [5]Hadassah Hebrew University Medical Center

Abstract: Introduction: Treatment resistance in Post-Traumatic Stress Disorder (PTSD) is common. Traumatic memories that underlie PTSD may be vulnerable to disruption during reconsolidation. Given that Electroconvulsive Therapy (ECT) is known to have amnestic side effects, this study examines whether the timed combination of traumatic memory re-activation using script driven imagery with Electroconvulsive Therapy (ECT) can improve symptoms of PTSD. Methods: Twenty-eight participants with severe depression and comorbid PTSD referred for ECT were randomized to receive a reactivation of a traumatic or non-traumatic memory using script driven imagery immediately prior to each ECT treatment. Primary outcomes were change in scores on the Modified PTSD Symptom Scale - Self Report (MPSS-SR) and the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5). We assessed the psychophysiologic response by continuously recording participants' heart rate (HR) with an ECG monitor as before, during, and after listening to the scripts. Assessment raters were blinded to treatment allocation. Additional exploratory analyses were conducted to examine how symptoms changed between groups on the CAPS-5 subscales (intrusion, avoidance, cognition and mood, arousal and reactivity, distress or impairment, global severity, and total number of symptoms) to look for symptom specificity. Results: In 25 patients who completed any post-ECT assessment, no significant group differences were found in the MPSS-SR or CAPS-5 scores from baseline to post-ECT assessments, nor at 3-month follow up. Both groups improved substantially at post-ECT and 3-month timepoints, with large effect sizes (Partial eta squared > 0.13). No significant differences were found between groups or over time in heart rate changes. PTSD symptom subscales or functioning subscales showed significant change across all timepoints but there were no between group differences.

Conclusions: ECT paired with pre-treatment traumatic memory reactivation was not associated with significant improvements in treating PTSD symptoms . This study highlights the challenges found in translating neuroscientific research in memory reconsolidation to clinical trials. Limitations of our intervention to find significant effects include the high prevalence of early life, chronic, developmental trauma in our participant sample. Our data provides support for the efficacy of ECT alone for improving symptoms of PTSD with comorbid depression. Our intervention demonstrated tolerability and feasibility, and further study is needed in larger sample sizes and optimization of parameters in ECT delivery, memory reactivation, and patient selection.

Learning Objectives:

1. To understand the neuroscientific basis for targeting memory reconsolidation in the treatment of posttraumatic stress disorder.
2. To learn about current and future research on memory reconsolidation interventions in clinical trials and patients with traumatic memories.

Literature References:

1. Andrade C, McCall WV, Youssef NA. Electroconvulsive therapy for post-traumatic stress disorder: efficacy, mechanisms and a hypothesis for new directions. Expert Rev Neurother 2016; 16(7):749-53.
2. Kroes MC, Tendolkar I, Van Wingen GA, Van Waarde JA, Strange BA, Fernández G. An electroconvulsive therapy procedure impairs reconsolidation of episodic memories in humans. Nat Neurosci 2014; 17(2):204-6.

*LOW INTENSITY FOCUSED ULTRASOUND AS A NON-INVASIVE COGNITIVE NEURAL PROSTHETIC: EARLY NEUROIMAGING FINDINGS

Taylor Kuhn*[1], *Norman Spivak[1], Sergio Becerra[1], Bianca Dang[1], Sonja Hiller[1], Nanthia Suthana[1], Martin Monti[1], Susan Bookheimer[1]*

[1]*University of California, Los Angeles*

Abstract: Objective: Neurostimulation is increasingly used in psychiatry and neurology. Common transcranial stimulation techniques (e.g. TMS) are unable to reach medial temporal lobe (MTL) regions directly. Deep brain stimulation (DBS), which can stimulate MTL regions, is an invasive technique requiring neurosurgery. Low intensity, transcranial focused ultrasound (tFUS) is a non-invasive technique with an extensive safety record and evidence showing it can excite deep neuronal activity in animals and primary sensory and motor cortices in humans. Therefore, this study sought to provide preliminary evidence that tFUS can selectively increase regional MTL perfusion.

Participants & Methods: A randomized, double-blind within-subject crossover study was conducted to investigate whether tFUS can selectively increase regional perfusion in the amygdala (AG) or entorhinal cortex (ERc) and their functionally associated regions. Arterial spin labeling (ASL) MRI was collected before and after FUS. Participants (N=6, age=58.3 + 2.52, 50% female) completed two tFUS sessions, two weeks apart, targeting either right AG or left ERc. Participants and statisticians were blinded to which brain region was targeted. ERc served as the control region for the AG and vice versa. Within subject, within-session, paired-samples t-tests were conducted comparing regional perfusion (ASL) before and after tFUS. Psychophysiological interaction analyses (PPI) assessed tFUS-related functional connectivity changes. Resulting statistical maps were then compared within subject, between tFUS sessions.

Results: tFUS resulted in increased perfusion in the targeted area and not in the control area. Increased perfusion was also seen in regions known to be functionally connected to the targeted area (e.g. AG and medial prefrontal). tFUS resulted in target-specific functional connectivity changes in the predicted direction (increased ERc, disrupted AG).

Conclusions: FUS appears to selectively increase regional perfusion and modulate functional connectivity of targeted MTL structures. Replication in larger samples is needed. Currently, ongoing work investigating the ability of FUS to directly enhance memory and emotion

regulation via modulation of the ERc and AG is ongoing. These preliminary findings offer exciting insight into the potential application of FUS as a non-invasive cognitive neural prosthetic with wide ranging implications as a therapeutic device for numerous patient populations.

Learning Objectives:

1. Develop understanding of the therapeutic possibilities of low intensity focused ultrasound.
2. Consider the ability to modify ultrasound effects on brain tissue by modifying ultrasound parameters.

Literature References:

1. Legon, W., Adams, S., Bansal, P., Patel, P. D., Hobbs, L., Ai, L., ... & Gillick, B. T. (2020). A retrospective qualitative report of symptoms and safety from transcranial focused ultrasound for neuromodulation in humans. Scientific reports, 10(1), 1-10.
2. Beisteiner, R., & Lozano, A. M. (2020). Transcranial ultrasound innovations ready for broad clinical application. Advanced Science, 7(23), 2002026.

*DIFFERENTIAL EFFECTS OF CHILDHOOD VS. ADULTHOOD TRAUMA IN CANNABINOID RECEPTOR TYPE 1 (CB1R) AVAILABILITY IN POST-TRAUMATIC STRESS DISORDER (PTSD): A REVIEW OF LITERATURE AND PILOT POSITRON EMISSION TOMOGRAPHY (PET) STUDY

Anahita Bassir Nia*[1], *Cyril D'Souza[1], Kelly Cosgrove[1], Robert Pietrzak[1], Ilan Harpaz-Rotem[1]*

[1]Yale University School of Medicine

Abstract: Background: Trauma-induced alterations in the endocannabinoid (eCB) system have been consistently reported in animal models but only few human studies of post-traumatic stress disorder (PTSD) are available. Nevertheless, there is no consensus on the direction of these changes both in animal and human studies. Given the high rates of recreational and medicinal cannabis use in individuals with PTSD, and promising preliminary studies to target eCB system in PTSD treatment, it is critical to understand the nature of the eCB system alterations in individuals with history of trauma and PTSD. The availability of a new high specific ligand for cannabinoid receptor type 1 (CB1R) makes it possible now to study the CB1R in vivo. Using [11C]OMAR an analog of rimonabant, and the high resolution tomograph (HRRT) scanner, we aimed at investigating the eCB in PTSD in humans.

Methods: To understand the current evidence, we made a comprehensive literature review of all available animal and human studies on the effects of trauma and PTSD on the eCB system. We attempted to clarify the contradictory results based on the potential confounding factors and tested our hypothesis in a pilot study of CB1R availability, using PET imaging and [11C]OMAR receptor antagonist radiotracer, in individuals with PTSD compared to healthy controls (sample size=18). The volume of distribution (VT) of [11C]OMAR was measured in different brain areas, which is linearly related to CB1R availability. Following our proposed theory, we compared the effects of childhood with adulthood trauma on the CB1R availability in individuals with PTSD. PTSD was evaluated using PTSD CheckList (PCL) and trauma was measured by Childhood Trauma

Questionnaire (CTQ) and The Early Trauma Inventory Self Report-Short Form (ETISRSF).

Results: We proposed that the current contradictory results of eCB system alterations in PTSD in animal and human studies are partly explained by differential effects of childhood vs. adulthood trauma on eCB system. Based on the current evidence, childhood trauma results in decreased and adulthood trauma results in increased presentations of cannabinoid receptor type 1 (CB1R), consistently in animal and human studies. Similarly, the results of our pilot study showed that CB1R availability is lower in PTSD with childhood trauma and higher in PTSD with adulthood trauma, compared to healthy controls, in all brain regions. The mean composite VT value was 1.27 (SD 0.17) in individuals with PSTD and childhood trauma, 1.63 (SD 0.14) in PTSD with adulthood trauma and 1.40 (SD 0.17) in healthy controls.

Conclusions: Our pilot study, consistent with available animal and human studies, suggests that among individuals with PTSD, childhood trauma associates with decreased availability of CB1R, whereas adulthood trauma associates with increased availability of CB1R. To the best of our knowledge, this is the first study reporting this, which has important clinical implications in recreational and medicinal cannabis use in PTSD, and in potential therapeutic uses of cannabinoids in PTSD treatment. Decreased presentations of CB1R in PTSD with history of childhood trauma, vs. its increased presentations in PTSD with adulthood trauma may result in opposing effects of cannabinoids in these two groups, which needs further investigations, both for recreational and

medicinal marijuana use and for novel pharmacological options for PTSD such as cannabidiol (CBD) and other cannabinoid modulators.

Learning Objectives:

1. To understand the endocannabinoid system alterations in post-traumatic stress disorder (PTSD).
2. To understand the childhood trauma associates with down-regulation of cannabinoid receptors.type 1 (CB1R) and adulthood trauma associates with up-regulation of CB1R , which has important.Clinical implications.

Literature References:

1. Hill MN, Campolongo P, Yehuda R, Patel S. Integrating Endocannabinoid Signaling and Cannabinoids into the Biology and Treatment of Posttraumatic Stress Disorder. Neuropsychopharmacology. 2018;43:80-102.
2. Bassir Nia A, Bender R, Harpaz-Rotem I. Endocannabinoid System Alterations in Posttraumatic. Stress Disorder: A Review of Developmental and Accumulative Effects of Trauma. Chronic Stress. (Thousand Oaks). 2019;3.

*THE ROLE OF CANNABIDIOL IN THE TREATMENT OF COCAINE USE DISORDER: A RANDOMIZED CONTROLLED TRIAL

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[1]*Centre hospitalier de l'Université de Montréal*

Abstract: Background: Cocaine is one the most popular drug globally with 19 million users, of which 3 million are diagnosed with a cocaine use disorder (CUD). At the moment, CUD can only be treated by psychosocial approaches that are associated with relatively poor treatment outcomes. Cannabidiol (CBD) has been highly touted as a potential treatment for cocaine and stimulant use disorders based on promising preclinical data. However, no study has yet

measured CBD efficacy to prevent cocaine use and relapse in humans, and whether the assumptions from preclinical studies about its anti-inflammatory properties are confirmed in humans is not known.

Objectives and methods: In a single-site double-blind randomized controlled trial, we assessed CBD efficacy for reducing craving and preventing relapse in individuals with CUD, and explored its effects on pro-inflammatory markers. Seventy-eight adult participants with CUD were randomized (1:1) to receive either 800 mg CBD (n=40) or placebo (n=38) for 92 days. They first underwent a 10-day in-patient detoxification period before being weekly followed as out-patients for 12 weeks. On day 8, we evaluated cocaine craving using the visual analogue scale before and after exposure to a drug use scenario and analyzed the data using a multiple linear regression model. Number of days before hospital discharge and the first day of cocaine use using self-report and urine drug screen were used to determine relapse and analyzed the data with a multivariate Cox proportional hazards model. We also measured anti- and pro-inflammatory markers from blood samples at day 8, weeks 4 and 12 and analyzed them using a generalized estimating equation.

Results: Our results show that participants treated with CBD and placebo had similar (mean ± standard deviation) drug-cue induced craving (CBD: 4.69±2.89; placebo: 3.21±2.78, confidence interval [CI]: -0.33-3.04, p=0.069, Bayes factor [BF] = 0.498). The risk of cocaine relapse was similar in CBD and placebo groups (Hazard Ratio [HR] = 1.20, CI = 0.65-2.20, p=0.512, BF=0.152). Finally, several inflammatory markers were lower in the CBD group compared with the placebo group, including IL-6 (p=0.022), VEGF (p=0.037), intermediate monocytes CD14+CD16+ (p=0.024) and NK CD56negCD16hi (p<0.001). Conversely, regulatory CD25+CD4+T cells (p=0.012) were higher in the CBD group compared with the placebo group. No significant group difference was observed for B lymphocytes.

Conclusion and relevance to the field: Our lack of CBD efficacy to reduce craving is in line with another clinical trial using a lower CBD dose (300 mg) showing similar negative results. Although CBD is not superior to placebo for treating CUD, it presents potentially interesting anti-inflammatory properties that could be helpful to address related comorbidities.

Learning Objectives:

1. Appreciate recent data on the efficacy of cannabidiol to treat craving and relapse in individuals with cocaine use disorder.
2. Understand the effects of cannabidiol on inflammation in this population.

Literature References:

1. Meneses-Gaya, C., Crippa, J. A., Hallak, J. E., Miguel, A. Q., Laranjeira, R., Bressan, R. A., Zuardi, A. W., and Lacerda, A. L. (2020) Cannabidiol for the treatment of crack-cocaine craving: an exploratory double-blind study. Braz J Psychiatry
2. Mongeau-Pérusse, V., Brissette, S., Bruneau, J., Conrod, P., Dubreucq, S., Gazil, G., Stip, E., and Jutras-Aswad, D. (2021) Cannabidiol as a Treatment for Craving and Relapse in Individuals with Cocaine Use Disorder: a Randomized Placebo-Controlled Trial. Addiction

*EARLY REDUCTION IN IRRITABILITY IS ASSOCIATED WITH IMPROVED TREATMENT OUTCOMES AMONG YOUTHS WITH DEPRESSION: FINDINGS FROM THE AMOD STUDY

Alaa Mohamed*[1], *Paul Croarkin[1], Manish Jha[2], Jennifer Vande Voort[1]*

[1]*Mayo Clinic,* [2]*Icahn School of Medicine At Mount Sinai*

Abstract: Purpose: Irritability is a common yet often understudied feature of depression. Recent studies of adults with depression have found that early treatment-related reduction in irritability predicts improved long-term treatment outcomes, including reduced levels of suicidal ideation. Here, we evaluated whether baseline-to-week-4 improvements scale predicted lower severity of depressive symptoms, including suicidal ideation, at subsequent visit (week-8).

Methods: Participants of Adolescent Management Of Depression (AMOD) study (aged 13-18 years) who had irritability-related items available were included (n=176). Irritability was assessed by adding a single-irritability-item each from Children's Depression Rating Scale-Revised (CDRS-R), Quick Inventory of Depressive Symptomatology Adolescent version (QIDS-A17), and the IMPACT Medication Side Effects Scale for Children scale. Severity of suicidal ideation was measured with the Columbia Suicide Severity Rating Scale (C-SSRS). Separate linear regression analyses with depression severity (CDRS-R) and suicidal ideation (C-SSRS) at week-8 as the dependent variable and baseline levels of irritability and baseline-to-week-4 changes in irritability as independent variables of interest were conducted. These analyses were repeated after controlling for overall depression severity (minus the irritability item), age and sex.

Results: The three irritability-related items loaded strongly on the same factor (loading ranging from 0.66-0.81) and were combined to compute a single irritability score (baseline mean = 7.4, standard deviation = 2.6, range: 1-13). Greater baseline-to-week-4 reduction in irritability was associated with lower level of overall depression [β = -1.83, 95% confidence interval (CI): -2.53, -1.14] and suicidal ideation (β = -0.52, 95% CI: -0.99, -0.05) at week-8. Higher baseline irritability was associated with levels of overall depression (β = 1.28, 95% CI: 0.61, 1.96) but not with suicidal ideation (β = 0.35, 95% CI: -0.11, 0.81) at week-8. The association between baseline-to-week-4 reduction in irritability and levels of depression severity at week-8 were significant (β = -0.68, 95% CI: -1.32, -0.03) even after controlling for baseline levels and baseline-to-week-4 changes in overall depression severity, age and sex. However, the association between early reductions in irritability and levels of suicidal ideation at week-8 were not significant (β = -0.05, 95% CI: -0.55, 0.46) after controlling for overall depression severity.

Conclusion: Early reductions in irritability were associated with lower levels of overall depression and suicidal ideation at subsequent visits. Developing treatments that specifically target irritability may improve long-term outcomes of youths with depression.

Learning Objectives:

1. Participants will understand the clinical utility of assessing irritability in children with MDD.
2. Participants will be able to evaluate the evidence of how an early reduction in irritability subcomponent can affect predictors of clinical outcomes in children with MDD.

Literature References:

1. Jha MK, Minhajuddin A, Fatt CC, Kircanski K, Stringaris A, Leibenluft E, Trivedi M. Association between irritability and suicidal ideation in three clinical trials of adults with major depressive disorder. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology. 2020.

2. Jha MK, Minhajuddin A, South C, Rush AJ, Trivedi MH. Irritability and Its Clinical Utility in Major Depressive Disorder: Prediction of Individual-Level Acute-Phase Outcomes Using Early Changes in Irritability and Depression Severity. The American journal of psychiatry. 2019;176:358-366.

Individual Research Reports: Chronic Stress Conditions and Symptoms

12:00 p.m. - 1:15 p.m.

*HOW SYMPTOMS OF PAIN, IRRITABILITY AND DEPRESSION RELATE TO EACH OTHER AND TO MEASURES OF SOCIAL FUNCTIONING, WORK PRODUCTIVITY AND QUALITY OF LIFE: FINDINGS FROM THE EMBARC AND STRIDE STUDIES AND THE VITALSIGN6 PROJECT

Manish Jha*[1], *Alan Schatzberg[2], Abu Minhajuddin[3], Cherise Chin Fatt[3], Taryn Mayes[4], Madhukar Trivedi[3]*

[1]Icahn School of Medicine At Mount Sinai, [2]Stanford, [3]University of Texas Southwestern Medical Center, [4]UT Southwestern Dallas

Abstract: Objective: Pain and depression are two of the leading causes of disability in the United States. They are often comorbid and may be associated with symptoms of irritability. The purpose of this report was to evaluate the associations among these symptom domains (pain, irritability, and depression) and understand how they relate to measures of functional impairment in three large samples of adults with depression or with substance use disorders.
Methods: Participants of two randomized controlled trials [Establishing Moderators and Biosignatures of Antidepressant Response in Clinical Care (EMBARC; n=251 with DSM-IV diagnosis of major depressive disorder; study-duration: 08/2011-12/2015) and STimulant Reduction Intervention Using Dosed Exercise (STRIDE; n=302 with DSM-IV diagnosis of stimulant abuse or dependence; study-duration: 07/2010-02/2013)], and treatment-seeking patients in primary care clinics from an ongoing quality-improvement project (VitalSign6; n=4370; project-duration: 08/2014-07/2019) were included. Baron and Kenny's approach was used to assess whether irritability accounted for the effect of pain on depression.

Results: Pain was positively correlated with irritability (EMBARC: r=0.22, p=0.0006; STRIDE: r=0.29, p<0.0001; and VitalSign6: r=0.26, p<0.0001) and depression (EMBARC: r= 0.10, p=0.11; STRIDE: r=0.20, p=0.0005; and VitalSign6: r=0.33, p<0.0001). Even after controlling for age, sex, race, and ethnicity, higher levels of pain were associated with higher levels of irritability in EMBARC [β=0.19, t=5.11, df=1, 244, p<0.001], STRIDE [β=0.18, t=5.50, df=1, 292, p<0.001] and VitalSign6 project (β=0.13, t=11.08, df = 1, 1885, p<0.001). The association between pain and depression were significant in STRIDE [β=0.09, t=3.86, df=1, 292, p<0.0001] and VitalSign6 project (β=0.11, t=11.08, df = 1, 1885, p<0.001) but not in EMBARC [β=0.05, t=1.83, df=1, 244, p=0.07].

Regression models, per Baron and Kenny Approach, demonstrated that irritability significantly accounted for the effect of pain on depression in EMBARC (Sobel test statistics =3.03, p=0.002), STRIDE (Sobel test statistics =4.19, p<0.001) and VitalSign6 (Sobel test statistics =10.14, p<0.001). Irritability accounted for 65.5%, 50.4%, and 40.7% of the effect of pain on depression in EMBARC, STRIDE, and VitalSign6, respectively.

Higher irritability was associated with poorer social functioning [t=4.73, df=1, 225, p<0.0001], lower quality of life [t= -7.39, df=1, 293, p<0.0001], and impaired productivity in work [t=2.50, df=1, 437, p=0.013] and non-work-related [t=5.75, df=1, 838, p<0.0001] activities even after controlling for the severity of concurrent pain and depression. Higher depression was associated with poorer social functioning [t=2.75, df=1, 225, p=0.006], lower quality of life [t= -3.83, df=1, 293, p=0.0002], and impaired productivity in work [t=7.71, df=1, 437, p<0.0001] and non-work-related [t=10.98, df=1, 838, p<0.0001] activities, even after controlling for the severity of concurrent pain and irritability. Pain was associated with non-work-related activity impairments [t=4.98, df=1, 838, p<0.0001] but not with work productivity impairment [t=1.76, df=1, 437, p=0.08], social functioning [t=1.87, df=1, 225, p=0.06], or quality of life [t= -0.77, df=1, 293, p=0.44] after controlling for severity of concurrent irritability and depression.

Conclusion: Pain is associated with symptoms of irritability and depression. Irritability accounts for a large proportion of the effect of pain on depression. Symptoms of pain, irritability, and depression are associated with functional impairments.

Learning Objectives:

1. Understand the role of irritability in accounting for the association between pain and depression.
2. Characterize the burden of pain, irritability, and depression on measures of social functioning and quality of life.

Literature References:

1. Jha MK, Minhajuddin A, South C, Rush AJ, Trivedi MH. Irritability and Its Clinical Utility in Major Depressive Disorder: Prediction of Individual-Level Acute-Phase Outcomes Using Early Changes in Irritability and Depression Severity. The American journal of psychiatry. 2019;176(5):358-366.
2. Jha MK, Minhajuddin A, Greer TL, Carmody T, Rush AJ, Trivedi MH. Early Improvement in Work Productivity Predicts Future Clinical Course in Depressed Outpatients: Findings From the CO-MED Trial. The American journal of psychiatry. 2016;173(12):1196-1204.

*RAPID AND SUSTAINED IMPROVEMENTS IN QUALITY OF LIFE AND FUNCTIONING WITH AXS-05, AN ORAL NMDA RECEPTOR ANTAGONIST, IN PATIENTS WITH MAJOR DEPRESSIVE DISORDER

Amanda Jones[1], Samantha Feliz[1], Cedric O'Gorman*[1], *Caroline Streicher[1], Zachariah Thomas[1], Herriot Tabuteau[1]Axsome Therapeutics Inc.*

Abstract: Background: Major depressive disorder (MDD) is a leading cause of disability. Depression significantly impairs functioning and quality of life (QoL). Studies with current therapies show functional improvement trails symptomatic benefit. Treatments which rapidly improve QoL and functioning, as well as depressive symptoms, are urgently needed.

AXS-05 (dextromethorphan-bupropion modulated delivery tablet) is a novel, oral, investigational NMDA receptor antagonist with multimodal activity being developed for MDD. The dextromethorphan component of AXS-05 is an uncompetitive antagonist of the NMDA receptor, an ionotropic glutamate receptor, and sigma-1 receptor agonist, and the bupropion component serves to increase the bioavailability of dextromethorphan.

Objective: To assess the effect of AXS-05 as compared to placebo on QoL and functioning in MDD patients.

Methods: GEMINI was a randomized, double-blind, placebo-controlled, trial, in which 327 adults with moderate or severe MDD were randomized 1:1 to AXS-05 (dextromethorphan 45 mg-bupropion 105 mg) or placebo treatment twice daily for 6 weeks. The primary endpoint was change from baseline in MADRS total score at Week 6. Key secondary endpoints assessed rapidity, at Week 1 and 2. QoL and functioning assessments included the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q-SF) and the Sheehan Disability Scale (SDS), respectively. The Q-LES-Q-SF is a self-reported, 16-item scale. The raw score is converted to a percentage of maximum possible score, with higher percentages reflecting better QoL. The SDS is a 3-domain questionnaire evaluating impairments in work, social life/leisure, and family life/home responsibility.

Results: AXS-05 rapidly, substantially, and durably improved depressive symptoms on the MADRS total score as compared to placebo, with statistical significance as early as Week 1, and at all timepoints thereafter including the primary timepoint of Week 6.

Baseline Q-LES-Q-SF scores were 34% for AXS-05 and 36% for placebo. Improvements from baseline were statistically significant for AXS-05 as compared to placebo beginning at Week 1 (9.04% and 5.79%, respectively, p=0.031) and at Week 2 (13.21% and 8.88%, respectively, p=0.017), Week 3 (16.63% and 11.50%, respectively, p=0.009), Week 4 (19.01% and 12.48%, respectively, p=0.002), and Week 6 (19.84% and 14.37%, respectively, p=0.011).

Baseline SDS total scores were 20.3 for AXS-05 and 19.3 for placebo. Improvements from baseline were statistically significant for AXS-05 as compared to placebo beginning at Week 2 (6.82 and 4.47, respectively, p=0.003) and at Week 3 (6.98 and 5.21, respectively, p=0.027), Week 4 (8.68 and 6.13, respectively, p=0.003), and Week 6 (8.87 and 6.25, p=0.002).

Conclusions: AXS-05 treatment resulted in rapid and substantial improvements in QoL and functioning in tandem with rapid antidepressant effects, starting at Week 1 and sustained through Week 6. These findings suggest that AXS-05, as a mechanistically novel medicine, rapidly improves depressive symptoms, quality of life, and functioning.

Learning Objectives:

1. To appreciate the effects of AXS-05 as compared to placebo on quality of life and functioning in patients with major depressive disorder.
2. To understand the novel mechanisms of action of AXS-05.

Literature References:

1. Rush AJ, Trivedi MH, Wisniewski SR, Nierenberg AA, Stewart JW, Warden D, et al: Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. Am J Psychiatry 2006; 11 (163):1905-1917
2. Substance Abuse and Mental Health Services Administration. Key Substance Use and Mental Health Indicators in the United States: Results from the 2019 National Survey on Drug Use and Health [Internet]. Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration; September 2020. Available from: https://www.samhsa.gov/data/

PERCEPTIONS OF SAFETY, SUBJECTIVE EFFECTS, AND BELIEFS ABOUT THE CLINICAL UTILITY OF LYSERGIC ACID DIETHYLAMIDE (LSD) IN HEALTHY PARTICIPANTS: QUALITATIVE RESULTS

Neiloufar Family[1], Peter Hendricks*[2]

[1]*Eleusis Health Solutions,* [2]*The University of Alabama at Birmingham*

Abstract: Background. Classic psychedelics may be effective in the treatment of a number of mental health conditions, however, scalable treatment approaches are needed to maximize access to these novel therapeutics. In the current study, perceptions of safety, subjective effects, and beliefs about the clinical utility of lysergic acid diethylamide (LSD) were evaluated among healthy participants (N = 31) administered between 50-100 μg LSD in an abridged treatment paradigm designed for real-world implementation.

Methods. Semi-structured interviews assessed participants' expectations, their experience, and their thoughts on the safety and efficacy of the study design. These interviews were transcribed for thematic analysis relating to perceptions of safety, subjective effects, and beliefs about the clinical utility of LSD.

Findings. Most participants felt safe throughout the study, with a minority reporting concerns related to having a challenging experience with LSD that diminished over time. Participants attributed their feelings of safety to the study structure and support of their attendants, which allowed them to "let go" and immerse themselves in the experience without preoccupation. Furthermore, participants reported transcendent, mystical-type experiences characteristic of classic psychedelics, with almost half highlighting the prominent role played by music during the acute period of drug action. Finally, participants endorsed support for the clinical utility of LSD in controlled environments, expressing the belief that LSD is a safe drug with the potential to help others.

Interpretation. The current findings support the potential feasibility of this scalable intervention paradigm in clinical settings.

Learning Objectives:

1. To describe participant experiences during an LSD interventional study.
2. Identify areas for development and focus in the development of scalable therapeutic interventions with psychedelics.

Literature References:

1. Johnson, M., Richards, W. and Griffiths, R. (2008) 'Human hallucinogen research: guidelines for safety.', Journal of psychopharmacology (Oxford, England), 22(6), pp. 603–20. doi: 10.1177/0269881108093587.
2. Kvale, S. and Brinkmann, S. (2009) 'Learning the Craft of Qualitative Research Interviewing', in InterViews: learning the craft of qualitative research interviewing.

MEDIATION OF THE RELATIONSHIP BETWEEN SUICIDE AND SLEEP BY PERSONALITY

Jessica Rohr*[2], *Katrina Rufino*[1], *Sanjay Mathew*[2], *Michelle Patriquin*[2]

[1]*University of Houston Downtown/The Menninger Clinic,* [2]*Baylor College of Medicine*

Abstract: Understanding the risk factors for suicidality is becoming more critical as rates increase. Sleep disturbance is highly related to future suicidal ideation. This study investigates a potential modifier of the relationship between sleep and suicide: personality. Normal personality traits are commonly understood to differentially impact the development of various psychiatric disorders as well as development of sleep problems. People higher on extraversion (Ex) and agreeableness (Ag) tend to be less prone to sleep issues; those high on neuroticism (Ne) tend to be at a higher risk. Evidence shows that treatment of sleep disturbances should integrate both psychological and pharmacological approaches; using personality traits to determine levels of risk can help to improve outcomes. We hypothesized that sleep problems at admission would be related to suicidal ideation at admission, and personality would mediate this relationship. Specifically, higher levels of Ne and lower levels of Ex and Ag should account for a portion of the variance between sleep and suicide. An exploratory hypothesis is whether this relationship differs across gender. Participants were 3300 inpatients at a psychiatric hospital (1769 male, 1637 female; mean age = 35.24, range = 17-89). Psychiatric diagnoses were determined using the Structured Clinical Interview for DSM-5 Axis I and Axis II Disorders, Research Version: 9.8% reporting persistent depressive disorder, 6.7% reporting bipolar disorder, 41.7% reporting major depressive disorder, 19.6% reporting GAD, and 13.3% reporting PTSD. The mean duration of inpatient hospitalization was 42.16 days, (range = 1-238 days). No sleep psychotherapy protocol is implemented at the hospital. Self-reported sleep disturbance was assessed using the Patient Health Questionnaire-9 (PHQ-9; "trouble falling or staying asleep, or sleeping too much") and suicidal ideation on the Columbia Suicide Severity Rating Scale (CSSRS). Personality factors were assessed using the Big Five Inventory (BFI). The PHQ-9, CSSRS, and BFI were administered at admission. Analyses controlled for age. Mediation analyses were used to determine whether personality factors accounted for any part of the relationship between suicide and sleep, correcting for age and gender. Partial mediation was found for Ne (p=.000), Ex (p=.000), Ag (p=.000), and conscientiousness (Co, p=.000) such that higher levels of Ne and lower levels of Ex, Ag and Co predict suicidality. Gender differences were explored by repeating the mediation analysis with sample separated into male and female groups. For women, the pattern for Ne (p=.000), Ex (p=.000) was similar. However, Ag was marginally significant (p=.02), and Co was no longer significant. For men, Ne (p=.000), Ex (p=.000) and Co were significant (all at p=.000); Ag was marginally significant (p=.02). Findings revealed that in this inpatient sample, personality traits significantly mediated the impact of sleep issues on suicidal ideation. Specifically, higher levels of Ne and lower levels of Ex, Ag, and Co partially mediate the relationship between sleep and SI. This relationship was similar across men and women, though other personality factors differed across gender in terms of the variance accounted for; the difference in the role of Co in the relationship bears further examination. This highlights the importance of using person-centered evidence-based therapy for sleep with pharmacological interventions, with special attention paid to potential gender differences and personality characteristics impacting the relationship between sleep and suicidality.

Learning Objectives:

1. To identify personality traits that impact the relationship between suicide and sleep.
2. To integrate personality theory into suicide and sleep treatment.

Literature References:

1. Allen MS, Magee CA, Vella SA. Personality, hedonic balance and the quality and quantity of sleep in adulthood. Psychol Health. 2016Apr;31(9):1091–107.
2. Hartwig EM, Rufino KA, Palmer CA, Shepard C, Alfano CA, Schanzer B, et al. Trajectories of self-reported sleep disturbance across inpatient psychiatric treatment

predict clinical outcome in comorbid major depressive disorder and generalized anxiety disorder. J Affect Disord.

Individual Research Reports: Using Molecular Physiology to Develop Novel Treatments and Biomarkers

12:00 p.m. - 1:15 p.m.

*CONVERGENT EVIDENCE FOR THE ANTIVIRAL EFFECTS OF SEVERAL FDA-APPROVED PHENOTHIAZINE ANTIPSYCHOTICS AGAINST SARS-COV-2 AND OTHER CORONAVIRUSES

Rodrigo Machado-Vieira*[1], *Joao Quevedo[1], Lokesh Shahani[1], Jair Soares[1]*

[1]McGovern Medical School, University of Texas Science Center in Houston

Abstract: In the present report, we provide the first convergent evidence from two validated datasets evaluating antiviral effects against different human coronavirus types, with a particular focus on SARS-CoV-2. We reviewed the NCATS approved drug collection (NPC) (2,677 drugs total, any formulation). We selected as criteria the presence of one or more parameters with high-quality evidence as well as at least 3 (out of 4) key parameters with any level of evidence. We hypothesized that antipsychotic drugs sharing the three-ring structure of the phenothiazine class, with different side chains, would display a unique pharmacological profile to convergently inhibit SARS-CoV-2. We conclude that several typical antipsychotics sharing the same phenothiazine skeleton may have antiviral effects against SARS-CoV-2. Further confirmatory in vivo and epidemiological studies are warranted.

Learning Objectives:

1. Evaluate in vitro effects of phenothiazines in COVID-19.
2. Explain mechanisms of action related to the in vitro antiviral effects.

Literature References:

1. Machado-Vieira R, Quevedo J, Shahani L, Soares JC. Convergent evidence for the antiviral effects of several FDA-approved phenothiazine antipsychotics against SARS-CoV-2 and other coronaviruses. Braz J Psychiatry. 2021 Jan 11:S1516-44462021005001201. doi: 10.1590/1516-4446-2020-0024. Epub ahead of print. PMID: 33440401.
2. Stip E, Rizvi TA, Mustafa F, Javaid S, Aburuz S, Ahmed NN, Abdel Aziz K, Arnone D, Subbarayan A, Al Mugaddam F, Khan G. The Large Action of Chlorpromazine: Translational and Transdisciplinary Considerations in the Face of COVID-19. Front Pharmacol. 2020 Dec 16;11:577678. doi: 10.3389/fphar.2020.577678. PMID: 33390948; PMCID: PMC7772402.

*BRUGADA SYNDROME AND RELATED CARDIAC CONDUCTION DISORDERS: A STRATEGY TO UNDERSTAND THE ETIOLOGY OF SUDDEN CARDIAC DEATH AMONG PATIENTS WITH SCHIZOPHRENIA AND PSYCHOTIC BIPOLAR DISORDER

Rishab Gupta*[1], *Tim Bigdeli*[2], *Mihaela Aslan*[3], *Philip Harvey*[4], *Ayman Fanous*[2], *Nina Schooler*[2]

[1]*Brigham and Women's Hospital, SUNY Downstate Medical Center,* [2]*SUNY Downstate Medical Center,* [3]*VA Connecticut Healthcare System,* [4]*University of Miami Miller School of Medicine*

Abstract: Background: Sudden Cardiac Death (SCD) is one of the leading causes of mortality among patients with Schizophrenia and is three times more common among them than in the general population. SCD is associated with number of clinical factors commonly seen in patients with psychotic disorders (schizophrenia and psychotic bipolar disorder), viz., poor lifestyle, psychotropic drugs (by prolonging QT interval via their effect on cardiac sodium channels), substance use, and metabolic syndrome leading to coronary artery disease. Although coronary artery disease underlies around 75%-80% of all cases of SCD, there is also a role for inherited conduction disorders.

One of the key causes of SCD in patients without structural heart disease is Brugada Syndrome (BrS), a complex arrhythmogenic disorder known to affect 1 in 2000 people. However, it is estimated to be ~10 times more common among patients with schizophrenia. Known genetic factors for BrS include mutations in CACNA1C and KCHN2, which have also been implicated in schizophrenia and bipolar disorder.

Approach: We postulate that a partially shared genetic basis of psychotic disorders and BrS may be contributing to the increased occurrence of SCD among patients with psychotic disorders. We reviewed the available evidence in support of this hypothesis, including results from the Schizophrenia Exome Sequencing Meta-analysis (SCHEMA) consortium (24K cases and 97K controls) and Psychiatric Genomic Consortium (PGC) with 34K cases and 45K controls.

Results: Among the 27 known BrS associated genes, 5 had nominally significant P-values in SCHEMA – HCN4 ($P<10^{-5}$) CACNA2D1 ($P<0.001$), ANK2 and CACNA1C ($P<0.01$), and ABCC9 ($P<0.05$). In addition to a replicated association with common variants in CACNA1C ($P<10^{-16}$), the landmark PGC genome-wide association study (GWAS) detected subthreshold associations in or near ANK2 ($P<10^{-4}$), and HCN4 and CACNA2D1 ($P<0.001$). We also investigated overlap at the level of curated gene sets, using results from the PGC and a recent study of 60K atrial fibrillation cases and 970K controls. We observed no overlap between enriched gene sets that survived correction for multiple testing in each study.

Conclusions: Leveraging publicly available summary statistics and large genomic data repositories, we evaluated the current evidence regarding possible shared genetic basis of schizophrenia with BrS and atrial fibrillation. We found supportive evidence for genetic association between schizophrenia and BrS. Based on these preliminary findings, we will describe a framework for dually modeling genetic and treatment-related influences on arrhythmias and SCD in the Veterans Affairs (VA) Cooperative Studies Program (CSP) #572, a detailed clinical study of more than 9K US veterans with schizophrenia or bipolar disorder focusing on the genetics of functional disability. We will also use available complete electronic health records (EHR) from VA database to extract treatment-related information of participants as well as reports of SCD for our proposed analysis.

Learning Objectives:

1. To systematically examine the shared genetic substrate between psychotic disorders (schizophrenia and psychotic bipolar disorder) and arrhythmias, and sudden cardiac death.
2. To highlight the complementary role of EHR-based data in the mechanistic understanding of psychotic disorders and co-morbid arrhythmias.

Literature References:

1. Blom MT, Cohen D, Seldenrijk A, et al.: Brugada syndrome ECG is highly prevalent in schizophrenia. Circ Arrhythm Electrophysiol 2014; 7:384–391
2. Refaat MM, Hotait M, London B: Genetics of sudden cardiac death. Curr Cardiol Rep 2015; 17:606

*TSPAN5 REGULATES SEROTONIN AND KYNURENINE LEVELS: PHARMACOGENOMIC MECHANISMS RELATED TO ALCOHOL USE DISORDER AND ACAMPROSATE TREATMENT RESPONSE

Ming-Fen Ho*[1], *Cheng Zhang[1], Lingxin Zhang[1], Lixuan Wei[1], Ying Zhou[2], Irene Moon[1], Jennifer Geske[1], Doo-Sup Choi[1], Joanna Biernacka[1], Mark Frye[1], Victor Karpyak[1], Zhexing Wen[2], Hu Li[1], Richard Weinshilboum[1]*

[1]Mayo Clinic, [2]Emory University

Abstract: Background: We previously reported that TSPAN5 SNPs were associated with plasma serotonin concentrations which were themselves correlated with selective serotonin reuptake inhibitor treatment outcomes in patients with major depressive disorder (MDD), and with alcohol use disoder (AUD) risk. A recent genome-wide association study (GWAS) of alcohol consumption in UK Biobank participants identified a series of genome-wide significant variants on chromosome 4. Strikingly, several of those SNPs (rs3114045, rs193099203 and rs9991733) are trans-eQTLs in the brain for TSPAN5 which maps to chromosome 4 (1). When the UK Biobank study results were stratified by sex, the rs114026228 SNP in TSPAN5 (p=3.60E-13) was the top signal associated with alcohol consumption in men. In addition, a recent GWAS meta-analysis demonstrated that TSPAN5 SNPs were associated with AUD risk in an African American population (2). It should also be pointed out that the TSPAN5 rs11947402 SNP which was originally identified from our GWAS for baseline plasma 5-HT concentrations in MDD patients was also associated with AUD risk (p=0.017) in that same AUD GWAS meta-analysis (2). As a result of this growing body of evidence that TSPAN5 may play a role in AUD risk, the present study was designed to explore the biological function of TSPAN5 with a focus on the tryptophan pathway using human iPSC-derived CNS cells exposed to either ethanol (EtOH) or acamprosate—an FDA approved medication for the treatment of AUD

Methods: Functional genomic studies were performed using five human induced pluripotent stem cell (iPSC) lines. The Mayo Clinic Center for the Individualized Treatment of Alcoholism recruited 443 AUD subjects with clinical data, and DNA samples were obtained at baseline and after 3 months of acamprosate treatment. Specifically, 300 European American subjects have their 3-month acamprosate treatment outcomes available.

Results: TSPAN5 mRNA expression was downregulated by ethanol and by acamprosate—an FDA approved drug for AUD therapy, resulting in decreased serotonin concentrations in iPSC-derived neuron culture media and the down-regulation of DDC, MAOA, MAOB, TPH1, and TPH2. Strikingly, these results were compatible with results obtained after the knockdown of

TSPAN5 expression in neurons. Very similar observations were also made in iPSC-derived astrocytes. Mass spectrometry identified proteins related to clathrin and other vesicle related proteins which interacted physically with TSPAN5, indicating that TSPAN5 might play a role in vesicular function in addition to regulating genes associated with serotonin biosynthesis and metabolism. RNA-seq data demonstrated that TSPAN5 knockdown in iPSC-derived astrocytes also significantly influenced kynurenine concentrations as well as the expression of genes associated with immune related pathways. Finally, we also determined that genetic variants that are associated with TSPAN5 expression might be biomarkers for abstinence length in AUD patients enrolled in the Mayo Clinic Center for the Individualized Treatment of Alcoholism clinical trial.

Conclusions: TSPAN5 is an alcohol responsive gene that plays a role in the regulation of 5HT and kynurenine concentrations. The functional genomic data from iPSC-derived CNS cells open a new avenue for understanding the biological role of TSPAN5 in AUD as well as acamprosate's mechanism of action. Our results highlight novel pharmacogenomic mechanisms underlying response to acamprosate therapy.

Learning Objectives:

1. Application of Patient-Specific iPSC Model Systems in Pharmacogenomics of Psychiatric Disorders.
2. Pharmacogenomics in alcohol use disorder and acamprosate treatment response.

Literature References:

1. Clarke TK, Adams MJ, Davies G, Howard DM, Hall LS, Padmanabhan S,
1. Murray AD, Smith BH, Campbell A, Hayward C, Porteous DJ, Deary IJ, McIntosh AM. Genome-wide association study of alcohol consumption and genetic overlap with other health-related traits in UK Biobank (N=112 117). Molecular Psychiatry. 2017;22:1376.
2. 2. Kranzler HR, Zhou H, Kember RL, Vickers Smith R, Justice AC, Damrauer S, Tsao PS, Klarin D, Baras A, Reid J, Overton J, Rader DJ, Cheng Z, Tate JP, Becker WC, Concato J, Xu K, Polimanti R, Zhao H, Gelernter J. Genome-wide association study of alcohol consumption and use disorder in 274,424
3. individuals from multiple populations. Nature Communications. 2019;10:1499.

*THE BIO-K STUDY OF BIOMARKERS OF RESPONSE TO INTRAVENOUS RACEMIC KETAMINE: CLINICAL OUTCOMES

Sagar Parikh*[1], *Jennifer Vande Voort[2], William Bobo[2], Dan Maixner[1], Vijay Tarnal[1], Mark Frye[2], Fernando Goes[3], Eric Achtyes[4], Brendon Watson[1], Daniela Lopez[1], Cortney Sera[1], Erica Vest-Wilcox[1], Cynthia Stoppel[2], Alexis Becerra[3], John Greden[1]*

[1]University of Michigan, [2]Mayo Clinic, [3]Johns Hopkins University, [4]Michigan State University College of Human Medicine

Abstract: Background: Meta-analytic data demonstrate that intravenous racemic ketamine is effective for treatment-refractory depression (TRD), usually using 40-minute infusions. Precise biomarker or clinical predictors of response have not been identified. Among the clinical issues are whether patient demographics, disease characteristics, or rate of administration of IV

ketamine modulates either efficacy or tolerability (side effects). Among biomarker predictors, we are examining mediators of neuroplasticity, particularly the mammalian target of rapamycin (mTOR) signaling pathway, as well as inflammatory markers. Here, we report clinical outcomes.

Methods: We conducted a four-site clinical trial of IV ketamine for TRD, administering 3 acute infusions dosed at 0.5 mg of ketamine per kg body weight to a maximum of 50 mg, within 11 days. Remission was defined as MADRS scores less than 9. Both 100-minute and 40-minute infusions were administered, enabling comparison of efficacy, side effects, safety, and tolerability.

Results: Seventy-four subjects completed the 3 acute phase infusions. Twenty-one participants had additional maintenance infusions, yielding a large number of both 100 minute and 40 minute infusions. Sample was 68% female with a mean age of 43.85 years and mean baseline MADRS of 29. After three infusions, 52% of the sample were in remission, with 55% of the sample reporting a greater than 50% decline in suicidality measured by the Beck Suicide Scale. Side effects were modest and transient. Almost no differences in efficacy or side effects were seen between 100 minute and 40 minute infusions. Biomarker assays are undergoing analysis, with preliminary results expected to be available at the time of presentation.

Conclusion: Substantial remission of depression symptoms and reduction in suicidality in TRD patients was seen in response to 3 infusions of IV ketamine over 11 days. Comparisons of 100 minute to 40 minute infusions did not reveal significant differences in efficacy or side effects, suggesting no advantage to slower infusions.

Learning Objectives:

1. Review the efficacy and side effects associated with administration of 3 infusions of racemic ketamine for TRD.
2. Explore differences in efficacy and side effects between slow (100 minute) and standard (40 minute) infusions.

Literature References:

1. Bobo WV, Vande Voort JL, Croarkin PE, et al: Ketamine for treatment-resistant unipolar and bipolar major depression: critical review and implications for clinical practice. Depress Anxiety 2016; 33:698–710
2. Matveychuk D, Thomas RK, Swainson J, et al. Ketamine as an antidepressant: overview of its mechanisms of action and potential predictive biomarkers. Ther Adv Psychopharmacol. 2020;10:2045125320916657. Published 2020 May 11. doi:10.1177/2045125320916657

*EFFECTS OF A KETOGENIC DIET ON WITHDRAWAL SYMPTOMS, ALCOHOL CRAVING AND BRAIN ENERGETICS DURING INPATIENT ALCOHOL DETOXIFICATION

Corinde Wiers*[1], *Leandro Vendruscolo[2], Jan-Willem van der Veen[3], Peter Manza[4], Ehsan Shokri-Kojori[4], Sara Turner[5], Shanna Yang[5], Dardo Tomasi[4], Kimberly Herman[4], Nancy Diazgranados[4], Gene-Jack Wang[4], Nora Volkow[4]*

[1]University of Pennsylvania, [2]NIH/NIDA, [3]NIH/NIMH, [4]NIH/NIAAA, [5]NIH/CC

Abstract: Participants with an Alcohol Use Disorder (AUD) show elevated levels of acetate metabolism in the brain at the expense of a decrease in brain glucose metabolism compared to non-dependent controls. While during alcohol intoxication plasma levels of acetate increase, during detoxification they decrease, which we hypothesize would result in an energy-deficient state in the brain that could contribute to withdrawal symptoms, enhanced neuronal excitability and neurotoxicity in AUD and proposed that a ketogenic diet (KD) could mitigate this. Here we studied the effects of KD on alcohol withdrawal, craving, and brain ketone concentrations in n= 33 AUD inpatients during alcohol detoxification, who were randomized into a KD (n=19; 4:1 ratio of fat: carbohydrate and protein) or Standard American (SA) diet (n=14; 50% carbs) intervention for 3 weeks. By providing a liquid diet, study procedures were double blind and there were no group differences in diet expectation at completion of the study, indicating that blinding was successful. During the first week when withdrawal symptoms were the strongest and required benzodiazepine dosing, we showed significantly lower use of benzodiazepines for the KD compared the SA diet and lower withdrawal scores (CIWA-Ar) at trend level in KD, which may have reflected the confounds from benzodiazepine use. Over the 3-week treatment, KD showed lower "wanting" for alcohol cues compared to SA, and KD showed a trend for reduced alcohol craving scores. Spectroscopic imaging (1H MRS) in the Anterior Cingulate Cortex (ACC) showed that KD participants compared to SA had higher levels of Acetone, Acetoacetate (AcAc), Glutamate and Glutamine, whereas lower Myo-inositol, and Choline. Weekly imaging with fMRI revealed that alcohol cue-induced reactivity was increased in the ACC in KD versus SA, consistent with enhanced control over alcohol craving. Here we show first evidence for beneficial effects of KD during alcohol withdrawal in AUD patients undergoing detoxification. This finding is in line with recent preclinical studies showing that metabolic ketosis induced by either a ketogenic diet or by a nutritional ketone ester can alleviate alcohol withdrawal symptoms.

Learning Objectives:

1. A high-fat low carbohydrate ketogenic diet lowered the need for benzodiazepines and withdrawal symptoms during detoxification in alcohol use disorder.
2. A ketogenic diet elevated ketone bodies and glutamate and glutamine in brain in AUD, which can be used as alternative energy to glucose.

Literature References:

1. Volkow ND, Wiers CE, Shokri-Kojori E, Tomasi D, Wang GJ, Baler R. Neurochemical and metabolic effects of acute and chronic alcohol in the human brain: Studies with positron emission tomography. Neuropharmacology. 2017;122:175-188
2. Dencker D, Molander A, Thomsen M, Schlumberger C, Wortwein G, Weikop P, Benveniste H, Volkow ND, Fink-Jensen A. Ketogenic Diet Suppresses Alcohol Withdrawal Syndrome in Rats. Alcoholism, clinical and experimental research. 2018;42:270-277.

***Clinical Updates in Psychopharmacology Session**

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

***CLINICAL UPDATES IN PSYCHOPHARMACOLOGY SESSION**

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

Overall Abstract: Sagar Parikh will provide an update on how to pick, present, and promote apps in your clinical practice. Stephan Taylor will provide an update on transcranial magnetic

stimulation for the treatment of depression, and Lori Davis provide an update on pharmacotherapy for post-traumatic stress disorder.

HOW TO PICK, PRESENT, AND PROMOTE APPS IN YOUR CLINICAL PRACTICE

Sagar Parikh, University of Michigan, Ann Arbor

Abstract: Apps for phones and other devices are ubiquitous, but which ones are truly beneficial? Apps are not regulated, and evidence of efficacy is limited. Frameworks for how to evaluate apps have emerged which provide guidance on how to choose apps, but where to start? This presentation highlights three key evaluation resources: MIND, Psyberguide, and the APA App Advisor. Integrating recommendations from these sites, evidence, and practical experience, we will review key apps: PTSD Coach, eMoods for bipolar disorder, Mindshift for CBT for adolescents, Moodshift for CBT for depression, and Headspace for stress and mindfulness. In addition, key apps useful as decision aids for the clinician will be reviewed: SMI Advisor for schizophrenia, MDCalc for diverse medical and psychiatric scales, and the CANMAT Bipolar Guidelines app. In addition to brief overviews of these apps, selecting the right patient for each app and how to introduce and monitor the app in practice will be explored.

Learning Objectives:

1. Identify key web resources where to learn how to evaluate apps, and identify suitable apps for specific indications.
2. Explore several key apps for patients, and also key apps that serve as useful decision aids for the clinician.

Literature References:

1. Lecomte T, Potvin S, Corbière M, Guay S, Samson C, Cloutier B, Francoeur A, Pennou A, Khazaal Y. Mobile Apps for Mental Health Issues: Meta-Review of Meta-Analyses. JMIR Mhealth Uhealth. 2020 May 29;8(5):e17458.
2. Carpenter-Song E, Acquilano SC, Noel V, Al-Abdulmunem M, Torous J, Drake RE. Individualized Intervention to Support Mental Health Recovery Through Implementation of Digital Tools into Clinical Care: Feasibility Study. Community Ment Health J. 2021 Feb 21:1–12.

UPDATE ON TRANSCRANIAL MAGNETIC STIMULATION FOR THE TREATMENT OF DEPRESSION

Stephan Taylor, University of Michigan

Abstract: Transcranial magnetic stimulation (TMS) was cleared by the FDA for the treatment of major depressive disorder in 2008. Since that time, 6 more TMS systems have been cleared, and the approved indications for TMS have expanded beyond unipolar depression to include bipolar depression, obsessive-compulsive disorder, migraine headache and smoking cessation. TMS involves the delivery of electromagnetic pulses to the brain, which stimulate underlying neurons by inducing electrical current in neurons. The precise effects of TMS stimulation on the brain depend upon a variety of factors, including the pulse shape, coil design and orientation, pattern and frequency of stimulation, location of stimulation and state of neural tissue being stimulated. All therapeutic use of TMS involves some form of repetitive stimulation (rTMS), and current therapies use either high frequency stimulation (10 or 20 Hz) to the left dorsolateral prefrontal cortex, or patterned stimulation designed to mimic theta and gamma frequencies in the brain (‘theta burst stimulation’). Multiple meta-analyses have

demonstrated efficacy for rTMS in the treatment of depression, usually in patients who have failed one or more course of antidepressant therapy. Response and remission rates in sham-controlled studies are on the order of 30% and 15%, respectively, whereas response rates in naturalistic, uncontrolled studies are in the range of 50%. With enormous flexibility in application, research is pursuing multiple avenues to improve efficacy, including rapid delivery of rTMS over days instead of weeks, pairing rTMS with psychotherapy and targeting rTMS in specific brain regions to specific patient types. As the new techniques mature and data show therapeutic benefits, TMS will continue to grow and become an increasingly important part of the therapeutic armamentarium to treat psychiatric disorders.

Learning Objectives:

1. Become acquainted with the basic technique and administration of transcranial magnetic stimulation (TMS) for the treatment of depression, including side effects and evidence for beneficial effects.
2. Understand the varieties of TMS treatment currently available for patients with depression.
3. Gain awareness of current research directions in TMS therapy.

Literature References:

1. Baeken, C., A. K. Brem, M. Arns, A. R. Brunoni, I. Filipcic, A. Ganho-Avila, B. Langguth, F. Padberg, E. Poulet, F. Rachid, A. T. Sack, M. A. Vanderhasselt and D. Bennabi (2019). "Repetitive transcranial magnetic stimulation treatment for depressive disorders: current knowledge and future directions." Curr Opin Psychiatry 32(5): 409-415.
2. Blumberger, D. M., F. Vila-Rodriguez, K. E. Thorpe, K. Feffer, Y. Noda, P. Giacobbe, Y. Knyahnytska, S. H. Kennedy, R. W. Lam, Z. J. Daskalakis and J. Downar (2018). "Effectiveness of theta burst versus high-frequency repetitive transcranial magnetic stimulation in patients with depression (THREE-D): a randomised non-inferiority trial." Lancet 391(10131): 1683-1692.
3. Brunoni, A. R., A. Chaimani, A. H. Moffa, L. B. Razza, W. F. Gattaz, Z. J. Daskalakis and A. F. Carvalho (2017). "Repetitive Transcranial Magnetic Stimulation for the Acute Treatment of Major Depressive Episodes: A Systematic Review With Network Meta-analysis." JAMA Psychiatry 74(2): 143-152.
4. McClintock, S. M., I. M. Reti, L. L. Carpenter, W. M. McDonald, M. Dubin, S. F. Taylor, I. A. Cook, J. O'Reardon, M. M. Husain, C. Wall, A. D. Krystal, S. M. Sampson, O. Morales, B. G. Nelson, V. Latoussakis, M. S. George, S. H. Lisanby, T. M. S. T. G. National Network of Depression Centers r, B. American Psychiatric Association Council on Research Task Force on Novel and Treatments (2018). "Consensus Recommendations for the Clinical Application of Repetitive Transcranial Magnetic Stimulation (rTMS) in the Treatment of Depression." J Clin Psychiatry 79(1).
5. Sehatzadeh, S., Z. J. Daskalakis, B. Yap, H. A. Tu, S. Palimaka, J. M. Bowen and D. J. O'Reilly (2019). "Unilateral and bilateral repetitive transcranial magnetic stimulation for treatment-resistant depression: a meta-analysis of randomized controlled trials over 2 decades." J Psychiatry Neurosci 44(3): 151-163.
6. Senova, S., G. Cotovio, A. Pascual-Leone and A. J. Oliveira-Maia (2019). "Durability of antidepressant response to repetitive transcranial magnetic stimulation: Systematic review and meta-analysis." Brain Stimul 12(1): 119-128.

PHARMACOTHERAPY FOR POST-TRAUMATIC STRESS DISORDER: NEW TRIALS AND NEW RESULTS

Lori Davis, Veterans Affairs Medical Center

Abstract: Post-traumatic stress disorder (PTSD) is a prevalent and costly mental disorder resulting from a life-threatening and/or sexually-traumatic event. The one-year prevalence is 3% for men and 6% for women in US civilians and 7% for men and 12% for women in US military populations. The US economic burden is estimated to be $232.2 billion overall, with $189.5 billion arising from civilian PTSD and $42.7 billion resulting from military-related PTSD. Thus, new and effective treatments for PTSD are urgently needed. Over the past five years, the pipeline for novel medications being tested in the treatment of PTSD has improved with exciting progress being made. With permission from sponsors and/or investigators, Dr. Davis will share details of the compounds being studied, design strategies, and results of recent ongoing and completed clinical trials.

Learning Objectives:

1. Following the presentation, participants will have a working knowledge of the prevalence and societal cost of post-traumatic stress disorder.
2. Following the presentation, participants will have a working knowledge of the new pharmaceutic agents that are being tested or have recently been tested for the treatment of post-traumatic stress disorder.

Literature References:

1. Lehavot K, Katon JG, Chen JA, Fortney JC, Simpson TL. Post-traumatic Stress Disorder by Gender and Veteran Status. Am J Prev Med. 2018;54(1):e1-e9.
2. Bryant RA. Post-traumatic stress disorder: a state-of-the-art review of evidence and challenges. World Psychiatry. 2019;18(3):259-269.

Panel Sessions

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

***NEXT-STEP TREATMENT CONSIDERATIONS IN PATIENTS WITH TREATMENT-RESISTANT DEPRESSION THAT RESPONDS TO LOW-DOSE INTRAVENOUS KETAMINE**

Sagar Parikh, University of Michigan, Ann Arbor

Overall Abstract: Numerous short-term randomized trials support the acute phase efficacy of low-dose intravenous (IV) ketamine for patients with treatment-resistant unipolar or bipolar depression (TRD). Ketamine's antidepressive effects generally have limited duration, highlighting the need for maintenance treatment following an acute-phase response. It is increasingly likely that psychiatrists will be called upon to manage the care of patients with TRD who have responded acutely to ketamine, and to recommend or initiate next-step treatments. However, there is a paucity of controlled evidence to guide best practices for managing patients with TRD who have had a positive initial response to ketamine. We review the available evidence supporting specific strategies for extending and maintaining acute antidepressive responses to low-dose IV ketamine in patients with TRD. We reviewed the evidence for the following approaches to treatment after IV ketamine: (a) Continued intravenous [IV] or intranasal ketamine (b) Intranasal esketamine (c) Oral ketamine (d) Other glutamatergic drugs (e) Electroconvulsive therapy (ECT) (f) Other neuromodulatory therapies

(g) Switching conventional antidepressants or mood stabilizing medications and (h) Continuation of effective psychotherapy. In the absence of specific randomized clinical trials, open-label studies were considered, along with primary efficacy and safety data for the other approaches. Expert opinion formed the basis of identifying potential treatment recommendations, without sufficient evidence or opinion to provide hierarchical recommendations of what might be considered first-line, second-line, or subsequent treatments. We highlight the most promising strategies to study, in order to clarify direction for future research.

Learning Objectives:

1. Clarify differences between using additional IV ketamine and moving to intranasal or oral ketamine, post successful treatment of acute depression with IV ketamine.
2. Identify non-ketamine options for maintaining remission after IV ketamine, particularly the use of conventional medications and neuromodulation.

CONTINUATION OF INTRAVENOUS (IV) RACEMIC KETAMINE: IS THE HORSE OUT OF THE BARN?

William Bobo, Mayo Clinic

Individual Abstract: The use of subanesthetic doses of IV racemic ketamine has brought with it the prospects of high clinical efficacy and rapid onset of therapeutic activity for depressed unipolar and bipolar depressed patients with a history of poor response to conventional antidepressants or mood stabilizing medications. Although the acute-phase antidepressive efficacy of IV ketamine for treatment-resistant depression has been established on the basis of numerous randomized trials, the same cannot necessarily be said for longer-term maintenance—that is, the provision of repeated doses of IV ketamine with the goal of extending a positive acute-phase treatment response. Here, we review the evidence for and against the continuation of IV racemic ketamine following a positive acute response in patients with treatment-resistant depression.

Learning Objectives:

1. Discuss the evidence supporting the continuation of IV racemic ketamine following a positive acute response in patients with treatment-resistant depression.
2. Enumerate the main safety concerns and unknown risks associated with the continuation of IV racemic ketamine following a positive acute response in patients with treatment-resistant depression.

Literature References:

1. Archer S, Chrenek C, Swainson J: Maintenance ketamine therapy for treatment-resistant depression. J Clin Psychopharmacol 2018; 38:380–384.
2. Phillips JL, Norris S, Talbot J, et al: Single, repeated, and maintenance ketamine infusions for treatment-resistant depression: a randomized controlled trial. Am J Psychiatry 2019; 176:401–409.
3. Vande Voort JL, Morgan RJ, Kung S, et al: Continuation phase intravenous ketamine in adults with treatment-resistant depression. J Affect Disord 2016; 206:300–304.
4. Wilkinson ST, Katz RB, Toprak M, et al: Acute and longer-term outcomes using ketamine as a clinical treatment at the Yale Psychiatric Hospital. J Clin Psychiatry 2018; 79:17m11731.

THE ROLE OF NEUROMODULATION IN PATIENTS WHO RECEIVE KETAMINE FOR TRD

Patricio Riva-Posse, Emory University School of Medicine

Individual Abstract: In recent years, ketamine (and more recently esketamine) have been used for patient with treatment-resistant depression. This new medication approach breaks away from the classical monoaminergic approach that dominated the last few decades of psychiatric biological treatments. Non-pharmacological approaches have been around for longer than pharmacology with treatments such as electroconvulsive therapy, and in recent years newer technologies such as rTMS, VNS (FDA-approved), and DBS (experimental). It is inevitable that patients with TRD will be exposed not only to ketamine, but to neuromodulation approaches in the course of their illnesses. There is still limited data supporting the combination of ketamine and neuromodulation treatments. Ketamine, used as an anesthetic, has been combined with ECT, but with poor evidence. There are ongoing trials discussing the combination of rTMS with ketamine.
We will discuss the current state of the art in TRD with regards to the combination of ketamine and neuromodulation approaches, discussing hypothetical synergistic mechanisms of action, complimentary uses and case reports will be described.

Learning Objectives:

1. To identify the potential benefits of combining neuromodulation treatments with ketamine in treatment resistant depression.
2. To review current state of the evidence in advanced stages of TRD supporting the combined use of ketamine and neuromodulation techniques.

Literature References:

1. Anderson, IM; Blamire, A; Branton, T; et al. Ketamine augmentation of electroconvulsive therapy to improve neuropsychological and clinical outcomes in depression (Ketamine-ECT): a multicentre, double-blind, randomised, parallel-group, superiority trial. Lancet Psychiatry 2017, 4 (5): 365-377
2. Leuchter, A; Espinoza, R; Suthana, N; et al. Synergistic effects of ketamine and theta burst stimulation in the treatment of major depressive disorder (MDD). Brain Stimulation 2017, 10 (2): 492

EFFICACY OF NON-KETAMINE GLUTAMATERGIC AGENTS IN THE TREATMENT OF MAJOR DEPRESSIVE DISORDER – THE PROMISE, THE PITFALLS, AND THE EVIDENCE

Fernando Goes, Johns Hopkins University School of Medicine

Individual Abstract: Although there remains controversy about Ketamine's specific mechanism of action, its primary role as an NMDA glutamate receptor antagonist has re-invigorated the search for alternative glutamatergic agents that may be more easily administered, with less dissociative effects or potential concerns for abuse. In this presentation, we will discuss novel compounds focused on the glutamatergic system that could provide greater ease of use and long-term feasibility for patients who respond to acute ketamine infusion. We will focus the discussion of compounds that have undergone, or are currently undergoing, large scale clinical trials such as riluzole, memantine, lanicemine, rapastinel and the combination of dextromethorphan/bupropion. Finally, we will also discuss the potential efficacy for the most widely studied glutamatergic compound, intranasal esketamine, as a

potential maintenance agent in subjects who have responded to IV acute phase racemic ketamine.

Learning Objectives:

1. To evaluate the efficacy of novel, non-ketamine, glutamatergic agents for the treatment of Major Depressive Disorder.
2. To compare the efficacy IV racemic ketamine with intranasal esketamine in the acute and long-term treatment of Major Depressive Disorder.

Literature References:

1. Wilkinson ST and Sanacora G: A new generation of antidepressants: an update on the pharmaceutical pipeline for novel and rapid-acting therapeutics in mood disorders based on glutamate/GABA neurotransmitter systems. Drug Discovery Today 2019; 24 (2): 606-615
2. Bahji A, Vazquez GH, Zarate CA: Comparative efficacy of racemic ketamine and esketamine for depression: a systematic review and meta-analysis. Journal of Affective Disorders, 2021; 278: 542-555

*INNOVATIVE TREATMENT STRATEGIES FOR TREATMENT RESISTANT MAJOR DEPRESSIVE DISORDER, BIPOLAR DISORDER AND SCHIZOPHRENIA

Roy Chengappa, University of Pittsburgh Medical Center

Overall Abstract: Treatment Resistant Major Depressive Disorder, Schizophrenia and Bipolar Disorder pose considerable challenges for symptom relief and even more importantly for functional recovery and reintegration into society by patients suffering from these illnesses. In terms of pharmacological or somatic treatments for these mental disorders, a few treatments have passed muster but do appear to provide benefits for some patients, but there remains a significant proportion of patients who remain "stuck" as it were in terms of symptom relief let alone experience even modest clinical outcomes. Non-pharmacological therapies may offer added benefits with few harmful effects, but typically are added only as adjunct to pharmacological or somatic treatments, or are added in the maintenance and relapse prevention phases of these disorders. This may not be altogether surprising given that we are dealing with treatment resistant severe mental illness.

Our panel of speakers and discussant will address newer strategies for treatment resistant major depressive disorder, and consider subgroups of patients with psychoses who may benefit from clozapine, a significantly underutilized drug even three decades after its approval, and the intriguing use of metformin, an insulin sensitizing medication to help convert several patients with treatment resistant bipolar depression to responders.

Several factors are responsible for clozapine underutilization, one factor includes the concern about neutropenia (benign ethnic neutropenia) among people of African descent. A study of African Americans in the USA and among Africans in Nigeria will be reviewed for the impact of ethnicity and genotype on absolute neutrophil counts and what this might mean for considering clozapine in patients with Schizophrenia of African descent. Data will be also presented on the outcomes of court ordered treatment with clozapine.

Treatment resistant bipolar disorder and more specifically bipolar depression remains highly recalcitrant to pharmacological manipulation, and somatic therapies such as electroconvulsive therapy is often utilized in this phase of the illness. One intriguing approach is the mitigation

of insulin resistance among patients with treatment resistant bipolar depression to provide symptom relief and improve general clinical outcomes. Our speaker will present the results of a placebo controlled trial of metformin which aids in reversing insulin resistance and review the results of this strategy in treatment resistant bipolar depression.

Esketamine has been approved by the FDA for treatment resistant major depression, and ketamine infusions continue to be used to treat major depressive episodes. Can the initial improvements be maintained while minimizing ongoing exposure to the drug, and is cognitive behavior therapy the answer to maintaining the improvement? Our speaker will present the results of a randomized trial of adding cognitive behavior therapy to treatment as usual versus treatment as usual following ketamine infusions.

Our discussant will bring forth his experience and knowledge of treatment resistant depression, bipolar depression and schizophrenia and ask speakers on what the data of their studies mean for practice or how they might inform future research endeavors.

Learning Objectives:

1. Participants will obtain knowledge on the results of a study done among African Americans in the USA and Africans in Nigeria that assessed on the impact of ethnicity and genotype on absolute neutrophil counts and its impact on the use of clozapine for treatment resistant schizophrenia. Participants will review and assess the clinical outcomes of patients treated with clozapine when ordered by the courts to undertake such treatment.
2. Participants will review and assess results of two randomized controlled trials, one assessing cognitive behavior therapy provided for 14 weeks for maintenance of benefits following ketamine infusions for treatment resistant major depressive disorder, and another 26 week study using metformin to reverse insulin resistance in treatment resistant bipolar depression and the impact of this reversal on bipolar depression symptoms and related outcomes.

COGNITIVE THERAPY MAY SUSTAIN THE ANTIDEPRESSANT EFFECTS OF INTRAVENOUS KETAMINE IN TREATMENT-RESISTANT DEPRESSION

Samuel Wilkinson, Yale School of Medicine

Individual Abstract: Introduction: Ketamine has emerged as a rapid-acting antidepressant, with the S-enantiomer (esketamine) receiving Food and Drug Administration (FDA) approval for treatment-resistant depression (TRD) in 2019. While ongoing treatment can prevent relapse, concerns exist regarding the feasibility and safety of long-term treatment.

Methods: Patients with TRD who were presenting for clinical ketamine treatment (0.5mg/kg intravenously) were enrolled in a randomized trial of cognitive behavioral therapy (CBT) following ketamine to improve longer-term outcomes. In Phase I, patients underwent 6 ketamine infusions given twice weekly. Responders (defined as those with ≥50% improvement in symptoms) were eligible to proceed to Phase II, where patients were randomly assigned to receive a 14-week course of CBT plus treatment-as-usual (TAU) or TAU alone.

Results: Forty-six (46) patients received one or more ketamine infusions during Phase I and 28 patients entered Phase II and were randomized. There was a significant interaction effect of time and treatment group as measured by the Quick Inventory of Depressive Symptomatology ($F=4.58$, $p=0.033$), favoring a greater sustained improvement in the CBT group. This corresponded to an effect size of Cohen's $d = 0.71$ (95% CI, -0.30 to 1.70) at end-of-study (14

weeks following last ketamine infusion). When measured by the Montgomery-Asberg Depression Rating Scale, the interaction effect was not significant (F=0.01, p=0.910), while the effect size was moderate, Cohen's d = 0.65 (95% CI, -0.55 to 1.82), at end-of-study.

Conclusion: Cognitive behavioral therapy may improve longer-term outcomes following intravenous ketamine in TRD. Large, well-powered studies are warranted to confirm this and to explore this potential approach to relevant FDA-approved medicines (i.e., esketamine) to minimize long-term exposure to the drug.

Learning Objectives:

1. To review and understand the potential benefits and risks of ketamine/esketamine for mood disorders.
2. To understand the limitations of long-term therapy with ketamine/esketamine.
3. To understand the research behind extending therapeutic effects of ketamine/esketamine while minimizing repeated exposure to the drug.

Literature References:

1. Cognitive Behavior Therapy May Sustain Antidepressant Effects of Intravenous Ketamine in Treatment-Resistant Depression. Wilkinson ST, Wright D, Fasula MK, Fenton L, Griepp M, Ostroff RB, Sanacora G. Psychother Psychosom. 2017;86(3):162-167. doi: 10.1159/000457960. Epub 2017 May 11.
2. Leveraging Neuroplasticity to Enhance Adaptive Learning: The Potential for Synergistic Somatic-Behavioral Treatment Combinations to Improve Clinical Outcomes in Depression. Wilkinson ST, Holtzheimer PE, Gao S, Kirwin DS, Price RB. Biol Psychiatry. 2019 Mar 15;85(6):454-465. doi: 10.1016/j.biopsych.2018.09.004. Epub 2018 Sep 20.

INSULIN RESISTANCE IN PATIENTS WITH BIPOLAR DISORDER: A NOVEL APPROACH TO TREATMENT RESISTANT BIPOLAR DEPRESSION

Jessica Gannon, University of Pittsburgh School of Medicine

Individual Abstract: Despite recent advances in treatment, bipolar depression remains one of the most challenging illnesses to treat in psychiatry and continues to be associated with significant patient morbidity and mortality. Insulin resistance (IR) and Type 2 Diabetes Mellitus (T2D) are present in more than half of all bipolar patients and have been associated with rapid cycling, a more chronic course of illness, and treatment refractory state. Untreated hyperinsulinemia may contribute to a chronic inflammatory state implicated in disease progression. Treatment of IR in bipolar depression, particularly where other treatments have failed, may thus improve clinical outcomes.

This hypothesis was tested in a 26 -week randomized, double-blind, parallel group prospective study of the efficacy of metformin as add-on treatment in patients with IR and non-remitting bipolar depression. The results of this trial will be presented here. Patients recruited were 18 years or older, carried a diagnosis of Bipolar (BD) I or II, had non-remitting BD as defined by the presence of moderate depressive symptoms (Montgomery-Åsberg Depression Rating Scale (MADRS) score ≥ 15 despite optimal, guideline compatible treatment) and were stable on optimal doses of mood stabilizing medications for at least 4 weeks. In addition, they also had IR as defined by a HOMA-IR≥ 1.8. Patients could not be diabetic or currently on metformin, amongst other exclusion criteria. Patients were randomized to treatment with placebo or metformin, titrated to full dose, up to 2000mg, over 2 weeks and then were maintained on full

treatment for 24 weeks thereafter. The primary outcome measure was change in MADRS score, with responders defined as having a 30% reduction in MADRS from baseline.

The efficacy and safety data for 45 randomized patients were reported; 20 were randomly assigned to metformin, and 25 to placebo. Baseline demographic and illness characteristics were similar between the randomized treatment groups as were baseline MADRS and secondary measure scores. There were no significant baseline differences in body weight, body mass index (BMI), fasting glucose or insulin serum between the randomized groups. Ten metformin treated patients (50%) no longer met insulin resistance criteria by week 14 compared to one (4%) placebo assigned patient (Fisher exact p = 0.0009). These converters (n = 11) achieved a significantly greater reduction in MADRS scores as compared to non-converters, beginning at week 6, and maintained this improvement through end of study. The size of the treatment effect (Cohen's d) for MADRS depression scores for converters was 0.52 at week 14, and 0.55 at week 26.

Pending replication, this early clinical trial suggests that the mitigation of insulin resistance by metformin significantly improves depressive symptoms in a significant percentage of treatment resistant bipolar patients.

Learning Objectives:

1. Recognize the association between treatment resistance in bipolar disorder and insulin resistance.
2. Discuss the putative benefit of metformin in insulin resistant individuals with treatment resistant bipolar depression.

Literature References:

1. Calkin CV, Ruzickova M, Uher R, Hajek T, Slaney C, Garnham J et al: Insulin resistance and outcome in bipolar disorder. Br J Psychiatry. Published online October 16, 2014. DOI: 10.1192/bjp.bp.114.152850.
2. Kemp DE, Gao K, Chan PK, Ganocy SJ, Findling RL, Calabrese JR: Medical comorbidity in bipolar disorder: relationship between illnesses of the endocrine/metabolic system and treatment outcome. Bipolar Disord 2010; 12(4):404-413.

ABSOLUTE NEUTROPHIL COUNT AND SEVERE NEUTROPENIA IN AFRICAN DESCENT PATIENTS TREATED WITH CLOZAPINE: RESULTS OF A SIX-MONTH MULTINATIONAL OPEN-LABEL CLINICAL TRIAL

Deanna Kelly, University of Maryland Baltimore

Individual Abstract: Introduction: Although clozapine is the most effective antipsychotic for treatment-resistant schizophrenia, it is markedly underutilized, particularly in the African American (AA) population. Low Absolute Neutrophil Counts (ANC), either at baseline or during treatment (a drop in ANC below 1500 cells/mm3) has been a significant barrier to clozapine use in AA patients, namely because these ranges were developed in White populations. More recently, it is known that the "ACKR1-null" C/C genotype (SNP rs2814778) on the ACKR1 gene (previously called Duffy Antigen Receptor for Chemokines (DARC) is associated with a lower normative ANC range as compared with those ween in White populations and low ANC in this population has been termed Benign Ethnic Neutropenia (BEN). In 2015 (subsequent to the beginning of this study), the Food and Drug Administration issued new guidelines (i.e., lower thresholds) for clozapine monitoring in people characterized

as having BEN, however the ranges of ANC variability and safety of clozapine have not been established in this ethnic group.

Methods: We recently completed the largest clinical trial of clozapine use in African descent patients. In this 6-month open label treatment study we examined clozapine safety and evaluated the relative fluctuations in ANC in participants with and without the "ACKR1-null" genotype. We examined weekly ANC during clozapine treatment and measured variability and ranges by genotype, sex, location, dosing and other characteristics. Genotyping was assayed using TaqManTM technology (Thermfisher Scientific).

Results: We enrolled 274 participants (N=150 Maryland and DC, 124 Sub-Saharan African) of which 227 completed 6 months of clozapine treatment (82.8%). We had 69 who were court ordered (25%). Of the 48 who discontinued 14 were from adverse events, 17 participant choice, 6 nonadherence, 2 lack of therapeutic response and 9 lost to follow up/prescriber choice. There was one case of severe neutropenia (<500 cells/mm3) (0.36%) which occurred at week 6 in the study and the participant recovered without sequelae. Of the participants to date with both alleles known and including the one case of severe neutropenia, >75% had the "ACKR1-null" genotype (aka "Duffy-null") (over 90% from the Sub-Saharan African population).

Conclusion: To our knowledge this is the largest prospective clozapine trial in African descent patients. We did not observe a higher risk of severe neutropenia (0.36%) despite normally occurring lower ANC in this ethnic group. The majority of participants in this trial had the "ACKR1-null" genotype with higher penetrance of this genotype seen in the Sub-Saharan African population. We will present comprehensive data on ANC fluctuations and ranges by genotype and other characteristics during clozapine treatment. Severe neutropenia, however, is rare during clozapine treatment in this ethnic group.

Learning Objectives: At the conclusion of this talk participants should be able to:

1. Discuss the risk of severe neutropenia and clozapine safety in African descent patients.
2. Understand the role of the ACKR1 (aka DARC) genotypes and Benign Ethnic Neutropenia characterization on neutrophil ranges in African descent patients treated with clozapine.

Literature References:

1. Richardson CM, Davis EA, Vyas GR, DiPaula BA, McMahon RP, Kelly DL. Evaluation of the Safety of Clozapine Use in Patients With Benign Neutropenia. J Clin Psychiatry 2016;77(11):e1454-e1459. doi: 10.4088/JCP.15m10315.
2. Campion P, Anbarasan D. Changes in Neutrophil Count After Antipsychotic Prescription Among a Retrospective Cohort of Patients With Benign Neutropenia. J Clin Psychopharmacol 2017;37(4):456-458. doi: 10.1097/JCP.0000000000000733.

*THERAPEUTIC POTENTIAL OF SELECTIVE OREXIN RECEPTOR ANTAGONISTS FOR PSYCHIATRIC DISORDERS

Manish Jha, Icahn School of Medicine At Mount Sinai

Overall Abstract: Psychiatric disorders are some of the leading causes of disability worldwide. Furthermore, deaths due to suicide have progressively increased over the past two decades. Yet, most drugs used for treatment of psychiatric disorders target monoamine neurotransmission. Therefore, there is an urgent need to identify novel mechanistically-guided treatments. In the two decades since their discovery, orexins (or hypocretins) have gained

prominent attention for their role in neuropsychiatric disorders. The effects of orexins are mediated by two distinct G protein–coupled receptors, orexin-1 receptor (OX1R) and orexin-2 receptor (OX2R). Two drugs targeting both these receptors (OX1R and OX2R; dual orexin receptor antagonists) have gained the United States Food and Drug Administration approval for treatment of insomnia. Research, led by the panelists of this proposed symposium, has laid the foundation for developing drugs that selectively block OX1R and OX2R for treatment of a range of psychiatric disorder, from aggression to anxiety, and from depression to addiction.
The first presentation will include novel research on the role of orexin signaling in preclinical rodent models and the therapeutic potential of selective OX2R antagonists in reducing aggression and related behaviors. The second presentation will include data on safety, pharmacokinetic and pharmacodynamic properties of a selective OX1R antagonist in first-in-human single and multiple ascending dose studies, and the efficacy of in reducing anxiety symptoms induced by the carbon dioxide challenge. The final presentation will elucidate the role of orexin system in substance use disorders including nicotine use disorders, and the development of selective OX1R antagonist for these disorders. These presentations will be discussed by a leading psychopharmacology researcher who will also engage the audience in a broader discussion for the potential of orexin system as the next frontier in drug discovery for psychiatric illnesses.

Learning Objectives:

1. Understand the role of orexin system in pathophysiology of neuropsychiatric disorders.
2. Identify the therapeutic potential of selective orexin receptor antagonists in treatment of psychiatric disorders.

TARGETING OREXIN SIGNALING TO REDUCE AGGRESSION

Scott Russo, Icahn School of Medicine At Mount Sinai

Individual Abstract: Heightened aggression is associated with a number of neuropsychiatric disorders including schizophrenia, mood disorders and autism. Such disruptions in social behavior are thought to result, in part, from inappropriate activation of brain reward systems in response to social stimuli. A series of nuclei within the ventral midbrain that control mood and emotion are known to encode certain aspects of aggressive and nonaggressive social interaction; however, little is known about the neural circuit mechanisms that directly modulate the motivational or rewarding component of social behavior. To address this question, we established a mouse behavioral model for investigating individual differences in social behavior. In this model, approximately 70% of outbred mice engage in aggressive behavior with a resident intruder and find such interaction rewarding, whereas the remaining 30% are not aggressive at all and find intruder interactions aversive. The lateral habenula (LHb) is a major hub within the brain's reward circuit and can encode information about positive and negative social stimuli. Interestingly, the LHb is differentially activated by intruder-based social interaction in aggressive and nonaggressive mice and we hypothesize that it plays a critical role in mediating social behavior. Indeed, our results show that the neuropeptide, orexin (also known as hypocretin) signals directly within the LHb to control initiation of aggressive social behavior and the valence of social interaction during the resident intruder paradigm in aggressive mice. A basic understanding of these circuits is absolutely critical for developing new treatment strategies for pathological aggression, an area of drug development that has lagged far behind other efforts in neuropsychiatry.

Learning Objectives:

1. Learn about how the brain's reward centers processes information about aggressive social behavior.
2. Learn about how orexin signaling within reward centers controls aggression.

Literature References:

1. Flanigan ME, Aleyasin H, Li L, Burnett CJ, Chan K, LeClair KB, Lucas EK, Matikainen-Ankney B, Durand-de Cuttoli R, Takahashi A, Menard C, Bouchard S, Pfau ML, Golden SA, Calipari ES, Nestler EJ, Dileone RJ, Yamanaka A, Huntley GW, Clem RL, Russo SJ. Orexin signaling in GABAergic lateral habenula neurons modulates aggressive behavior. Nat Neurosci. 2020 May;23(5):638-650.
2. Golden SA, Heshmati M, Flanagan M, Christoffel DJ, Guise K, Pfau ML, Aleyasin H, Menard C, Zhang H, Hodes GE, Bregman D, Khibnik L, Tai J, Rebusi N, Krawitz B, Chaudhury D, Walsh JJ, Han MH, Shapiro ML, Russo SJ. Basal forebrain projections to the lateral habenula modulate aggression reward. Nature. 2016 Jun 29;534(7609):688-92.

ANXIOLYTIC ACTIVITY OF THE OREXIN-1 RECEPTOR ANTAGONIST JNJ-61393215 IN PRECLINICAL AND HUMAN PANIC MODELS

Mark Schmidt, Janssen Pharmaceutica N.V.

Individual Abstract: Orexin neurons originating in the perifornical and lateral hypothalamic area project to anxiety- and panic-associated neural circuitry and are highly reactive to anxiogenic stimuli. Preclinical evidence suggests that the orexin system and particularly the orexin-1 receptor (OX1R), may be involved in the pathophysiology of panic and anxiety. Selective OX1R antagonists thus may constitute a potential new treatment strategy for panic- and anxiety-related disorders.

Here, we characterized a novel selective OX1R antagonist, JNJ-61393215, and determined its affinity and potency for human and rat OX1R in vitro. We also evaluated the safety, pharmacokinetic and pharmacodynamic properties of JNJ-61393215 in first-in-human single and multiple ascending dose studies. Finally, the potential anxiolytic effects of JNJ-61393215 were evaluated both in rats and in healthy humans using a CO2 inhalation challenge to induce panic symptoms.

JNJ-61393215 showed anxiolytic activity in both preclinical and human anxiety CO2 challenge models without inducing sedation and with overall an acceptable tolerability profile.

These results suggest that selectively inhibiting the OXR1 may be a novel therapeutic approach for anxiety disorders and potentially other psychiatric conditions

Learning Objectives:

1. Understand the role of the orexin system in the pathophysiology of different psychiatric disorders.
2. Understand the translational data indicative of anxiolytic activity of the selective orexin-1 inhibitor JNJ-61393125.

Literature References:

1. Salvadore G, Bonaventure P, Shekhar A, et al: Translational evaluation of novel selective orexin-1 receptor antagonist JNJ-61393215 in an experimental model for panic in rodents and humans. Transl Psychiatry 2020;10:308.

2. Recourt K, de Boer P, Zuiker R, et al: The selective orexin-2 antagonist seltorexant (JNJ-42847922/MIN-202) shows antidepressant and sleep-promoting effects in patients with major depressive disorder. Transl Psychiatry 2019;9:216.

OREXIN-1 RECEPTOR ANTAGONISTS FOR THE TREATMENT OF NICOTINE DEPENDENCE

Paul Kenny, Icahn School of Medicine at Mount Sinai

Individual Abstract: Background: Orexin-1 receptors (OX1Rs) regulate the motivation to seek and consume nicotine, opioids, cocaine and other drugs of abuse in laboratory rodents, but underlying mechanisms are unclear. Here, we identify a novel brain circuit through which OX1Rs exerts control over drug-seeking behaviors and describe progress toward the development of a patient-ready OX1R antagonist as novel smoking cessation agents.
Methods: Intravenous nicotine self-administration and Intracranial self-stimulation thresholds were used to assess the motivational and reward-related properties of nicotine, respectively. DREADDs were used to chemogenetically activate or inhibit targeted neurons. Fiber photometry was used to monitor orexin neuron activity in vivo. CHO cells stably expressing OX1Rs or OX2Rs were generated and used to identify novel potent and selective OX1R antagonists, using intracellular calcium response to orexin-A peptide as our primary cell-based functional assay. Standard cell-based ADME-Tox (Absorption, Distribution, Metabolism, Excretion and Toxicity) and in vivo pharmacokinetic procedures were used to optimize drug-like physiochemical features of our novel OX1R antagonists. Good Laboratory Practice (GLP)-compliant rat and dog studies were conducted to assess the toxicological profile of our lead OX1R antagonist in laboratory animals. A Phase 1 clinical trial was performed to assess the safety profile of our lead OX1R antagonist in healthy human volunteers.

Results: We found that pharmacological or genetic disruption of OX1 receptor-mediated transmission decreased the motivation to consume nicotine, and attenuated relapse-like reinstatement of extinguished nicotine-seeking responses, in mice, rats or monkeys. A population of previously unidentified OX1R-regulated neurons we identified in thalamus. We found that these neurons regulated the inhibitory actions of OX1R antagonists on nicotine intake and relapse-like nicotine-seeking behaviors in mice and rats. These thalamic neurons do not regulate reward-related actions of nicotine, but instead regulate the apparent "value" of the drug. Based on these findings, we initiated a drug discovery campaign to develop OX1R antagonists and advance them to human clinical assessment as smoking cessation agents. We identified a highly potent and selective OX1R antagonist that displayed favorable drug-like physiochemical properties. This lead compound reduced nicotine intake and relapse-like nicotine seeking in laboratory rats and monkeys. GLP-compliant rat and dog toxicological studies established a safety window for our lead compound that was sufficiently favorable to initiate Phase 1 clinical trials. Progress on safety assessments of our lead compound in human volunteers will be described.

Conclusions: OX1 receptors regulate the motivational properties of nicotine through a novel thalamic circuit. Targeting this circuit using patient-ready OX1R antagonists may represent an exciting new strategy to facilitate smoking cessation in human tobacco users. This same OX1R-based strategy may also be beneficial for the treatment of individuals dependent upon opioids of psychomotor stimulants.

Learning Objectives:

1. Understand the role for orexin transmission in regulating the motivational properties of nicotine and other drugs of abuse.
2. Understand progress toward the development of novel orexin-based therapeutics for the treatment of tobacco dependence and dependence upon other addictive substances.

Literature References:

1. Harris GC, Wimmer M, Aston-Jones G. A role for lateral hypothalamic orexin neurons in reward seeking. Nature. 2005;437:556-559.
2. Hollander JA, Lu Q, Cameron MD, Kamenecka TM, Kenny PJ. Insular hypocretin transmission regulates nicotine reward. Proc Natl Acad Sci U S A. 2008;105:19480-19485.

*WOMEN'S BRAIN FORUM

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

Overall Abstract: Sex and gender differences in Alzheimer's Disease (AD) have been increasingly described and recognized by the scientific community. These include differences in risk factors, biomarkers, symptoms, progression and response to treatment.
However, whether and how such differences should be integrated into clinical practice or in the design of clinical trials for AD, is currently unclear.

Women's Brain Project is a Swiss-based international non-profit organization focused on sex and gender determinants of brain and mental health as a gateway to precision medicine. In this panel, new and novel evidence in this field will be presented and discussed. First the panel will provide an overview of gender medicine and precision medicine in the context of neurology and AD; next, the panel will discuss sex differences in fluid and imaging biomarkers and why they are relevant for clinical practice. The panel will also provide a clinical perspective on the implications of sex differences for prevention and diagnosis. Finally, the panel will discuss how sex differences can be integrated into regulatory processes.

Learning Objectives:

1. How a careful consideration of sex and gender aspects might help improving clinical management of patients with Alzheimer's Disease.
2. How sex and gender differences in biomarkers and disease presentation should be accounted for when planning clinical trials for Alzheimer's Disease.

SEX AND GENDER SPECIFIC PRECISION MEDICINE FOR NEUROLOGY AND PSYCHIATRY - THE WORK OF THE WOMEN'S BRAIN PROJECT

Maria Teresa Ferretti, Women's Brain Project

Individual Abstract: Cumulating evidence has indicated that, in brain disorders, patient variability exists, and that pathological mechanisms are often shared between different syndromes. Precision medicine, as applied in oncology, might provide substantial progress in the field, from molecular diagnosis to tailored treatments.
In this regard, sex and gender differences are emerging as leading features driving patient heterogeneity in a variety of brain diseases, including Alzheimer. These differences offer therefore a useful starting point to discuss potential applications of precision medicine in neurology.

Taking the example of Alzheimer's Disease, in this talk I will introduce the concept of gender medicine and precision medicine, as opposed to shallow medicine. I will discuss their relevance for clinical trial design and development of digital health technologies for Alzheimer and the work that the non-profit organization Women's Brain Project is doing in this field.

A proper understanding of sex and gender-differences will be key towards a precision medicine paradigm in Alzheimer's, beyond a 'one size fits all' approach and towards sustainability.

Learning Objectives:

1. Familiarise with sex and gender differences in neurology and psychiatry.
2. Discuss precision medicine applications to neurology and psychiatry.

Literature References:

1. Sex differences in Alzheimer disease — the gateway to precision medicine
2. Maria Teresa Ferretti, Maria Florencia Iulita, Enrica Cavedo, Patrizia Andrea Chiesa, Annemarie Schumacher Dimech, Antonella Santuccione Chadha, Francesca Baracchi, Hélène Girouard, Sabina Misoch, Ezio Giacobini, Herman Depypere & Harald Hampel for the Women's Brain Project and the Alzheimer Precision Medicine Initiative
3. Nature Reviews Neurology volume 14, pages457–469(2018), https://www.nature.com/articles/s41582-018-0032-9
4. Sex and gender differences in Alzheimer's disease: current challenges and implications for clinical practice
5. Position paper of the Dementia and Cognitive Disorders Panel of the European Academy of Neurology M. T. Ferretti J. Martinkova E. Biskup T. Benke G. Gialdini, Z. Nedelska K. Rauen V. Mantua D. Religa J. Hort A. Santuccione Chadha R. Schmidt First published: 13 February 2020 https://doi.org/10.1111/ene.14174 https://onlinelibrary.wiley.com/doi/abs/10.1111/ene.14174

INCORPORATING SEX DIFFERENCES FOR ACCURATE CLINICAL INTERPRETATION OF CEREBROSPINAL FLUID AND BLOOD-BASED BIOMARKERS OF ALZHEIMER'S DISEASE AND RELATED DEMENTIAS

Michelle Mielke, Mayo Clinic

Individual Abstract: The development of cerebrospinal fluid (CSF) and blood-based biomarkers for Alzheimer's disease (AD) and related dementias is rapidly progressing. Some CSF markers are currently used clinically to aid in diagnosis and prognosis. In addition, several blood-based biomarkers of AD pathology are nearing clinical use, including primary care, for either screening or diagnostic purposes. However, one critical aspect not typically considered in the assay development of these biomarkers, or in their clinical interpretation, is sex and gender. For some markers, concentrations may differ by sex. For other markers concentrations might not differ by sex, but the impact or interpretation may differ depending on the context of use (e.g., diagnostic vs prognostic). Physiological differences between women and men can also impact biomarker levels. This talk will first discuss the state of the field for sex differences in fluid biomarkers for Alzheimer's disease. Additional discussion will focus on factors that contribute to these sex differences and that need to be considered for the most accurate clinical interpretation of the biomarker levels.

Learning Objectives:

1. To understand how sex can affect the measurement or interpretation of biofluid-based biomarkers.

2. To understand some sex differences in neuroimaging biomarkers of Alzheimer's disease and related disorders.

Literature References:

1. Mielke MM:. Consideration of sex differences in the measurement and interpretation of Alzheimer disease-related biofluid-based biomarkers. J Appl Lab Med 2020;5(1):158-69. PMCID: PMC7246149
2. Nebel RA, Aggarwal NT, Barnes LL, Gallagher A, Goldstein JM, Kantarci K, Mallampalli MP, Mormino EC, Scott L, Yu WH, Maki PM, Mielke MM: Understanding the impact of sex and gender in Alzheimer's disease: a call to action. Alzheimers Dement 2018;14(9):1171-83. PMCID: PMC6400070

SEX-DIFFERENCES IN NEUROPSYCHIATRIC SYMPTOMS AMONGST YOUNG-ONSET AND LATE-ONSET ALZHEIMER'S DISEASE

Carmela Tartaglia, University of Toronto Faculty of Medicine

Individual Abstract: Over 50 million people are affected with dementia and 60-70% of the cases are due to Alzheimer's Disease (AD). Late-onset AD (LOAD) accounts for most AD cases and its prevalence increases with age (Scheltens 2016). Young-onset Alzheimer's disease (YOAD) is diagnosed when someone develops AD before the age of 65 and represents up to 10% of all AD cases. In addition to the ongoing investigations into sex differences in prevalence of AD, there is intensive research into sex-related biological differences and gender-related environmental factors that may affect presentation and progression of disease. Although AD is a cognitive disorder, neuropsychiatric symptoms (NPS) are common. NPS are often evident as the disease progresses but can also be present at the onset (Petrovic 2007). More than 80% of patients with AD develop at least one NPS over the course of the disease(Lyketsos 2002). These symptoms include, but are not limited to, agitation, depression, anxiety, hallucinations and apathy (Kiely 2018). NPS can complicate the disease course and impact both patients and their caregivers as they are associated with early institutionalization (de Vugt 2005), increased mortality (Peters 2015) as well as increased caregiver burden (Chiao 2015). NPS in YOAD can delay diagnosis as these patients are often misdiagnosed with a psychiatric rather than a neurodegenerative disease (Bature 2011). Investigating the incidence of NPS in AD is complicated by sex-related differences in NPS in non-demented patients. Females have twice the lifetime rates of depression and most anxiety disorders except obsessive–compulsive disorder and bipolar disorder, which have similar prevalence(Gater 1998). However, even for these disorders, males and females have differences in disease presentation and course. Subclinical anxiety and depression symptoms are also more common in females(Hankin 2009). A better understanding of NPS in AD and how they differ between YOAD and LOAD as well as between males and females could help in diagnosis and management of these distressing symptoms.

We assessed the prevalence of NPS in YOAD and LOAD in the National Alzheimer's Coordinating Center database. We found significant differences in frequency of NPS in YOAD vs. LOAD with more anxiety and depression in YOAD than LOAD (Gumus 2021). However, when we compared YOAD and LOAD by sex we found that depression was higher in YOAD females versus LOAD females while anxiety was higher in YOAD males compared to LOAD males. Comparisons in the YOAD group revealed that females showed higher prevalence of disinhibition and euphoria. Males did not have a higher frequency of any NPS compared to females. Comparison in LOAD revealed that LOAD females had higher frequency of

irritability compared to LOAD males while LOAD males had more hallucinations. When we combined YOAD and LOAD, hallucinations, although rare (3%), were more frequent in males while irritability was more frequent in females.

When comparing AD and psychiatric medication usage amongst females and males, more males than females were on acetylcholinesterase inhibitors and memantine (35 vs. 28% and 16 vs 11%, respectively). When we divided the YOAD and LOAD group, we found no difference in medication usage between males and females but more LOAD males than females were on memantine. Interestingly there was no difference in usage of anti-depressant or anxiolytics despite differences in frequency of these symptoms between the sexes.

In conclusion, we show differences in the incidence of various NPS between YOAD and LOAD males and females. Improvement in recognition of sex-differences as it relates to the NPS in AD as well as their interaction with age will facilitate precision medicine and targeted therapies.

Learning Objectives:

1. Understand sex-differences in neuropsychiatric symptoms in AD.
2. Age effect interacts with sex-differences to differentiate neuropsychiatric symptoms in young-onset and late-onset AD.

Literature References:

1. Lyketsos CG, Lopez O, Jones B, Fitzpatrick AL, Breitner J, DeKosky S. Prevalence of neuropsychiatric symptoms in dementia and mild cognitive impairment: results from the cardiovascular health study. JAMA. 2002 Sep 25;288(12):1475–83.
2. Peters ME, Schwartz S, Han D, Rabins PV, Steinberg M, Tschanz JT, et al. Neuropsychiatric symptoms as predictors of progression to severe Alzheimer's dementia and death: the Cache County Dementia Progression Study. Am J Psychiatry. 2015 May;172(5):460–5.

REGULATORY PERSPECTIVE ON GENDER/SEX DIFFERENCES IN ALZHEIMER'S DISEASE (AD) CLINICAL TRIALS

Florence Butlen-Ducuing, European Medicines Agency

Individual Abstract: Sex and gender differences, although not fully understood yet, have been reported in many medical conditions. Amongst CNS disorders, those have been shown to be particularly prominent in a number of diseases and notably in AD. Thus, based on this example for which the evidence is thought to be best understood, this presentation aims at raising further awareness on those sex and gender aspects as well as discussing potential implications on clinical drug development programs from the regulatory perspective.

Learning Objectives:

1. To learn about the challenges in the development of precision medicines in CNS.
2. To learn about potential implications of sex and gender differences in the methodology of clinical trials in CNS and in AD in particular.

Literature References:

Denny JC, Collins FS. Precision medicine in 2030-seven ways to transform healthcare. Cell. 2021 Mar 18;184(6):1415-1419.

Shansky RM. Sex Differences in the Central Nervous System. Academic Press. Ed Elsevier 1st edition 2015: 1-428.

Workshops

11:00 a.m. - 1:00 p.m.

*OVERCOMING BARRIERS TO THE IMPLEMENTATION OF NOVEL TREATMENTS FOR MOOD DISORDERS

Samuel Wilkinson, Yale School of Medicine

Overall Abstract: Mood disorders represent a huge public health burden and are the largest cause of disability worldwide. Recent advances in diverse fields such as neuropharmacology and digital technology are bringing forth new therapeutic approaches that may help address this unmet need for improved care of mood disorders. However, as some of these treatments are move from the research phase to the clinical phase, we are understanding some difficulties and obstacles that impede the implementation of these treatments. For example, the Food and Drug Administration (FDA) recently approved new therapies (esketamine, brexanolone) for mood disorders that have novel mechanisms of action and different routes of administration compared with traditional antidepressant drugs. For psychiatrists and other clinicians who treat patients with mood disorders, adoption of these new treatments may require fundamental changes to the organization and reimbursement of their medical practice. Existing treatments that are often reserved for refractory mood disorders—electroconvulsive therapy, racemic ketamine, transcranial magnetic stimulation—also have different routes of administration compared to standard antidepressants.

Many of these treatments also have unique challenges to administration and implementation. Other novel pharmacological treatment options and novel service delivery approaches (i.e., collaborative care, digital therapeutics, etc.) will face similar challenges. This workshop brings together perspectives from academia, industry, patient advocacy groups, and administrators to discuss optimal ways to overcome barriers to the implementation of novel, evidence-based therapies for mood disorders.

Dr. Samuel T. Wilkinson (Yale) will speak on overall barriers to interventional psychiatry treatments, including electroconvulsive therapy, racemic ketamine, and esketamine nasal spray.

Dr. Jill Harkavy-Friedman (American Foundation for Suicide Prevention) will speak on challenges to receiving treatment from the perspective of patients and families and potential ways that other stakeholders can assist patients and families to overcome these challenges.

Dr. Abigail Nash (Janssen, manufacturer of esketamine) will discuss the challenges in the development of therapies for refractory mood disorders and targeting patients with major depressive disorder with active suicidal ideation with intent.

Dr. Ilse Weichers (Veterans Health Administration) will discuss challenges and opportunities to implementing novel therapeutics in large healthcare system.

As the discussant, Dr. Gerard Sanacora (Yale) will synthesize common themes, barriers and possible solutions to move the field forward to improve the implementation of evidence-based therapies for mood disorders.

Learning Objectives:

1. To be able to describe the potential barriers to implementing new treatment / pharmacologic approaches to depression that have different routes of administration compared to standard antidepressants.

2. To be able to describe potential solutions to overcoming barriers to the implementation of these treatments

OVERCOMING BARRIERS TO THE IMPLEMENTATION OF NOVEL TREATMENTS FOR MOOD DISORDERS IN AN INTERVENTIONAL PSYCHIATRY SETTING

Samuel Wilkinson, Yale School of Medicine

Individual Abstract: Interventional Psychiatry is emerging as a subspecialty of psychiatry focusing on interventional modalities for diagnostic and therapeutic means with substantial potential in the management of neuropsychiatric disorders. Interventional therapeutics include electroconvulsive therapy (ECT), racemic ketamine, esketamine nasal spray, as well as transcranial magnetic stimulation. These therapeutic modalities are often difficult to implement because of the need for specialized training, space and medical observation requirements, complex methods for billing and reimbursement, and interaction with other specialists (anesthesia). Dr. Wilkinson will speak on the barriers to building a clinical service that offers these therapeutic interventions in order to integrate recent advances in therapeutics into clinical settings. He will discuss potential solutions and ways that the Yale Interventional Psychiatry Service has been able to successfully integrate many of these treatment modalities coherently. Racemic ketamine and esketamine nasal spray will be used as case examples.

Learning Objectives:

1. 1. To learn and be able to describe the barriers to implementing novel treatments for mood and other neuropsychiatric disorders in the interventional setting.
2. To learn of potential solutions for overcoming these barriers.

Literature References:

1. Jilka S, Murray C, Wieczorek A, et al. Exploring patients' and carers' views about the clinical use of ketamine to inform policy and practical decisions: mixed-methods study. BJPsych Open. 2019 Jul 30;5(5):e62. doi: 10.1192/bjo.2019.52.
2. Wilkinson ST, Howard DH, Busch SH. Psychiatric Practice Patterns and Barriers to the Adoption of Esketamine. JAMA. 2019 Aug 2. doi: 10.1001/jama.2019.10728. [Epub ahead of print].

REDUCING SUICIDE RISK: INTERVENTIONS AND BARRIERS TO CARE

Jill Harkavy-Friedman, American Foundation for Suicide Prevention

Individual Abstract: Suicide is the tenth leading cause of death with 48,344 individuals dying by suicide in 2018. Suicide is complex, with multiple contributors often converging with stressors in the context of access to lethal means. Suicide risk is not stagnant, it crescendos and diminishes depending on many biological, psychological, social and environmental factors. During a suicidal crisis, the individual experiences intense pain and all their efforts are focused on stopping the pain.

Thinking becomes less flexible and the individual does not have access to their usual coping capacities. Treatments are available to assist people in managing suicidal ideation and behavior over time, so they don't get to the point of crisis. If they do reach crisis point, rapid interventions and limiting access to lethal means are key. Rapid and sustained effective care is essential, especially since the highest risk for suicide is after an emergency department visit or

psychiatric hospitalization. When substance use is co-morbid, which is often the case, the need for novel treatments is clear. A model for understanding suicide, approaches to working with the suicidal individual and barriers to care will be discussed. With suicide rates rising, we must translate what we have learned from research into practice.

Learning Objectives:

1. To describe a model for suicidal behavior.
2. List at least two treatments available for individuals with suicidal ideation and behavior.
3. Enumerate barriers to care for the suicidal person.

Literature References:

1. D'Anci KE, Uhl S, Giradi G, et al. Treatments for the Prevention and Management of Suicide: A Systematic Review. Ann Intern Med. 2019;171:334–342.
2. Van Heeringen K Mann J.The neurobiology of suicide.Lancet Psychiatry. 2014; 1: 63-72 Méndez-Bustos P, Calati R, Rubio-Ramírez F, Olié E, Courtet P, and Lopez-Castroman J.
3. Effectiveness of Psychotherapy on Suicidal Risk: A Systematic Review of Observational Studies 6 2021 ASCP Annual Meeting Front Psychol. 2019; 10: 277

DIFFICULTIES IN THE DEVELOPMENT OF THERAPIES FOR SUBSETS OF PATIENTS WITH CHALLENGING TO TREAT MAJOR DEPRESSIVE DISORDER

Abigail Nash, Janssen Pharmaceuticals

Individual Abstract: Major depressive disorder (MDD) is the leading cause of disability worldwide and is associated with a 10-year reduction in life expectancy. Despite widespread availability of numerous pharmacologic treatment options and several somatic therapies, patients with MDD continue to experience negative outcomes, including treatment resistance (failure to respond to at least 2 different antidepressants in the current depressive episode) and acute suicidal ideation or behavior. In the phase 3 clinical development program for esketamine nasal spray (ESK), over 1,700 adults with treatment-resistant depression (TRD) and over 260 adults with MDD and active suicidal ideation with intent received ESK. The TRD program consisted of 3 short-term (acute), randomized, double-blind, active-controlled studies; 1 long-term, double-blind, relapse prevention study; and an up to 1 year open-label, long-term safety study. The program supporting the indication in adults with MDD and acute suicidal ideation or behavior (MDSI) was comprised of 2 identically designed short-term, randomized, double-blind global clinical trials.

This session will focus on the difficulties in developing a treatment for these two subsets of patients with challenging to treat depression which entailed a novel treatment paradigm and route of administration. Most patients with TRD or MDSI are currently treated with traditional oral antidepressants or adjunctive medications. ESK requires twice weekly intranasal dosing sessions during the first 4 weeks of treatment as well as a required 2-hour post-dose monitoring period and adherence to a REMS program to support safe and appropriate use. Additionally, although these patient populations are recognized by clinicians in practice, the lack of consensus regarding the definitions of TRD and MDSI have added to the challenges.

Dr. Nash will briefly review the clinical development program and regulatory challenges.

Learning Objectives:

1. Understanding the challenges of developing a new treatment for moderately to severely ill subsets of patients with major depressive disorder.

2. Understanding the challenges to implementing a new treatment paradigm into clinical practice.

Literature References:

1. Kim, J, Farchione T, Potter, A, et al. Esketamine for treatment-resistant depression – first FDA-approved antidepressant in a new class. N Engl J Med. 2019 Jul 4;381(1):1-4.
2. Fu, D-J, Ionescu, DF, Li, X, et al. Esketamine Nasal Spray for Rapid Reduction of Major Depressive Disorder Symptoms in Patients Who Have Active Suicidal Ideation With Intent: Double-Blind Randomized Study (ASPIRE I). J Clin Psychiatry. 2020 May 12;81(3):19.

LESSONS LEARNED FROM IMPLEMENTATION OF KETAMINE AND ESKETAMINE AT THE VETERANS HEALTH ADMINISTRATION

Ilse Wiechers, Department of Veterans Affairs

Individual Abstract: Mood disorders represent one of the most common behavioral health disorders and are now the most common cause of disability worldwide. Direct costs of care for mood disorders, including its impact on the course of other chronic medical disorders (i.e., diabetes, heart disease), number well over billions of dollars per year. Employers and communities alike also bear the indirect cost of loss productivity, increased disability duration, and absenteeism and presenteeism as a result of mood disorders. Given high rates of suboptimal response to antidepressant treatments, there is a need for novel approaches to treatment resistant mood disorders. Dr. Wiechers will discuss the challenges and opportunities of implementing novel antidepressant therapeutics in a large integrated healthcare system (Veterans Health Administration). She will discuss special considerations for quality and safety monitoring as well as policy and clinical operations. Dr. Wiechers will discuss additional factors that can facilitate implementation of novel therapeutics in a large healthcare organization.

Learning Objectives:

1. Understand elements of quality, safety, policy and clinical outcomes that play into the decision-making process of the implementation for novel therapeutics.
2. Articulate factors that can facilitate adoption of novel therapeutics in large healthcare organizations.

Literature References:

1. Sanacora, G, Frye, MA, McDonald W, et. al. A Consensus Statement on the Use of Ketamine in the Treatment of Mood Disorders. JAMA Psychiatry 2017 Apr 1;74(4):399-405
2. VA/DoD Clinical Practice Guideline for the Assessment and Management of Patients at Risk for Suicide. Version 2.0 - 2019.
3. VA/DoD Clinical Practice Guideline for the Management of Major Depressive Disorder. Version 3.0 - 2016.

MID CAREER WORKSHOP

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

Overall Abstract: This workshop will focus on career decisions and transitions. The workshop will feature an interactive discussion format with panelists from several different career arenas including academia, industry, clinical settings, and government (funding and regulatory agencies). Career paths represented will include research, clinical, teaching, and regulatory components. It is expected that topics will broadly impact participants across work settings.
The workshop will be interactive and dynamic. The workshop will start with each panelist providing a 5-minute introduction including a brief career summary and selected career highlights and challenges. After introductions, a question and answer session will begin. Questions will be solicited both prior to the event as well as invited in person throughout the workshop

PRESENTERS:
Ross Baker, Otsuka
Tiffany Farchione, US Food and Drug Administration
Mark Rapaport, University of Utah Neuropsychiatric Institute
Ivan Montoya, DHHS/National Institute on Drug Abuse
Colin Sauder, Karuna Therapeutics

***USING MENTAL HEALTH APPS FOR MOOD DISORDERS: A PRACTICAL PRIMER FOR CLINICIANS**
Sagar Parikh, University of Michigan, Ann Arbor

Overall Abstract: We are proposing a workshop to teach the busy clinician how to pick and use the best websites and apps for mood disorders. The use of the internet via websites, and apps, are now an integral part of e-health strategies to monitor and improve mental health. Depression and anxiety are disorders that are particularly well resourced with websites and apps providing assessment and treatment. Some web-tools and apps have proper efficacy data collected in randomized clinical trials as well as more basic studies. However, unlike medications, websites and apps are not regulated, so the clinician has three challenges (1) knowing how to evaluate e-health tools, (2) knowing which tools have some efficacy and (3) how to apply such tools in routine clinical practice. This workshop, conducted by physicians experts in e-health, continuing medical education, and implementation / dissemination, allows clinicians to overcome all three challenges. Firstly, an overview of key websites and apps for mood disorders is provided. Next, the evaluation framework for apps as recently published by the American Psychiatric Association is reviewed. Finally, highly rated websites and apps are reviewed, both providing an overview of evidence but more importantly, through demonstration of the actual application of the website or app during a simulated patient encounter. Through live demonstration and additional use of videos created of how an app opens and functions on a phone, individuals get exposure to practical use of the website and app. For mood monitoring, we review the MoodFx app as well the Michigan Depression Toolkit. For monitoring and psychoeducation and self-management strategies, we review the Michigan Depression Toolkit in detail. For CBT as applied to depression and anxiety, we demonstrate use of the Moodgym. For stress, depression, and anxiety relief employing Mindfulness and related strategies, we employ the Headspace app. We also provide practical strategies about matching these tools to patients and how to integrate these tools with standard pharmacotherapy and psychotherapy.
Learning Objectives:

1. Clarify the best websites and apps for mood and anxiety disorders.
2. Demonstrate how to use mental health websites and apps for mood disorders in a typical patient encounter, integrating these tools with medications and psychotherapy.

THE BEST OF E-HEALTH: KEY WEBSITES AND APPS FOR MOOD AND ANXIETY EXPLAINED WITH LIVE DEMONSTRATION

Sagar Parikh, University of Michigan, Ann Arbor

Individual Abstract: Many websites provide information and resources for mental health disorders; some provide more specific treatment strategies, primarily self-help strategies derived from evidence-based treatments like CBT. Tens of thousands of apps for mood and anxiety disorders have also been developed, mostly without expert mental health clinician involvement. This workshop presentation will review key elements of e-health (websites and apps) as applied to mental health, with specific attention to the MoodFx website / app as well as the Michigan Depression Toolkit as excellent resources for measurement-based care; both of these resources are free to the public. For psychoeducation and self-management strategies, the Michigan Depression Toolkit will be will reviewed, along with its capacity to assist families and employers in strategies to help ill individuals. Beyond summarizing the strengths of these tools, this workshop will review how to match a patient to a resource, and most importantly, how to use such resources at the point of care. Blending e-health tools with standard treatments like medications and psychotherapy provides reinforcement that improves adherence to treatment. For some tools, RCTS have demonstrated that application of e-health tools improves clinical outcomes, both in those relying only on self-help strategies, but particularly in those receiving brief encouragement and guidance in the context of regular clinical care. The tools will be demonstrated live in the session; where possible, individuals will be encouraged to use the websites or apps during the session to allow for an integrated "theory and practice" session.

Learning Objectives:

1. Identify characteristics of good websites in terms of credibility, privacy, and efficacy.
2. Demonstrate how to apply key e-health tools in a typical clinical encounter for mood or anxiety problems.

Literature References:

1. Bidargaddi N, Schrader G, Klasnja P, Licinio J, Murphy S. Designing m-Health interventions for precision mental health support. Transl Psychiatry. 2020 Jul 7;10(1):222.
2. Porras-Segovia A, Díaz-Oliván I, Gutiérrez-Rojas L, Dunne H, Moreno M, Baca-García E. Apps for Depression: Are They Ready to Work? Curr Psychiatry Rep. 2020 Feb 5;22(3):11.

PICKING AND USING AN APP FOR MOOD DISORDERS

Wegdan Abdelmoemin, CAN-BIND, St. Michael's Hospital, Toronto

Individual Abstract: In this practical session, we aim to educate the clinician on the principles of selecting an appropriate mental health app for their patients using live demonstrations and hands-on exercises. Evaluating the safety, efficacy, and usefulness of an app will be approached by reviewing the APA app evaluation framework. The session will then focus on real-time demos of 2 treatment-based applications namely MoodGym and Headspace. We will explore the various CBT modules of MoodGym sharing tips on how to best utilize this tool in

practice. The Headspace demo will highlight the aspects of the app that clinicians can recommend and use to facilitate meditative and mindfulness therapies. The session will allow time for discussion and interaction throughout.

Learning Objectives:

1. Principles of picking an app through the APA app evaluation framework.
2. App demonstration (MoodGym and Headspace).

Literature References:

1. Howells, A., Ivtzan, I., & Eiroa-Orosa, F. J. (2016). Putting the 'app'in happiness: a randomised controlled trial of a smartphone-based mindfulness intervention to enhance wellbeing. Journal of Happiness Studies, 17(1), 163-185.
2. Torous, J., Luo, J., & Chan, S. R. (2018). Mental health apps: what to tell patients. Curr Psychiatry, 17(3), 21-25.

EARLY CAREER WORKSHOP: HOW TO GIVE A VIRTUAL TALK

Rebecca Hendrickson, VA Puget Sound Health Care System

Overall Abstract: Giving talks is core part of science and teaching. Increasingly, talks and lectures are delivered virtually. What strategies for giving talks are the same in a virtual environment, and what strategies are different?

In this participatory workshop, we will hear from two experts in the field, Dr. Deng of the NIMH and Dr. Heldt from the UCLA School of Medicine. Drs. Deng and Heldt will address both core concepts of giving an excellent talk, and how methods do and do not differ in a virtual environment. Then, Dr. Nasca from Rockefeller and Dr. Piacentino from NIAAA will each present a brief scientific talk, and the presenters and workshop participants will examine how the principles of scientific presentations in general and of virtual presentations in particular apply to these two examples.

Learning Objectives:

1. Describe the principles of effective oral presentations in science, and be ready to apply them to your own talks.
2. Know how these principles do and do not change when presenting over a virtual platform.

BEST PRACTICES IN ONLINE TEACHING FOR MEDICAL AND SCIENTIFIC EDUCATORS

Jonathan Heldt, David Geffen School of Medicine at UCLA

Individual Abstract: The impact of the COVID-19 pandemic on medical and scientific education has been profound. Social distancing requirements forced most academic institutions to make major changes to the structure of all forms of learning, including didactic education. Evidence suggests that many departments transitioned away from in-person learning to remote learning, including both synchronous (livestreamed) and asynchronous (prerecorded) forms. While remote learning is not new, the COVID-19 pandemic forced its adoption to a greater extent and higher speed than ever before. The urgency of the situation forced many institutions to implement remote learning within the span of a single week despite the existence of multiple longstanding barriers to adoption and without the opportunity to orient either instructors or learners to the new format.

With this in mind, this session is focused on reviewing the data on best practices in online teaching. This session will include three key components: presentation of survey data about attitudes regarding remote learning both at our institution and others, a review of the literature on the efficacy of remote learning, and an introduction to specific remote teaching tools. During this session, we will review the following best practice principles for online teaching:

1. Understand the literature on remote learning. Many educators perceive remote learning to be less effective than in-person learning. Reviewing the literature supporting the efficacy of remote learning may help to improve attitudes towards its use.

2. Implement active learning. Active learning is an effective method of keeping learners engaged and is associated with increased knowledge retention. We will review several active learning resources (e.g, PollEverywhere and Kahoot) and demonstrate their use within the session itself.

3. Encourage learners to turn their cameras on. We encourage educators to request that all learners turn their cameras on at the beginning of each lecture to help with engagement while being flexible for those who can't.

4. Use trust generators. Trust generators are specific techniques that educators can use to foster a sense of trust between teachers and learners. Given that online platform such as Zoom may be associated with challenges in interpersonal connection, use of trust generators such as selective vulnerability, similarity of interests, and showing concern can be beneficial.

5. Use storytelling as a medium. Because listening to a story is an imaginative act, storytelling may survive the transition to remote learning better than other forms of teaching. This is consistent with data supporting the use of storytelling as a method of changing beliefs, attitudes, and behaviors.

6. Think of remote learning as its own medium with inherent weaknesses and strengths. Finally, we find it helpful to acknowledge that remote learning platforms such as Zoom are inherently different than in-person lectures. In areas where remote learning platforms are less intuitive than in-person teaching, specific features (such as the whiteboard function and breakout rooms in Zoom) may help to bridge the gap. In other areas, remote learning platforms provide features such as the chat function that are not available with in-person teaching.

Learning Objectives:

1. By the end of this session, attendees will be able to compare and contrast in-person learning to remote learning on a variety of metrics including efficacy, convenience, and connection.
2. By the end of this session, attendees will be able to implement at least one online active learning tool into their next teaching session.

Literature References:

1. Pei L, Wu H. Does online learning work better than offline learning in undergraduate medical education? A systematic review and meta-analysis. Med Educ Online. 2019 Dec;24(1):1666538.
2. Freeman S, Eddy SL, McDonough M, Smith MK, Okoroafor N, Jordt H, et al. Active learning increases student performance in science, engineering, and mathematics. Proc Natl Acad Sci U S A. 2014 Jun 10;111(23):8410-5.

THE BINGING BABOONS OF BALTIMORE: GUT MICROBIOME AND METABOLOME IN A NON-HUMAN PRIMATE MODEL OF CHRONIC EXCESSIVE ALCOHOL DRINKING

Daria Piacentino, Clinical Psychoneuroendocrinology and Neuropsychopharmacology Section, National Institute on Drug Abuse and National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health

Individual Abstract: Excessive alcohol use is a serious public health problem. In the United States, each year, it accounts for one in 10 deaths among adults aged 20-64 years. Excessive alcohol use includes: (1) binge drinking (drinking too much, too fast), a pattern of drinking that brings blood alcohol levels (BALs) to 0.08 g/dL, or above, in about 2 hours and corresponds to 0.8-1 g/kg of body weight or >4 drinks/occasion for men and >3 drinks/occasion for women; (2) heavy drinking (drinking too much, too often), defined as drinking >14 drinks/week for men and >7 drinks/week for women. Binge and heavy drinking increase the risk of alcohol use disorder (AUD). Excessive alcohol use produces changes in the fecal microbiome and metabolome in both rodents and humans. Yet, these changes can be observed only in a subgroup of the studied populations, and reversal does not always occur after abstinence. We aimed to analyze fecal microbial composition and function in a translationally relevant baboon model of chronic heavy drinking that also meets binge criteria (drinking too much, too fast, and too often), i.e., alcohol ~1 g/kg and BALs ≥0.08 g/dL in a 2-hour period, daily, for years. We compared three groups of male baboons (Papio anubis): L=Long-term alcohol drinking group (12.1 years); S=Short-term alcohol drinking group (2.7 years); C=Control group, drinking a non-alcoholic reinforcer (Tang®) (8.2 years). Fecal collection took place during 3 days of Drinking (D), followed by a short period (3 days) of Abstinence (A). Fecal microbial alpha- and beta-diversity were significantly lower in L vs. S and C (p's<0.05). Members of the commensal families Lachnospiraceae and Prevotellaceae showed a relative decrease, whereas the opportunistic pathogen Streptococcus genus showed a relative increase in L vs. S and C (p's<0.05). Microbiota-related metabolites of aromatic amino acids, tricarboxylic acid cycle, and pentose increased in L vs. S and C (FDR-corrected p<0.01), with the latter two suggesting high energy metabolism and glycolysis in the gut lumen in response to alcohol. Consistent with the long-term alcohol exposure, mucosal damage markers (N-acetylated amino acids) increased in L vs. S and C (FDR-corrected p<0.01). Overall, S showed few differences vs. C, possibly due to the long-term chronic alcohol exposure needed to alter the normal gut microbiota. In the three groups, the fecal microbiome barely differed between conditions D and A, whereas the metabolome shifted in the transition from condition D to A. In conclusion, changes in the fecal microbiome and metabolome occur after significant long-term excessive drinking and are only partially affected by acute forced abstinence from alcohol. These results provide novel information on the relationship between the fecal microbiome and metabolome using a unique non-human primate model of chronic excessive alcohol drinking (up to 15 years) in controlled experimental conditions. These conditions included consistent and reliable alcohol self-administration and BALs, controlled food intake, regulated weight gain, identical housing and exposure to stimuli, and lack of confounders (e.g., geographic location, diet, cigarette smoking, illicit drugs, medications) that are commonly and inevitably present in humans. Furthermore, baboons, differently from rodents, are phylogenetically close to humans and have comparable alcohol absorption and metabolism. Importantly, the validity of this baboon model has been extensively demonstrated in previous studies testing clinically-relevant alcohol behaviors and pharmacotherapies for AUD, including baclofen and naltrexone. Thus, this model bridges the gap between rodent and human data, advancing knowledge in alcohol research.

Learning Objectives:

1. In a baboon model of chronic excessive alcohol drinking, there were significant changes in the fecal microbiota of the long-term alcohol drinking group (up to 15 years), whereas relatively short-term alcohol drinking (~3 years) did not significantly alter it. Compared to the control group, long-term and, less frequently, short-term alcohol drinking led to significant alterations in microbiota-related metabolites.
2. Our baboon model of chronic excessive alcohol drinking is translationally relevant. While several confounders may be present in humans due to variability in lifestyle and exposure to environmental factors, our study was conducted in a controlled experimental setting, which allows us to have confidence that the observed changes in the fecal microbiome and metabolome can be attributed directly to the chronic excessive alcohol exposure.

Literature References:

1. Temko, J. E., Bouhlal, S., Farokhnia, M., Lee, M. R., Cryan, J. F., & Leggio, L. (2017). The Microbiota, the Gut and the Brain in Eating and Alcohol Use Disorders: A 'Ménage à Trois'? Alcohol and alcoholism (Oxford, Oxfordshire), 52(4), 403–413.
2. Weerts, E. M., Fantegrossi, W. E., & Goodwin, A. K. (2007). The value of nonhuman primates in drug abuse research. Experimental and clinical psychopharmacology, 15(4), 309–327.

SCIENTIFIC PRESENTATION FROM THE AUDIENCE'S PERSPECTIVE

Zhi-De Deng, National Institute of Mental Health

Individual Abstract: Oral presentation of research at a conference or seminar is a core part of scientific communication for researchers and academics. The key to a successful presentation is to understand the audience's interpretive process. In order to fulfill the audience's expectation, there are several critical questions that the presenter must answer from the audience's perspective. Generally, the audience will ask: 1) Who is the presenter? 2) What story is the presenter trying to tell? 3) Why should I care? The first question concerns an aspect of academic presentation that is seldom discussed, that is the persona of the presenter. One of the most important elements in creating expectation is what kind of person the audience believes the presenter is and the relationship between the presenter and their scientific work. We will discuss techniques for developing and conveying the presenter's persona and style. The second question emphasizes storytelling. Although the primary goal of a scientific presentation is not to tell a story, the narrative structure of stories can be an effective vehicle for facilitating learning and transfer of information since human beings are programmed to respond to stories. In this part, we will discuss how to package the presentation in a story framework, and dramatic structures that catches the audience's attention. We will also explore several techniques that are often employed in advertising that are intended to maximize the impact of the story and connection with the audience.

Learning Objectives:

1. Identify two advertising techniques that are potentially useful in enhancing their presentation.
2. Discuss why storytelling can be an effective vehicle for facilitating learning.

Literature References:

1. Guber, P. "The Four Truths of the Storyteller," Harvard Business Review. December 1, 2007. URL: https://hbr.org/2007/12/the-four-truths-of-the-storyteller

2. Hollis, N. “Why Good Advertising Works (Even When You Think It Doesn’t)” URL: https://www.theatlantic.com/business/archive/2011/08/why-good-advertising-works-even-when-you-think-it-doesnt/244252/

ROLE OF MITOCHONDRIA IN THE EPIGENETIC REGULATION OF GLUTAMATERGIC FUNCTION: A NOVEL THERAPEUTIC APPROACH FOR MAJOR DEPRESSIVE DISORDERS

Carla Nasca, The Rockefeller University

Individual Abstract: A major challenge in the development of better antidepressants is the identification of molecular mechanisms linked to specific pathophysiological features of major depressive disorder (MDD). Recent studies suggested the pivotal mitochondrial metabolite acetyl-L-carnitine (LAC) as a new epigenetic modulator of glutamatergic function and a promising therapeutic target for clinical endophenotypes of MDD. In rodent models of depression, LAC leads to a rapid and persistent antidepressant-like response by increasing acetylation of specific histones and the expression of key genes of the glutamate (mGlu2 receptors) and insulin signaling pathways important for brain plasticity. 2) in patients with depression, LAC levels are decreased compared to age/sex-matched controls, with the lowest levels of LAC in patients with treatment-resistant depression. Specifically, the LAC-deficient endophenotype of MDD is characterized by greater severity of symptoms, early age of onset, a history of non-response to monoaminergic medication. Based upon these compelling preclinical and clinical evidence, the current work aimed at determining the neurobiological targets and pathways of this novel mitochondrial endophenotype of MDD using the innovative technology of exosomes.

We used a computational approach and leveraged recent methodological advances in exosome biology that enable the study of in-vivo molecular targets and pathways in the otherwise inaccessible human brains. 93 subjects were recruited at the Department of Psychiatry & Behavioral Sciences at Stanford and the Mood and Anxiety Disorders Program at the Icahn School of Medicine at Mount Sinai. All patients with MDD were in an acute episode during study participation. No differences were observed between subjects with MDD (n=64) and HC (n=29) with respect to demographic characteristics.

We herein report increased concentration of the insulin receptor substrate-1 (IRS-1) in specific brain-enriched exosomes of subjects with MDD as compared with age- and sex-matched HC ($p=0.036$), and sex-differences in serine-312 phosphorylation of IRS-1 in these discrete exosomes ($p=0.02$ in women, $p=0.31$ in men). These changes were specific to brain-enriched exosomes, no difference was observed in the pool of total circulating exosomes. Using regression analyses and hierarchical clustering approaches, we found that the increased phosphorylation of IRS-1 in brain-enriched exosomes was greater in subjects with MDD ($p=0.01$, $r=0.5$) and was associated with suicidality and anhedonia. Our data also suggest that a relationship between central and peripheral insulin resistance (IR) in HC subjects, but not in subjects with MDD. Importantly, these same subjects with MDD and potential brain IR were previously characterized by aberrant mitochondrial metabolism of LAC, which we recently discovered as an epigenetic modulator of glutamatergic function.

To our knowledge, this is the first in-vivo evidence for brain IR in potential mitochondrial endophenotypes of MDD. Our data also suggest that combining computational tools with the novel nanotechnology of exosomes to study in-vivo molecular mechanisms otherwise inaccessible in the human brain will aid in developing biological models of depression based

upon integrated measures of brain and systemic functions. These findings provide a starting point for creating mechanistic framework of regulation of brain plasticity and support further exploration of specific aspects of mitochondrial metabolism as a promising biological pathway that may help to develop individualized therapeutic strategies for treatment-resistant endophenotypes of depression.

Learning Objectives:

1. Novel mitochondrial mechanism of epigenetic regulation underlying the effects of stress on brain structure and function.
2. Combining computational tools with the novel nanotechnology of exosomes to identify in-vivo molecular targets and mechanisms in the otherwise inaccessible human brain.
3. How integrating basic and translational neuroscience can lead to the development of more effective personalized treatments for psychiatric illnesses such as depression.

Literature References:

1. Nasca C*, Bigio B, Zelli D, et al: Role of the astroglial glutamate exchanger xCT in ventral hippocampus in resilience to stress. Neuron 2017 2:402-413
2. Nasca C*, Dobbin J, Bigio B, et al: Insulin receptor substrate in brain-enriched exosomes in subjects with major depression: on the path of creation of biosignatures of central insulin resistance. Nature Molecular Psychiatry 2020 10.1038/s41380-020-0804-7

Panel Sessions

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

EFFICACY AND SAFETY RESULTS FROM THE FIRST PIVOTAL PHASE 3 RANDOMIZED CONTROLLED TRIAL OF MDMA-ASSISTED PSYCHOTHERAPY FOR TREATMENT OF SEVERE CHRONIC PTSD

Berra Yazar-Klosinski, Multidisciplinary Association for Psychedelic Studies

Overall Abstract: Posttraumatic stress disorder (PTSD) is a prevalent mental health condition with substantial impact on daily functioning that lacks sufficient treatment options. Previous research has led to the U.S. FDA's designation of 3,4-methylenedioxymethamphetamine (MDMA) as a Breakthrough Therapy for treatment of PTSD when administered as an adjunct to psychotherapy. Here we report the findings of the first randomized, double-blind, Phase 3 trial assessing the efficacy and safety of 3 sessions with a flexible dose of MDMA or placebo administered under direct observation to participants with severe PTSD (n = 100) as an adjunct to psychotherapy. Change in PTSD symptoms, measured by the gold standard Clinician-Administered PTSD Scale according to DSM-5 (CAPS-5), and functional impairment, measured by the Sheehan Disability Scale (SDS), were assessed by a central, blinded Independent Rater Pool at baseline and following each treatment session by live video ratings. Vital signs were measured during experimental sessions. Adverse events (AEs), concomitant medications, and suicidal ideation and behavior measured by the Columbia Suicide Severity Rating Scale (C-SSRS), were tracked throughout the study. The primary endpoint was 18 weeks post-randomization. Results from primary and secondary endpoints measured by change in CAPS-5 and SDS with a Mixed Model Repeated Measures (MMRM) analysis, psychotherapy with placebo-subtracted Cohen’s d effect size, and a responder analysis will be

presented. There were three serious AEs of suicidal ideation or behavior reported. MDMA was well tolerated, with some treatment emergent AEs occurring at greater frequency for the MDMA group during and after experimental sessions. Panelists will present important considerations for development of clinical practice guidelines for MDMA-assisted psychotherapy as a first-line treatment for PTSD. Risk/benefit considerations and cost effectiveness analyses based on Phase 2 publications and results from the pivotal Phase 3 clinical trial will be elucidated. Training requirements for risk mitigation by prescribers and other healthcare providers applied during the Clinical Development Program will be discussed. If Phase 3 results demonstrate that MDMA-assisted psychotherapy significantly attenuates PTSD symptomatology and associated functional impairment, these results will form the basis for marketing authorization applications worldwide, including among patients suffering from the dissociative subtype of PTSD, co-morbid depression, history of alcohol and substance use disorders, and adverse childhood experiences.

Learning Objectives:

1. Explore clinician training requirements developed by the sponsor to ensure risk mitigation during commercial rollout of MDMA-assisted psychotherapy for treatment of PTSD.
2. Review risk/benefit considerations and cost effectiveness of MDMA-assisted psychotherapy based on placebo-controlled clinical trials.

SAFETY AND EFFICACY OF MDMA-ASSISTED PSYCHOTHERAPY FOR THE TREATMENT OF SEVERE CHRONIC PTSD: RESULTS FROM THE FIRST PIVOTAL INTERNATIONAL MULTI-CENTER PHASE 3 RANDOMIZED CONTROLLED TRIAL

Corine de Boer, MAPS Public Benefit Corporation

Individual Abstract: The MAPP1 multi-site, randomized, double-blind study was designed to assess the efficacy and safety of MDMA assisted psychotherapy versus psychotherapy with placebo control in participants diagnosed with at least severe PTSD. Participants meeting DSM-5 criteria for current PTSD with a symptom duration of 6 months or longer at screening and a CAPS-5 Total Severity Score of 35 or greater at baseline were recruited at 15 sites across US, Canada, and Israel. Exclusion criteria included primary psychotic disorder, bipolar disorder 1, dissociative identity disorder, eating disorders with active purging, major depressive disorder with psychotic features, pregnancy or lactation, and any medical condition that could make receiving a sympathomimetic drug harmful due to increased in blood pressure and heart rate, including uncontrolled hypertension, history of arrhythmia, or marked baseline prolongation of QT interval. Full inclusion and exclusion criteria are included in the study protocol is available at maps.org/research/mdma/ptsd/phase3.

A flexible dose of MDMA or placebo, followed by a supplemental half-dose unless contraindicated, was administered during the ~12-week treatment period with manualized psychotherapy in three blinded monthly experimental sessions. The treatment period was preceded by three non-drug preparatory sessions and each experimental session was followed by three integrative sessions of non-drug psychotherapy.

Change in PTSD symptoms, measured by the gold standard Clinician-Administered PTSD Scale according to DSM-5 (CAPS-5), and functional impairment, measured by the Sheehan Disability Scale (SDS), were assessed by a central, blinded Independent Rater Pool at baseline and following each treatment session by live video ratings. Vital signs were measured during

experimental sessions. Adverse events (AEs), concomitant medications, suicidal ideation and behavior, measured by the Columbia Suicide Severity Rating Scale (C-SSRS), were tracked throughout the study.

The primary efficacy objective of this clinical trial was to evaluate the efficacy of MDMA-assisted psychotherapy for PTSD compared to inactive placebo plus psychotherapy, based on comparison of CAPS-5 Total Severity Score at Visit 3 (Baseline) to Visit 19 (18 weeks post Baseline).

Due to COVID-19 the study was terminated early. A total of 90 participants were randomized 1:1 to receive either MDMA or placebo- assisted psychotherapy. Baseline demographic data were similar between groups. The average participant age was 43 years (SD 12.7) and 38 (10.4) in the MDMA and placebo group, respectively with an average of 20 years of PTSD diagnosis duration. Average CAPS-5 score at baseline was 44.0 (SD 6.0) and 44.2 (6.2) in the MDMA and placebo group, respectively.

There were three serious AEs of suicidal ideation or behavior reported. MDMA was well tolerated, with some treatment emergent AEs occurring at greater frequency for the MDMA group during and after experimental sessions. No increase in suicidality was observed in the MDMA group. Detailed safety results will be presented. Primary and secondary endpoints measured by change in CAPS-5 and SDS with a Mixed Model Repeated Measures (MMRM) analysis, psychotherapy with placebo-subtracted Cohen's d effect size, and a responder analysis will be presented. The importance of the observed results for the treatment of PTSD will be discussed including further plans for the development of the MDMA-assisted psychotherapy modality.

Learning Objectives:

1. Review safety profile of MDMA in the context of MDMA-assisted psychotherapy for the treatment of PTSD.
2. Review the efficacy of MDMA-assisted psychotherapy for the treatment of PTSD.

Literature References:

1. Feduccia AA, Jerome L, Mithoefer A et al: Breakthrough for Trauma Treatment: Safety and Efficacy of MDMA-Assisted Psychotherapy Compared to Paroxetine and Sertraline. Frontiers in Psychiatry 2019 Sep 12;10:650.
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 2019 Sep;236(9):2735-2745.

PEER-REVIEWED CLINICAL PRACTICE GUIDELINES FOR MEDICAL AND PSYCHIATRIC EVALUATION AND MANAGEMENT PRIOR TO MDMA-ASSISTED PSYCHOTHERAPY FOR TREATMENT OF PTSD

Alia Lilienstein, MAPS Public Benefit Corporation

Individual Abstract: Before any drug, surgery, or treatment is prescribed, a physician must evaluate the safety of the proposed therapy in the context of the patient's history, comorbidities, and concomitant medications, to assess the risk/benefit ratio, and mitigate risk as possible in order to optimize patient care. Prescribers refer to the drug label and published study reports for relevant safety and efficacy information. These data are generated during the clinical

studies, which require strict inclusion and exclusion criteria in order to precisely characterize the safety and efficacy profile of the investigational compound. Treating physicians therefore commonly lack complete guidance, as they encounter a broader range of clinical scenarios in the real world than were allowed for in the clinical studies. Clinical Practice Guidelines (CPG) are tools intended to bridge the gap between clinical trial protocols and real-world use, by providing a systematic aid to help providers make complex medical decisions.

The anticipated clinical pathway for a patient seeking MDMA-assisted psychotherapy for PTSD begins when a patient is identified as a potential candidate for therapy, likely by a therapist, PCP, or psychiatrist. The patient will then be referred to a provider with the credentials to prescribe MDMA; this will likely consist of a combination of appropriate licensure and REMS certification. REMS will specify safe-use conditions for the drug/therapy session(s), but, as is always the case, pre-treatment medical evaluation and management will be outside of the purview of the REMS. Patients with PTSD experience a high rate of comorbidities and often are taking numerous medications, and CPG will aid the prescribing physician in evaluating and optimizing the patient prior to MDMA-assisted psychotherapy. In addition, external healthcare providers that are not included in the REMS will also benefit from CPG, for educational purposes and to be able to identify patients for which the treatment modality may be beneficial. Ultimately, the prescriber assumes medicolegal responsibility for any complications that may arise, and adherence to peer-reviewed CPG will minimize exposure to findings of malpractice.

CPG should present evidence from the literature, and when necessary, expert opinion, supporting decision-making around treating patients with complex medical and psychiatric histories. While all possible medical histories cannot reasonably be covered, guidance should be provided on how to approach patients with medical conditions which may be impacted by the physiologic effects of MDMA, such as certain cardiovascular and cerebrovascular conditions, neurologic conditions, pulmonary compromise, renal and hepatic impairment, both insulin-dependent and non-insulin-dependent diabetes, immunosuppression, chronic infectious disease, and cancer. Approaches to managing patients with psychiatric histories should also be examined, to include personality disorders, substance use disorders, psychotic disorders, eating disorders, and history of suicidality. Known and potential drug-drug interactions should also be discussed.

As MDMA-assisted psychotherapy for the treatment of PTSD moves toward approval, there is an urgent need to develop CPG to support pre-treatment medical and psychiatric evaluation and management.

Learning Objectives:

1. Understand the likely steps of the clinical pathway of medical evaluation and management of patients prior to MDMA-assisted psychotherapy for the treatment of PTSD.
2. Recognize the importance of Clinical Practice Guidelines in bridging the information gap between clinical trial protocols and real-world use.

Literature References:

1. Institute of Medicine 2011. Clinical Practice Guidelines We Can Trust. Washington, DC: The National Academies Press. https://doi.org/10.17226/13058.
2. Mithoefer MC, Feduccia AA, Jerome L, Mithoefer A, Wagner M, Walsh Z, Hamilton S, Yazar-Klosinski B, Emerson A, Doblin R. 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. 2019;236:2735-2745.

THE ROLE OF THE MDMA THERAPY TRAINING PROGRAM IN TRAINING FUTURE CLINICIANS

Marcela Ot'alora G., MAPS

Individual Abstract: MDMA-assisted psychotherapy is currently provided by trained mental health and medical practitioners working on approved clinical research protocols at facilities that meet government regulatory requirements for drug storage. As Phase 3 trials continue, data is being collected to support a New Drug Application (NDA) to the U.S. Food and Drug Administration (FDA) in 2022 with the hopes of making MDMA-Assisted Psychotherapy into an approved prescription treatment. The MDMA Therapy Training Program is a pre-requisite for conducting MDMA-Assisted Psychotherapy as a part of an approved clinical trial and is expected to continue as a required training for clinicians offering MDMA-Assisted Psychotherapy post-approval. The MDMA Therapy Training Program teaches competencies that have been implemented in all MAPS-sponsored MDMA-assisted psychotherapy trials with effective results. The principals of this modality are based on the belief that the participant is the agent of change, and that MDMA combined with psychotherapy can best help support the participant's healing process. The MDMA Therapy Training Program will supplement the planned Risk Evaluation and Mitigation Strategy (REMS) program to ensure that practitioners offer this treatment in a safe, effective, and ethical manner. This presentation will focus on critical themes that have emerged from the Phase 3 trial that should be taken into consideration when providing training and clinical supervision to healthcare providers as the treatment modality transitions to fit into current clinical practice.

Learning Objectives:

1. Explore clinician training requirements developed by the sponsor to ensure risk mitigation and enable clinician adoption during commercial rollout of MDMA-assisted psychotherapy for treatment of PTSD.
2. Explore clinician qualifications during commercial rollout of MDMA-assisted psychotherapy for treatment of PTSD.

Literature References:

1. Clare S: Cultivating Inner Growth: The Inner Healing Intelligence in MDMA-Assisted Psychotherapy. MAPS Bulletin 2018: 28 (3)
2. MAPS: Treatment Manual of MDMA-assisted psychotherapy. https://s3-us-west-1.amazonaws.com/mapscontent/research-archive/mdma/TreatmentManual_MDMAAssistedPsychotherapyVersion+8.1_22+Aug2017.pdf Accessed 09Nov2020.

THE COST-EFFECTIVENESS OF MDMA-ASSISTED PSYCHOTHERAPY FOR THE TREATMENT OF CHRONIC, TREATMENT-RESISTANT PTSD

Elliot Marseille, University of California, San Francisco

Individual Abstract: Background: Chronic posttraumatic stress disorder (PTSD) is a disabling condition that generates considerable morbidity, mortality, and both medical and indirect social costs. Treatment options are limited. A novel therapy using 3,4-

methylenedioxymethamphetamine (MDMA) has shown efficacy in six phase 2 trials. Its cost-effectiveness is unknown.

Methods and findings: To assess the cost-effectiveness of MDMA-assisted psychotherapy (MAP) from the U.S. health care payer's perspective, we constructed a decision-analytic Markov model to portray the costs and health benefits of treating patients with chronic, severe, or extreme, treatment-resistant PTSD with MAP. In six double-blind phase 2 trials, MAP consisted of a mean of 2.5 90-minute trauma-focused psychotherapy sessions before two 8-hour sessions with MDMA (mean dose of 125 mg), followed by a mean of 3.5 integration sessions for each active session. The control group received an inactive placebo or 25 – 40 mg. of MDMA, and otherwise followed the same regimen. Our model calculates net all-cause medical costs, mortality, quality-adjusted life-years (QALYs), and incremental cost-effectiveness ratios (ICERs). Efficacy was based on the pooled results of six randomized controlled phase 2 trials with 105 subjects (average duration of PTSD, 197.9 months (SD, 139.1) and 222.6 months (SD, 208.5) in controls and treatment groups respectively); and a four-year follow-up of 19 subjects. Other inputs were based on published literature and on assumptions when data were unavailable. We modeled results over a 30-year analytic horizon and conducted extensive sensitivity analyses. Our model calculates expected medical costs, mortality, quality-adjusted life-years (QALYs), and incremental cost-effectiveness ratio. Future costs and QALYs were discounted at 3% per year. For 1,000 individuals, MAP generates discounted net savings of $103.2 million over 30 years while accruing 5,553 discounted QALYs, compared to continued standard of care. MAP breaks even on cost at 3.1 years while delivering 918 QALYs. Making the conservative assumption that benefits cease after one year, MAP would accrue net costs of $7.6 million while generating 288 QALYS, or $26,427 per QALY gained.

Conclusion: MAP provided to patients with severe or extreme, chronic PTSD appears to be cost-saving while delivering substantial clinical benefit. Third-party payers are likely to save money within three years by covering this form of therapy.

Learning Objectives:

1. MDMA-Assisted Psychotherapy is not only cost-effective but will save health system money when provided to patients with severe / extreme, chronic, treatment-resistant PTSD.
2. These results are robust to a wide range of values and assumptions about the costs and consequences of providing MDMA-Assisted Psychotherapy.

Literature References:

1. Mithoefer, M. C., A. A. Feduccia, L. Jerome, A. Mithoefer, M. Wagner, Z. Walsh, S. Hamilton, B. Yazar-Klosinski, A. Emerson and R. Doblin (2019). "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.
2. Ivanova, J. I., H. G. Birnbaum, L. Chen, A. M. Duhig, E. J. Dayoub, E. S. Kantor, M. B. Schiller and G. A. Phillips (2011). "Cost of post-traumatic stress disorder vs major depressive disorder among patients covered by medicaid or private insurance." Am J Manag Care 17(8): e314-323.

***HOW TO MAXIMIZE PSYCHOPHARMACOLOGY EDUCATION AND TRAINING OF STUDENTS, RESIDENTS, AND EARLY CAREER PSYCHIATRISTS**

Madhukar Trivedi, UT Southwestern Medical Center

Overall Abstract: The field of psychopharmacology is going through a transformational change. For the first time in over half a century, the Food and Drug Administration has approved antidepressants with novel non-monoaminergic mechanisms of action. A new generation of medications have either gained approval or are in development. Similarly, psychedelics have ushered a new era of medication-assisted psychotherapy that promises long-term improvement for patients with a range of psychiatric disorders, from anxiety, mood, and stress-related disorders to substance use disorders. Together with emerging trends where primary care clinicians and physician extenders (such as psychiatric nurse practitioners and physician assistants) are providing a large portion of psychiatric care, residents and early career psychiatrists are being called upon to take care of individuals with difficult-to-treat serious mental illnesses.

Therefore, the proposed panel aims to bring together leaders in psychopharmacology education and research who will elucidate challenges in psychopharmacology training and identify potential solutions. In the first presentation, Dr Saunders will speak about the role of educating psychiatry trainees in measurement-based care (MBC) in diagnostic and outcome assessment, and describe the change management process used to incorporate and sustain the use of MBC methods in a training clinic. She will present data demonstrating that MBC methods can improve accurate diagnosis of treatment-resistant depression (TRD) and identify patients who are in need of more intensive management including TRD-specific pharmacotherapy. In the second presentation, Dr. Macaluso will present findings of a nationwide survey of psychopharmacology training in residency programs which include common topics that trainees feel are not adequately covered (such as drug-drug interactions) and potential opportunities to bridge the psychopharmacology knowledge gap (such as case-based learning and online modules). In the third presentation, Dr. Ross will present on a novel curriculum to teach psychopharmacology to trainees and introduce the concept of a "prescriber's workshop". Dr. Ross's presentation will discuss pros and cons of this curriculum, and the challenges and outcomes from its implementation at multiple institutions. In the fourth presentation, Dr. Brenner will discuss themes relevant to psychopharmacology training across a range of training experiences – from medical studies to residents, from early career attendings to clinical supervisors. He will discuss challenges from an academic psychiatry perspective including how to advise early career faculty on keeping up with psychopharmacology and what is the role of psychiatrists in the era of mid-level physician extenders. He will elaborate on strategies that may be successful in providing greater representation to trainees and clinicians on committees that guide departmental education mission (such as the grand rounds committee and journal clubs) and in educating interested trainees and clinicians with masterclass series in teaching and supervising psychopharmacology practice. Dr. Mathew will summarize the presented findings and lead an engaging and thought-provoking discussion with panelists and attendees.

Learning Objectives:

1. Understand the challenges in psychopharmacology education of trainees and early career psychiatrists.
2. Identify opportunities to engage in and impart evidence-based psychopharmacology training.

INTEGRATING PSYCHOPHARMACOLOGY INTO THE IDENTITY AND ROLES OF 21ST CENTURY PSYCHIATRY RESIDENTS

Adam Brenner, The University of Texas Southwestern Medical Center

Individual Abstract: Our profession has historically struggled to successfully integrate psychopharmacology into a cohesive identity and role as general psychiatrists. We first experienced the resistance to any displacement of time for psychotherapy training and practice, followed by economic pressures leading to ultra-brief 'medication management' appointments. The use of the term 'medication management' may have contributed to a diminution of both the psychiatrist's expertise and the importance of oversight of all the patient's treatment modalities. We now find ourselves in a healthcare landscape where advanced practice providers are a rapidly increasing presence, spurred by psychiatrist shortages and by financial incentives for institutions and insurers. In this new context, how should we conceptualize the place of psychopharmacology in the identity of the psychiatrist?

In our training program and department, we see the expertise of the psychiatrist as indispensable in two kinds of roles, and these roles then determine the approach to psychopharmacology: First, as the clinician directly treating complex, treatment resistant patients. Second, as the team leader/medical director who oversees care provided by a multidisciplinary team that may include primary care providers, psychiatry APPs, social workers, psychologists, case managers, nurses, and others.

In the first role, the psychiatrist must remain at the cutting edge of the evidence base, and this is always where the evidence is most preliminary, incomplete, and sometimes flawed. The psychiatrist must have the skills to critically assess the quality of the available evidence, to understand the strengths and limitations of different kinds of studies. The goal is to be a both a cautious and an optimistic advisor to very ill patients, and to avoid prescription that is driven by the fads generated by the enthusiasm of 'experts' and the marketing opportunities of pharmaceutical companies.

In the second role, the psychiatrist is also immersed in the evidence base, but with much more emphasis on teaching the essential evidence in her/his supervision of other providers and leadership of team meetings. In addition, the psychiatrist in this role focuses on a very challenging integrative expertise – the patient needs someone who can understand prescribing within the 'big picture'.

At a minimum this means the neuroscience of brain circuits responding to medication or stimulation, in the context of comorbid physical illnesses that both contribute to and are worsened by psychiatric conditions. Those psychiatric and physical illnesses are often caused and/or exacerbated by social determinants, so that preventing recurrences means a treatment team that can address experiences of trauma, social isolation, economic deprivation, and injustice/inequity. And finally there is the individual patient, struggling to put their neurobiologic and social experiences into a narrative that can provide meaning, or scaffolding to help bear their pain and inform their choices. The result is psychopharmacology informed by translational neuroscience, the patient's socioeconomic situation, and the meaning of medications to the patient.

In this presentation I will discuss the use of didactic seminars on conceptualizing patients, journal clubs that focus on critical thinking, general psychiatry clinic (not med management),

electives in treatment resistant clinics, and learning the teaching and management skills to lead multidisciplinary teams.

Learning Objectives:

1. The attendee will be able to describe the challenges of integrating psychopharmacology into emerging new roles for psychiatrists.
2. The attendee will be able to critique different approaches to training psychiatry residents in psychopharmacology for roles as an expert in treatment resistance and complex patients, and as a leader/teacher of multidisciplinary team care.

Literature References:

1. Bracken P et al: Psychiatry Beyond the Current Paradigm. The British Journal of Psychiatry (2012) 201, 430–434. doi: 10.1192/bjp.bp.112.109447
2. Craddock N, Kerr M, Thapar A: What is the core expertise of the psychiatrist?The Psychiatrist (2010), 34, 457 -460, doi: 10.1192/pb.bp.110.030114

IMPLEMENTING MEASUREMENT-BASED CARE IN THE CLINIC: ROLE OF TEAM EDUCATION IN OUTCOME MEASUREMENT

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

Individual Abstract: Accurate diagnosis of psychiatric disorders is critical for improving treatment of mental illness. Measurement-based care (MBC) – the use of standardized assessment measures to assist with diagnosis and follow outcome – has been shown to improve diagnosis and treatment, however adoption has been slow in psychiatric clinic settings. Several barriers dampen the effective implementation of MBC, including lack of education of clinicians about using the tools in clinical care. The implementation of the Penn State Psychiatric Clinical Assessment and Rating Evaluation System will be described, with a focus on the process used to educate clinicians including early-career attending psychiatrists, trainee psychiatrists, therapists, and advanced practice providers. Data on diagnosis and outcome from the PCARES registry (N=3721) will be shared to illustrate the benefits of MBC. In a subset of the PCARES sample (N=493), significant agreement occurred between a structured interview and clinical diagnoses for Major Depressive Disorder (MDD), Bipolar Disorder (BD), Generalized Anxiety Disorder and Panic Disorder. Initial psychopathological symptom complexity predicted improved diagnostic agreement for individuals with MDD at the first follow-up visit. Diagnostic agreement for BD at the initial visit was predicted by lower symptom burden and better social, physical and occupational functioning. Individual-level predictors of difficult-to-treat depression were identified in patients with repeated visits within a year, including demographic, psychiatric and functioning factors. Identification of the at-risk population can assist clinicians in tailoring treatment to algorithms for difficult-to-treat depression earlier in care.

Learning Objectives:

1. The participant will be able to list 3 benefits of using MBC in clinic.
2. The participant will be able to describe the process used to educate clinicians in MBC.

Literature References:

1. Waschbusch DA, Pearl A, Babinski DE, Essayli JH, Koduvayur SP, Liao D, Mukherjee D, Saunders EFH. Developing Measurement-Based Care for Youth in an Outpatient Psychiatry Clinic: The Penn State Psychiatry Clinical Assessment and Rating Evaluation System for Youth (PCARES-Youth). Evidence-Based Practice in Child and Adolescent Mental Health. 2020;5:67-82.

2. Zandi PP, Wang YH, Patel PD, Katzelnick D, Turvey CL, Wright JH, Ajilore O, Coryell W, Schneck CD, Guille C, Saunders EFH, Lazarus SA, Cuellar VA, Selvaraj S, Dill Rinvelt P, Greden JF, DePaulo JR. Development of the National Network of Depression Centers Mood Outcomes Program: A Multisite Platform for Measurement-Based Care. Psychiatr Serv. 2020;71:456-464.

NATIONAL PRACTICES IN TEACHING PSYCHOPHARMACOLOGY IN PSYCHIATRY RESIDENCY PROGRAMS: RESULTS OF A NATIONWIDE SURVEY

Matthew Macaluso, The University of Alabama At Birmingham

Individual Abstract: Objective: The goal of this study is to survey psychiatry residents throughout the United States in order to understand program practices for teaching psychopharmacology and resident perceptions of the same, including potential gaps in curriculum.

Methods: During the month of August 2020, we emailed survey invitations to program directors of every psychiatry residency program in the United States. The initial email contact instructed program directors to forward their residents the invitation to participate in the survey. REDCap, a web-based database designed to house data in a secure environment, was used to administer the survey, which included an online consent to participate. Survey questions assessed resident education on psychopharmacology including teaching methods and resources used by programs. The survey also assessed resident perceptions of the quality of psychopharmacology teaching in their program, as well as potential gaps in curriculum. Responses were deidentified for analysis.

Results: Of the 201 residents who responded to the survey invitation, a total of 200 residents (99.5%) consented to participate. However, 56 of these residents did not answer any survey questions. Therefore, a total of 144 residents who consented and answered survey questions were included in the analysis. 15.1% of respondents were PGY1 (n = 19), 23.0% PGY2 (n = 29), 28.6% PGY3 (n = 36), 24.6 % PGY4 (n = 31), 7.1% PGY5 (n = 9), and 1.6% (n=2) PGY6, with 12.5% choosing not to identify their year in training (n = 18). The most common psychopharmacology topics residents felt were not adequately covered in the curriculum include drug-drug interactions (40.9%), cognitive enhancers (40.9%), child and adolescent psychopharmacology (35.5%), clinical trial design (36.4%), and pharmacokinetics/pharmacodynamics (38.2%). In addition, 25.7% of residents surveyed indicated they were not taught about informed consent when prescribing psychotropic drugs. The most common barriers to teaching psychopharmacology were time limitations and other competing topics. Approximately half of participants reported that non-psychiatrists teach psychopharmacology in their programs. Traditional didactics remain the most common form of teaching method occurring in 98.6% of programs surveyed. Case based learning was the second most common form of teaching occurring in 52.8% of programs surveyed. 75% of programs surveyed used methods where residents partner directly with faculty to teach psychopharmacology didactics (ie, residents were actively asked to present cases, present portions of the material, or engage in a flipped classroom approach). 61.8% of residents surveyed desire a case-based learning format be added to their residency program, while 56.3% wished for more interactive seminars, and 44.4% would like the addition of online modules. Participants generally desired didactic formats unavailable in their programs. For example,

those who answered not having case-based didactics desired more case-based learning ($p<0.0001$).

Discussion/conclusions: Understanding national trends in teaching methodology and content will be useful for individual programs and educators when evaluating local/personal practices. The results suggest residents prefer more interactive methods of teaching psychopharmacology be incorporated into their programs such as case-based learning. Several gaps in curriculum were uncovered, with 25% of programs not teaching about informed consent.

Learning Objectives:

1. Assess psychopharmacology education across psychiatry residency programs in the United States with the goal of identifying best practices.
2. Understand resident perceptions of their education on psychopharmacology across psychiatry residency programs in the United States.

Literature References:

1. Zisook S, Benjamin S, Balon R, Glick I, Louie A, Moutier C, Moyer T, Santos C, Servis M. Alternate Methods of Teaching Psychopharmacology. Academic Psychiatry volume 29, pages141–154(2005)
2. American Society of Clinical Psychopharmacology Model Psychopharmacology Curriculum, for Psychopharmacology Teachers for Primary Care Clinicians, 2nd Edition, 2015, ASCP, 5034A Thoroughbred Lane, Brentwood, TN 37027.

PSYCHOPHARMACOLOGY "PRESCRIBER'S WORKSHOP:" THE DESIGN, IMPLEMENTATION, AND DISSEMINATION OF A MODEL CURRICULUM

David Ross, Yale School of Medicine

Individual Abstract: Historically, psychopharmacology classes are often taught by lecture. As residents rotate to outpatient clinics they begin to function more independently, rarely seeing patients in concert with supervisors. These two factors may serve as barriers to optimal acquisition and assessment of the full range of skills that encompass the act of good prescribing, respectively.

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

In this workshop we will introduce the model of a psychopharmacology "prescriber's workshop" and describe how the curriculum has been adapted and implemented at multiple institutions. We will discuss pros and cons of this approach and how to optimize the value and accessibility of model curriculum resources.

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

1. Describe limitations of traditional approaches to teaching psychopharmacology.
2. Describe a model for combining existing knowledge-based learning objectives with skills- and experience-based objectives.

Literature References:

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

CRO PANEL: CLINICAL TRIALS ON MARS IN A REGULATORY ENVIRONMENT...VIRTUAL, APPS, AND ALL OF THE ABOVE

Timothy Peters-Strickland, PPD Biotech

Overall Abstract: Data collection in our clinical trials is being challenged on multiple fronts. Sometimes, it feels like we are living on Mars with the constant changes. The COVID-19 pandemic and advances in technology are requiring us to adapt and approach our participants differently.

Restrictions related to the public health emergency required a proactive effort from regulators in adapting clinical trials to be conducted remotely while maintaining GCP compliance, participants' safety, and trial integrity. As a result of operational needs and Agency guidance, many clinical trials that were ongoing during the public health emergency implemented decentralized trial activities. Many of us used digital health technologies to obtain data from trial participants in their homes, at work, or at local health care environments. The ability to obtain continuous data, or to evaluate patient functioning in their own environment, may provide richer information than might be obtained at the investigational site.

Many of these changes will likely become permanent alterations with respect to trial design and may catalyze a transition toward mostly (or fully) remote trials. Although many current performance-based assessments of cognition, social cognition and functioning were designed for in-person administration by trained raters, a transition to fully self-administered remote assessments has the potential to increase the accuracy and validity of our clinical data.

In the real world, smart phones provide an exceptional opportunity to broaden the availability of cost-effective care, high-quality care for a wide range of individuals. While cognitive behavior therapy (CBT) has been proven to be an effective treatment for many disorders like Body Dysmorphic Disorder (BDD), access to CBT therapists trained in BDD is limited and out of reach for many individuals geographically and financially. Thus, developing and testing smartphone apps could be an important way to increase dissemination of this empirically supported treatment.

Learning Objectives:

1. Understand the general regulatory principles for the implementation of decentralized clinical trials and the use of digital health technologies for remote data acquisition.
2. Understand the challenges of remote delivery of performance-based assessments and app-delivered therapies in the domains of clinical symptoms, neurocognition and social cognition.

A REGULATORY PERSPECTIVE ON DECENTRALIZED CLINICAL TRIALS AND ON THE USE OF DIGITAL HEALTH TECHNOLOGIES FOR THE REMOTE ACQUISITION OF DATA IN CLINICAL INVESTIGATIONS

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

Individual Abstract: The restrictions related to the COVID-19 public health emergency required a proactive effort from regulators to assist sponsors in adapting various aspects of clinical trials to be conducted remotely while maintaining GCP compliance, participants' safety, and trial integrity. As a result of operational needs and Agency guidance, many clinical trials that were ongoing during the public health emergency implemented decentralized trial activities.

In addition to providing guidance on the conduct of clinical trials of medical products during the COVID-19 pandemic, the FDA Center for Drug Evaluation and Research (CDER) has been developing guidance on the conduct of decentralized clinical trials (DCTs), as well as on the use of digital health technologies (DHTs) for remote data acquisition in clinical investigations.

DCTs may involve different levels of decentralization. In fully decentralized clinical trials, all activities take place at locations remote from the investigator. In hybrid DCTs, some activities involve in-person visits by trial participants at the investigator's traditional trial site, and other visits or activities are conducted remotely from the investigator.

Advances in communication technology and digital health technologies (DHTs) have expanded the types of trial-related activities that can be performed without in-person visits at traditional clinical trial sites.

DHTs may be used to obtain data from trial participants in their homes, at work, or at local health care environments. The ability to obtain continuous data, or to evaluate patient functioning in their own environment, may provide richer information than might be obtained at the investigational site.

In this presentation I will briefly describe potential advantages and limitations of DCTs as compared to traditional trials, as well as barriers to their implementation. Next, I will provide examples in the therapeutic area of psychiatry and general principles useful for the implementation of DCTs, including remote assessment of outcome measures. Finally, I will discuss the challenges in the use of DHTs in drug development, highlighting FDA resources and mechanisms for interacting with the Agency.

Learning Objectives:

1. General principles for the implementation of decentralized clinical trials.
2. General principles for the use of digital health technologies for remote data acquisition in clinical trials.

Literature References:

1. US Department of Health and Human Services, Food and Drug Administration. FDA guidance on conduct of clinical trials of medical products during COVID-19 pandemic: guidance for industry, investigators, and institutional review boards. Accessed November 12, 2020.
2. US Department of Health and Human Services, Food and Drug Administration. Use of electronic informed consent in clinical investigations—questions and answers: guidance for institutional review boards, investigators, and sponsors. Published December 2016. Accessed May 17, 2016.

3. Cummings SR. Clinical Trials Without Clinical Sites. JAMA Intern Med. Published online March 01, 2021. doi:10.1001/jamainternmed.2020.9223
4. Lenze EJ, Mattar C, Zorumski CF, et al. Fluvoxamine vs placebo and clinical deterioration in outpatients with symptomatic COVID-19: a randomized clinical trial. JAMA. 2020;324(22):2292-2300.

HOW TO DEVELOP AND TEST A SMARTPHONE-APP: A NEW TREATMENT FOR BODY DYSMORPHIC DISORDER

Sabine Wilhelm, Harvard Medical School

Individual Abstract: Most individuals with mental disorders do not receive any treatment at all, and those who do often face challenges accessing high quality care. The ubiquity of smart phones in the general population provides an exceptional opportunity to broaden the availability of cost-effective care for a wide range of individuals. However, while there are over 10,000 apps dedicated to the improvement of mental health, only few were developed with expert input or are supported by efficacy data. Thus, the efficacy of most mental health apps remains questionable. The current presentation will discuss how to develop and test a smartphone app, using the example of a new cognitive behavioral treatment app for Body Dysmorphic Disorder (BDD). BDD is a severe and common disorder characterized by a preoccupation with a perceived appearance flaw. While cognitive behavior therapy (CBT) has been proven to be an effective treatment (Wilhelm et al 2019) access to CBT therapists trained in BDD is limited and out of reach for many individuals geographically and financially. Thus, developing and testing smartphone apps could be an important way to increase dissemination of this empirically supported treatment. The current talk will focus on the development and testing of a smartphone CBT app for BDD, which will illustrate the issues clinical scientists have to consider when developing apps, including remote safety assessments, and design considerations to keep the patients engaged while also maintaining the fidelity of treatment. We (Wilhelm, et al, 2020) developed the first smartphone-delivered CBT for BDD via user-centered design, combining stakeholder input from clinical psychologists, engineers, design experts, and BDD patient consultants. We then completed a 12-week open trial (N = 10), and collected data on feasibility, acceptability, and treatment outcome. Patient feedback and attrition rates (0%) showed that smartphone-based CBT for BDD appears to be feasible, acceptable, and satisfactory. Results also indicated that app -based CBT for BDD improved BDD symptoms, BDD-related insight, functional impairment, and quality of life; scores from baseline to post-treatment improved with large to very large effects; depression improved with a medium effect. The response rate was very high, 90% of participants were treatment responders at post-treatment. Thus, our initial trial showed that a mobile app CBT for BDD has promise as a cost effective and scalable treatment. Next steps, including a larger randomized controlled trial for BDD (n=80), as well as the development and testing of app-based CBT for other disorders and use cases, will be discussed.

Learning Objectives:

1. Describe how to develop engaging, safe and powerful mental health mobile apps.
2. Cite evidence from a clinical trial that smartphone-based treatments can be effective.

Literature References:

1. Wilhelm S, Weingarden H, Greenberg JL, et al:. Development and Pilot Testing of a Cognitive Behavioral Therapy Digital Service for Body Dysmorphic Disorder. Behav Ther 2020; 51(1): 15-26.

2. Wilhelm S, Weingarden H, Ladis I, et al: . Cognitive-behavioral therapy in the digital age: Presidential Address. Behav Ther 2020; 51(1): 1-14.

CLINICAL TRIAL DESIGN CONSIDERATIONS FOR REMOTE CLINICAL TRIALS

Philip Harvey, University of Miami Miller School of Medicine

Individual Abstract: The COVID-19 pandemic has affected the ability of researchers to conduct clinical trials in person and required multiple adaptations. Some of these adaptations will likely become permanent alterations to trial design and may catalyze a transition toward mostly or fully remote trials in the future. In clinical trials, clinical and performance-based assessments are commonly implemented. Many current performance-based assessments of cognition, social cognition, and functioning were designed for in-person administration by trained raters, even when measures include largely automated stimulus delivery. Further, in-person functional and clinical assessments are already handicapped by inaccurate or variable administration on the part of site personnel, and by the burden and expense required to staff and train reliable raters. A transition to fully self-administered remote assessments has the potential circumvent these issues while increasing the accuracy and validity of these observations. The challenges in fully remote performance-based assessments include ensuring that the participant understands and adheres to the testing procedures and that the participant is not assisted or replaced by someone else. Many previously successful remote procedures such as cognitive training do not rely on single-observation assessments, making after the fact correction of errors feasible as part of a longer-stream of data collection. In terms of data currently available, this presentation will focus on validity and adherence to remotely delivered Ecological Momentary Assessments (EMA) of mood and psychosis as well as association of measures of social context to clinician ratings of negative symptoms. EMA embedded single-task cognitive and social cognitive measures have also proven feasible with high levels of adherence and excellent convergence with in-person assessments. Finally, the presentation will discuss strategies and levels of success in transitioning in-person technology based cognitive and functional capacity assessments (e.g., tablet-based Brief Assessment of Cognition [BAC] and Virtual Reality Functional Capacity Assessment Task [VRFCAT]) to remote delivery, including which performance domains present minimal remote challenges (verbal episodic and working memory) versus those with greater apparent challenges (tests of processing speed). As remote trials are the next likely step in clinical research, a positive focus on ensuring validity is required and data regarding feasibility and convergence with standard measures are central to this effort.

Learning Objectives:

1. Understanding the challenges of remote delivery of performance based assessments designed to be administered by an examiner.
2. Appreciating the successes to date in remote assessments in domains of clinical symptoms, neurocognition, and social cognition.

Literature References:

1. Parrish EM, Kamarsu S, Harvey PD, Pinkham A, Depp CA, Moore RC. Remote Ecological Momentary Testing of Learning and Memory in Adults With Serious Mental Illness [published online ahead of print, 2020 Nov 21]. Schizophr Bull. 2020;sbaa172. doi:10.1093/schbul/sbaa172

2. Depp CA, Kamarsu S, Filip TF, et al. Ecological momentary facial emotion recognition in psychotic disorders [published online ahead of print, 2021 Jan 12]. Psychol Med. 2021;1-9. doi:10.1017/S0033291720004419

*INNOVATION AND TECHNOLOGY IN EDUCATION

Mark Rapaport, University of Utah Neuropsychiatric Institute

Overall Abstract: The intent of this panel is discuss how technologies are modifying our educational environment. The use of remote learning techniques, asynchronous learning approaches, and just-in-time interventions is radically reshaping education. We will use the lecture by Dr. Cohen to focus this discussion.

Learning Objectives:

1. To discuss the impact of new technologies on the presentation of information to different audiences.
2. To discuss the similarities and differences in needs of different types of audiences.

FROM BOOKS TO BEDSIDE: IMPLEMENTING EVIDENCE-BASED CARE FOR THOSE WITH SERIOUS MENTAL ILLNESS

Amy Cohen, American Psychiatric Association

Individual Abstract: COVID-19 continues to transform care for serious mental illness (SMI). The move to online and virtual platforms has created both new opportunities as well as challenges for those seeking to apply evidence-based practice (EBP) in frontline clinical work. This talk will explore novel educational strategies used by the Clinical Support System for Serious Mental Illness (also known as SMI Adviser) to help frontline clinicians care for those with SMI. This APA led and SAMHSA funded uses mobile apps, virtual communities, accredited education, direct clinical consultations, and a vast knowledgebase to help clinicians implement EBP across all practice settings. The work of SMI Adviser can serve as a template for other educational initiatives seeking to support mental health clinicians across disease states.

Learning Objectives:

1. Identify tools to support evidence-based care for those with schizophrenia, bipolar disorder, and recurrent major depression.
2. Describe innovative educational strategies for engaging front-line clinicians in acquiring knowledge and skills for evidence-based practice.

Literature References:

1. Cohen, A. N., & Gorrindo, T. (2020). New Tools for Implementing Evidence-Based Care for Serious Mental Illness. Focus (American Psychiatric Publishing), 18(4), 432–435. https://doi.org/10.1176/appi.focus.20200023
2. Wisniewski, H., Gorrindo, T., Rauseo-Ricupero, N., Hilty, D., & Torous, J. (2020). The Role of Digital Navigators in Promoting Clinical Care and Technology Integration into Practice. Digital biomarkers, 4(Suppl 1), 119–135. https://doi.org/10.1159/000510144

***Keynote Plenary**

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

*KEYNOTE PLENARY SESSION: INTEGRATING NEW AND NOVEL TREATMENTS INTO CLINICAL PRACTICE

Susan Kornstein, Virginia Commonwealth University

Overall Abstract: This Keynote Plenary Session will focus on the 2021 annual meeting theme of integrating new and novel treatments into clinical practice. Dr. Luca Pani will discuss new models for the evaluation of specialized medicinal products coming to market, such as advance therapy medicinal products (ATMPs), orphan drugs, and digital therapies. Dr. Edward Nunes will address new compounds and new approaches to treating substance use disorders, including implanted formulations of buprenorphine and naltrexone for the treatment of opioid use disorder and combination treatment strategies for stimulant use disorder. Dr. Sarah Lisanby will consider the opportunities and obstacles to incorporating new developments in neuromodulation into research and clinical settings. Finally, Dr. Samantha Meltzer-Brody will highlight recent advances in treatment options for postpartum depression, specifically the use of the two neuroactive steroid GABAAR-positive allosteric modulators brexanolone and zuranolone.

NEW MODELS FOR THE EVALUATION OF SPECIALISED MEDICINAL PRODUCTS: BEYOND CONVENTIONAL HEALTH TECHNOLOGY ASSESSMENT AND PRICING

Luca Pani, University of Miami

Abstract: New specialised therapeutics products coming to market, such as advanced therapy medicinal products (ATMPs), orphan drugs and digital therapies differ from traditional therapies in terms of how they are manufactured and administered, as well as the potentially transformative benefits they may provide. The current health technology assessment (HTA) process that has been used for traditional therapies, such as small molecule drugs and antibodies, does not work adequately for specialised therapeutics, with a key issue being the generation of sufficient evidence to adequately capture the full long-term benefits. The objectives of this presentation are to discuss why the current HTA process is inadequate for evaluating these new therapies, how evidence should be continuously generated and presented to regulators and payers to support their use, and to propose new approaches to pricing models. This will enable payers to have an affordable, risk-mitigated means of funding new therapies in a timely manner, thus guaranteeing patient access to new, potentially life-saving therapies, while providing manufacturers with a return on their investment. Without new approaches or adaptation of existing frameworks, certain ATMPs may not reach patients in some or all countries, or be at risk of withdrawal from the market.

Learning Objectives:

1. The audience will appreciate how and why continuous evidence generation and new approaches to pricing models will be required in the very near future to support the use of specialized therapeutics.

Literature References:

1. Sverdlov O, van Dam J, Hannesdottir K, Thornton-Wells T. Digital Therapeutics: An Integral Component of Digital Innovation in Drug Development. Clinical pharmacology and therapeutics. 2018; 104: 72-80.
2. Pammolli F, Righetto L, Abrignani S, Pani L, Pelicci PG, Rabosio E. The Endless Frontier? The Recent Upsurge of R&D Productivity in Pharmaceuticals. J Transl Med. 2020; 18: 162.

NEW COMPOUNDS AND NEW APPROACHES TO TREATING SUBSTANCE USE DISORDERS

Edward Nunes, NYSPI - Columbia University

Abstract: The opioid epidemic continues to escalate, worsened by widespread illicit fentanyl, while stimulant use disorders are also escalating, both cocaine use and methamphetamine. General strategies for pharmacotherapy of substance use disorders include agonists, partial agonists, antagonists, and indirect modulators of response to substances. For opioid use disorder, there is a clear target, the mu opioid receptor, mediating both reinforcing (euphoria) and toxic (respiratory depression, overdose and death) effects of opioids. Agonist (methadone), partial agonist (buprenorphine), and antagonist (naltrexone) at the mu receptor are highly effective as treatments when taken, though strategies to improve adherence are needed. Cocaine and methamphetamine do not present as clear molecular targets. Many medications from a range of classes, including antidepressants, anticonvulsants, and stimulants have been tested, and to date there are not clearly established effective medications. New developments in the pharmacotherapy of opioid and stimulant use disorders will be discussed. Extended-release injected or implanted formulations of buprenorphine and naltrexone circumvent the need daily adherence to medication taking, and clinical trials supporting their effectiveness are promising. For stimulant use disorders, where the effect sizes for single treatments have been modest, combinations of treatments with complementary mechanisms have shown promise, including naltrexone plus bupropion for methamphetamine use disorder, topiramate plus extended release amphetamine for cocaine use disorder, and antidepressants plus the behavioral treatment contingency management. Ketamine, which has emerged as an effective antidepressant with novel mechanism, has also shown promise for substance use disorders.

Learning Objectives:

1. Understand mechanisms of pharmacotherapies for substance use disorders, including agonist, partial agonist, antagonist, and indirect modulators of drug response.
2. Understand the pharmacokinetics and evidence of efficacy for extended release injected or implanted formulations of buprenorphine and naltrexone for treatment of opioid use disorder, and understand how these new formulations may be applied in clinical practice.
3. Understand the main findings of clinical trials of combination treatment strategies for stimulant use disorders, and implications for clinical practice.

Literature References:

1. Haight BR, Learned SM, Laffont CM, Fudala PJ, Zhao Y, Garofalo AS, Greenwald MK, Nadipelli VR, Ling W, Heidbreder C; RB-US-13-0001 Study Investigators. Efficacy and safety of a monthly buprenorphine depot injection for opioid use disorder: a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2019 Feb 23;393(10173):778-790. doi: 10.1016/S0140-6736(18)32259-1. Epub 2019 Feb 18. PMID: 30792007
2. Lofwall MR, Walsh SL, Nunes EV, Bailey GL, Sigmon SC, Kampman KM, Frost M, Tiberg F, Linden M, Sheldon B, Oosman S, Peterson S, Chen M, Kim S. Weekly and

Monthly Subcutaneous Buprenorphine Depot Formulations vs Daily Sublingual Buprenorphine With Naloxone for Treatment of Opioid Use Disorder: A Randomized Clinical Trial. JAMA Intern Med. 2018 Jun 1;178(6):764-773. doi: 10.1001/jamainternmed.2018.1052. PMID: 29799968

3. Lee JD, Nunes EV Jr, Novo P, Bachrach K, Bailey GL, Bhatt S, Farkas S, Fishman M, Gauthier P, Hodgkins CC, King J, Lindblad R, Liu D, Matthews AG, May J, Peavy KM, Ross S, Salazar D, Schkolnik P, Shmueli-Blumberg D, Stablein D, Subramaniam G, Rotrosen J. Comparative effectiveness of extended-release naltrexone versus buprenorphine-naloxone for opioid relapse prevention (X:BOT): a multicentre, open-label, randomised controlled trial. Lancet. 2018 Jan 27;391(10118):309-318. doi: 10.1016/S0140-6736(17)32812-X. Epub 2017 Nov 14. PMID: 29150198
4. Levin FR, Mariani JJ, Pavlicova M, Choi CJ, Mahony AL, Brooks DJ, Bisaga A, Dakwar E, Carpenter KM, Naqvi N, Nunes EV, Kampman K. Extended release mixed amphetamine salts and topiramate for cocaine dependence: A randomized clinical replication trial with frequent users. Drug Alcohol Depend. 2020 Jan 1;206:107700. doi: 10.1016/j.drugalcdep.2019.107700. Epub 2019 Nov 1. PMID: 31753736
5. 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. doi: 10.1056/NEJMoa2020214. PMID: 33497547
6. Dakwar E, Nunes EV, Hart CL, Foltin RW, Mathew SJ, Carpenter KM, Choi CJJ, Basaraba CN, Pavlicova M, Levin FR.A Single Ketamine Infusion Combined With Mindfulness-Based Behavioral Modification to Treat Cocaine Dependence: A Randomized Clinical Trial. Am J Psychiatry. 2019 Nov 1;176(11):923-930. doi: 10.1176/appi.ajp.2019.18101123. Epub 2019 Jun 24. PMID: 31230464

INCORPORATING NEW DEVELOPMENTS IN NEUROMODULATION DEVICES INTO RESEARCH AND PRACTICE: OBSTACLES AND OUTLOOK FOR THE FUTURE

Sarah Lisanby, NIH/NIMH

Abstract: Neuromodulation devices span our oldest (e.g. electroconvulsive therapy, ECT) to our newest (e.g. transcranial magnetic stimulation, TMS; deep brain stimulation, DBS; transcranial direct current stimulation, tDCS; focused ultrasound, FUS; etc) somatic treatment modalities in psychiatry. Each of these tools has unique features in terms of how they are delivered to the brain, how deeply they penetrate, how focal they are, how invasive they are, and their mechanisms of action. Their applications are quite diverse as they can be used as tools of discovery and/or as therapeutic interventions. These devices have taken different pathways in their incorporation into research and practice and are at different stages in the product development lifecycle. Some of these tools followed a rational design process whereby a new device was built and tested, iteratively re-designed to be fit for specific research or therapeutic purposes, and then tested in clinical trials. As an example, TMS began as a research tool for probing physiology and was later developed as a clinical treatment for depression, obsessive compulsive disorder (OCD), and smoking cessation. In contrast, ECT was already in clinical use for decades and is now being re-engineered to improve their safety and efficacy. Examples of this reverse engineering include magnetic seizure therapy (MST) and individualized low amplitude seizure therapy (iLAST) which were designed to improve the focality of stimulation and reduce adverse side effects of ECT.

One of the most fundamental challenges to developing neuromodulation tools and to their incorporation into research and practice is the need to re-conceptualize and standardize how we quantify, individualize, and report the "dose" of neuromodulation. Key elements of the dose of neuromodulation include the strength and spatial distribution of the delivered energy in the brain, the temporal aspects of the pulse and stimulation pattern, and the physiological state of the brain during stimulation. In addition to describing all of the elements that determine the dose delivered to the head, the dose that the brain is actually exposed to is highly subject to variability as a consequence of interindividual differences in anatomy and physiology. Examples of new approaches to enhance spatial precision include computational modeling of the electric field induced in the brain of each individual, and connectivity-based targeting to enable engagement of distributed networks and to inform patient selection based on baseline biotypes derived from fMRI or EEG measures. Examples of new approaches to enhance temporal precision include optimizing pulse shape and width (e.g. ultrabrief pulse ECT and controllable pulse TMS), optimizing stimulation pattern (e.g. theta burst stimulation, TBS), and closed-loop systems that trigger stimulation based on on-line recording of brain state. Examples of new approaches to enhance contextual precision include on-line cognitive task performance and simultaneous cognitive behavioral therapy and TMS.

As we seek to incorporate these new developments in neuromodulation into research application, we face a number of obstacles such as rigor and reproducibility in technique within and across labs, consistency in nomenclature and reporting, the problem of inference, and training needs for researchers. There is the additional challenge of how to decide when the field is ready to pivot from developing/validating the tool to using the tool to study other scientific questions. Incorporation of new developments into clinical practice presents its own set of obstacles such as FDA and CMS approvals, training in patient selection, operator training, staging of neuromodulation relative to other modalities, and the need for professional practice guidelines to inform care. Each of these challenges will be illustrated with examples, and an outlook for the future impact of neuromodulation in research and practice will be presented.

Learning Objectives:

1. Attendees will be able to discuss the opportunities and obstacles to incorporating new developments in neuromodulation into research and clinical settings.

Literature References:

1. Bikson M, Brunoni AR, Charvet LE, Clark VP, Cohen LG, Deng ZD, Dmochowski J, Edwards DJ, Frohlich F, Kappenman ES, Lim KO, Loo C, Mantovani A, McMullen DP, Parra LC, Pearson M, Richardson JD, Rumsey JM, Sehatpour P, Sommers D, Unal G, Wassermann EM, Woods AJ, Lisanby SH. Rigor and reproducibility in research with transcranial electrical stimulation: An NIMH-sponsored workshop. Brain Stimul. 2018 May - Jun;11(3):465-480.
2. Deng ZD, Luber B, Balderston NL, Velez Afanador M, Noh MM, Thomas J, Altekruse WC, Exley SL, Awasthi S, Lisanby SH. Device-Based Modulation of Neurocircuits as a Therapeutic for Psychiatric Disorders. Annu Rev Pharmacol Toxicol. 2020 Jan 6;60:591-614.
3. Fried PJ, Santarnecchi E, Antal A, Bartres-Faz D, Bestmann S, Carpenter LL, Celnik P, Edwards D, Farzan F, Fecteau S, George MS, He B, Kim YH, Leocani L, Lisanby SH, Loo C, Luber B, Nitsche MA, Paulus W, Rossi S, Rossini PM, Rothwell J, Sack AT, Thut G, Ugawa Y, Ziemann U, Hallett M, Pascual-Leone A. Training in the practice of noninvasive brain stimulation: Recommendations from an IFCN committee.

Clin Neurophysiol. 2020 Dec 3:S1388-2457(20)30575-7. doi: 10.1016/j.clinph.2020.11.018. Epub ahead of print. PMID: 33549501.
4. Peterchev AV, Wagner TA, Miranda PC, Nitsche MA, Paulus W, Lisanby SH, Pascual-Leone A, Bikson M. Fundamentals of transcranial electric and magnetic stimulation dose: definition, selection, and reporting practices. Brain Stimul. 2012 Oct;5(4):435-53.
5. Rossi S, Antal A, Bestmann S, Bikson M, Brewer C, Brockmöller J, Carpenter LL, Cincotta M, Chen R, Daskalakis JD, Di Lazzaro V, Fox MD, George MS, Gilbert D, Kimiskidis VK, Koch G, Ilmoniemi RJ, Pascal Lefaucheur J, Leocani L, Lisanby SH, Miniussi C, Padberg F, Pascual-Leone A, Paulus W, Peterchev AV, Quartarone A, Rotenberg A, Rothwell J, Rossini PM, Santarnecchi E, Shafi MM, Siebner HR, Ugawa Y, Wassermann EM, Zangen A, Ziemann U, Hallett M. Safety and recommendations for TMS use in healthy subjects and patient populations, with updates on training, ethical and regulatory issues: Expert Guidelines. Clin Neurophysiol. 2021 Jan;132(1):269-306. doi: 10.1016/j.clinph.2020.10.003. Epub 2020 Oct 24. PMID: 33243615.

BREXANOLONE AND ZURANOLONE TREATMENT IN PATIENTS WITH POSTPARTUM DEPRESSION

Samantha Meltzer-Brody, University of North Carolina School of Medicine, Chapel Hill

Abstract: This presentation will review the burden of postpartum depression (PPD) and highlight recent advances in treatment options, specifically on the use of the 2 neuroactive steroid (NAS) ɣ-aminobutyric acid receptor (GABAAR)-positive allosteric modulators to treat PPD, brexanolone injection (BRX) and the orally administered zuranolone (SAGE-217; ZRN). PPD is a major depressive episode with peripartum onset and is one of the most common medical complications during and after pregnancy. In the United States, estimates of new mothers experiencing symptoms of PPD vary by state, from 10% to 24%, with an average of 13.2%. PPD impacts the wellbeing of the mother and her family, in part because it can impair the expected bonding between the mother and infant that is important for development. PPD is also associated with maternal mortality resulting from suicide, and physical and behavioral deficits in the children, if left untreated.

Several mechanisms have been implicated in the pathophysiology of PPD, including abrupt decline in the endogenous NAS; allopregnanolone concentrations following childbirth and related changes in GABAAR regulation; dysfunctional signaling in GABA and altered functional network connectivity; and hypothalamic-pituitary-adrenal axis dysfunction. Enhancing GABAergic inhibition may restore excitatory/inhibitory balance to regulate brain network activity, which has been proposed to reduce depressive symptoms. The circulating levels of allopregnanolone, an endogenous neuroactive steroid and GABAAR-positive allosteric modulator, rise over the course of pregnancy and drop rapidly following birth.

BRX, a first-in-class, intravenous formulation of allopregnanolone, is approved by the US Food and Drug Administration for the treatment of adults with PPD. BRX was evaluated in 3 randomized placebo-controlled trials (RCTs) in PPD (HUMMINGBIRD Studies NCT02614547, NCT02942004, and NCT02942017). The safety and efficacy of ZRN, an oral investigational compound, was evaluated in a Phase 3 RCT in PPD (ROBIN Study, NCT02978326) of a 14-day treatment with ZRN 30 mg vs placebo (N=153) in women with severe PPD. Both treatments achieved their respective primary endpoints of a reduction in

depressive symptoms as measured by a change from baseline in the 17-item Hamilton Rating Scale for Depression (HAM-D17) compared with placebo (BRX at Hour 60; ZRN at Day 15). Additional secondary and post-hoc analyses of the BRX and ZRN RCTs supported the primary endpoint results showing that BRX and ZRN treatments provide rapid (BRX: Hour 8, ZRN: Day 3) and sustained improvement in depressive symptoms (all time points measured to Day 30 for BRX and Day 45 for ZRN) in women with PPD as measured by HAM-D17 total score.

The ongoing phase 3 SKYLARK study (NCT04442503) is evaluating the efficacy and safety of ZRN 50 mg vs placebo (planned enrollment N=192) in women with severe PPD, and data is anticipated at the end of 2021. Taken together, these results help support the use of BRX and the development of ZRN as treatments for adult women with PPD.

Learning Objectives:

1. To understand the prevalence of PPD in the United States and worldwide.
2. To recognize the burden of disease associated with PPD and the importance of effective treatment strategies.
3. To review the objectives and designs of brexanolone and zuranolone PPD studies.
4. To assess results from the PPD development program of brexanolone and zuranolone.

Literature References:

1. Bauman BL, Ko JY, Cox S, et al. Vital signs: postpartum depressive symptoms and provider discussions about perinatal depression — United States, 2018. MMWR Morb Mortal Wily Rep. 2020;69(19):575-581. doi: 10.15585/mmwr.mm6919a2
2. Meltzer-Brody S, Colquhoun H, Riesenberg R, et al. Brexanolone injection in post-partum depression: two multicentre, double-blind, randomized, placebo-controlled, phase 3 trials. Lancet. 2018;392(10152):1058-1070. doi: 10.1016/S0140-6736(18)31551-4
3. Kanes S, Colquhoun H, Gunduz-Bruce H, et al. Brexanolone (SAGE-547 injection) in post-partum depression: a randomised controlled trial. Lancet. 2017;390(10093):480-489. doi: 10.1016/S0140-6736(17)31264-3
4. Deligiannidis K, Meltzer-Brody S, Gunduz-Bruce H, et al. Effect of zuranolone vs placebo in postpartum depression: a randomized clinical trial. JAMA Psych. 2021. In press.

Friday, June 4, 2021

Regulatory Plenary & Panel Q&A

11:00 a.m. - 1:00 p.m.

REGULATORY PLENARY

Linda Brady, DNBBS/NIMH/NIH

Overall Abstract: The past decade has seen tremendous innovation in digital health technologies (DHTs) for capturing data that are of importance to many different stakeholders – consumers, clinicians, researchers, healthcare providers, industry, and regulators. DHTs include a range of technologies from hardware (e.g., wearable devices and sensors) to software (e.g., mobile phone apps that enable consumers to monitor their own health and participate in

studies), as well as telemedicine platforms and artificial intelligence to support clinical decision making.

DHTs have untapped potential for use in intervention development and clinical trial paradigms as relatively low cost, objective, and scalable technologies to improve outreach and inclusion of a broader and more diverse community of participants. Potential uses for DHTs include digital phenotyping, collection of continuous data, monitoring of disease progression, capturing real-time information about patients' experience outside of the clinic, and the measurement of novel endpoints for assessing the efficacy of novel interventions. Studies involving psychiatric disorders may particularly benefit from DHTs, given the traditional reliance on outcome measures that depend on patient recall as well as the importance of assessing behavioral outcomes. Psychiatric clinical trials represent an area of opportunity for rigorous testing and assessment of the value of DHTs, both to improve the diversity and inclusion of study participants as well as to measure real-world outcomes to assess whether novel interventions provide benefits that are meaningful to patients.

The Foundation for NIH (FNIH) Biomarkers Consortium recently held a workshop to explore the use of DHTs in drug development (https://fnih.org/our-programs/biomarkers-consortium/digitalmonitoring), and the National Academies of Science, Engineering and Medicine (NASEM) held a follow-on workshop focused on CNS disorders (https://www.nationalacademies.org/our-work/the-role-of-digital-health-technologies-in-drug-development-a-workshop). In addition, the Clinical Trials Transformation Initiative (CTTI) led efforts to clarify a pathway for developing novel endpoints from DHTs to drive more efficient clinical trials (https://www.ctti-clinicaltrials.org/projects/novel-endpoints). As a result of these concerted efforts, the FDA launched a digital health center of excellence (https://www.fda.gov/news-events/press-announcements/fda-launches-digital-health-center-excellence) and has developed regulatory guidance to accelerate the development of digital health products (https://www.fda.gov/medical-devices/digital-health-center-excellence/guidances-digital-health-content).

This session is a venue to learn about how these efforts have advanced the use of innovative DHTs in drug and device development for psychiatric disorders, both in academic research and in clinical trial paradigms. Specific emphasis will be on strategies for the development of DHTs in the context of the U.S. FDA and the European Medicines Agency (EMA) regulatory environments.

Mike Davis, FDA will provide an overview of DHTs in psychiatric drug development, highlighting issues related to the use of DHTs within drug development programs, recent FDA guidance and resources, and mechanisms for interacting with the Agency. He will highlight issues related to the development of DHTs as therapeutic devices, as well as regulatory guidance on the use of DHTs as outcome measures within clinical trials.

Celso Arango will review two academic clinical trials funded by the European Commission under the Innovative Medicines Initiative, highlighting the use of DHTs in these studies and how to optimize dialogues with regulators, patients, and researchers to implement DHTs in clinical trials.

The session chair will then moderate an interactive discussion on opportunities and challenges for implementing DHTs in clinical trials for psychiatric disorders and the levels of evidence to validate their context(s) of use. Discussants will include: the speakers; the panel of discussants from the FDA Center of Drug Evaluation, the FDA Center for Devices and Radiologic Health,

the FDA Digital Health Center of Excellence, and the EMA; and questions from ASCP attendees.

REGULATORY PERSPECTIVES ON THE USE OF DIGITAL HEALTH TECHNOLOGIES IN PSYCHIATRIC TREATMENT AND IN DRUG DEVELOPMENT

Michael Davis, US Food and Drug Administration

Abstract: Digital health technologies (DHTs) have been defined by their use of computing platforms, connectivity, software, and sensors for health care and related uses. DHTs may also be used to develop or study medical products. Examples of DHTs include sensors intended to track drug ingestion, software applications intended to deliver behavioral therapy, artificial intelligence algorithms intended to identify subpopulations in clinical trials, and wearable sensors for the measurement of clinical events.

Considering the recent marked increase in development of DHTs to deliver psychiatric treatments as well as for use in clinical trials, regulatory agencies are developing new frameworks and regulatory pathways for advancing and realizing the potential of digital health. Accordingly, the FDA Center for Devices and Radiological Health (CDRH) has granted marketing authorization for three Class II device classifications (novel device types): computerized behavioral therapy device for psychiatric disorders; digital therapy device for Attention Deficit Hyperactivity Disorder; and digital therapy device to reduce sleep disturbance for psychiatric conditions. CDRH has also launched the Digital Health Center of Excellence, which aims to align and coordinate digital health work across FDA.

The FDA Center for Drug Evaluation and Research (CDER) is developing guidance on the use of DHTs for remote data acquisition in clinical investigations, as well as guidance on the conduct of decentralized trials, which frequently use DHTs to engage and assess remote study participants. CDER has also recently launched the Innovative Science and Technology Approaches for New Drugs (ISTAND) pilot program to encourage development of drug development tools (DDTs) that may be out of scope for existing DDT qualification programs, and tools that leverage DHTs are highlighted as example submissions to the ISTAND program.

In this presentation, I will first provide an overview of DHTs, highlighting recent marketing authorizations as examples. Next, I will discuss issues related to the use of DHTs within drug development programs, focusing on potential benefits as well as challenges that may be encountered by sponsors. Finally, I will highlight useful guidance and FDA resources, as well as mechanisms for interacting with the Agency, both in the context of developing DHTs for use as therapeutic devices as well as for seeking regulatory guidance on the use of DHTs as outcome measures within clinical trials.

Learning Objectives:

1. Using case examples, attendees will learn about how different types of DHTs are regulated at FDA.
2. Attendees will learn about the potential benefits as well as challenges in using DHTs within drug development programs.
3. Attendees will learn about mechanisms for interacting with FDA regarding DHTs, focusing on their potential use as outcome measures within clinical trials.

Literature References:

1. Izmailova ES, Wagner JA, Ammour N, Amondikar N, Bell-Vlasov A, Berman S, Bloomfield D, Brady LS, Cai X, Calle RA. Remote digital monitoring for medical product development. Clinical and Translational Science. 2021;14:94-101.

DIGITAL HEALTH TECHNOLOGIES IN CNS CLINICAL TRIALS: THE RESEARCHER'S EXPERIENCE

Celso Arango, Institute of Psychiatry and Mental Health Hospital General Universitario Gregorio Marañón, IiSGM, School of Medicine Universidad Complutense de Madrid, CIBERSAM

Abstract: The use of digital health technologies (DHTs) in clinical trials has grown exponentially. Clinical trials for psychiatric disorders face many challenges, notably due to subjective diagnostic systems leading to heterogeneity in the definition of patient populations and the clinical measures used in trials, as well as a lack of biomarkers. Some of those challenges make DHTs very appealing for clinical trials in psychiatry. In this context, digital health technologies (DHTs), in combination with clinical observation and existing subjective tools, could enhance CNS drug research and development. DHTs allow remote measurement of patient data, such as specific behaviors (e.g., social isolation), aspects of psychopathology and cognition, physiological parameters, and motor skills, by means of sensor-based devices, mobile applications, or wearables. The promising use of DHTs in pharmacological and non-pharmacological trials could reduce subjectivity and retrospective memory bias, enrich patient populations, reduce heterogeneity, allow continuous, objective, remote measurement of highly variable outcomes, facilitate collection of real-world evidence, and facilitate decentralized trials (so relevant in the context of the COVID-19 pandemic).
The reality is that there is not yet a structured, unified process for development of DHTs, as there is for medicinal products. There is also no standard framework for clinical validation or consensus on how to design or conduct studies to validate DHTs. It is particularly important to consider the role of the DHT and also the construct it measures in the clinical context of the study population or in relation to the expected treatment effect.

In this talk, I will review two academic clinical trials funded by the European Commission under the Innovative Medicines Initiative (IMI) program: PRISM (Psychiatric Ratings using Intermediate Stratified Markers) and AIMS-2-TRIALS (Autism Innovative Medicine Studies - 2 - Trials). I will go over the interaction with regulators and practicalities involved in the use of DHTs in these two studies with different psychiatric populations (e.g., schizophrenia, Alzheimer's disease, autism spectrum disorder). I will cover topics such as how to optimize dialogue with regulators reactions of patients and researchers to sometimes unexpected challenges in the implementation DHTs, and various practicalities in actual clinical trials.

Learning Objectives:

1. Using real studies, attendees will learn potential uses of DHTs in clinical trials in psychiatry.
2. Attendees will learn from an academic researcher's experience in interacting with regulators (EMA) regarding the use of DHTs.
3. Attendees will learn about practical challenges in using DHTs in clinical trials in psychiatry.

Literature References:

1. Valentina Mantua, Celso Arango, Pavel Balabanov, Florence Butlen-Ducuing. Digital health technologies in clinical trials for central nervous system drugs: an EU regulatory perspective. Nat Rev Drug Discov. 2021 Feb;20(2):83-84.
2. Kas MJ, Penninx B, Sommer B, Serretti A, Arango C, Marston H A quantitative approach to neuropsychiatry: The why and the how. Neurosci Biobehav Rev. 2019 Feb;97:3-9.
3. Jongs N, Jagesar R, van Haren NEM, Penninx BWJH, Reus L, Visser PJ, van der Wee NJA, Koning IM, Arango C, Sommer IEC, Eijkemans MJC, Vorstman JA, Kas MJ. A framework for assessing neuropsychiatric phenotypes by using smartphone-based location data. Transl Psychiatry. 2020 Jul 1;10(1):211.

Federal Agency Updates Plenary

1:15 p.m. - 3:45 p.m.

FEDERAL AGENCY UPDATES PLENARY

Madhukar Trivedi, UT Southwestern Medical Center

Overall Abstract: The COVID-19 pandemic presented increases in psychiatric conditions, particularly substance use disorders. Despite the overwhelming circumstances, however, scientific research has provided advancements. The ASCP is proud to highlight several programs that have proved themselves leaders in addressing psychiatric challenges. This plenary will provide research highlights and Institute updates across fedearl agencies. Dr. Koroshetz will discuss the National Institute of Neurological Disorders and Stroke's efforts to develop non-addictive pain treatment and symptomatic therapy in brain disorders, as well as cognitive decline and dementia. Dr. Josh Gordon of the National Institute of Mental Health will present the Institute's current drug development efforts. Next, Dr. Koob of the National Institute on Alcohol Abuse and Alcoholism will address research and treatments necessary to understand the relevant relationships between alcohol addiction and human suffering caused by the COVID-19 pandemic. Finally, Dr. Volkow of the National Institute on Drug Abuse will conclude by providing updates on research targeting the United States' opioid crisis and the structural challenges facing those with substance abuse disorders.

UPDATE FROM NINDS

Walter Koroshetz, National Institute of Neurological Disorders and Stroke (NINDS)

Abstract: Three major programs to bring to the attention of ASCP: 1) NINDS leads the component of the Helping to End Addiction Long Term (HEAL) Initiative that focuses on the development and testing of non-addictive treatments for pain. 2) The BRAIN Initiative, which is co-led with NIMH is revolutionizing our understanding of information processing in neural networks. This work promises to elevate measures of network activity as targets for the development of symptomatic therapy in many brain disorders. 3) NINDS also has ambitious programs to understand how to understand cognitive decline and dementia due to vascular disease, synucleinopathy and fronto-temporal dementia.

Learning Objectives:

1. Understand the very specialized research opportunities in developing and testing pain treatments; neural circuit mapping, monitoring and modulation; and cognitive/behavioral disorders.

Literature References:

1. Hsu NS, Fang HY, David KK, Gnadt JW, Peng GCY, Talley M, Ward JM, Ngai J, Koroshetz WJ. 2020 The promise of the BRAIN initiative: NIH strategies for understanding neural circuit function. Current Opinion in Neurobiology 65: 162-166.

AN UPDATE ON DRUG DEVELOPMENT AT NIMH

Josh Gordon, National Institute of Mental Health

Abstract: Following on the substantial achievements of the past year, the NIMH continues to encourage and support drug development efforts across the spectrum of mental illness. Dr. Gordon will provide updates regarding these efforts, including support for both pre-clinical and clinical studies.

Learning Objectives:

1. Attendees will be informed regarding current drug-development efforts supported by NIMH.
2. Attendees will understand the experimental therapeutics approach and its position within the drug development continuum.

Literature References:

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

ALCOHOL USE DISORDER AS A COPING RESPONSE: HYPERKATIFEIA, DEATHS OF DESPAIR AND COVID-19

George Koob, National Institute of Health – NIAAA

Abstract: Alcohol use disorder (AUD) causes an enormous amount of human suffering, loss of productivity and cost to our medical care system and the nation's economy. Recent developments, including an increase in "deaths of despair" in the United States, increases in alcohol use by some individuals as a result of the 2019 coronavirus disease (COVID-19) pandemic, and limited availability of in-person treatment and recovery support, raise concerns about the use of alcohol and other drugs in an effort to cope with distress. A heuristic framework for studying addiction, characterized by a three-stage cycle—binge/intoxication, withdrawal/ negative affect, and preoccupation/anticipation—provides a starting point for exploring the intersection between alcohol addiction, deaths of despair, and social isolation that are caused by the COVID-19 pandemic. As such, advances in the science of alcohol use disorders can lead the way to better diagnosis, treatment and prevention of this significant public health problem. Using these heuristic frameworks, current challenges include addressing the intersection of pain, hyperkatifeia and negative reinforcement with deaths of despair impacts, and addressing the continuing challenges of women and alcohol, older adults and alcohol, pain and alcohol, and sleep and alcohol. In addition, using telehealth for prevention and treatment may help address continuing challenges in closing the treatment gap. Addressing such challenges will facilitate the implementation of evidence-based treatment for AUD in primary care, mental health, and other health care settings.

Learning Objectives:

1. To understand the interface and impact of AUD in the U.S with the effects of the Covid-19 pandemic and deaths of despair, and the challenges for treatment.

Literature References:

1. U.S. Department of Health and Human Services (HHS), Office of the Surgeon General, Facing Addiction in America: The Surgeon General's Report on Alcohol, Drugs, and Health. Washington, DC: HHS, November 2016.
2. 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.

AMERICA'S OPIOID CRISIS: CHALLENGES AND SCIENCE-BASED SOLUTIONS

Nora Volkow, National Institute on Drug Abuse

Abstract: The misuse of and addiction to opioids—including prescription pain relievers, heroin, and synthetic opioids such as fentanyl—has resulted in a national crisis of overdose deaths that we have not been able to control. In parallel, an alarming resurgence in stimulant use--including cocaine and methamphetamine—is further contributing to the rise in overdose fatalities. This crisis is now exacerbated by the COVID-19 pandemic which has resulted in increased drug use and relapse of those in treatment and highlights the urgency to characterize the unique social and structural challenges faced by those with substance use disorders and to develop strategies to overcome them. This presentation will highlight such challenges as the increased use of fentanyl by itself or in combination with other opioids or stimulant drugs like cocaine and methamphetamine. It will also focus on how NIH researchers are using scientific advances to address the opioid crisis amidst the COVID pandemic, which includes the development of new medications and formulations to help treat opioid use disorders and overdoses; prevention strategies to mitigate an individual's vulnerability to addiction; and implementation science to guide optimal deployment of therapeutic interventions including the use of telehealth in diverse settings (healthcare, justice setting, rural communities).

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

1. Describe the current state of the opioid crisis in the U.S.
2. Appreciate the added social challenges facing those with substance use disorders during the COVID-19 pandemic.
3. Better understand some of the unique structural challenges facing those with substance use disorders during the COVID-19 pandemic.

Literature References:

1. Volkow ND. Collision of the COVID-19 and Addiction Epidemics. Ann Intern Med 2020 Jul 7;173(1):61-62. doi: 10.7326/M20-1212. Epub 2020 Apr 2.
2. Wang QQ, Kaelber DC, Xu R, Volkow ND. COVID-19 risk and outcomes in patients with substance use disorders: Analyses from electronic health records in the United States.
3. Mol Psychiatry 2020 Sep 14: :1-10. doi: 10.1038/s41380-020-00880-7. Online ahead of print.

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

Holly Ramsawh, Patient-Centered Outcomes Research Institute

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

Learning Objectives:

1. To familiarize the audience with comparative clinical effectiveness research and current mental/behavioral health funding opportunities.

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

Panel Sessions

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

*THE PURSUIT OF CLINICAL TRANSLATION IN MENTAL HEALTH: INNOVATIVE QUANTITATIVE METHODS FOR WEARABLE, GENETIC, AND NEUROIMAGING DATA

Michelle Patriquin, Baylor College of Medicine

Overall Abstract: Although there is continued momentum towards a more integrative, psychobiological framework for clinical research in mental health (e.g., via NIMH RDoC), the clinical utility of the DSM-5 (as well as ICD-11) has helped to maintain its position as the dominating diagnostic system that guides clinical practice. The subjective-based (e.g., self-report, observation) characterization of mental health disorders via the DSM-5 or ICD-11 leads to nosological and biological conflation with diagnoses demonstrating high comorbidity (e.g., anxiety and depression). Novel therapeutic developments have been stymied by stagnant or bottlenecked processes due to the focus on symptom-based (subjective report) metrics rather than focus on psychobiological targets (e.g., pharmaceutical companies pivoting away from mental health due to clinical trial failures). As such, this diverse and multidisciplinary panel will discuss innovative clinical translation methods and findings, as well as tangible clinical implications, of objective data from wearables, genetic, and neuroimaging studies. In particular, Dr. Patriquin will discuss her recent work regarding utilizing wearables data – collected in real-time – on an inpatient psychiatric unit to predict suicide risk via time-lagged Bayesian modeling and provide an alternative method to assess current patient safety (i.e., is a patient alive; is a patient not harming themselves). Dr. Meyers will discuss her use of polygenic risk scores derived from large-scale GWAS of neuropsychiatric traits (e.g., alcohol use disorder, cannabis use disorder, PTSD) with neurocognitive and clinical outcomes (e.g., substance use disorders, PTSD, impulsivity). Regarding neuroimaging, Dr. Lauharatanahirun will discuss her research where she builds intelligent systems (through algorithm development) that leverage neural and behavioral determinants of risk-taking as targets for future

personalized clinical interventions. Deriving accurate clinical meaning from these data requires accurate and innovative approaches to mathematically connecting these data. Thus, the panel will also include Dr. Lee who will review his empirical work that uses novel statistical approaches (e.g., latent growth mixture modeling; big data [data mining] for forecasting treatment outcomes with biological data) for effective clinical translation. The integration of remote, passively-acquired objective data with neuroimaging, genetic, and clinical data is critical for releasing the bottleneck and stagnation of mental health treatment development. The overarching goal of this panel is to highlight creative new ways these data can be meaningfully linked to improve and personalize our mental health care.

Learning Objectives:

1. Develop an understanding of new quantitate methods to link biological and clinical mental health data.
2. Understand the clinical utility and actions that can be accurately triggered by biological data.

WEARABLES: A LIFESAVING SOLUTION TO AN UNSOLVED PROBLEM? CLINICAL TRANSLATION OF WEARABLES DATA TO IMPROVE INPATIENT PSYCHIATRY SAFETY

Michelle Patriquin, Baylor College of Medicine

Individual Abstract: The initial 90-days post-discharge from an inpatient psychiatric hospital is the highest risk period for suicide (Chung et al., 2017). We previously theorized that inpatient safety precautions might be contributing to this high-risk period and generate an effect, the Safety-Sleep-Suicide Spiral (Gazor et al., 2020). We have hypothesized that since Q-15 checks and 1:1 observation frequently disturb or interrupt sleep, and we have empirically demonstrated that sustained sleep disturbances are associated with increased suicidal ideation for patients admitted inpatient (Hartwig et al., 2019), this system maybe creating a positive feedback loop that further contributes to suicidal ideation and post-discharge being a high-risk period for suicide. Given the critical role that sleep plays in the mitigation of suicide risk, reducing the nighttime sleep disturbances caused by safety precautions, using alternative methods could interrupt the compounding effect of the Safety-Sleep-Suicide Spiral. In this presentation, I will discuss one highly promising alternative method: continuous monitoring via wearable technology. Data will be presented from an ongoing study (N = 11 at present; 5 = male, 4 = female; Mage = 24.09) examining objective and subjective sleep measures and their relationship with suicide risk (measured via the Suicide Behaviors Questionnaire-Revised, SBQ-R) in adults with anxiety and depression. Objective sleep is measured via actigraphy (ActiGraph wGT3X-BT) continuously for a patient's entire length of stay (4-6 weeks) in an inpatient psychiatric hospital. Subjective sleep is measured through weekly self-report of nighttime sleep disturbance on the Pittsburgh Sleep Quality Index (PSQI) and daytime sleepiness on the Epworth Sleepiness Scale (ESS). Initial results demonstrate that increased suicide risk on the SBQ-R is associated with shorter objective total sleep time (TST) measured via the actigraph. Results will be expanded to include using time-lagged Bayesian modeling to quantify the compounding effect of Q15 checks on increased sleep problems and suicide risk hypothesized by the Safety-Sleep-Suicide Spiral. I will discuss the promise of translating wearables data in order to improve inpatient outcomes monitoring and provide a less invasive real-time safety assessment. Prior to this clinical translation, significant research is needed to improve the predictive power of wearable-based metrics as they relate to suicide risk and safety, as well as the development of clinically actionable visualization of these data. These challenges will also be discussed. Considering that current inpatient techniques are resource

intensive and often disturb sleep, however, wearable-based technology could revolutionize the way we ensure the safety and generate the best outcomes for our patients.

Learning Objectives:

1. Develop an understanding of how wearables data can be used to improve inpatient psychiatry safety monitoring.
2. Learn a new method for effective clinical translation of wearables data to quantify the compounding effect of the Safety-Sleep-Suicide Spiral in inpatient.

Literature References:

1. Hartwig, E.M., Rufino, K.A., Palmer, C.A., Shepard, C., Alfano, C.A., Schanzer, B., Mathew, S.J., & Patriquin, M.A. (2019). Trajectories of self-reported sleep disturbance across inpatient psychiatric treatment predicts clinical outcome in comorbid major depressive disorder and generalized anxiety disorder. Journal of Affective Disorders, 251, 248-255. doi: 10.1016/j.jad.2019.03.069
2. Gazor, A., Mathew, S.J., & Patriquin, M.A. (2020). Q-15 checks and 1:1 observations: Are we exacerbating the problem we are trying to prevent? Journal of Affective Disorders, 263, 552. doi: 10.1016/j.jad.2019.11.018

NEUROECONOMICS OF THE RISKY BRAIN: REAL WORLD RISKY BEHAVIOR AND CLINICAL APPLICATION

Nina Lauharatanahirun, Pennsylvania State University

Individual Abstract: Adolescence is a transformative period of development involving significant neurobiological changes and health risk behaviors (e.g., substance use, reckless driving, risky sexual behavior) that negatively impact health. Given the deleterious consequences of risk-taking during adolescence, effective prevention and intervention strategies must be developed in order to help adolescents make optimal choices that in turn support their health and well-being. In this presentation, Dr. Lauharatanahirun will present work that leverages neuroeconomic models and diverse brain imaging methodologies (e.g., functional magnetic resonance imaging, fMRI; electroencephalography, EEG) to better understand the neurocognitive mechanisms underlying adolescent risky decision making both inside and outside of the laboratory. First, Dr. Lauharatanahirun will present data from a laboratory study (N=159) where she uses neuroeconomic models in conjunction with fMRI to map the brain regions involved in the processing of risk in the environment. She will show that adolescents' neural encoding of economic risk can provide a potential explanation for why some adolescents are more likely to make maladaptive risky choices. Next, she will present work that reveals how these computational lab approaches can be utilized to predict risky behavior in the real world. Results will be presented from a real world driving study where dyads (N=22) drove in naturalistic conditions along Interstate-95 in a fully instrumented vehicle that recorded time-synchronized, multi-sensor data including mobile EEG data. Although EEG lacks the spatial resolution of fMRI, it provides an ambulatory method for assessing neural activity in real world contexts. She will show that neuroeconomic models developed in the lab are able to predict real-world risky driving, and present potential neural mechanisms supporting this behavior. Finally, Dr. Lauharatanahirun will discuss how neuroeconomic models can inform computational architectures underlying artificial intelligence that interact with human decision-makers within mobile platforms. The ultimate aim of this research line is to develop mobile health interventions that can be adapted in real-time and in response to individual neurobehavioral attributes.

Learning Objectives:

1. Understand the advantages of using functional neuroimaging methods for illuminating potential neural mechanisms of risky decision making.
2. Understand how neural and behavioral determinants in the lab can be used in a new computational architecture to support mobile health interventions.

Literature References:

1. Lauharatanahirun, N., Maciejewski, D., Holmes, C., Deater-Deckard, K., Kim-Spoon, J., & King-Casas, B. (2018). Neural correlates of risk processing among adolescents: Influences of parental monitoring and household chaos. Child Development, 89(3), 784-796.
2. Kim-Spoon, J., Lauharatanahirun, N., Peviani, K., Brieant, A., Deater-Deckard, K., Bickel, W. K., & King-Casas, B. (2019). Longitudinal pathways linking family risk, neural risk processing, delay discounting, and adolescent substance use. Journal of Child Psychology and Psychiatry, 60(6), 655-664.

PATHWAYS OF RISK FOR SUBSTANCE USE DISORDERS AND RELATED PSYCHOPATHOLOGY: TRAUMA, POLYGENIC RISK, AND NEURAL CONNECTIVITY

Jacquelyn Meyers, State University of New York Downstate Medical Center

Individual Abstract: Substance use disorders (SUD; e.g., alcohol, cannabis, opioid) and comorbid psychiatric disorders are known to be influenced by social-environmental (e.g., trauma exposure), polygenic, and neurodevelopmental risk factors. One potential pathway by which trauma exposure may increase risk for psychopathology is via effects on developmental trajectories of brain functioning, which in turn may increase risk for SUD and related psychiatric conditions. Furthermore, trauma related atypical neural development may be exacerbated by genetic risk. However, no prior studies have examined if polygenic risk indexing risk for SUD and/or related psychiatric disorders moderates the impact of trauma on brain functioning and resulting risk for psychopathology. Further, this has not been done in a longitudinal paradigm over adolescence and young adulthood, an important period for brain development and onset of mental health problems. This gap in the literature calls for use of deeply phenotyped, genetically informative, longitudinal studies assessing neurodevelopmental trajectories, to further our understanding of how trauma exposure, polygenic risk, and their interplay increase risk for SUD and related psychiatric disorders. In this presentation, Dr. Meyers will present data drawn from the Collaborative Study on the Genetics of Alcoholism's prospective study (51% female, ages 12-22 at baseline), a longitudinal, developmental study of adolescent and young adult offspring of families densely affected with SUD who have been followed biennially since 2004. Data is currently available on 3,911 participants (57.8% trauma exposed) with 14,495 total assessments, including repeated measures of clinical interview, genome-wide association data, and brain functional activity data. In this presentation, she will present data on the impact of trauma on trajectories of neural connectivity with distal outcomes of young adult SUD and related disorders (e.g., PTSD). Next, she will demonstrate how we can leverage large-scale GWAS of SUD to examine the interactive influences of polygenic risk scores with trauma on neural trajectories and risk for SUD and related problems. Preliminary findings indicate differential trajectories of neural connectivity are observed among those exposed to trauma, which in turn are associated with increased risk for young adult SUD and PTSD. Further, polygenic risk for SUD increases the association of trauma exposure with neural connectivity, SUD and PTSD. Effects were particularly robust among females and those with a family history of SUD. Together with our previous work, these data suggest that individuals exposed to trauma may exhibit dysfunction

and/or delays in frontal lobe development, involving synaptic pruning and/or cortical maturation. These same problems in brain development may be associated with increased risk for SUD and PTSD. While these preliminary results support the hypothesis that changes in neurocognitive development related to trauma exposure may increase risk for SUD and related psychopathology in young adulthood, much remains to be further understood.

Learning Objectives:

1. To gain a global understanding of potential etiological pathways to substance use disorders, involving trauma exposure, polygenic, and neurodevelopmental risk factors.
2. To evaluate the hypothesis that changes in neurocognitive development related to trauma exposure, along with genomic risk factors, may increase risk for substance use disorders and related psychopathology.

Literature References:

1. Meyers JL, V. McCutcheon, A. Pandey, C. Kamarajan, S. Subbie, D. Chorlian, J.E. Salvatore, L. Almasy, A. Anokhin, L. Bauer, A. Bender, D.M. Dick, H.J. Edenberg, V. Hesselbrock, J. Kramer, S. Kuperman, A. Agrawal, KK. Bucholz and B. Porjesz. Early Sexual Trauma Exposure and Neural Response Inhibition in Adolescence and Young Adults: Trajectories of Frontal Theta Oscillations during a Go/NoGo Task. J Am Acad Child Adolesc Psychiatry 2019 Feb;58 (2):242-255. PMID: 20738551.
2. Meyers JL, Chorlian DB, Johnson EC, Pandey AK, Kamarajan C, Salvatore JE, Aliev F, Subbie-Saenz de Viteri S, Zhang J, Chao M, Kapoor M, Hesselbrock V, Kramer J, Kuperman S, Nurnberger J, Tischfield J, Goate A, Foroud T, Dick DM, Edenberg HJ, Agrawal A, Porjesz B. Association of Polygenic Liability for Al-cohol Dependence and EEG Connectivity in Adolescence and Young Adulthood. Brain Sciences. 2019 Oct 17;9(10). PMID: 31627376.

A SYNTHESIS OF VARIABLE-CENTERED APPROACH AND PERSON-CENTERED APPROACH FOR AN EFFECTIVE FORECASTING OF HEALTH OUTCOMES AND CLINICAL TRANSLATION

Jaehoon Lee, Texas Tech University

Individual Abstract: Much of the extant literature proceeds from what could be called a "variable-centered approach," in that the findings represent an 'averaged' estimate of the relationships among variables observed in a sample of the target population. As an example, a study may demonstrate that "on average" patients enhanced their mental health with fewer depressive symptoms over the course of psychiatric hospitalization. Obviously, such finding is much valuable in its own right, but this study ignores the possibility that the patients may come from different subpopulations where biological basis and susceptibility to the treatment differ considerably. Alternatively, a "person-centered approach" aims to identify subgroups within the sample that share a common biological, behavioral, and/or social profile. This approach views individuals in a more holistic fashion and provides an opportunity to address complex interactions among variables that would be difficult to detect by using traditional variable-centered analytic techniques. The presenter will demonstrate how these two different approaches are merged into an analysis of health outcomes, promoting the strengths of each approach in a clinical study. In the first stage, growth mixture modeling (GMM) is conducted to classify patients into a small number of classes, each manifesting a unique pattern of change in mental illness during hospital stay. The shape of change (linear, quadratic, or cubic, etc.) and the optimal number of change trajectories (classes) are determined by comparing competing models with regards to goodness-of-fit and classification accuracy (e.g., entropy,

Bayesian Information Criterion, likelihood-ratio tests). This person-centered analysis informs the subsequent variable-centered analysis about the existence of distinct classes of patients who share similar longitudinal trajectories of mental illness over the course of inpatient treatment. In the second stage, machine learning—deep neural networks (DNN)—is utilized to forecast health outcomes of new incoming patients admitted to the hospital. The forecasting proceeds as follows. First, incoming patients are classified into one of identified trajectories of mental illness based on their demographic information (only) available at admission. Second, the classification of patients is updated every time when additional medical/medication information (e.g., prescription, dosage) and behavior observations (e.g., depression, anxiety, suicidal ideation and attempts) become available. The performance of DNN (i.e., classification accuracy) is verified through k-fold cross-validation, where (a) the original sample of new patients is randomly partitioned into k equal-sized subsamples; (b) k – 1 subsamples are used to train the machine and the remaining 1 subsample is used to test the machine; (c) this process is repeated k times; and (d) k results are combined together. This validation process reduces the risk for overfitting and selection bias and gives an insight on how the DNN will generalize to a new cohort of patients. This new way of synthesizing two different approaches is a powerful tool for predicting health outcomes in an early stage of the treatment and thus useful for customizing services to individual patients and shortening hospital stay for psychiatric care. This presenter will also offer methodological guidelines and suggestions for applied researchers in clinical settings.

Learning Objectives:

1. Learn how to merge a person-centered approach and a variable-centered approach into an analysis of health outcomes, promoting the strengths of each approach in a clinical study.
2. Learn the potentials of this new analysis for predicting health outcomes in an early stage of the treatment and thus useful for customizing services to individual patients and shortening hospital stay for psychiatric care.

Literature References:

1. Vandenberg, R. J., & Stanley, L. J. (2009). Statistical and methodological challenges for commitment researchers: Issues of invariance, change across time, and profile differences. In H.J. Klein, T.E. Becker, & J.P. Meyer (Eds.), Commitment in organizations: Accumulated wisdom and new directions (pp. 383–416). Florence, KY: Routledge/Taylor and Francis Group.
2. Nylund, K. L., Asparouhov, T., & Muthén, B. O. (2007). Deciding on the number of classes in latent class analysis and growth mixture modeling: A Monte Carlo simulation study. Structural Equation Modeling, 14, 535-569

FAILED VERSUS NEGATIVE CLINICAL TRIALS: DIFFERENTIATING ABSENCE OF EVIDENCE FROM EVIDENCE OF ABSENCE

Joseph Goldberg, Icahn School of Medicine at Mount Sinai

Overall Abstract: When an experimental treatment is found in a clinical trial to not differ significantly from placebo, or from an active comparator, one must interpret whether the experimental drug truly lacks efficacy (considered a negative trial, and usually discouraging expenditure of resources for further investigation) or whether non-separation from placebo (or the active comparator) occurs for reasons other than inherent lack of efficacy in the drug of interest (termed a failed trial). Failed trials commonly spur thinking about unexpectedly high placebo response rates. Clinical trialists often rely on active comparator arms to detect inflated

placebo response rates, strive to minimize such events via specifying enrollment criteria and devising study designs aimed to deflate placebo responsivity. Predictors of placebo responsiveness can vary across disorders as well as by other features of study design. However, many factors in addition to placebo responsivity and sample inclusion/exclusion criteria contribute to the failure to detect a "true" drug-placebo difference. These include characteristics such as excessively long study durations, underpowering (and expectations of superiority versus noninferiority), sample enrichment, attrition, choice (and non-redundancy) of symptom severity measures for enrollment versus primary outcome, and study site experience, among others. This symposium will examine distinctions between negative versus failed clinical trials with examples across several specific major psychiatric conditions, with a focus on (a) recognizing the likelihood that an observed non-difference is real or spurious, (b) appreciating methodological contributors that can obscure detection of true drug-placebo differences, and (c) "misapplications" of an investigational drug for a particular disease state or phenomenon (e.g., negative versus positive symptoms in schizophrenia; mania versus depression in bipolar disorder; or differential acute versus prophylactic efficacy in any recurrent condition. Implications will be discussed for optimal study designs, as well as how best to draw valid inferences from a failed versus negative trial with regard to ongoing development (or cessation) of an otherwise promising investigational compound.

Learning Objectives:

1. Participants will understand and recognize clinical and methodological factors associated with failed versus negative pharmacotherapy trials in major depression, schizophrenia, and bipolar disorder.
2. Attendees will be able to identify when a failed clinical trial likely has eclipsed a true drug effect, and whether further investigation is warranted through future studies using modified designs.

CRITICAL REVIEW OF EVIDENCE AMONG MODERN REGULATORY ANTIDEPRESSANT CLINICAL TRIALS

Arifulla Khan, Northwest Clinical Research Center

Individual Abstract: The Kefauver-Harris Act of 1963 signed by President Kennedy in 1963 heralded a new era for pharmacotherapy. This act simply gave all the authority about all human research to the US FDA and had a built-in requirement to show efficacy for all drugs to be approved for sale in the US, besides the primary focus of safety. Neither the MAO Inhibitors nor the tricyclic antidepressants had to undergo the regulatory testing that was fully developed by the FDA about 40 years ago.

On the other hand, all the currently commonly used antidepressants such as SSRIs, SNRIs, NMDA antagonists and various classes of antidepressants including bupropion and other agents have had to meet the stringent and newly developed criteria to show efficacy. It was obvious 20 years ago, that even among the newly approved and marketed antidepressants, although widely popular, performed poorly in the regulatory trials as more than 50% of these trials did not achieve statistically significantly superiority over placebo.

Among the more recently antidepressant clinical trials for the seven monotherapy antidepressants (trazodone ER, desvenlafaxine, duloxetine, escitalopram, vilazodone, levomilnacipran, vortioxetine) the success rate is about 68%, with the results of many trials being either 'failed' or 'negative and well below the powered/planned 80% expectancy of success.

In this context, we will review the data from 106 antidepressant clinical trials that include 135 treatment arms for 16 approved antidepressants available via the Freedom of Information Act from US FDA archives. We will evaluate the factors that seem to impact trial outcomes including understanding of the 'positive, 'failed' and 'negative' among these trials.

Learning Objectives:

1. Understand the differences between regulatory antidepressant trials compared to non-regulatory trials.
2. Appreciate the potential depression between various classes of antidepressants.

Literature References:

1. Khan. A, Mar. K, Faucett. JF, Schilling. S, Brown. WA. Has the rising placebo response impacted antidepressant clinical trial outcome? Data from the US Food and Drug Administration 1987-2013. World Psychiatry 2017;16:181–192
2. Khan. A, Mar, K, Brown WA. The conundrum of depression clinical trial: one size does not fit all. Int Clin Psychopharmacology. 33: 239-248, 2018

THE PERILS OF PLACEBO: DEVELOPING MEDICATIONS FOR PERSONS WITH SCHIZOPHRENIA

Leslie Citrome, New York Medical College

Individual Abstract: It is often remarked on how promising medication interventions for persons with schizophrenia can perform so well in Phase 2 clinical trials and yet fail to demonstrate efficacy when compared with placebo in larger Phase 3 studies. In the past several years this has been observed with novel compounds such as pomaglumetad methionil, bitopertin, and encenicline. Even approved second-generation antipsychotics have not been immune to this phenomenon, and subject to unexpected results. For example, asenapine was approved for the treatment of acute schizophrenia on the basis of 2 out of 4 placebo-controlled trials, where one of the studies considered 'positive' for asenapine was actually a Phase 2 study where the active control, risperidone, failed to demonstrate efficacy despite a therapeutic dose. Iloperidone was also approved for schizophrenia based on 2 out of 4 clinical trials, with disagreement between the US Food and Drug Administration and the manufacturer as to which studies were considered 'positive' for iloperidone. Attempts have been made to determine what is standing in the way of successful clinical trials in persons with schizophrenia. Examples of obstacles include the heterogeneity of the study population, enrollment of patients not meeting the spirit of the protocol, quality issues with assessments, and insufficient attention to differentiating between a "therapeutic alliance" when treating patients vs. a "research alliance" when enrolling and assessing subjects in a research protocol. A recent meta-regression analysis examined drug-response and placebo-response in terms of effect size. and included 167 trials (28,102 participants). Publication year, the number of participants and sites, mean dose, minimum severity threshold as an inclusion criterion, chronicity, industry sponsorship, type of rating scale, diagnostic criteria, and number of medications had a different impact on drug and placebo response. However, baseline severity, duration of wash-out, study duration, and study region affected drug and placebo response in a similar way without a net effect on effect sizes. These and other factors will need to be considered when designing and executing clinical trials in persons with schizophrenia.

Learning Objectives:

1. Be aware of the challenges in studying persons with schizophrenia in placebo-controlled trials.

2. Understand some of the ways to increase the probability of differentiating study drug from placebo in clinical trials in persons with schizophrenia.

Literature References:

1. Leucht S, Chaimani A, Mavridis D, Leucht C, Huhn M, Helfer B, Samara M, Cipriani A, Geddes JR, Davis JM. Disconnection of drug-response and placebo-response in acute-phase antipsychotic drug trials on schizophrenia? Meta-regression analysis. Neuropsychopharmacology. 2019 Oct;44(11):1955-1966.
2. Gopalakrishnan M, Zhu H, Farchione TR, Mathis M, Mehta M, Uppoor R, Younis I. The Trend of Increasing Placebo Response and Decreasing Treatment Effect in Schizophrenia Trials Continues: An Update From the US Food and Drug Administration. J Clin Psychiatry. 2020 Mar 3;81(2):19r12960.

REASONS FOR CLINICAL TRIAL FAILURE IN BIPOLAR DISORDER

Joseph Goldberg, Icahn School of Medicine at Mount Sinai

Individual Abstract: In 2019, the failure of two randomized industry trials with brexpiprazole for acute mania serves as a reminder that unexpectedly high placebo response rates -- even for a condition as traditionally placebo-unresponsive as hospitalized mania – can obscure accurate signal detection. For patients across all phases of bipolar disorder, an examination of unsuccessful clinical trials helps shed light on reasons for failed versus negative outcomes. Important examples include the following: (a) failure to assure acute responsivity before randomization to relapse prevention - as seen in a large, multi-site failed trial of maintenance efficacy for divalproex (where failure to enrich the study group for divalproex responsivity in acute mania before randomization likely contributed to lack of a significant difference from placebo (and where ~40% of placebo recipients remained episode-free for up to year)); (b) failure of acute enrichment to detect relapses of either polarity – because the polarity of an index episode strongly predicts the polarity of relapse, maintenance trials that enroll subjects only during acute mania tend to enrich for low likelihood of a depressive relapse or recurrence, with consequent failure of separation from placebo, as evident in maintenance studies of both oral and long-acting injectable aripiprazole; (c) unbalanced randomization – failed trials can arise when randomization does not sufficiently account for important moderators of treatment outcome, such as manic- versus depressive- polarity proneness, episode number, or past year rapid cycling; (d) excessive trial length – in bipolar disorder, placebo responsivity has been shown to increase by about 15% for each additional study week, a factor that likely accounted for obliteration of initially-observed drug-placebo differences in two randomized trials of aripiprazole for acute bipolar depression; (d) rebound effects after drug discontinuation – an increased risk for rapid relapse after abrupt cessation of lithium or antidepressants could inflate relapse risk in placebo arms, a consideration that has been noted in some randomized trials of lithium prophylaxis failure. Other factors that may contribute to failed trials in bipolar depression include poor choice of primary outcome ratings scales, as suggested by use of the Hamilton rather than Montgomery-Asberg Rating Scales for depression in an initial large industry trial of lamotrigine for acute bipolar depression. Scales that fail to capture reverse neurovegetative features also may lack sensitivity to detect changes in atypical presentations of bipolar depression. Finally, and arguably most challenging of all, involves the need for study designs that adequately account for differences due to treatment versus the natural course of illness, as exemplified in the failed STEP-BD randomized trials of antidepressants (bupropion or paroxetine) versus placebo augmentation of antimanic drugs in bipolar depression.

Learning Objectives:

1. To recognize differences between, and examples of, failed versus randomized trials across all phases of bipolar disorder.
2. To describe the impact on detecting drug-placebo differences when clinical trials utilize add-on therapy designs, fail to enrich samples for acute responsivity before entering maintenance therapy phases, ignore discontinuation effects of pre-enrollment medications, and fail to balance randomization for key moderators of outcome such as baseline severity, rapid cycling, predominant polarity proneness, and degree of treatment resistance.

Literature References:

1. 1.McElroy SL, Bowden CL, Collins MA, et al. Relationship of open acute mania treatment to blinded maintenance outcome in bipolar I disorder. J Affect Disord 2008; 107(1-3): 127-133
2. Mahableshwarkar AR, Calabrese JR, Macek TA, et al. Efficacy and safety of sublingual ramelteon as adjunctive therapy in the maintenance treatment of bipolar I disorder in adults: a phase 3, randomized controlled trial. J Affect Disord 2017; 221: 275-282

***ASCP/AFSP**

Madhukar Trivedi, UT Southwestern Medical Center

Overall Abstract: The ever-increasing suicide-related mortality rates highlight the urgency to develop effective treatments, especially among adolescents and young adults. Delayed development of novel therapeutics has been a result of limited understanding of the mechanisms of increased suicide risk. This panel led by Drs. Trivedi and Friedman will present novel research currently bridging the gap in our knowledge of the intricacies of suicidality. First, Dr. Christianne Esposito-Smythers will present the necessary considerations in clinical trials research with adolescents and their families. Next, Dr. Barbara Stanley will address recent developments in intervention research. Finally, Dr. Louisa Sylvia will present the importance of widening the efforts of mood disorder research to include those who experience suicidal thoughts and the intricacies of managing suicidality in online studies.

Learning Objectives:

1. To understand the nuances in suicide research, particularly regarding youth, mood disorders, and virtual studies.
2. Discuss the strengths of recent research projects and plan future endeavors to identify treatments.

BEST PRACTICES FOR INCLUDING ADOLESCENTS WITH SUICIDAL BEHAVIOR IN CLINICAL RESEARCH

Christianne Esposito-Smythers, George Mason University

Individual Abstract: Adolescents who report suicidal thoughts and behavior are commonly excluded from clinical research. Yet, there are a number of best practices that can be employed to safely retain these youth in research studies. This presentation will provide an overview of these practices with a particular focus on including youth with suicidal thoughts and behavior and their families in clinical trials research. The primary focus will include a review of ethical

and safety practices, such as unique informed consent and assent considerations, risk monitoring and management protocols, research clinical competencies, and management of legal risk in the context of research. Unique design considerations as well as lessons learned from conducting clinical trials research with this population will also be discussed. This presentation will conclude with a discussion of reasons to include youth at risk for suicidal behavior and their families in clinical research studies.

Learning Objectives:

1. To obtain an understanding of best practices for ethically and safety retaining adolescents with suicidal ideation and behavior in clinical research.
2. To obtain knowledge about design considerations unique to clinical trials research with adolescents with suicidal ideation and behavior and their families.

Literature References:

1. Bai S, Babeva KN, Kim MI, et al: Future directions for optimizing clinical science & safety: Ecological momentary assessments in suicide/self-harm research. J Clin Child Adolesc Psyc 2021; 50(1):141–153
2. Fisher CB, Pearson JL, Kim S, et al: Ethical issues in including suicidal individuals in clinical research. IRB: Ethics Human Res 2002; 24(5): 9-14
3. King CA, Kramer, AC: Intervention research with youths at elevated risk for suicide: Meeting the ethical and regulatory challenges of informed consent and assent. Suicide Life Threat Behav 2008; 38(5):486–497
4. Nock, MK, Kleiman, EM, Abraham M, et al: Consensus statement on ethical & safety practices for conducting digital monitoring studies with people at risk of suicide and related behaviors. Psych Res Clin Prac 2020; xx:1–10
5. Pearson JL, Stanley B, King CA, et al: Intervention research with persons at high risk for suicidality: Safety and ethical considerations. J Clin Psychiatry 2001; 62(suppl 25):17–26

CONSIDERATIONS FOR INCLUDING SUICIDAL INDIVIDUALS IN CLINICAL TRIALS

Barbara Stanley, Columbia University

Individual Abstract: Suicidal individuals comprise a significant proportion of those who experience major depression, bipolar disorder, schizophrenia and borderline personality disorder. In fact, suicidality are diagnostic criteria for depression and borderline personality disorder. Yet pharmacotherapy and psychosocial intervention trials frequently exclude suicidal participants leading to significant problems in generalizability of findings and increased likelihood that unexpected adverse events may occur after approval of a medication or dissemination of a psychosocial intervention. This presentation will provide a rationale for inclusion of suicidal individuals in trials, describe at what stage of testing it is appropriate and the ways in which "suicidal" participant can be defined. Furthermore, we will discuss methodological and ethical considerations when the targeted outcome is prevention of suicidal behavior or suicidal ideation vs. when the outcomes are disorder-specific, e.g. reduction in depression symptoms for Major Depression.

Learning Objectives:

1. To describe strategies for including suicidal individuals in clinical trials.
2. To discuss considerations for specific inclusion, exclusion and removal decisions for suicidal trial participants.

Literature References:

1. Pearson JL, Stanley B, King CA, Fisher CB. Intervention research with persons at high risk for suicidality: safety and ethical considerations.J Clin Psychiatry. 2001;62 Suppl 25:17-26.
2. Oquendo MA, Stanley B, Ellis SP, Mann JJ. Protection of human subjects in intervention research for suicidal behavior.Am J Psychiatry. 2004 Sep;161(9):1558-63. doi: 10.1176/appi.ajp.161.9.1558

INCLUDING AND MANAGING INDIVIDUALS AT-RISK FOR SUICIDAL IDEATION AND BEHAVIORS IN ONLINE STUDIES OF MOOD DISORDER

Louisa Sylvia, Massachusetts General Hospital

Individual Abstract: Approximately one in every two individuals with a mood disorder will experience suicidal ideation at some point in their life (Asnis et al., 1993) with 12-month prevalence rates ranging from 14.1-20.1% (Han et al., 2015; Wiebenga etal., 2021). Moreover, the incidence of suicidal behavior is about 20- to 40-fold higher when individuals are depressed compared to when they are euthymic (Isometsa, 2014) highlighting that the risk is very state-dependent (Rihmer, 2007).

Despite the heightened risk of death by suicide in mood disorders, persons with suicidality are underrepresented in clinical trials. Iltis et al (2020) examined exclusion criteria in 28 antidepressant efficacy trials from 2000 through 2013 and found that 24/28 trials excluded individuals with suicidality, while four did not mention suicidality at all. This practice creates uncertainty about the safety and efficacy of treatments for a crucial segment of the depressed population. In addition, excluding individuals with suicidal ideation at baseline from research studies does not ensure that participants will not experience suicidal ideation over the study duration and can seriously affect the generalizability of any findings to individuals with mood disorders. We conducted a randomized study to compare whether online, asynchronous cognitive behavioral therapy (CBT) or online asynchronous mindfulness-based cognitive therapy (MBCT) (both adjunctive to activity monitors) increase daily physical activity (relative to activity monitors alone) in individuals with a history of depression and at-risk for cardiovascular disease. Given the risk of suicidal ideation over the duration of the 6-month study, we consulted with stakeholders (e.g., individuals with mood disorders, clinicians, researchers, advocacy group members) to develop procedures to monitor and manage suicidality remotely (as all study procedures were conducted online without any contact with study staff). We found that 46.4% (N=235) among all 506 consented participants reported a history of suicidal ideation (i.e., endorsed the question “During the worst period in your life of at least two weeks when you felt depressed or uninterested, did you repeatedly consider hurting yourself, feel suicidal, or wish you were dead?”). We also found at study entry that 6.5% (N=33) of participants reported having severe depressive symptoms (i.e., score>20 on the PHQ-9) and 23.1% (N=117) had at least “several days” in the past two weeks of suicidal ideation (i.e., “Thoughts that you would be better off dead or of hurting yourself in some way”). We will discuss the procedures, developed collaboratively with our stakeholders, for monitoring suicidal thoughts and behaviors for this online study as well as what to do when suicidal intent and behaviors are endorsed.

Learning Objectives:

1. Understand the importance of including individuals who endorse suicidal thoughts and behaviors in studies of mood disorders.
2. Learn how to monitor suicidal thoughts and behaviors in online studies.
3. Discuss procedures to manage changes and increases in suicidal thoughts and behaviors during online studies of individuals with mood disorders.

Literature References:

1. Iltes, A.S., McCall, W.V., & Deria, R. (2020). Suicidallity, depression, and the FDA: Health inequities and the ethical conduct of research. Journal of Clinical Psychiatry, 81(2), 19.
2. Isometsä E. Suicidal Behaviour in Mood Disorders—Who, When, and Why? The Canadian Journal of Psychiatry. 2014;59(3):120-130.
3. Wiebenga, J. X. M., Dickhoff, J., Mérelle, S. Y. M., Eikelenboom, M., Heering, H. D., Gilissen, R., van Oppen, P., & Penninx, B. W. J. H. (2021). Prevalence, course, and determinants of suicide ideation and attempts in patients with a depressive and/or anxiety disorder: A review of NESDA findings. Journal of Affective Disorders, 283, 267–277.
4. Han, B., Compton, W. M., Gfroerer, J., & McKeon, R. (2015). Prevalence and correlates of past 12-month suicide attempt among adults with past-year suicidal ideation in the United States. The Journal of Clinical Psychiatry, 76(3), 295–302.
5. Rihmer, Z. (2007). Suicide risk in mood disorders. Current opinion in psychiatry, 20(1), 17-22.
6. Asnis, G. M., Friedman, T. A., Sanderson, W. C., Kaplan, M. L., Van Praag, H. M., & Harkavy-Friedman, J. M. (1993). Suicidal behaviors in adult psychiatric outpatients: I. Description and prevalence. The American Journal of Psychiatry, 150(1), 108–112.

*EARLY INTERVENTION IN SCHIZOPHRENIA: ADVANCES TO PREVENT RELAPSE AND HOSPITALIZATION

Nina Schooler, SUNY Downstate Medical Center

Overall Abstract: Few studies of early intervention services (coordinated specialty care-CSC) in schizophrenia have conducted outcome assessment beyond two years and a major question has been the sustained impact once the intervention is reduced or discontinued. In addition, CSC impact on hospitalization rates and medication adherence has been inconsistent. Utilization of long-acting injectable antipsychotics has generally been low in such studies.
This symposium will provide new data from recent large studies in first episode and early phase psychosis. Nina Schooler (SUNY Downstate) will present five-year data from the RAISE-ETP study, which found sustained advantages for those patients receiving CSC compared to usual care. Delbert Robinson (Zucker School of Medicine) will present data on the risk factors associated with hospitalization in the RAISE-ETP study and also data from a CMS sponsored study involving the use of an integrated program using smartphone and web-based cognitive behavioral therapy, illness management techniques, family support and medication decision support to reduce rates of hospitalization in newly discharged patients with schizophrenia. John Kane (Zucker School of Medicine) will present data from a large, simple, cluster randomized trial comparing the use of a once monthly long-acting antipsychotic (LAI) to clinician's choice of antipsychotic at 39 community mental health centers in the U.S. showing a significant delay in time to first hospitalization with LAIs. Robert Rosenheck (Yale) will present an analysis of

RAISE-ETP data suggesting that CSC substantially improved the main trial outcomes compared to usual care for patients in the highest SES quartile, but had small and statistically nonsignificant benefits for the remaining 75 percent of patients. Intervention participation rates and several potential moderators did not explain this disparity. Together these talks will provide major insights into the treatment of early phase psychosis.

Learning Objectives:

1. Understand the similarities and differences between short and long term outcomes of early intervention services in psychosis/schizophrenia as well as the characteristics of individuals that may moderate those effects.
2. Learn about the results of an RCT comparing a long-acting antipsychotic to clinician and patient choice to early phase schizophrenia patients

LONG TERM EFFECTS OF EARLY INTERVENTION SERVICES FOR FIRST EPISODE PSYCHOSIS: OUTCOMES OVER FIVE YEARS FROM THE RECOVERY AFTER A 1ST EPISODE OF SCHIZOPHRENIA-EARLY TREATMENT PROGRAM (RAISE-ETP)

Nina Schooler, SUNY Downstate Medical Center

Individual Abstract: Background: Early intervention services (EIS) for first episode psychosis (FEP) are now implemented worldwide and these integrated and team-based treatment programs improve FEP outcomes while patients are participating. EIS service and treatment models provide care for limited periods followed by return to standard services. Cross sectional follow-up studies conducted after EIS participation ends have not been able to find advantages compared with standard care. The RAISE-ETP study was the first US-based, multi-center randomized clinical trial to compare an EIS, labeled NAVIGATE, to usual clinical care. Those who received NAVIGATE experienced significant improvement in symptoms and functioning compared to those who received usual care during the initial two-year treatment period. We now report clinical outcomes covering five years, a time frame that includes services after EIS participation ended.

Methods. RAISE-ETP was a cluster randomized clinical trial conducted at 34 US sites; 17 sites provided NAVIGATE to 223 participants and 17 sites provided usual clinical care to 181 participants. NAVIGATE was available until the last randomized subject had the opportunity for two years of services. Participants were assessed every six months for up to 60 months by masked, centralized assessors utilizing live two-way video and with the Heinrichs-Carpenter Quality of Life Scale (QLS) and the Positive and Negative Syndrome Scale (PANSS).

Results. Participants had a mean age of 23 years and the majority were male; (78% in NAVIGATE and 66% in usual care). The mean opportunity for NAVIGATE treatment was 33.8 (SD=5.1) months; the longest 44.4 months. Analysis of missing data patterns suggested use of a not missing at random (NMAR) approach instead of the more commonly used missing at random (MAR) approach. A NMAR shared parameter analysis of QLS total scores revealed a significant overall treatment by time interaction ($p<0.001$) with a 13.14 unit difference favoring NAVIGATE over the full five-year study. A comparable analysis of the PANSS total score also revealed a significant overall treatment by time interaction ($p<0.002$) with a 7.73 unit difference favoring NAVIGATE over the full 5-year study.

Conclusions. The RAISE-ETP study provides compelling evidence of a substantial benefit in quality of life and in symptom outcomes of the NAVIGATE EIS compared with usual care for

FEP over 5 years, a period with both EIS and non-EIS treatment. Our ability to detect these advantages in contrast to earlier EIS follow-up studies may be due to our longitudinal assessment model that provided periodic assessment over the full five-year study in contrast to a cross-sectional evaluation, as well as differences in the statistical approaches used by the studies.

Learning Objectives:

1. Learn about long term outcomes of early intervention services for first episode psychosis in both the US and other countries.
2. Understand the effects of treatment model, study design and statistical methods that may influence the results of studies in first episode psychosis.

Literature References:

1. Correll C, Galling B et al. Comparison of Early Intervention Services vs Treatment as Usual for Early-Phase Psychosis A Systematic Review, Meta-analysis, and Meta-regression. JAMA Psychiatry 2018: 75;555-565
2. Schooler NR. Long-term outcomes of psychosis: naturalistic follow-up after initial hospitalization. (Editorial) Am J Psychiatry 2017:174; 1030-1031

PREVENTING HOSPITALIZATION AS A TREATMENT TARGET FOR SCHIZOPHRENIA INTERVENTIONS

Delbert Robinson, Hofstra NS-LIJ School of Medicine

Individual Abstract: Background: Despite treatment advances in other domains, inpatient psychiatric hospitalization rates for individuals with psychosis remain high. Even with early intervention services, a third or more of individuals with first-episode psychosis are hospitalized over the first 2 years of treatment. Interventions to reduce hospitalization are important from a patient and family perspective but also from a public health perspective as hospitalization is a major cost component of schizophrenia care.

Method: The RAISE-ETP study, reviewed in the first presentation, followed 404 participants with first-episode schizophrenia-spectrum disorders at 34 sites. Univariate and multivariate baseline and time-varying covariate analyses were conducted to identify predictors of hospitalization during the first 2 years of follow-up. The primary outcome measure for RAISE-ETP was quality of life. The specific aim of the 10 site Improving Care and Reducing Cost (ICRC) project was to test a novel, multicomponent, and technology-enhanced approach to relapse prevention in outpatients following a psychiatric hospitalization. The relapse prevention program included in-person, individualized relapse prevention planning and smartphone and web-provided cognitive behavioral therapy, illness management techniques, family support and medication decision support. Participants were between 18 and 60 years old; had a diagnosis of schizophrenia, schizoaffective disorder, or psychotic disorder not otherwise specified; and were currently hospitalized or had been hospitalized within the past 30 days. The first participant cohort (N = 89) received standard care; the second cohort (N = 349) the experimental intervention. Follow-up duration was 6 months.

Results: In RAISE-ETP, risk analyses revealed significant predictors of hospitalization to be: the number of hospitalizations before study entry, duration of untreated psychosis, and time-varying days of substance misuse, presence of Positive and Negative Syndrome Scale positive symptoms, and beliefs about the value of medication. In ICRC, days of hospitalization were reduced by a mean of 4.25 (95% CI: 0.21, 8.29; p=0.039) days during follow-up in the

intervention compared to the control condition. Mean estimated days of hospitalization during 6 months for the control group were 15.93 and 11.68 for the intervention group.

Conclusions: The ICRC results show that technology-assisted treatment can reduce the need for inpatient hospitalization. Using a recent estimate of hospital costs to be $1358 per hospital day, our findings suggest a decrease in hospitalization costs of $5772 per participant over the 6 month period. The RAISE-ETP results suggest that targets for future intervention development specific to preventing hospitalizations in first-episode psychosis include reducing the duration of untreated psychosis and prior hospitalizations, minimizing residual symptoms, preventing substance misuse and facilitating adherence in medication taking.

Learning Objectives:

1. At the completion of the presentation, the listener will be able to describe the effect of the Improving Care and Reducing Cost project on days of psychiatric inpatient hospitalization.
2. At the completion of the presentation, the listener will be able to describe the intervention targets for preventing psychiatric inpatient hospitalization that were identified in the RAISE-ETP study.

Literature References:

1. Brunette MF, Rotondi AJ, Ben-Zeev D, et al.: Coordinated Technology-Delivered Treatment to Prevent Rehospitalization in Schizophrenia: A Novel Model of Care. Psychiatr Serv 2016; 67:444–447
2. Robinson DG, Schooler NR, Rosenheck RA, et al.: Predictors of Hospitalization of Individuals With First-Episode Psychosis: Data From a 2-Year Follow-Up of the RAISE-ETP. Psychiatr Serv 2019; 70:569–577

THE USE OF LONG-ACTING ARIPIPRAZOLE VS TREATMENT AS USUAL IN EARLY PHASE SCHIZOPHRENIA: RESULTS FROM THE PRELAPSE TRIAL

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

Individual Abstract: Background/Rationale: Hospitalization rates in early phase psychosis remain high with non-adherence presenting a major risk factor. Long-acting injectable antipsychotics (LAIs) have shown effectiveness in addressing this concern in both mirror image and cohort studies. However, randomized controlled trials (RCTs) have reported mixed results. RCTs can change the ecology of care and do not reflect "real world" conditions, particularly when adherence is a focus of study. The large simple trial (LST) is one way to address such concerns.

Methods: The PRELAPSE trial was a LST involving cluster randomization of 39 US clinics (19 provided. Inclusion criteria: DSM5 schizophrenia; <5 yrs lifetime antipsychotics; age 18–35 yrs; informed consent. Rating scale assessments were done at baseline, 12 and 24 months. Data on hospitalizations/ER visits LAI aripiprazole monohydrate (AM) and 20 treatment as usual (TAU)). The primary hypothesis was that AM treatment would significantly delay time to first hospitalization were obtained by phone every other month. AM-specific training was provided to AM sites to facilitate use of AM.

Results: 489 subjects were included: 234 AM, 255 TAU; mean age 25; 75% male; 44% African-American, 35% Caucasian. 46.0% had <=1 yr lifetime antipsychotic exposure. 14% of subjects declined participation due to LAI treatment. 91% of eligible subjects received at least one AM treatment within three months. 52 AM subjects had at least one hospitalization

(22.2%) vs 90 TAU subjects (35.3%). The hazard ratio for AM for time to first hospitalization, under the proportional hazards assumption, was HR=0.56 (95% CI = 0.34, 0.92), p=0.02. The estimated survival probabilities and 95% CIs from the Cox model were 0.73 (0.65, 0.83) for AM subjects and 0.58 (0.50, 0.67) for TAU subjects. The number needed to treat (NNT) to prevent a hospitalization was 6.67 subjects treated with AM relative to TAU.

Conclusion: The results demonstrate that with focused training of the clinical staff a large proportion of first episode and early phase schizophrenia patients will accept a trial of a long acting injectable formulation of antispsychotic medication. The use os such formuations (in this case aripiprazole monohydrate) is associed with a significant reduction in the risk of hospitalization with an NNT of 7. Such a strategy should be considered more frequently in early phase illness.

Learning Objectives:

1. To provide attendees with an overview of relapse risk in early phase schizophrenia.
2. To present data on the impact of long acting injectable formulations on risk of relapse in early phase illness.

Literature References:

1. Takeuchi H, Siu C, Remington G, et al: Does relapse contribute to treatment resistance? Antipsychotic response in first vs. second episode schizophrenia. Neuropsychopharmacology 2019; 22:1036-1042
2. Kane JM, Robinson DG, Schooler NR, et al. Comprehensive verus usual community care for first episode psychosis: 2-year outcomes from the NIMH RAISE Early Treatment Program. Am J Psychiatry 2016; 173:362-372

SOCIOECONOMIC STATUS AND THE EFFECTIVENESS OF COORDINATED SPECIALTY CARE FOR FIRST EPISODE PSYCHOSIS

Robert Rosenheck, Yale Medical School

Individual Abstract: Objective: Socioeconomic status (SES) may be an important moderator of the effectiveness of early intervention in psychosis but has not been previously examined in a randomized trial. We investigated the role of SES as a moderator of the effectiveness of early intervention for first episode psychosis. Methods: We conducted a secondary analysis of the RAISE-ETP Trial, a cluster-randomized trial comparing a coordinated specialty care (CSC) intervention called NAVIGATE with usual community care. We constructed a patient SES index based on parental education, parental occupational prestige, and race/ethnicity. After identifying correlates of SES, we used OLS regression analysis to estimate treatment effects on the major study outcomes across quartiles of the SES distribution. We also examined whether factors such as the duration of untreated psychosis (DUP) and NAVIGATE participation could account for the observed difference in effectiveness by SES. Results: The trial sample had a similar SES distribution to the US population, and SES was positively correlated with all mental health outcomes and several potential moderators at baseline. CSC substantially improved the main trial outcomes compared to community care for patients in the highest SES quartile but had small and statistically insignificant benefits for the remaining patients. Intervention participation rates and several potential moderators did not explain this disparity. Conclusions: CSC may be the most effective for high-SES. Additional research is needed to understand why CSC is less effective for moderate-SES and low-SES patients and to develop methods to increase effectiveness for these patients.

Learning Objectives:

1. At the end of this presentation participants will understand how to evaluate socio-economic status among people with psychoses.
2. At the end of this presentation participants will understand the independent effect of SES on the effectiveness of coordinated specialty care for first episode psychosis.

Literature References:

1. Rosenheck RA, Leslie D, Sint K, Lin H, Robinson DG, Schooler NR, Mueser KT, Penn DL, Addington J, Brunette MF, Correll C, Estroff SE, Marcy P, Robinson J, Azrin S, Goldstein AB, Severe JB, Rupp A, Schoenbaum M, Kane JM. Cost-Effectiveness of Comprehensive, Integrated Care for First Episode Psychosis in the NIMH RAISE Early Treatment Program. Schizophenia Bulletin. 2016; 42(4):896-906. PMID: 26834024
2. Rosenheck R, Estroff S, Sint K, Lin H, Mueser KT, Robinson DG, Schooler NR, Kane JM. and the RAISE ETP Investigators. Incomes and Outcomes: Social Security Disability Benefits in First Episode Psychosis. American Journal of Psychiatry 2017; 174(9):886-894PMID: 28427286

ON-DEMAND PANEL

SULFORAPHANE AS A POTENTIAL ADD-ON TREATMENT STRATEGY FOR SCHIZOPHRENIA AND AUTISM: BASIC AND CLINICAL EXPERIMENTAL FINDINGS

Robert C. Smith, NYU Medical School

Overall Abstract: There is evidence that biochemical abnormalities associated with oxidative stress, reduced ani-oxidant capacity, overactivity of inflammatory markers and abnormalities in HDAC activity and overactivity in methylation of some promotor genes, such GAD67, may be involved in the underlying pathophysiology of schizophrenia and autism. Sulforaphane (SFN: 1-isothiocyanato-4-methylsulfinylbutane) is an organosulfur isothiocyanate derived from a glucosinolate precursor (glucoraphanin) found primarily in the cruciferous vegetable broccoli, which has chemical properties both as an antioxidant and an HDAC inhibitor, and some of its epigenetic effects also resulted in decreasing the expression of several methylation enzymes DNMT1 and DNMT3a and DNMT3b. There are some studies in mice showing that treatment with sulforaphane can ameliorate or reverse cognitive deficits and histological changes induced by PCP. One double-blind clinical study involving 29 subjects with autism showed that sulforaphane significantly improved patient's scores on 2 autism behavioral scales. In the proposed symposium we will review the biochemical and pharmacokinetic properties of sulforaphane and its sources, and present results from three double-blind placebo controlled studies of sulforaphane effects in patients with schizophrenia and autism. John Fahey will discuss the biochemical properties of sulforaphane and his studies of pharmacokinetics, absorption and bioavailability along with biochemical correlates of efficacy from preliminary studies. Hua Jin will present results from a study of sulforaphane done with 151 subjects in china diagnosed with first-episode schizophrenia. In that study we found statistically significant effects of sulforaphane on reducing cognitive deficits schizophrenia on several domains measured on the MATRICS Battery- Spatial Working Memory, Reasoning and Problem Solving, and Verbal Learning. Faith Dickerson will present results from a study of sulforaphane patients with chronic schizophrenia, where preliminary results show effects of

the treatment on working memory. Since there are no generally effective add-on drugs for treating cognitive deficits in schizophrenia, these results with sulforaphane may have clinical significance if additional studies confirm our findings. Robert Smith will present the results form a study of 106 subjects with autism in China who received sulforaphane or placebo for 12 weeks; the sulforaphane subjects showed significant improvement on the OSU autism rating scale (OASR) on both total scores and several of the subscale scores as well as on the CGI improvement scale.. Sulforaphane showed benefit cal effects in subjects with and without severe cognitive impairment.Side effects of sulforaphane in all the studies were minimal. Sulforaphane has already been established as an effective drug for treating some cancers. This symposium will show its potential for treatment of two neuropsychiatric diseases and encourage further research in this area.

Learning Objectives:

1. The participants will learn about the major biochemical mechanisms through which sulforaphane may exert some of its physiological or clinical effects.
2. The participants will learn about the potential ability of sulforaphane to reduce some specific symptoms in patients with schizophrenia and autism spectrum disorder.

SULFORAPHANE FROM BROCCOLI FOR NEUROPSYCHIATRIC DISORDERS: OVERVIEW OF BIOCHEMISTRY, SAFETY, BIOAVAILABILITY, AND MECHANISMS OF EFFICACY

Jed Fahey, Johns Hopkins University School of Medicine

Individual Abstract: Sulforaphane (SF) is a phytochemical from broccoli, derived from a stable and abundant precursor glucoraphanin (GR) and. It is an isothiocyanate with over 3000 published studies that examine its efficacy in rodent and other mechanistic disease models. SF is known in particular for its antibacterial, antifungal, antioxidant, and cytoprotective properties. SF is formed by the conversion of the vacuole-entrained precursor GR, to SF, mediated by myrosinase, an enzyme that is compartmentalized and sequestered in the cell, until released upon cell lysis. GR is also converted to SF by the microbiota in the gastrointestinal tract. SF is rapidly absorbed by the GI tract and it rapidly distributes to cells throughout the body. It is a highly promising agent currently under preclinical and clinical evaluation for disease prevention. Depending on its use, SF (and GR) can be considered foods, dietary supplements, or natural product-based drugs. We and others have generated extensive animal and human clinical evidence on the bioavailability of both GR and SF.

We will review studies from our own and other groups exploring the underlying biochemical abnormalities associated with neurodevelopmental illness, and discuss how the underlying biochemical effects of sulforaphane that may counteract these deficits, and which types of markers may be useful in monitoring in treatment strategies and clinical trials.

Several basic physiological pathways have been associated with neurodevelopmental and/or neurodegenerative conditions. To name a few, they include: redox metabolism/oxidative stress including reduced glutathione synthesis, mitochondrial dysfunction and low oxidative phosphorylation, increased lipid peroxidation, immune dysregulation, neuroinflammation, febrile illness associated with the heat shock response, and synaptic dysfunction. There is extensive evidence from in vitro and clinical studies, that SF counteracts many of these same

biochemical and molecular abnormalities. Importantly, SF is a food-sourced small molecule that can cross the blood-brain-barrier and quickly reach the CNS to exert its protective effects. There have been over 50 clinical trials to date examining pharmacokinetics, pharmacodynamics, and disease mitigation of SF.

We have identified biomarkers that can be used to assess the functioning of these pathways that could even guide novel treatment strategies to correct these biochemical abnormalities or to improve core and associated symptoms of some of these conditions. A key mechanism of action of SF is the activation of the transcription factor Nrf2, which regulates the expression of at least 2% of the coding human genome, inducing an extensive array of cytoprotective responses. Upon its interaction with specific cysteine residue sensors on the cytoplasmic tether peptide Keap1, SF frees Nrf2 to translocate to the nucleus and activate transcription of a coordinate set of genes coding for phase 2 detoxification enzymes. Separately, SF also has potent anti-inflammatory, heat shock-response-inducing, and histone deacetylase (HDAC) inhibiting properties.

Sulforaphane may have a broad range of potential uses in treating many medical conditions. The information on sulforaphane's pharmacokinetics and biochemistry, and the biochemical markers that may be utilized in future clinical studies, provide basic information which will help participants better understand and interpret the potential mechanisms underlying sulforpahane's clinical effects in studies reported in this symposium.

Learning Objectives:

1. To understand the biogenic relationship of sulforaphane to its biologically inert precursor, found in the common cruciferous vegetable broccoli.
2. To understand the variability in bioactivity from the perspectives of microbiome, metabolism, bioavailability, source, matrix, and mode of action.

Literature References:

1. Yagishita Y, Fahey JW, Dinkova-Kostova AT and Kensler TW: Broccoli or sulforaphane: is it the source or dose that matters? Molecules 2019; 24, 3593; doi:10.3390/molecules24193593.
2. Liu H, Zimmerman AW, Singh K, Connors SL, Diggins E, Stephenson KK, Dinkova-Kostova AT, Fahey JW: Biomarker exploration in human peripheral blood mononuclear cells for monitoring sulforaphane treatment responses in Autism Spectrum Disorder. Scientific Reports 2020; 10:5822 https://doi.org/10.1038/s41598-020-62714-4.

EFFICACY OF ADD-ON SULFORAPHANE FOR IMPROVING COGNITION AND SYMPTOMS IN FRIST-EPISODE SCHIZOPHRENIA: A RANDOMIZED DOUBLE-BLIND STUDY

Hua Jin, University of California at San Diego and VA San Diego Healthcare System

Individual Abstract: Background: Cognitive symptoms are common and associated with significant dysfunction in schizophrenia. Oxidative stress, inflammation and epigenetic modifications involving HDAC and methylating enzymes have been implicated in some of the risk factors or underlying pathophysiology of schizophrenia. Sulforaphane has chemical properties both as an antioxidant and an HDAC inhibitor. One published study suggests it have

beneficial effects in autism. Studies in PCP animal models of schizophrenia suggest it may be effective on improving some of the cognitive deficits and underlying pathophysiological abnormalities in schizophrenia. However, no large sample trials have been done to examine the efficacy of sulforaphane in treating cognitive and psychotic symptoms in schizophrenia. The objective of the current study was to determine the efficacy and safety of sulforaphane as an add-on treatment for patients with first episode schizophrenia and particularly its effects on cognitive symptoms.

Methods: This double-blind randomized trial was conducted from November 2016 to June 2019 in 4 psychiatric institutions in China. Patients with first-episode schizophrenia with minimum PANSS >75 were enrolled and followed for 22 weeks. The patients were randomized to 3 groups (low and high doses of sulforaphane vs placebo) and symptomatic and cognitive assessments were done at multiple time points. The Avmacol® tables contained glucoraphanin and active myrosinase which converted to sulforaphane with the estimated delivery of approximately 48 and 72 umol of sulforaphane daily in the low and high dose group. The primary outcome was change in the MATRICS Composite score and secondary outcome changes in MATRICS Domain scores. Additional secondary outcomes were change PANNS Total score PANSS 5-factor scores, and change in side-effect scales scores.

Results: A total of 172 patients with first-episode of schizophrenia were enrolled and randomized into 3 study groups and 151 patients had at least 1 follow up evaluation. In the mixed -model intention-to-treat analysis, sulforaphane significantly improved performance scores on several Domains of the MATRICS battery, spatial working memory (P= 0.004), reasoning-problem solving (P= 0.063), and verbal learning (P= 0.031) (Overall effect sizes d=.26-.35). It did not improve global cognitive function as measured by the MATRICS overall composite score. There were no effects on PANSS symptom scores. Sulforaphane was well tolerated and side effects were very low and infrequent.

Conclusion: If these positive effects of sulforaphane on selected aspects of cognitive function in schizophrenia can be replicated, it may be useful as an add-on treatment for reducing cognitive deficits in schizophrenia. Cognition is a different aspect of schizophrenia than symptoms, and it's possible that even a small benefit in cognition, added to that produced by standard treatment, could make a clinical important difference, if these findings replicate in additional studies.

Learning Objectives:

1. Sulforaphane, as a nutritional supplement, could improve cognitive symptoms in treating schizophrenia.
2. Sulforaphane is very safe and tolerated as an add-on treatment for patients with schizophrenia.

Literature References:

1. Singh K, Connors SL, Macklin EA, Smith KD, Fahey JW, Talalay P, Zimmerman AW. Sulforaphane treatment of autism spectrum disorder (ASD). Proc Natl Acad Sci U S A. 2014;111:15550-15555.
2. Shiina A, Kanahara N, Sasaki T, Oda Y, Hashimoto T, Hasegawa T, Yoshida T, Iyo M, Hashimoto K. An Open Study of Sulforaphane-rich Broccoli Sprout Extract in Patients with Schizophrenia. Clin Psychopharmacol Neurosci. 2015;13:62-67.

SULFORAPHANE AS A TREATMENT FOR AUTISM: REPORT OF A RANDOMIZED DOUBLE-BLIND STUDY IN SUBJECTS WITH AND WITHOUT SEVERE COGNITIVE IMPAIRMENT

Robert C. Smith, NYU Medical School

Individual Abstract: Background: Some underlying biochemical abnormalities in Autism Spectrum Disorder (ASD) may be associated with oxidative stress and lower antioxidant capacity, depressed glutathione synthesis, reduced mitochondrial function and oxidative phosphorylation, increased lipid peroxidation, and increased neuroinflammation. Sulforaphane (SNF) has chemical properties which may counteract some of these deficits. A double-blind study in the US found that sulforaphane ameliorated several measures of ASD symptoms, a finding supported by some open trials. We present results from a larger double-blind study of sulforaphane effects on children with ASD in China.

Methods: 108 children, ages 5-15, with a diagnosis of ASD, were enrolled in a 12 week randomized double blind study of sulforaphane or matched placebo, using Avmacol® tablets (Nutrimix Laboratories). Dosage was based on weight ranging from 2 ,4, 6 or 8 tablets /day. Outcomes measures, evaluated at bassline and weeks 4, 8 and 12, included a clinician rated scale, Ohio State Autism Rating Scale (OARS-4),Clinical global Improvement (CGI-I) and several caregiver rated scales- Social Responsiveness Scale (SRS), Repetitive Behavior Scale – Revised (RBS-R), and social relatedness sub-scale from the Autism Behavior checklist. Side-effects were rated using the SAFTEE scale and laboratory measures collected at baseline and 12 weeks. Statistical analysis used intent to treat mixed model analysis of covariance, using both differences score from baseline and actual scores at each time point.

Results: 94 patients were available for analysis of treatment effects if they had at least one post drug treatment study evaluation. The intent to treat mixed model analysis showed that sulforaphane improved ratings more than placebo on the clinician rated CGI-I ($P<.0001$) and on the OARS with significant decreases on OARS total average scores ($P=0.002$) and sub-scores of impaired social interaction ($P=.0006$) and communication barriers ($P=.003$) but not stereotyped behaviors ($P=0.300$). 90% of SFN treated subjects showed at least mild improvement or better (score 3 or less) on the CGI-I by week 12 compared to 41% of PLO subjects. However, there were no significant changes in scores on the caregiver rated scales (SRS, RSR, Autism Checklist (social relating behavior sub-scale). For OARS total average difference scores, and impaired social interaction scores, patients over 10 yrs. of age showed a greater decrease than younger patients. For OARS scores patients with lower surrogate IQ scores ($IQ<60$ score) showed a greater improvement that patients with higher scores ($IQ\geq60$ score) although the interaction effects of IQ and treatment effect were not statistically significant. Side effects were low; there were few difference between between placebo and sulforaphane groups on SAFTEE scale and no clinically significant difference between the groups on changes in routine laboratory values.

Conclusions: Sulforaphane produced significant decrease in autism scores on a clinician rated scale with some significant reductions in symptoms occurring as early as 8 weeks of treatment. The SNF treatment was safe and well tolerated. We cannot fully assess reasons for the lack of changes in parent-caregiver rated scores. However, it may be due to the (a)relatively short length of treatment, since the initial Zimmerman study reported maximum changes in some of these scales at 18 weeks' treatment, and/or (b) our ASD subjects were in a highly supportive

educational placement that facilitated robust additional observations of professional staff that were elicited during clinician administered ratings with input from other support providers beyond family.

Learning Objectives:

1. Particpatins will learn about the effects of sulforaphane on social and communication deficits associated with autism spectrum disorder.
2. Participations will earn about the potentially greater effects of sulforaphane in chains autism patients with more severe cognitive impairments and the clinical implications of this finding.

Literature References:

1. Singh K, Connors SL, Macklin EA, Smith KD, Fahey JW, Talalay P, Zimmerman AW. Sulforaphane treatment of autism spectrum disorder (ASD). Proc Natl Acad Sci U S A. 2014;111:15550-15555.
1. 2 Liu H, Zimmerman AW, Singh K, Connors SL, Diggins E, Stephenson KK, Dinkova-Kostova AT, Fahey JW. Biomarker Exploration in Human Peripheral Blood Mononuclear Cells for Monitoring Sulforaphane Treatment Responses in Autism Spectrum Disorder. Scientific Reports. 2020;10.

EFFICACY OF ADD-ON SULFORAPHANE FOR IMPROVING SYMPTOMS AND COGNITION IN SCHIZOPHRENIA: A RANDOMIZED DOUBLE-BLIND STUDY

Faith Dickerson, Sheppard Pratt

Individual Abstract: Background: The consumption of cruciferous plants such as broccoli and cauliflower has been associated with a reduced risk of cancer and other chronic diseases. This beneficial effect has been ascribed largely to the plants' high content of glucosinolates which are converted to isothiocyanates such as sulforaphane. Sulforaphane crosses the blood brain barrier and has antioxidant and anti-inflammatory activities. A previous trial in males with autism found that adjunctive sulforaphane was associated with improvements in some indicators of social functioning and aberrant behavior. The primary aim of the current study was to evaluate the safety and efficacy of an adjunctive sulforaphane nutraceutical for individuals with schizophrenia in a placebo-controlled, randomized double blind trial.

Methods: Individuals with schizophrenia or schizoaffective disorder, most of whom had long-standing illness and who had residual psychotic symptoms of at least moderate severity were randomized to receive 6 tablets per day of 16 mg of glucoraphanin, which is metabolized following ingestion yielding approximately 100 micromoles of sulforaphane, or identical-appearing placebo added to usual psychiatric medications. The study duration was 16 weeks following a 2 week placebo run-in. The primary outcome was change in the severity of psychiatric symptoms, measured biweekly by the Positive and Negative Syndrome Scale (PANSS) over the double-blind phase. The secondary outcome was change in cognitive functioning, measured by the MATRICS Consensus Cognitive Battery (MCCB), from the beginning to the end of the trial. Mixed effects models were used to evaluate the relationship between the administration of the sulforaphane precursor and change in symptoms or cognitive functioning during the study period. Exploratory analyses were performed to examine the

association between levels of the sulforaphane metabolite, dithiocarbamate, in urinary samples and changes in the outcome measures.

Results: A total of 64 participants were randomized (mean age 44.0 (±12.0) years); 58 participants completed the 18 weeks of the trial. There were no significant differences in the change of positive, negative, general, or total PANSS symptom scores between groups (Coefficient = .7754, 95% CI -5.304, 6.855, p=0.803; Coefficient = .0003, 95% CI -2.551, 2.552, p=1.0; Coefficient = .9197, 95% CI -1.259, 3.099, p=0.408; Coefficient = -.0311785, 95% CI .1320388, .0696817, p=0.545, respectively). There was also no significant improvement in MCCB total or domain scores by treatment group in the entire cohort. However, there was a significant association between glycophorin treatment and improvement in the MCCB working memory domain in individuals with urine concentrations of dithiocarbamate of > 1 mmol/L (Wald Test, F(2, 47) = 4.35. p = 0.0185). Reasons for the differences in sulforaphane metabolism are not known with certainty but may be related to host genetics, the composition of the gastrointestinal microbiome, or medication compliance. The study medication was well tolerated with no significant difference in the number of adverse events between groups.

Conclusions: The trial did not demonstrate an overall benefit of adjunctive sulforaphane for psychiatric symptoms or cognition in schizophrenia. Sulforaphane may result in improvement in working memory for the subset of persons who generate dithiocarbamate following treatment

Learning Objectives: At the end of this presentation, the audience member will be able to:

1. Define the rationale for a trial of sulforaphane in schizophrenia.
2. Describe the design and the results of the trial presented.

Literature References:

1. Singh K, Connors SL, Macklin EA, Smith KD, Fahey JW, Talalay P, Zimmerman AW.Sulforaphane treatment of autism spectrum disorder (ASD). Proc Natl Acad Sci U S A. 2014 Oct 28;111(43):15550-5. doi: 10.1073/pnas.1416940111. Epub 2014 Oct 13.
2. Palliyaguru DL, Yuan JM, Kensler TW, Fahey JW. Isothiocyanates: Translating the Power of Plants to People. Mol Nutr Food Res. 2018 Sep;62(18):e1700965. doi: 10.1002/mnfr.201700965. Epub 2018 Mar 26.

Wednesday, June 2, 2021

Poster Session I

W1. PHARMACOLOGIC TREATMENT OF ATTENTION DEFICIT HYPERACTIVITY DISORDER AND THE RISK OF NEW-ONSET PSYCHOSIS IN A GEOGRAPHICALLY-DEFINED COHORT OF YOUTH: PRELIMINARY FINDINGS

Andrew Pines[1], Rana Elmaghraby[2], Coombes Brandon[2], Jennifer Geske[2], Matej Markota[2], William Bobo[2]*

[1]Mayo Clinic Arizona, [2]Mayo Clinic

Abstract: Objectives: Epidemiological studies have suggested increased risk of new-onset psychosis in children and adolescents with Attention Deficit Hyperactivity Disorder (ADHD) who are treated with psychostimulant medications (1). A recent study by Moran and colleagues found that youth with ADHD who were treated with amphetamines had a significantly higher risk of new-onset psychosis compared to methylphenidate-treated youth (2). The risk of developing psychosis in other groups of ADHD medications is poorly understood. This population-based study aims to compare the risk of new-onset psychosis between four different groups of ADHD medications.

Methods: We used the Rochester Epidemiology Project (REP) to evaluate patients who were i) between 6-18 years of age, ii) between 1/1/2005 and 12/31/2018; iii) were diagnosed with ADHD during that time, and iv) were prescribed at least one of the following four groups of ADHD medications: amphetamine, methylphenidate, atomoxetine, and alpha agonists (clonidine or guanfacine). All subjects with any psychotic diagnosis prior to receiving the first qualifying ADHD medication were excluded. The primary outcome was a newly diagnosed psychosis, defined as having a relevant International Classification of Diseases 9 or 10 diagnostic code. For purposes of preliminary results, the risk of new-onset psychosis conditioned on ADHD medication class, expressed as odds ratios, were estimated using logistic regression. Four separate analyses were performed, each testing for risk of psychosis in a specific group of ADHD medications compared to youth treated with the other three medication groups.

Results: We identified 4,599 youth (3,210 male) who met inclusion criteria of which 152 (106 males, 69.7%) were classified as having new-onset psychosis. Both genders had the same risk of developing psychosis (both 3.3%, p=0.99). Ever treated with atomoxetine group was associated with significantly higher risk of psychosis compared to never treated with atomoxetine group (OR=2.3, 95% CI=1.4-3.9). Such effect was not found for amphetamines (OR=1.3, 95% CI=0.8-2.1), methylphenidate (OR=1.1, 95% CI=0.7-1.7), or alpha agonists (OR=1.2, 95% CI=0.7-2.0). In a combined analysis of all four groups of medications, atomoxetine remained significantly associated with psychosis (OR=2.4, 95%CI =1.7-3.5); amphetamines (OR=1.3 95% CI = 0.9-1.8), methylphenidate(OR=1.5, 95% CI =0.9-2.3), and alpha agonists (OR=1.3, 95%CI = 0.9-1.9) did not reach significance.

Conclusion: Our preliminary results agree with previously published findings that ADHD medications are associated with increased risk for new-onset psychosis. Surprisingly, we found the risk of new-onset psychosis to be greatest in patients prescribed atomoxetine. Our final analysis will be based on Cox proportional hazard models of time until psychosis after first treatment for ADHD, and will account for cumulative exposure to each of the four groups of medications, sex, and race. The preliminary findings presented here have several important limitations, including lack of data on severity of ADHD, cumulative doses of medications, or detailed timing between receiving ADHD medications and developing psychosis.

W2. TOWARD OPERATIONALIZING DEFICIENT EMOTIONAL SELF-REGULATION IN NEWLY-REFERRED ADULTS WITH ADHD: A RECEIVER OPERATING CHARACTERISTIC CURVE ANALYSIS

Joseph Biederman[*1], Maura Disalvo[1], Ronna Fried[2], Mai Uchida[1], Thomas Spencer[1], Stephen V. Faraone[3]*

[1]Massachusetts General Hospital, [2]MGH/Harvard Medical School, [3]SUNY Upstate Medical University

Abstract: Hypothesis/Objective: Low frustration tolerance, impatience, and quickness to anger have long been associated with attention-deficit/hyperactivity disorder (ADHD), and deficits in emotion regulation have been included as associated features of ADHD in the DSM. A growing body of research suggests that deficient emotional self-regulation (DESR) is common and morbid among ADHD patients. Despite this, uncertainties remain about how to best operationalize DESR at the individual level. The main aim of the present study was to assess whether high and low levels of DESR in adult ADHD patients can be operationalized and whether they are clinically useful.

Methods: A total of 441 newly referred 18- to 55-year-old adults of both sexes with DSM-5 ADHD completed self-reported rating scales. We operationalized DESR using the eight-item Emotional Dysregulation (ED) subscale of the Barkley Current Behavior Scale. We used receiver operating characteristic (ROC) curves to identify the optimal cut-off on the Barkley ED Scale to categorize patients as having high- versus low-level DESR and compared demographic and clinical characteristics between the groups.

Results: We averaged the optimal Barkley ED Scale cut-points from the ROC curve analyses across all subscales and arrived at an average optimal cut-off score of 8 to identify high levels of DESR. We then categorized ADHD patients as having high- (N=191) or low-level (N= 250) DESR based on total Barkley ED Scale scores ≥8 or <8, respectively. Those with high-level DESR had significantly more severe symptoms of ADHD, executive dysfunction, autistic traits, levels of psychopathology, and worse quality of life compared with those with low-level DESR. There were no major differences in outcomes among medicated and unmedicated patients.

Conclusions: Our results identify a robust association between DESR and ADHD that correlated with impaired quality of life and a wide range of functional impairments. High levels of DESR are

common in adults with ADHD and, when present, represent a burdensome source of added morbidity and disability worthy of further clinical and scientific attention.

W3. USING A TEXT MESSAGING INTERVENTION TO IMPROVE ADHERENCE TO STIMULANTS IN INDIVIDUALS WITH ADHD

Joseph Biederman[*1]*

[1]*Massachusetts General Hospital*

Abstract: Hypothesis/Objective: Although large datasets document that stimulants decrease the risk for many adverse ADHD-associated outcomes, compliance with stimulants remains poor. The studies presented examined the effectiveness of a novel ADHD-centric text-messaging-based intervention aimed to improve adherence to stimulant medications in both children and adults with ADHD.

Methods: We conducted two separate studies: one in children largely from the primary care setting (N=87) and one in adults largely from the primary care setting (N=117). Patients who received the text messaging intervention were children (ages 6-12) and adults (ages 18-55) who were prescribed a stimulant medication for ADHD treatment. Comparators were age- and sex-matched pediatric patients and age-, race-, and sex-matched adult patients from the same healthcare organization's electronic medical record (EMR) who had been prescribed stimulant medications over a similar time period. We determined whether patients had timely prescription refills, defined as refilled within 37 days, using prescriptions documented in the EMR.

Results: In children, 85% of the SMS intervention group refilled their prescriptions in a timely manner compared to only 62% of patients receiving treatment as usual (TAU) (OR=3.46, 95% CI: 1.82, 6.58; $p<0.001$). The number needed to treat (NNT) statistic was computed as five, meaning for every five pediatric patients who receive the text messaging intervention, we can keep one adherent with their stimulant medication. In adults, 81% of the SMS intervention group refilled their prescriptions in a timely manner compared to only 36% of patients receiving TAU (OR=7.54, 95% CI: 4.46, 12.77; $p<0.001$). The NNT statistic was three, meaning for every three adult patients who receive the text messaging intervention, we can keep one adherent with their stimulant medication.

Conclusions: These data indicate that an innovative ADHD-centric text messaging intervention significantly improved adherence to treatment with stimulants in ADHD. Findings provide strong support for the utility of this readily accessible, inexpensive, and widely available technology to improve the poor rate of adherence to stimulant treatment in children and adults with ADHD. To the best of our knowledge, these studies are the first digital health interventions aimed at improving adherence to stimulant medication for children and adults with ADHD.

W4. GLIAL FIBRILLARY ACIDIC PROTEIN, VASCULAR ENDOTHELIAL GROWTH FACTORS, AND S100B CHANGES IN SERUM WITH TRANSCRANIAL MAGNETIC

STIMULATION TREATMENT IN DEPRESSED PATIENTS ASSOCIATED WITH CLINICAL OUTCOME

Andrew Fukuda[1], Lauren Hindley[2], Jee Won Diane Kang[2], Eric Tirrell[1], Audrey Tyrka[3], Linda Carpenter[3]*

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Abstract: Background: Transcranial magnetic stimulation (TMS) therapy is effective for treatment resistant depression (MDD) but the exact therapeutic mechanism of action is still being investigated. Astrocytic contributions to the pathophysiology of depression have started garnering attention but has not been explored much in TMS treatment. Our study examined serum levels of three astrocytic proteins: S100 Calcium Binding Protein B (S100B), Glial Fibrillary Acidic Protein (GFAP), and Vascular endothelial growth factor (VEGF), before and after TMS in MDD to investigate their potential roles in the mechanism of TMS.

Methods: Serum was collected from a naturalistic population of 35 patients (40% male, 60% female) with MDD at two timepoints: prior to receiving first session of TMS and after the 30th session (end of the acute phase treatment course). Protein concentrations were determined via Enzyme-linked Immunosorbent Assay (ELISA) and all samples were run in duplicates. Inventory of Depressive Symptomatology Self Report (IDS-SR) was used as a measure of depression symptom severity, clinical response, and remission. TMS was given at standard 10 Hz delivered to the dorsolateral left prefrontal cortex daily at 120% maximum intensity relative to their motor threshold for a minimum of 3000 pulses.

Results: There was a positive correlation between % change in IDS-SR and % change in GFAP ($r=.561$, $p<0.05$), and VEGF ($r=.358$, $p<0.05$). Amongst those who remitted, VEGF increased from pre to post TMS (% change +12.30%) whereas VEGF decreased in nonremitters (% change -9.24%) ($p=0.054$). This same pattern was observed when comparing VEGF changes between responders (+9.35%) and non-responders (-12.42%) ($p<0.05$). Similarly, GFAP also increased in responders (+151.18%) but decreased in non-responders (-41.10%) ($p<0.05$). S100B did not correlate with depression severity changes, nor did they differ between those with different clinical outcomes. The protein levels did not differ by sex or with age.

Conclusions: Patients with a successful treatment with TMS had significantly greater increase in VEGF and GFAP from pre to post treatment compared to non-responders and a larger increase was associated with greater improvement in depressive symptoms after TMS. These patterns were not seen in S100B. The functional implications of the differential changes in these astrocytic proteins are yet to be elucidated, but data from basic science hint at neuroinflammation, angiogenesis, synaptic remodeling, and blood brain permeability changes. This pilot study provides promising exploratory data showing that GFAP and VEGF is an important mediator in the mechanism behind TMS' antidepressant effects.

W5. ESTIMATING INDIVIDUALIZED TREATMENT RULES FOR REDUCING RECIDIVISM AMONG CRIMINAL JUSTICE-INVOLVED ADULTS WITH MENTAL ILLNESS

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Abstract: Criminal justice-involved people with mental illness are a heterogeneous group with diverse symptoms, risk factors, and other treatment-relevant characteristics. Data from clinical trials with this group can be used to understand treatment effect heterogeneity, i.e., determine which treatment works best for whom to reduce recidivism. The optimal dynamic treatment rule (ODTR) framework offers an approach for understanding which kinds of patients respond best to specific treatments. Recently, there has been a proliferation of methods for estimating the ODTR, including work by van der Laan and Luedtke using the Super Learner algorithm (a data-adaptive machine learning method of optimally combining candidate algorithms that has been extensively used in prediction problems) to estimate ODTRs. This presentation serves two purposes: 1) to review the ODTR SuperLearner and 2) to illustrate a practical application of the ODTR SuperLearneron data collected from an ongoing randomized clinical trial comparing Cognitive Behavioral Therapy(CBT) versus Treatment as Usual (TAU) in a sample (n=720) of criminal-justice involved patients with mental illness. Estimating the ODTR on this data helps inform for whom CBT works best to reduce recidivism, instead of Treatment As Usual (TAU; mostly psychiatric services). Preliminary results from the ODTR analysis show people with lower levels of substance abuse, higher education, and minimal psychiatric symptoms benefit more from CBT; people with higher levels of substance abuse, low education, and severe psychiatric symptoms benefit more from TAU. However, estimated outcomes if treatment were assigned using the ODTR algorithm (i.e., in an individualized way) were not significantly different from outcomes if all had been assigned treatment or no treatment. While this may indicate an absence of strong heterogeneous treatment effects by the measured variables or combinations of the variables, it may also reflect limitations in power to detect such effects due to preliminary sample sizes. This work contributes to understanding the toolbox of methods that can be used to advance the field of precision public health, and ultimately improve patient outcomes.

W6. COMPARISON OF ACCELEROMETER-BASED QUALITY OF REST METRIC TO PSG-DERIVED SLEEP EFFICIENCY

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Abstract: Objective: The aim of this analysis was to apply a novel cluster-based methodology for quantifying a rest quality metric to triaxial accelerometer data from an in-lab sleep study, and to compare this rest quality metric to gold-standard polysomnography (PSG) sleep stage classification and night-level sleep metrics. Accelerometer data was collected for patients with serious mental illness (SMI) and healthy volunteers via a torso-worn patch that can be used as part of a digital medicine system. Because sleep quantity and quality are important behavioral metrics for SMI patients, correlation between established sleep metrics and logistically simpler portable actimetry could enable more readily available insights into patients' clinical statuses.
Methods: Data was collected from 73 subjects (42 with SMI and 31 healthy volunteers) across a total of 220 nights in the sleep lab. For the accelerometer data, body orientation angle and step-

count records were used to differentiate rest from non-rest data points. The data was then partitioned into 15-minute non-overlapping time intervals. For the data from each night, K-means clustering (K=2) was used to identify the patient's rest-reference (RR) and deviation-from-reference (DFR) cluster. A rest quality score of zero was assigned to all points in the RR cluster, while the rest quality score for each point in the DFR cluster was defined as the Euclidean distance between that point in the DFR cluster and the RR cluster's center. The total rest quality score for each window was defined by summing all scores within that interval. The mean and standard deviation of this total rest quality score, as well as the mean and standard deviation of its first temporal derivative, were calculated across each night. Binary, i.e., sleep versus wake, PSG sleep stage classifications were made at 30-second without regard to sleep stage. The PSG data was consolidated into 15-minute intervals that coincided with the rest quality intervals by calculating the fraction of 30-second "wake" events within that interval. These PSG intervals were then compared to the interval-level rest quality data. Additionally, the sleep efficiency, i.e., fraction of intervals classified as sleep by PSG, across each night was compared to the nightly rest metrics that were derived. Data analysis was completed using Python.

Results: At the nightly level, the standard deviation of the first derivative of the rest quality metric exhibited a relationship to sleep efficiency. Nights with very high sleep efficiency had a smaller standard deviation in the rest quality first derivative, and nights with low sleep efficiency had larger standard deviations in this rest metric. Using a binary classification, where sleep efficiency and the rest quality derivative standard deviation thresholds were defined as their respective nightly medians, the rest quality metric accurately classified 65% of nights as either high or low PSG-derived sleep efficiency.

Conclusions: This work aimed to assess the correlation between a novel, accelerometer-based rest quality metric and PSG-derived sleep efficiency. Nightly features related to this rest metric mapped reasonably well to nightly sleep efficiency. This analysis, combined with the accelerometer's ability to identify when a subject is lying down, demonstrates the potential ability of this rest quality metric to provide information about both sleep quality and quantity using only the temporally sparse accelerometer data already available on this portable digital medicine system. Such accelerometer-based metrics, which do not require in-lab PSG data, could enable correlation between sleep and clinical outcomes for a much larger population of SMI patients.

W7. THE EFFICACY OF LUMATEPERONE IN PATIENTS WITH BIPOLAR DEPRESSION WITH AND WITHOUT MIXED FEATURES

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Abstract: Background: Mixed features during bipolar depression are common, associated with a more severe illness presentation, as well as higher rates of non-recovery, recurrence, and chronicity. Lumateperone (LUMA), a mechanistically novel antipsychotic that simultaneously modulates serotonin, dopamine, and glutamate neurotransmission, is FDA-approved for the

treatment of schizophrenia and is being investigated in adults with bipolar depression. A Phase 3 randomized, double-blind, parallel-group, placebo (PBO)-controlled multinational study (Study 404, NCT03249376) established the efficacy, safety, and tolerability of LUMA 42-mg monotherapy in patients with bipolar I or bipolar II disorder experiencing a major depressive episode (MDE). A post hoc analysis of Study 404 evaluated the efficacy of LUMA in patients with bipolar depression with mixed features.

Methods: The 6-week study evaluated the safety and tolerability of LUMA in patients aged 18–75 years with DSM-5-defined diagnosis of bipolar I or bipolar II disorder who were experiencing a current MDE (Montgomery-Åsberg Depression Rating Scale [MADRS] Total score ≥20 and a Clinical Global Impression Scale-Bipolar Version-Severity [CGI-BP-S] score ≥4 for depression and overall bipolar illness). Patients were required to have a Young Mania Rating Scale (YMRS) score ≤12 at screening and baseline. The primary and key secondary efficacy endpoints were change from baseline to Day 43 in MADRS Total score and CGI-BP-S score, respectively. For post hoc analyses, patients were categorized as having mixed features (YMRS Score ≥4) or not having mixed features (YMRS Score <4) at baseline. Comparisons between treatment groups for change from baseline in MADRS and CGI-BP-S scores were analyzed using a mixed-effects model for repeated measures.

Results: Of the intent-to-treat population (n=376), 41% had mixed features (LUMA, 73; PBO, 83). Mean baseline MADRS Total score for patients with mixed features (LUMA, 31.6; PBO, 30.5) and patients without mixed features (LUMA, 30.4; PBO, 30.1) indicated moderate-to-severe depression. LUMA compared with PBO showed significant improvement for both patients with mixed features (least square mean difference [LSMD]=−4.4, 95% CI [−7.26, −1.52]; P=.0030) and patients without mixed features (LSMD=−4.2, 95%CI [−6.46, −1.92]; P=.0004) as evidenced by change from baseline to endpoint in MADRS Total score. Improvement in CGI-BP-S scores for LUMA vs PBO were similar in patients with mixed features (LSMD=−0.7, 95%CI [−1.43, −0.05]; P=.0369) and with non-mixed features (LSMD=−1.0, 95%CI [−1.62, −0.47]; P=.0004). Rates of treatment-emergent mania (LUMA, 2; PBO, 4) and hypomania (LUMA, 1; PBO, 1) were low. Mean change in YMRS scores were -1.1 and -0.6 for LUMA and PBO, respectively.

Conclusion: In this post hoc analysis of a Phase 3 clinical trial, LUMA compared with PBO demonstrated significant and clinically meaningful efficacy in patients with bipolar depression with or without mixed features.

W8. LURASIDONE IN THE TREATMENT OF COMORBID ANXIETY SYMPTOMS IN BIPOLAR DEPRESSION

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Abstract: Background: Anxiety and subsyndromal manic symptoms often occur during episodes of depression. The objective of this post-hoc analysis was to investigate the relationships between symptoms of anxiety and depression, and their implications for treatment response to lurasidone

in patients with bipolar depression presenting with comorbid anxiety and subsyndromal manic symptoms.

Methods: This post-hoc analysis included pooled data from two placebo-controlled studies of lurasidone as monotherapy (20-60 mg/d and 80-120 mg/d) and as adjunctive therapy (20 to 120 mg/day flexibly dosed) with lithium or valproate in patients with bipolar depression. A "psychic anxiety" symptom component was assessed by a sum of HAM-A items 1-6 and item 14 for mental agitation and psychological distress. A "somatic anxiety" symptom component was assessed by a sum of HAM-A item 7-13 for physical complaints related to anxiety.

Results: Anxious symptoms were highly prevalent in patients with bipolar depression at study baseline, with 100% (n=824) having at least one psychic anxiety symptoms, and 88.5% (n=729) having at least one somatic anxiety symptom.

The proportion of patients with any degree of sleep disturbance symptoms as measured by the individual items assessing sleep was 94.9% on the MADRS, 95.1% on the HAM-A, and 76.3% on the YMRS. Lurasidone was associated with significant improvement in the psychic anxiety component score from baseline to week 6 as monotherapy (LS mean change -4.58, $p<0.001$ for 20-60 mg/d; LS mean change -4.40, $P<0.01$ for 80-120 mg/d; vs. -2.87 for placebo) and as adjunctive therapy with lithium/valproate (LS mean change -5.72 vs. -4.42 for lithium/valproate plus placebo, $P<0.01$).Lurasidone was also numerically but non-significantly associated with improvement in the somatic anxiety component score from baseline to week 6 as monotherapy for the low dose arm (mean change -1.89, P=0.09 for 20-60 mg/d; mean change -1.70, P=NS for 80-120 mg/d; vs. mean change -1.40 for placebo) and as adjunctive therapy with lithium/valproate (LS mean change -2.30 vs. -1.58 for lithium/valproate plus placebo, $P<0.01$).

The presence of the "decreased need for sleep" symptom (YMRS item 4) at baseline significantly moderated the effect of lurasidone monotherapy 20-60 mg/d (vs. placebo) treatment, leading to significantly greater lurasidone effect size for improvement in HAM-A total score (Cohen's d=0.55, $P<0.001$), somatic anxiety component score (d=0.35, P=0.008), and psychic anxiety component score (d=0.58, $P<0.001$) in the presence (vs. absence) of sleep disturbance symptoms. There was a significant association between changes in the "decreased need for sleep" symptom and changes in the HAM-A psychic and somatic anxiety component scores with lurasidone monotherapy 20-60 mg/d (vs. placebo) or adjunctive with lithium or valproate (vs. placebo plus lithium or valproate) treatment. Remission of anxiety symptoms (HAMA <= 18) mediated functional remission (all SDS domains <= 3) with lurasidone (vs. placebo) treatment ($P<0.05$).

Conclusion: Results of this post-hoc analysis suggest that lurasidone was efficacious in treating both psychic and somatic anxiety in adults with bipolar depression. Co-occurring sleep disturbance symptoms moderated the effect of lurasidone on anxiety. Remission of anxiety symptoms was also associated with functional recovery.

W9. ADJUNCTIVE LUMATEPERONE (ITI-007) IN THE TREATMENT OF BIPOLAR DEPRESSION: RESULTS FROM A RANDOMIZED CLINICAL TRIAL

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Abstract: Background: Approved treatments for bipolar depression are limited and associated with a spectrum of undesirable side effects. Lumateperone (lumateperone tosylate, ITI-007), a mechanistically novel antipsychotic that simultaneously modulates serotonin, dopamine, and glutamate neurotransmission, is FDA-approved for the treatment of schizophrenia. In a recent phase 3 clinical trial (Study 404, NCT NCT03249376), lumateperone 42-mg monotherapy significantly improved depressive symptoms in patients with a major depressive episode (MDE) associated with both bipolar I and bipolar II disorder. This Phase 3 randomized, double-blind, placebo-controlled multinational study (Study 402, NCT02600507) investigated the efficacy and safety of lumateperone adjunctive therapy to lithium or valproate in patients with bipolar I or bipolar II disorder experiencing an MDE (bipolar depression).

Methods: Patients (18–75 years) with a clinical diagnosis of bipolar I or bipolar II disorder who were experiencing a MDE with a Montgomery-Åsberg Depression Rating Scale (MADRS) Total score ≥20 and a Clinical Global Impression Scale-Bipolar Version-Severity (CGI-BP-S) score ≥4 at screening and baseline were randomized 1:1:1 to adjunctive placebo, lumateperone 28 mg, or lumateperone 42 mg with lithium or valproate for 6 weeks. The primary and key secondary efficacy endpoints were change from baseline to Day 43 in MADRS total score and CGI-BP-S Depression scores, respectively. Safety assessments included treatment emergent adverse events, laboratory parameters, vital signs, extrapyramidal symptoms (EPS), and suicidality.

Results: In this study, 528 patients received treatment (placebo, 175; lumateperone 42 mg, 177; lumateperone 28 mg, 176) and 430 completed the 6-week study. Patients in the lumateperone 42-mg group had significantly greater improvement on MADRS total score as indicated by mean change from baseline to Day 43 compared with placebo (least squares mean difference [LSMD] −2.4; 95% confidence interval [CI] −4.42, −0.37; P<.05), with numerical improvements in the lumateperone 28-mg group compared with placebo (LSMD −1.7; 95% CI, −3.65, 0.32; P=.10). There were significantly greater mean improvements in CGI-BP-S Depression score compared with placebo for patients treated with lumateperone 42 mg (LSMD −0.3; 95% CI −0.59, −0.09; P<.01) and lumateperone 28 mg (LSMD, −0.3; 95% CI, −0.50, −0.01; P<.05). Lumateperone treatment was well tolerated, with minimal risk of EPS, metabolic, and prolactin side effects.

Conclusion: Lumateperone 42 mg demonstrated efficacy as an adjunctive treatment to lithium or valproate, significantly improving depressive symptoms in patients with bipolar depression. Lumateperone was generally safe and well tolerated with no new safety concerns. These results suggest that lumateperone 42 mg may be a promising new adjunctive treatment to lithium or valproate for depression associated with bipolar I or bipolar II disorder.

W10. RIZATRIPTAN INDUCED MANIA IN CHRONIC BIPOLAR AFFECTIVE DISORDER

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Abstract: Comorbid migraine in the course of bipolar disorder has been reported as highly prevalent and associated with increased morbidity [1, 2]. Different pathophysiologic mechanisms and neurotransmitter systems play a role in the pathogenesis of bipolar affective disorder and migraine, which include serotonergic system (HT(1B/1D) receptors) and dopaminergic system [3]. The main advances for acute migraine treatment in the recent decades have been triptans [4]. Rizatriptan (Reference ID: 3059739) is a 5-HT1 receptor agonist of the triptan class of drugs developed by Merck & Co. for the treatment of migraine headaches [5]. Rizatriptan benzoate presumably exerts its therapeutic effects in the treatment of a migraine headache by binding to 5-HT1B/1D receptors located on intracranial blood vessels and sensory nerves of the trigeminal system. Multiple factors may contribute to precipitating bipolar mania/hypomania in susceptible individuals [6]. A review of the available literature elicited no cases of Rizatriptan precipitating hypomania and/or mania, and one case of Frovatriptan induced hypomania [7]. Here we present a case of mania induced by Rizatriptan in a patient with chronic bipolar disorder.
Ms. A is a 33-year-old woman who was seen and followed as an outpatient. She was diagnosed with bipolar I disorder and maintained on oral Depakote 750mg daily and IM monthly Abilify Aristida 882mg. The patient was last seen 3 weeks prior with a Young Mania Rating Scale (YMRS) of 5, with no hypomanic or mixed episodes in the previous 9 months. Patient had a migraine headache, lasted 18 hours, which was aggravated by work/school stressors and associated with nausea, photophobia and phonophobia. Patient took 2 pills of Rizatriptan 10 mg – prescribed by her neurologist. The same day patient started to develop insomnia, irritability, and racing thoughts. 2 days later her condition worsened, and she developed pressured speech, and increased somatic preoccupation, and a YMRS score of 27. She was subsequently hospitalized for observation and resumed on her same home treatment. Her symptoms resolved completely 3 days after hospitalization without changing her psychiatric medication.

W11. IS THERE A PANDEMIC ASSOCIATED CHANGE IN ENROLLMENT SEVERITY IN PEDIATRIC CNS TRIALS?

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Abstract: Background: The effect of the COVID-19 worldwide pandemic on subjects in non-COVID related CNS clinical trials is as of yet unknown and the subject of much speculation and interest. For pediatric CNS trials that began prior to the pandemic, regulators including IRBs and Ethics Committees have generally allowed trial continuation of enrolled subjects, if deemed safe, and have instructed sponsors to tag data collected during the pandemic and track any required administration venue changes (remote telemedicine visits as compared to in-clinic, for example). Many sponsors chose to suspend enrollment of new subjects, but many did not. In psychiatry trials, there is justified concern about a potential cohort effect of enhanced fear, anxiety, or grief associated with the pandemic, and it is unclear whether this will result in changes in the severity and characteristics of patients enrolling into trials and whether and if so how this may interact with response to the drugs under study. To begin to examine potential effects of the global pandemic on pediatric trials data, we examined efficacy scale severity data from in-person screening visits from 3 varied-indication CNS pediatric trials in the first 3 months vs. the remaining 9 months of

2020, using end of March as a reasonable date for pandemic lockdown for most countries. This methodology of defining the pandemic onset has been used by other authors for adult psychiatric trials (Kott and Daniel, 2020).

Method: We examined the severity data from screening visits from 3 disparate pediatric CNS indication studies that had begun screening prior to 2020 and were continuing to screen throughout 2020. Two of the studies were child psychiatric (1 psychosis and 1 mood) and 1 was child neurologic (neuromuscular). Scales were different for each study (primary efficacy for 2 and secondary efficacy for one that did not not administer the primary measure at screening). Studies were multisite, under the aegis of separate industry sponsors and conducted internationally with respective IRB/EC approvals. For each of the three studies, separately, scores from January through March 2020 (pre-pandemic) were compared to scores from April through December 2020 (pandemic) via independent sample unequal size parametric analysis.

Results: A total of 194 screening visits were examined for the year 2020: 72 of them prior to April 1st "pre-pandemic" and 122 conducted between April 1st and December 21st "pandemic." For each of the three studies, no significant difference was found for screening scores conducted in the "pre-pandemic" vs "pandemic" timeframes. Numerically, means were virtually identical across the two timeframes; in two of the three studies means reflected slightly lower severity (nonsignificant) in the pandemic timeframe than in the pre-pandemic timeframe (for the third study the mean values were numerically and statistically identical across timeframes).

Conclusions: Our study is preliminary and must be interpreted as such. As more data are gathered the effect of the pandemic on pediatric CNS trials data will grow. The effect of "lockdown status" for children with mental and neurological disorders may be different from that of children without such disorders – these questions remain to be examined. It may be the case that children have more resilience than adults to constrictions placed by lockdown or may be less aware of or concerned by the pandemic. The data, though limited, do provide some reason for cautious optimism for the integrity of CNS pediatric trials that span the pre-pandemic and pandemic timeframes.

W12. A NOVEL APPROACH TO PROVISIONAL DIAGNOSIS OF PREMENSTRUAL EXACERBATION OF DEPRESSION

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Abstract: Introduction: Faced with an acute exacerbation of depression (X) clinicians often consider medication adherence, concomitant medications, and intercurrent medical illness. In young women, recurrent menstrual-related X (mrX) should also be considered and, prior to any treatment change, date of last menses (LMP) documented. Accurate assessment of mrX has been impeded by lack of clinically useful methodologies: prospective symptom ratings of X are burdensome and self-report has little predictive validity. We provide proof-of-concept for a simple, novel approach to screening depressed, cycling women for mrX, using LMP.

Methods: Subjects were enrolled between April 1996 and July 1999 in consecutive clinical trials of antidepressant efficacy. Each had a diagnosis of DSM-IV depressive disorder or dysthymia.The

sample comprised the 35 spontaneously menstruating women (menses within the last 2 months and no treatment with gonadal hormones), of whom 34 had LMP documented. X was defined as a clinically significant increase in depressive severity by clinical global impression, operationalized as a 6-pt increase in HAMD-17 from one visit to the next. Day of the cycle was operationalized as days since LMP (d+) and, where available, days until onset of next menses (d-). The distribution of X was evaluated across a standardized 28-d cycle, anchored to menses, using circular statistics1. We calculated the circular mean and confidence angle, as well as the mean resultant length (MRL) of the composite vector. MRL varies from 0 to 1, representing the concentration of data around the mean. Rayleigh's z test for uniformity was conducted. A subanalysis was conducted of visits with both d+ and d- in order to increase physiological validity. Days 15-28 were plotted using d-, whereas remaining days 1 through 14 were plotted using d+.

Results: Thirty-four women attended 183 visits. Excluding one X on d+44 for presumed anovulation and reassigning one X on d+35 to d+28, ten women (29%) had X during 14 visits (7.7%). X clustered at an average of 4.3 (SD = 2.9) days prior to onset of menses (MRL = .54; $p < .025$, see figure). When date of next menses was available, X occurred at 3.3 (2.8) mean days prior to menses (MRL = .77; $p < .01$). Within the 2 cycles of the studies, two women had repeated X with both d+ and d- data. X fell on d-4 and d-5 or on d+1 and d-3; the 3 X with followup data all resolved by the next visit. X appeared in all active treatment groups.

Discussion: The strength of the relationship between X and the cycle suggests that perhaps half of all X in premenopausal women are in fact mrX, consistent with prior evidence2. The prior probability of X falling between d-5 and d+1 is 21%; the probability of 2 successive X in that interval is <5%. In this small study, two women had repeated, self-resolving X in the vulnerable timeframe, suggesting comorbidity with severe premenstrual dysphoria, which occurs at a rate of 3-9% 3. Documentation of LMP and the clinician's impression of increased severity of illness can increase the reliability of the provisional diagnosis of mrX, especially when examined prospectively. Treatment of women suffering a likely mrX with a transient dose (or increase) of an SSRI is supported both clinically4, 5 and pharmacologically6.

W13. ATTENDING TO THE PATIENT WITH MAJOR DEPRESSION: PREFERENCES FOR CLINICAL TRIAL METHODOLOGIES AND COVID19 MITIGATIONS

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Abstract: Introduction: The continued significant attrition rate within antidepressant randomized clinical trials (RCTs) has long been recognized, with Khan et al. (2000) finding the mean rate to be 37%, and more recently as high as 48% within RCTs of smartphone apps among subjects with major depressive disorder (MDD; Torous et al., 2020). The consequences of such poor RCT retention are extensive, including biased study results, reduced power, lower internal validity, less generalizability, and higher study costs (Liu et al., 2018). Researchers have examined reasons for

poor accrual within MDD RCTs, such as study design (Rutherford et al., 2013), but a thorough review of the literature yielded no investigation specifically surveying MDD patients regarding retention. Exploring these factors is essential toward minimizing participants' attrition (Page & Persch, 2013). In addition, given that study procedures are currently being considered and even implemented because of COVID19, it is crucial to explicitly survey these patients on such design matters to enhance their retention.
Methods: Patients currently experiencing a major depressive episode per the DSM-5 (APA, 2013) before study entry completed the Research Participant Preference Survey (RPPS), a 10-point Likert 45-item questionnaire focusing on various methodological, site operational, and assessment procedures that motivate general participation and continued enrollment in a trial, and specifically during the current COVID19 pandemic. The RPPS was completed at five US research sites (three in the West coast and two in the East) from May 2020 through December 2020.
Results: A total of 66 subjects completed the RPPS, with a mean of 1.47 previous MDD clinical trial participation. Preferences that strongly motivated enrolling and continued study participation included having the opportunity to discover new or improve antidepressants (M=7.68), study compensation (M=7.89), access to mental health care (M=7.52), site staff explaining the study rather than just receiving study information from the Consent Form (M=7.83), and site staff courtesy and respect (M=9.03). Wilcoxon pairwise comparisons indicated that study initiation and retention were significantly enhanced by shorter on-site study visits ($p<.001$), visits occurring every other week compared to multiple times a week ($p=.001$), and more on-site assessments versus engaging in Zoom or Skype calls while the subject is at home ($p=.003$) or having a lab staff member conduct such procedures at the subject's home ($p=.05$) during COVID19. Participants had a significant preference for clinician-administered computer/tablet assessments than paper ($p=.044$). An example of demographic-related findings indicated that, per an analysis of variance, racial minorities over their Caucasian counterparts significantly preferred paper assessments ($p=.031$).
Conclusions: Data from the current study indicate clear preferences that motivate subjects to enroll and not drop from clinical trial participation. These findings are informative to trial developers, such as knowing retention may be significantly hindered if a trial requires subjects to participate in longer duration study visits. Also, while sponsors and CROs may develop COVID19 remote study procedural contingency plans, subjects preferred assessments be conducted on site rather than at their homes. Potential explanation for our findings as well as study limitation will be discussed in the poster.

W14. EFFECTIVENESS OF LORAZEPAM IN CONJUNCTION WITH STEROIDS AND IMMUNOSUPPRESSANT IN TREATMENT OF CATATONIA SECONDARY TO SYSTEMIC LUPUS ERYTHEMATOSUS CEREBRITIS (SLE-C) – A CASE REPORT

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Abstract: Background: Catatonia is a neuropsychiatric syndrome that was described early by Karl Kahlbaum in 1874. Although the etiology remains largely unknown, the treatment of catatonia secondary to mental illness with lorazepam is associated with 66%-100% efficacy in previous studies. The DSM-V added a new entity of "catatonic disorder due to another medical condition,"

a possible cause of it is neuropsychiatric systemic lupus erythematosus. Previous studies explored the use of steroids and benzodiazepines to treat catatonia. Yet, few reports exist about the effectiveness of such medications in patients with active brain lesions secondary to SLE. We report an SLE-C case showing a sporadic response to the combination of lorazepam, steroids, and hydroxychloroquine.

Case Report: Ms. A is an 18-year-old female patient with no significant past medical history other than premature birth at 26 weeks without subsequent developmental delay, who presented to our hospital with chest pain of one day as well as a few weeks of subacute changes in mood and behavior, manifested as depressed mood, passive suicidal ideation, and psychomotor retardation. At the initial presentation, the patient had persistent tachycardia, catatonic-like symptoms (including blunted affect, mutism, posturing, and muscle resistance), together with impairment in her neurocognitive assessment, Mini-Mental Status Examination score (MMSE) was 19/30. Her magnetic resonance imaging (MRI) of the brain showed recent right frontal lobe white matter changes on T2 weighted images. Workup showed elevated erythrocyte sedimentation rate (ESR), low C3 and C4, high anti-nuclear antibody (ANA) titer, positive anti-double-stranded DNA antibodies, as well as pericardial effusion on echocardiogram. We started her on methylprednisolone 60mg IV q12h and hydroxychloroquine 200mg PO daily. Still, her response was slow with fluctuating motor and verbal abnormalities, anxiety, and intermittent paranoid ideation. Following initial responsiveness to the lorazepam challenge, we gradually increased her dose from 1mg IV q8h to 3mg PO/IV q8h, which showed a sporadic response. Her Bush Francis Catatonic Rating Scale (BFCRS) was fluctuating between 8-11/69. Over her hospital stay (4 weeks), she improved moderately with continued steroids, hydroxychloroquine, and lorazepam.

Discussion: In our case, lorazepam only showed moderate efficacy in treating catatonia due to SLE cerebritis, contrary to its effectiveness in treating catatonia secondary to affective or psychotic disorders. Such effect was potentiated with the addition of steroids and hydroxychloroquine. Although the pathophysiology remains mostly unknown, we propose using lorazepam in conjunction with steroids and hydroxychloroquine to treat such cases. The response to such regimen could be explained by cytokines' involvement in the context of cerebritis secondary to SLE.

W15. A MINDFULNESS AND PEER MENTORING PROGRAM TO IMPROVE ADHERENCE TO MEDICATION ASSISTED TREATMENT FOR OPIOID USE DISORDERS (THE MIND AND MENTORS PROGRAM [MIMP])

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Abstract: Although medication assisted therapy (MAT) for opioid use disorders (OUD) is safe and effective and is currently considered the gold standard for treating OUD, adherence to MAT regimens remains a challenge. Initial studies have demonstrated efficacy of mindfulness-based interventions as adjunctive treatment for substance use disorders (SUD) while reducing substance use and cravings. Additionally, non-randomized pilot studies suggest that mindfulness-based interventions may be effective in reducing symptoms of depression and anxiety in individuals

undergoing MAT for OUD. In addition, peer recovery support services delivered by individuals in recovery from SUD have also been found to be effective in reducing relapse rates, increasing treatment retention and improving relationships with treatment providers and social supports.6 Nonetheless, recent studies that have used a combination of therapy and MAT have yielded mixed results, thereby necessitating further exploration.7-8 Several factors, including depression, anxiety, stress, and cravings affect adherence to MAT and other SUD treatment regimens because they increase likelihood of relapse.9-12 Additionally, physiologic stress reactivity and drug cue reactivity, often measured by the hormone cortisol, have been shown to be predictors of relapse. The goal of our present study is to determine the effectiveness of a mindfulness-based intervention that also utilizes peer mentors in addition to professional substance abuse therapists (the Minds and Mentors program [MiMP]) in improving adherence to MAT for OUD and reducing relapse rates in a sample of individuals with OUD who are also on MAT versus a twelve-step facilitation (TSF) program. This study was recently funded by the National Institutes of Health's National Center for Complementary and Integrative Health (NCCIH) under the Helping to End Addiction Long-term (HEAL) Initiative. The MiMP is a 12-week intervention that uses group therapy and meets once a week for about an hour and half. We hypothesize that participants in MiMP will demonstrate better adherence (primary outcomes measures), reduced relapse and cravings reduced depression, anxiety, and stress, and improved social support (secondary outcomes measures), and reduced cortisol levels and reactivity to drug cues (exploratory outcome measures). This study will utilize an individually randomized group treatment design. Data collection will occur at baseline (T0), end of treatment (T1), and at 3 (T2), 6 (T3), and 12 (T4) months follow-up. The findings of the study have the potential to impact policy and practice changes related to treatment of OUD and strategies to improve adherence to MAT. This intervention has the potential to ultimately decrease morbidity and mortality in individuals with OUD by decreasing relapse and other comorbid psychosocial outcomes such as depression, anxiety, and stress. Furthermore, this study may help in the identification of individuals who are more reactive to stress, and who may need treatments that incorporate additional elements focused on stress reduction.

W16. STRESS AND COPING WITH THE COVID-19 PANDEMIC: A SURVEY OF PSYCHIATRIC PATIENTS AT CLINICAL TRIAL SITES

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Abstract: Recent research on the COVID-19 pandemic suggests that individuals who suffer with serious mental illness (SMI) are at heightened risk of infection and have increased mortality, due to their illness or lack of access to healthcare. As a consequence, progress in developing new treatments for the SMI has been disrupted, with many interruptions and holds places on clinical trials in psychiatry due to concerns regarding the pandemic and its risks to SMI patients. To investigate this further, we conducted, a multi-site cross-sectional survey of 94 clinical trial patients diagnosed with bipolar disorder (n=23), major depressive disorder (n=27), or schizophrenia (n=44) in three geographically-distinct clinical trial sites (Maryland, Georgia and Florida) between June and September 2020. The survey collected data on COVID health service

utilization, COVID knowledge and concerns, risk perceptions, use of precautionary measures, and psychological distress. Prevalence rates were calculated for sample characteristics and demographics, and low vs high stress groups were compared on survey variables using the Pearson's Chi Squared Test of Independence. The results from the surveys indicate that COVID19 knowledge, awareness, and the use of precautionary safety measures (i.e. handwashing, personal protective equipment, and social distancing) were robust and mirrored the general population. While the majority of patients reported experiencing moderate or extreme levels of distress (61.5%, n=56), high levels of stress were correlated with positive coping skills. These findings suggest that clinical trial patients with SMI can participate safely in clinical trials despite the increase safety risks posed by the COVID-19 pandemic.

W17. TOLCAPONE TREATMENT FOR COGNITIVE AND BEHAVIORAL SYMPTOMS IN BEHAVIORAL VARIANT FRONTOTEMPORAL DEMENTIA: A PLACEBO-CONTROLLED CROSSOVER STUDY

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Abstract: Background: There are currently no disease-targeted treatments for cognitive or behavioral symptoms in patients with behavioral variant frontotemporal dementia (bvFTD).
Objective: To determine the effect of tolcapone, a specific inhibitor of Catechol-O-Methyltransferase (COMT), in patients with bvFTD.

Methods: In this randomized, double-blind, placebo-controlled, cross-over study at two study sites, we examined the effect of tolcapone on 28 adult outpatients with bvFTD. The primary outcome was reaction time on the N-back cognitive test. As an imaging outcome, we examined differences in the resting blood oxygen level dependent (BOLD) functional magnetic resonance imaging (fMRI) signal intensity between subjects on placebo versus tolcapone performing the N-back test. Secondary outcomes included measures of cognitive performance and behavioral disturbance using the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), Neuropsychiatric Inventory-Questionnaire (NPI-Q), and Clinical Global Impressions scale (CGI).

Results: Tolcapone was well tolerated, and no patients dropped out. The most frequent treatment-related adverse event during tolcapone treatment was elevated liver enzymes (21%). There were no significant differences between tolcapone treatment and placebo in the primary or imaging outcomes. However, there were significant differences between RBANS total scores ($p < 0.01$), NPI-Q total scores ($p = 0.04$), and CGI total scores ($p = 0.035$) between treatment conditions which were driven by differences between baseline and tolcapone conditions. Further, there was a trend toward significance between tolcapone and placebo on the CGI ($p = 0.078$).

Conclusions: Further study of COMT inhibition and related approaches with longer duration of treatment and larger sample sizes in frontotemporal lobar degeneration-spectrum disorders may be warranted.

W18. ELECTROCONVULSIVE THERAPY CHANGES IMMUNOLOGICAL MARKERS IN PATIENTS WITH MAJOR DEPRESSIVE DISORDER

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Abstract: Background: Major depressive disorder (MDD) is a highly prevalent and disabling condition. Electroconvulsive therapy (ECT) is the most effective treatment option, although its mechanism of action is not fully understood. Elucidating the mechanism of action could further increase the efficacy and tolerability of ECT as well as promote acceptance of the treatment. Over recent decades, findings suggest that the immune system and gut microbiome play a role in the pathophysiology of MDD. More recently, ECT has been associated with changes in immune markers, indicating a role in ECT's mechanism of action.

Objectives: This systematic review aimed to summarize the human clinical trials correlating ECT with levels of immune markers. Our goal is to understand the effect ECT has on markers of neuroinflammation in patients suffering from MDD. Data sources: We conducted an electronic search of the literature in Medline (Pubmed), Embase (Elsevier), and PsycINFO (EBSCO) databases. We used a mix of keywords and controlled vocabulary representing MDD, ECT, gut microbiome, and the immune system. Study eligibility criteria: Included studies were those that evaluated ECT in patients with MDD, used immune or microbiome markers as outcome measures, and were published in English. Animal studies, incorrect intervention or outcomes, or without full text available were excluded. Studies from database inception to January 13, 2021, were considered. Study appraisal and synthesis methods: References were uploaded into Covidence, a systematic review screening tool, where a single reviewer screened all the titles and read the abstractsfound in the search (n = 646, after removal of 142 duplicates). Applying the inclusion/exclusion criteria, 474 articles were excluded. A full-text review was conducted on the remaining 172 studies, resulting in 145 studies excluded. The resulting 27 were organized into a table by study type and methodology, sample characteristics, ECT parameters, and main study findings.

Results: MDD is associated with a pro-inflammatory profile at baseline and some profiles may predict seizure quality and treatment outcome. In many studies, biomarkers normalized over time with ECT, especially in responders. Peripheral levels of interleukin-6 (IL-6) acutely increase following ECT, then decrease back to baseline or normalize with time. Decreased IL-6 has been shown to correspond with an improvement of psychomotor retardation after ECT and was associated with increased hippocampal volume. Additional inflammatory markers evaluated were tumor necrosis factor-alpha (TNF-alpha), c-reactive protein (CRP), interferon-gamma (IFN-gamma), IL-8, leukocyte G protein, among others. TNF-alpha data is inconsistent. Higher CRP

levels at baseline predict a larger reduction in depressive symptoms while lower baseline levels predict relapse. IFN-gamma was shown to decrease acutely after ECT, approaching that of controls. The kynurenine pathway, as a mediator between the gut microbiome and brain function, was relatively unchanged.

Limitations: Most studies had small sample sizes. Further, time points of specimen acquisition, clinical measures, and ECT procedures/parameters varied across studies.

Conclusions: Findings indicate that MDD is frequently associated with a pro-inflammatory profile at baseline and that ECT elicits immunological changes. As ECT is the most effective treatment for major depression and may normalize inflammation over time, the immunomodulatory effects of ECT may contribute to its mechanism of action.

W19. RAPID EFFECTS OF AXS-05, AN ORAL NMDA RECEPTOR ANTAGONIST, IN MAJOR DEPRESSIVE DISORDER: RESULTS FROM TWO RANDOMIZED, DOUBLE-BLIND, CONTROLLED TRIALS

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Abstract: Background: AXS-05 (dextromethorphan-bupropion modulated delivery tablet) is a novel, oral, investigational NMDA receptor antagonist with multimodal activity being developed for major depressive disorder. The dextromethorphan component of AXS-05 is an uncompetitive antagonist of the NMDA receptor, an ionotropic glutamate receptor, and sigma-1 receptor agonist, and the bupropion component serves to increase the bioavailability of dextromethorphan.
Objectives: To evaluate the rapidity of clinical effect of AXS-05 in the treatment of major depressive disorder.

Methods: AXS-05 was evaluated in two double-blind, randomized, controlled, 6-week trials. The GEMINI trial was placebo-controlled and the ASCEND trial used bupropion as the control. The primary efficacy variable in both was change in the MADRS total score. Here we examine the efficacy in the first 2 weeks of treatment.

Results: AXS-05 met the primary endpoint in both studies. In GEMINI (N=327), starting at Week 1, AXS 05 was superior to placebo on: mean MADRS improvement (7.3 vs. 4.9; p=0.007), MADRS response (≥50% improvement; 15% vs. 7%; p=0.035), CGI-I (22% vs. 13%; p=0.035), CGI-S (0.7 vs. 0.4; p=0.013) and Q-LES-Q-SF (9.0% vs. 5.8%; p=0.031). At Week 2, AXS-05 was superior to placebo on MADRS remission (≤10; 17% vs. 8%; p=0.013) and on the Sheehan Disability Scale (6.8 vs. 4.5; p=0.003). In ASCEND (N=80), starting at Week 1, AXS-05 was superior to bupropion on: CGI-I (18% vs. 3%; p=0.045) and MADRS-6 response (≥50% improvement; 16% vs. 3%; p=0.044). From Week 2, AXS-05 was superior to bupropion on: mean MADRS improvement (12.5 vs. 7.8; p=0.024), MADRS remission (≤10; 26% vs. 3%; p=0.004), and CGI-S (1.41 vs. 0.9; p=0.049).

Conclusions: AXS-05 demonstrated rapid and statistically significant improvements in depression at Weeks 1 and 2 in placebo- and active- controlled trials. In both studies, rapid remission from

depressive symptoms was achieved by Week 2 and maintained over the 6-week treatment period. The novel mechanisms of action of AXS-05 may contribute to these rapid antidepressant effects.

W20. EFFECTS OF AXS-05, AN ORAL NMDA RECEPTOR ANTAGONIST WITH MULTIMODAL ACTIVITY, ON PATIENT REPORTED DEPRESSIVE SYMPTOMS IN MAJOR DEPRESSIVE DISORDER: RESULTS FROM THE GEMINI PHASE 3 DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL

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Abstract: Background: Major depressive disorder (MDD) is chronic and disabling disorder. Two-thirds of patients have an inadequate response to current first-line therapies and the majority of these inadequate responders also fail second-line therapy. Current oral antidepressants are associated with prolonged time to clinically meaningful response (up to 6-8 weeks).
AXS-05 (dextromethorphan-bupropion modulated delivery tablet) is a novel, oral, investigational NMDA receptor antagonist with multimodal activity being developed for MDD. The dextromethorphan component of AXS-05 is an uncompetitive antagonist of the NMDA receptor, an ionotropic glutamate receptor, and sigma-1 receptor agonist, and the bupropion component serves to increase the bioavailability of dextromethorphan. Patient reported outcomes (PROs) are directly reported by the patient without interpretation by a clinician, therefore providing an assessment of the benefit of treatment from the perspective of the patient.

Objective: To evaluate the patient-reported antidepressant effects of AXS-05 compared to placebo.

Methods: GEMINI was a randomized, double-blind, placebo-controlled trial, in which 327 adults with moderate or severe MDD were randomized 1:1 to AXS-05 (dextromethorphan HBr 45 mg and bupropion HCl 105 mg) or placebo treatment twice daily for 6 weeks. The primary endpoint was change from baseline in MADRS total score at Week 6. On the primary endpoint, AXS-05 rapidly, substantially, and durably improved depressive symptoms on the MADRS vs. placebo, with statistical significance demonstrated as early as Week 1, and at all timepoints thereafter including the primary endpoint of Week 6.

Two PROs for depression were used in this trial: the Quick Inventory of Depressive Symptomatology (Self-Report) (QIDS-SR-16), and the Patient Global Impression of Improvement (PGI-I) for depression. The PROs in the GEMINI trial complement the clinician-reported measures, including the MADRS and CGI-I, used in this trial.

Results: At baseline, QIDS-SR-16 scores were 16.2 for AXS-05 and 15.8 for placebo. Improvements from baseline on the QIDS-SR-16, were statistically significant for AXS-05 vs. placebo beginning at Week 1 (-3.7 points and -2.3, respectively, $p=0.016$) and at Week 2 (-5.8 and -3.5, respectively, $p<0.001$), Week 3 (-6.5 and -4.1, respectively, $p<0.001$), Week 4 (-7.5 and -4.7, respectively, $p<0.001$), and Week 6 (-7.8 and -5.4, respectively, $p=0.001$).

Percentages of patients reporting very much or much improved on PGI-I were statistically significant for AXS-05 vs. placebo beginning at Week 1 (13.5% vs. 4.9%, respectively, p=0.008) and at Week 2 (30.0% vs. 18.2%, respectively, p=0.015), Week 3 (43.2% vs. 18.2%, respectively, p<0.001), Week 4 (46.9% vs. 28.0%, respectively, p=0.001), and Week 6 (47.2% vs. 31.3%, respectively, p=0.007).

Conclusions: Patients receiving treatment with AXS-05 reported rapid, substantial, and statistically significant improvements in depressive symptoms consistent with clinician-reported measures (MADRS, CGI-I), starting at Week 1 and sustained through Week 6. These findings suggest that AXS-05, as a mechanistically-novel medicine, rapidly and substantially improves depressive symptoms as observed by clinicians and as reported by patients.

W21. EXPLORING THE RELATIONSHIP BETWEEN HETEROGENEOUS SYMPTOMS OF MAJOR DEPRESSIVE DISORDER AND ANTIDEPRESSANT RESPONSE: PRELIMINARY FINDINGS

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Abstract: Intro: Major Depressive Disorder (MDD) is a highly heterogeneous disorder with varied presentations. This may point to the heterogeneity of response and suboptimal outcomes to first, second, and even third-line treatments (1). Thus, identifying whether certain antidepressants yield favourable responses to specific symptoms may improve and personalize treatment plans. This study is a preliminary step in determining whether baseline items in the 17-item Hamilton Depression Rating Scale (HAM-D) may predict antidepressant response (2).

Methods: Archival data from 13 clinical trials evaluating the efficacy of antidepressants in the treatment of MDD were pooled together for analyses. Due to differences in protocols, only treatment arms with a fixed dose between 6 - 8 weeks were included in the analyses. The subsequent dataset (N = 3051) included HAM-D data on duloxetine (n = 2199), paroxetine (n = 585) and escitalopram (n = 267). Within each drug subset, participants were categorized into responders (total HAM-D reduction greater than 50%) and non-responders (total HAM-D reduction less than 50%). Welch two-sample T-Tests were employed to determine whether there was a significant difference between responders and non-responders prior to receiving treatment for each item on the HAM-D.

Results: The mean differences in total HAM-D scores at baseline were negligible in duloxetine (Mresponders= 21.88, Mnonresponders = 21.72), paroxetine (Mresponders= 21.54, Mnonresponders = 21.79), and escitalopram (Mresponders= 20.60, Mnonresponders = 20.99) groups.

In the duloxetine treatment arm, responders had significantly lower ratings of depressed mood, $t(2093) = 2.0$, $p < 0.05$, feelings of guilt, $t(1604) = 3.96$. $p < 0.0005$, suicide, $t(1600) = 3.7$, $p < 0.0005$, somatic anxiety, $t(1993)$, $p < 0.05$ and work and activities $t(1692) = 2.97$, $p < 0.05$ compared to non-responders on the HAM-D. Responders also had significantly greater ratings for

hypochondriasis, $t(2049) = -3.58$, $p < 0.0001$ and insight, $t(1817) = -2.96$, $p < 0.005$, compared to non-responders.
In the paroxetine treatment arm, responders scored significantly lower than non-responders on HAM-D ratings of the following items: feelings of guilt, $t(463) = 2.39$, $p < 0.05$, suicide $t(451) = 2.19$, $p < 0.05$, work and activities, $t(446) = 2.35$, $p < 0.05$. Furthermore, paroxetine responders had significantly greater scores for retardation than non-responders, $t(447) = -2.14$, $p < 0.05$.
In the escitalopram group, responders scored significantly lower on weight loss, $t(198) = 2.3$, $p < 0.05$ than non-responders on HAM-D scores.
Conclusion: Minimal differences in pretreatment total HAM-D scores across groups suggest that total scores provide poor insight into who may respond best to a drug. Thus, we investigated individual symptoms on the HAM-D scale. Our preliminary findings indicate that certain presentations of MDD may respond better to an antidepressant than others. Notably, these findings suggest that treatment response may be determined by both highly endorsed and under-endorsed symptoms, as seen in duloxetine responders with mild feelings of guilt, yet poorer insight. Further analyses will aim to elucidate whether individual items and symptom clusters can predict outcomes to specific antidepressants. As such, we aim to employ linear discriminant analysis, taking into consideration dosage, multiple timepoints from pre-to-post treatment, remission, sample size, and placebo groups to investigate whether such symptom clusters exist.

W22. EARLY LIFE ADVERSE EVENTS AS CHARACTERIZED VIA THE CHILDHOOD TRAUMA QUESTIONNAIRE IN A NATURALISTIC SAMPLE OF TREATMENT RESISTANT DEPRESSION RECEIVING TRANSCRANIAL MAGNETIC STIMULATION THERAPY

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Abstract: Background: Transcranial magnetic stimulation (TMS) is effective for those with unsatisfactory response to pharmacotherapy and psychotherapy for depression (MDD). Adverse early life events such as childhood trauma has been shown to have lasting effects on the health and treatment outcomes for many illnesses including MDD. Little is known regarding the relationship between childhood trauma and TMS for MDD. The aim of the study was to investigate the relationship between the severity and types of childhood adverse events with TMS clinical outcomes.
Methods: Childhood Trauma Questionnaire (CTQ), a questionnaire to assess severity and type of childhood trauma, was collected in a naturalistic setting from patients receiving TMS for treatment resistant MDD. Inventory of Depressive Symptomatology Self Report (IDS-SR) was used as a measure of depression symptom severity, clinical response and remission. Treatment was given at 10 Hz stimulation to the dorsolateral left prefrontal cortex at 120% maximum intensity relative to their motor threshold for 3000-4000 pulses/daily for 6 weeks.

Results: Data from 117 clinic patients receiving TMS for the first time who completed CTQ from February 2017 to October 2020 were collected and analyzed. 66.7% (n=78) were female and average age at start of TMS was 46.69. 66.7% (n= 78) of the patients had at least one moderate to severe level of trauma in one of the 5 categories of trauma, and 52.1% (n=61) had moderate or

severe level of trauma in two or more categories. Of the 117 patients, 49.6% (n=58) had experienced moderate or severe emotional abuse, 42.7% (n=50) emotional neglect, 34.1% (n=40) sexual abuse, 28.8% (n=33) physical abuse, and 27.3% (n=32) physical neglect. Overall patients with more severe trauma showed less improvement in depressive symptoms after TMS as seen via a statistically significant negative correlation between IDS-SR % change and CTQ overall total score ($r=-.251$, $p<0.01$). Specifically, patients with more severe trauma in the physical abuse ($r=-.245$, $p<0.01$) and physical neglect ($r=-.251$, $p<0.01$) had less magnitude of improvement in depression. Non-responders had significantly higher mean scores in physical abuse (9.35±4.72 vs 7.29±3.37, $p<.01$), sexual abuse (11.15±7.43 vs 8.48±6.41, $p<.05$), and physical neglect (8.89±4.12 vs 7.35±2.75, $p<.05$) compared to responders. Patients with physical neglect tended to be non-responders as shown via a significant chi-square association between non-response and physical neglect ($\chi=8.623$, $p<0.05$); and those with sexual abuse tended to be non-remitters ($\chi=9.214$, $p<0.05$).

Discussion: Our result was in accordance with other studies that have shown that the presence of childhood adverse events impacting treatment outcome in various disorders including depression. Furthermore, our data show that certain types of trauma may have more impact on TMS outcomes than others. Based on these results, future studies examining the possible biological pathways and mechanisms contributing to the differences in severely depressed patients with and without certain types of childhood trauma could lead to a more personalized treatment algorithm leading to improved efficacy of TMS.

W23. IMPACT OF COVID-19 PANDEMIC AMONG PATIENTS WITH MDD IN A US COMMERCIALLY INSURED POPULATION: A SURVEY STUDY

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Abstract: Objective: Assess the impact of the COVID-19 pandemic among patients with major depressive disorder (MDD).

Methods: Survey-eligible, commercially-insured patients, aged 18–64 years, with >1 medical claim for MDD and treated with antidepressants during 12/1/2018–11/30/2019, were identified from claims in the HealthCore Integrated Research Database. Consenting, qualified patients completed an internet-based survey that included the PHQ-9 depression scale, PROMIS GH-10 health-related quality of life questionnaire, demographic/clinical characteristics, and questions related to the impact of the COVID-19 pandemic. A COVID-19 Pandemic Impact (CPI; not yet validated) score, ranging from 0-60, with increasing scores indicating greater impact of the pandemic , was calculated by adding responses of the 6 individual CPI questions. Based on score distribution, 3 CPI levels were defined to maximize differences between low and high impact levels: Low Pandemic Impact (LPI)=lowest quartile scores 0–10; Medium Pandemic Impact (MPI)=interquartile scores 11–30; High Pandemic Impact (HPI)=highest quartile scores 31–60.

Chi-square tests and ANOVA testing were used to assess unadjusted differences among CPI groups as appropriate.

Results: Of 900 patients who completed the survey; 78% were female, 92% were white, non-Hispanic, 87% had attended at least some college, 57% were married, 74% were employed with a mean age varying across CPI levels (LPI=48; MPI=45; HPI=43; p<0.001). Compared to LPI and MPI patients, HPI patients reported significantly more generalized anxiety disorder (LPI=59%; MPI=67%; HPI=79%; p<0.001), fatigue (LPI=36%; MPI=49%; HPI=54%; p<0.001), and sleep problems (LPI=45%; MPI=54%; HPI=61%; p=0.005). HPI-level patients reported significantly higher PHQ-9 symptom scores (LPI=4.9 MPI=7.4; HPI=10.1; p<0.001) and significantly lower GH-10 physical (LPI=49; MPI=47; HPI=44; p<0.001) and mental health summary norm scores (LPI=47; MPI=43; HPI=40; p<0.001). Among COVID-19 pandemic related behaviors, HPI patients reported significantly more alcohol use (LPI=17%; MPI=27%; HPI=38%; p<0.001), drug use (LPI=2%; MPI=4%; HPI=13%; p<0.001), tobacco use (LPI=6%; MPI=9%; HPI=15%; p=0.012), unhealthy mindless eating (LPI=32%; MPI=58%; HPI=83%; p<0.001), and sedentary behavior (LPI=48%; MPI=72%; HPI=81%; p<0.001) than patients in the LPI and MPI groups. HPI patients reported significantly more access-to-care issues than MPI and LPI patients in terms of missing scheduled visits with mental healthcare providers (LPI=8%; MPI=17%; HPI=26%; p<0.001), changing mental healthcare provider in-person visits to telehealth visits (LPI=44%; MPI=53%; HPI=61%; p=0.005), and avoiding or being unable to make a visit to a healthcare facility for an urgent mental health issue (LPI=7%; MPI=10%; HPI=18%; p=0.001).

Conclusion: Impact of the COVID-19 pandemic varied among patients with MDD. High CPI is associated with lower age, increased depression symptomatology, lower health-related quality of life, increased alcohol use, drug use, unhealthy eating habits and sedentary behavior, and greater access to care issues. Additional investigation is needed to determine long-term effects of the impact of the COVID-19 pandemic on health behaviors and overall depression.

W24. TREATMENT WITH ZURANOLONE IN COMBINATION WITH STANDARD OF CARE ANTIDEPRESSANT IN THE PHASE 3, OPEN-LABEL, LONGITUDINAL SHORELINE STUDY IN PATIENTS WITH MAJOR DEPRESSIVE DISORDER

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Abstract: Introduction: Zuranolone (ZRN; SAGE-217) is an investigational, oral, neuroactive steroid (NAS) ɣ-aminobutyric acid receptor type A (GABAAR) positive allosteric modulator (PAM) being studied as a treatment for patients with Major Depressive Disorder (MDD).1 ZRN has pharmacology distinct from benzodiazepines, which target only synaptic GABAAR, by targeting both synaptic and extra-synaptic GABAAR.2 The ongoing phase 3, open label, 1-year

longitudinal SHORELINE study (NCT03864614) is evaluating the safety, tolerability, and need for repeat dosing with ZRN in patients with MDD.

Objectives: To present interim safety and efficacy of ZRN 30 mg (ZRN30) in a subset of patients with MDD vs those treated with ZRN30 in combination with a standard of care (SOC) antidepressant therapy (ADT).

Methods: An interim analysis from July 2020 evaluated 801 patients with MDD, aged 18-75, with Hamilton Depression Rating Scale (HAMD-17) total score ≥20 and Montgomery–Åsberg Depression Rating Scale (MADRS) total score ≥28 at screening, who received ZRN30 or ZRN 50 mg (ZRN50) for 14 days. Use of pre-existing SOC ADT is permitted provided patients were on a stable dose for ≥60 days prior to Day 1. Patients who achieved a HAMD-17 response (≥50% improvement) at Day 15 were followed for 48 weeks and were eligible to receive retreatment based on standardized assessments. The primary endpoint was safety and tolerability assessed by adverse events and clinical measures. The interim safety data set comprised patients receiving ZRN30 throughout their participation in the study (n=677). Secondary endpoints including rates of retreatment, change from baseline in HAMD-17 total score, HAMD-17 response (≥50% improvement) and remission (HAMD-17 total score ≤7) were assessed in the efficacy data set (patients who only received ZRN30 and completed the first cycle of treatment; n=640). This analysis evaluated the impact of an SOC ADT used in combination with ZRN30 compared to ZRN30 alone on study outcomes.

Results: In the interim safety dataset 41.4% (280/677) of patients who received ZRN30 throughout their participation in the trial were also receiving stable dose SOC ADT. During treatment cycle 1, the number of ZRN30 patients with ≥1 treatment-emergent adverse events (TEAEs) was similar between patients taking concomitant SOC ADT compared with those who were not (157/280 [56.1%] vs 266/397 [67.0%], respectively). TEAEs leading to study drug discontinuation were low in both groups (4/280 [1.4%] vs 10/397 [2.5%], respectively). In the interim efficacy dataset the change from baseline (SD) in HAMD-17 was -15.1 (7.3) for patients taking ZRN30 with concomitant SOC ADT (n=270) and -14.7 (6.9) in those receiving ZRN30 only (n=370) at Day 15 of treatment cycle 1. Similar HAMD-17 response rates of 70.0% (191/270) and 72.2% (267/370) and remission rates of 37% (100/270) and 41.9% (155/370) were observed at Day 15 for patients taking ZRN30 with concomitant SOC ADT, and those who were receiving ZRN30 only, respectively. The proportion of patients requiring retreatment and time between retreatment, for those requiring it, was not affected by use of ZRN30 with concomitant SOC ADT at baseline in the previous treatment cycle.

Conclusions: This interim analysis suggests that safety and efficacy of zuranolone is not affected when used in combination with a SOC ADT. Ongoing studies will further evaluate zuranolone administered either “as needed” as monotherapy or in combination with an SOC antidepressant for treatment of MDD.

W25. CHANGES IN METABOLIC PARAMETERS AND BODY WEIGHT IN PATIENTS WITH AND WITHOUT PRE-DIABETES: POOLED ANALYSIS OF SHORT- AND LONG-TERM CLINICAL STUDIES OF ADJUNCTIVE BREXPIPRAZOLE IN MAJOR DEPRESSIVE DISORDER

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Abstract: Background: Many atypical antipsychotics are associated with metabolic adverse effects, which increase the risk for drug-related diabetes mellitus (1). Brexpiprazole is a serotonin–dopamine activity modulator with a pharmacology that may limit the risk for diabetes and weight gain. In a previous study of adults with major depressive disorder (MDD), adjunctive brexpiprazole was associated with small changes in metabolic parameters and moderate weight gain during short- and long-term treatment (2).The aim of this post hoc analysis was to analyze the effect of adjunctive brexpiprazole on metabolic parameters and body weight in adults with MDD with and without pre-diabetes at baseline, based on pooled data from three short-term studies and one long-term extension study.

Methods: The short-term studies (NCT01360645, NCT01360632, NCT02196506) were randomized, double-blind, placebo-controlled studies in outpatients with MDD (DSM-IV-TR criteria) and inadequate response to 1–3 prior antidepressant treatments (ADTs) plus 1 prospective ADT. Patients were randomized to adjunctive brexpiprazole (fixed doses in the range of 1–3 mg/day) or placebo for 6 weeks. The long-term study (NCT01360866) was a 52-week (amended to 26 weeks), open-label, uncontrolled study of adjunctive brexpiprazole 0.5–3 mg/day (flexible dose). Mean changes from baseline and categorical shifts in fasting metabolic parameters (cholesterol, triglycerides, glucose) and body weight were analyzed by pre-diabetes status. 'Pre-diabetes' was defined as a glycated hemoglobin (HbA1C) level of ≥5.7% and <6.5% at baseline; patients with HbA1C <5.7% at baseline were classed as 'normal HbA1C'.

Results: In the analysis of short-term study data, the pre-diabetes subgroups comprised 182 patients treated with ADT + brexpiprazole and 136 patients treated with ADT + placebo; corresponding numbers in the normal HbA1C subgroups were 545 and 390. Mean changes from baseline in metabolic parameters after 6 weeks of ADT + brexpiprazole treatment were small in the normal HbA1C subgroup (all ≤4 mg/dL), and negligible or beneficial in the pre-diabetes subgroup (all ≤0 mg/dL). In the analysis of long-term study data (short-term studies plus long-term extension; up to 58 weeks), the pre-diabetes subgroup comprised 642 patients and the normal HbA1C subgroup comprised 1,920 patients. Mean changes in metabolic parameters from baseline to Week 52 were generally small (all <6 mg/dL) and similar between the subgroups, except for triglycerides: pre-diabetes subgroup, 8.49 mg/dL; normal HbA1C subgroup, 19.99 mg/dL. There were no notable differences between subgroups in the incidence of favorable and unfavorable shifts in metabolic parameters. Considering body weight, the mean increases at last visit of the short-term studies in the pre-diabetes subgroups were 1.6 kg (ADT + brexpiprazole) and 0.4 kg (ADT + placebo); corresponding values in the normal HbA1C subgroups were 1.5 kg and 0.4 kg. During long-term treatment (up to 58 weeks), the mean body weight increase at last visit was 2.4 kg in the pre-diabetes subgroup and 3.0 kg in the normal HbA1C subgroup.

Conclusion: Adjunctive brexpiprazole was associated with small changes in metabolic parameters and moderate weight gain during short- and long-term treatment. Results were comparable

between subgroups with and without pre-diabetes, suggesting that adjunctive brexpiprazole has a limited impact on the metabolic profile in patients with MDD regardless of pre-diabetes status.

W26. UPDATE ON THE LANDSCAPE DEVELOPMENT PROGRAM OF ZURANOLONE FOR THE TREATMENT OF MAJOR DEPRESSIVE DISORDER

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Abstract: Introduction: Zuranolone (ZRN; SAGE-217) is an investigational, oral neuroactive steroid (NAS) positive allosteric modulator (PAM) of synaptic and extra-synaptic ɣ-aminobutyric acid type A receptors (GABAAR), making its pharmacology distinct from benzodiazepines which target only synaptic GABAAR.1 The LANDSCAPE development program is designed to evaluate the efficacy and safety of ZRN in MDD.

Objectives: To present the study rationales, designs, and updates from the LANDSCAPE development program of ZRN.

Methods: Completed or currently active studies in the LANDSCAPE program consist of 2 completed (one phase 2 and one phase 3) and three ongoing phase 3 studies that evaluate ZRN as monotherapy, add-on, or as-needed therapy in patients with MDD. The phase 2, randomized, double-blind, placebo-controlled study (NCT03000530) examined the efficacy and safety of 14-day treatment with ZRN 30 mg vs placebo (n=89). The phase 3 MOUNTAIN study (NCT03672175) examined the efficacy and safety of 14-day treatment with ZRN 20 mg or 30 mg vs placebo (n=581) followed for up to 6 months after treatment. The ongoing phase 3 WATERFALL study (NCT04442490) is assessing the efficacy and safety of a 14-day treatment of ZRN 50 mg vs. placebo followed for 42 days after treatment initiation (planned enrollment n=370). The phase 3 SHORELINE study (NCT03864614) is an ongoing, open-label, 1-year, naturalistic, longitudinal study evaluating the safety, tolerability, and need for retreatment with ZRN 30 mg or 50 mg (planned enrollment n=900). The phase 3 CORAL study (NCT04476030) is designed to assess a 14-day treatment with ZRN 50 mg as a rapid response therapy vs placebo when co-initiated with a new standard of care antidepressant therapy (planned enrollment n=424).

Results: In the phase 2 study (NCT03000530), ZRN met its primary endpoint of an improvement in depressive symptoms in adults with MDD based on the change from baseline at Day 15 on the HAMD-17.2 The MOUNTAIN study showed a rapid reduction of depressive symptoms at Day 3 with 14-day ZRN 30 mg treatment vs placebo but did not meet its predefined primary endpoint (Day 15). Post-hoc analyses in patients with baseline HAMD-17 score ≥24 and a measurable plasma concentration demonstrated that ZRN 30 mg separated from placebo at Day 3, with significant improvements observed at all measured timepoints through Day 15, which suggests that 30 mg is the minimally effective dose. Thus, the LANDSCAPE program was expanded to include 50-mg dosing cohorts in the ongoing studies. An interim data cut from the open-label SHORELINE study (July 2020) reported safety and tolerability data consistent with prior ZRN studies. The majority (70.8%) of patients who initially responded to ZRN 30 mg (HAMD-17)

required no re-treatments (44.5%) or 1 re-treatment (26.3%) over the 1- year study period. At Day 15 following the first 14-day treatment course, the mean (SD) change from baseline in HAMD-17 total score for patients treated with ZRN 30 mg (n=640) was -14.9 (7.1). Topline data from the WATERFALL and CORAL studies are anticipated in the 1st and 2nd half of 2021, respectively.

Conclusions: The LANDSCAPE development program is a large, multi-study clinical program for zuranolone treatment in patients with MDD. Utilizing the unique characteristics of zuranolone as a NAS GABAAR PAM, the program is designed to assess rapid response and sustained treatment effects.

W27. LONG-TERM SAFETY OF ESKETAMINE NASAL SPRAY IN PATIENTS WITH TREATMENT-RESISTANT DEPRESSION: INTERIM RESULTS OF THE SUSTAIN-3 STUDY

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Abstract: Background: Esketamine nasal spray (ESK) plus a newly initiated oral antidepressant (AD) has demonstrated robust efficacy and an acceptable safety profile in managing treatment-resistant depression (TRD). However, long-term (>1 year) safety data are limited.

Methods: This ongoing phase 3, open-label extension study is being conducted to evaluate the long-term safety (and efficacy) of individualized, intermittently-dosed ESK in conjunction with an oral AD in patients with TRD. Patients (≥18 years) who previously participated in 1 of 6 phase 3, "parent" studies of ESK (NCT02417064, NCT02418585, NCT02493868, NCT02497287, NCT02422186, NCT03434041 [US sites]) entered either the 4-week induction (IND) phase or the long-term optimization/maintenance (OP/M) phase of this study based on their status at the end of the parent study. In the IND phase, eligible patients self-administered (under supervision) ESK (28 [starting dose age ≥65 years], 56, or 84 mg) as a flexible dose, twice-weekly for 4 weeks. In OP/M phase, eligible patients received interval dosing of ESK individualized to the severity of their depression. Safety evaluations included treatment-emergent adverse events (TEAEs) and cognition (using a computerized cognitive test battery [Cogstate] and the Hopkins Verbal Learning Test-Revised). Interim safety results from the extension study are reported herein (data cutoff: 20 May 2020; ~4 years from study initiation).

Results: A total of 1148 patients (458 entered at IND; 690 entered at OP/M) were enrolled in the study. Of 458 patients who entered the IND phase, 420 (91.7%) continued to the OP/M phase. Of 1110 patients who participated in the OP/M phase, 306 (27.6%) discontinued the study, primarily due to AEs (n=54), lack of efficacy (n=48), and other reasons (n=135; e.g., symptom improvement, scheduling/logistical conflicts, etc.). The median total duration of exposure, including exposure in the preceding parent study, was approximately 3 years (35.8 [range: 0, 57] months). In total, 1064 patients experienced ≥1 TEAEs (IND: 346/458, 75.5%; OP/M: 1024/1110, 92.3%). The most

common TEAEs (≥10% of patients) in IND phase were dissociation (21.2%), dizziness (20.5%), nausea (17.7%), vertigo (16.8%), dysgeusia (bad/altered taste) (16.6%), and headache (15.1%), and in OP/M phase were headache (31.2%), dizziness (29.8%), nausea (28.1%), dissociation (22.3%), somnolence (21.8%), nasopharyngitis (21.5%), dysgeusia (18.6%), vertigo (16.8%), anxiety (14.4%), back pain (14.3%), vomiting (13.6%), diarrhea (12.3%), increased blood pressure, urinary tract infection (each 12.1%), upper respiratory tract infection (11.3%), and blurred vision (10.1%). Most TEAEs were mild or moderate in severity. Long-term exposure to ESK did not reveal any additional safety signals of concern related to bladder-, lower urinary tract-, or hepatic-related TEAEs. There were 4 (0.3%) deaths, none considered by the investigator as related to ESK. Cognition remained stable or showed a trend for small, averaged improvement among patients during the IND and OP/M phases, with the exception of a slight slowing of reaction times in patients aged ≥65 years, consistent with results of another longitudinal trial.

Conclusion: This interim analysis suggests that long-term treatment (~3 years) with ESK+AD has acceptable safety and tolerability. No new or unexpected safety concerns emerged during 3-year intermittently-dosed treatment with ESK.

W28. INTRANASAL ESKETAMINE EFFECTIVELY TREATS TREATMENT-RESISTANT DEPRESSION IN ADULTS REGARDLESS OF BASELINE IRRITABILITY

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Abstract: Background: Irritability is an important yet underrecognized symptom in adults with major depressive disorder (MDD); its association with clinical features in adults with treatment-resistant major depression (TRD) is poorly understood. Furthermore, the impact of irritability on clinical outcomes in adults with TRD treated with esketamine nasal spray (ESK) has not been evaluated.

Methods: This was a post hoc analysis of pooled data from 2 similarly designed 4-week, double-blind, phase 3 studies: TRANSFORM-1 (NCT02417064) and TRANSFORM-2 (NCT02418585). Adults with TRD (n = 560) were randomly assigned to ESK (fixed or flexible dose) plus a newly initiated oral antidepressant (AD; ESK + AD) or placebo nasal spray (PBO) plus a newly initiated oral AD (AD + PBO). Baseline irritability was assessed with Item 6 of the Generalized Anxiety Disorder 7-item (GAD-7) scale and was characterized as high, varying, or low based on the consistency of responses above or below cutoff at screening and baseline; participants were considered to have high irritability if they reported "becoming easily annoyed or irritable" for over half the days or nearly every day over the past 2 weeks (score ≥2). The extent to which baseline irritability and treatment impacted changes in mean depression severity (measured using Montgomery Asberg Depression Rating Scale [MADRS] total score) was evaluated by repeated measures mixed model analyses. Rates of treatment response (≥50% decrease from baseline in MADRS total score) and remission (MADRS total score ≤12) over the course of the 4-week study were examined using multiple logistic regression analyses. Incidence of adverse events (AEs) was also evaluated.

Results: Of 560 participants with TRD, 296 (52.9%) had high irritability at screening and baseline, 130 (23.2%) had low irritability at both visits, and 134 (23.9%) had varying levels of irritability (i.e., Item 6 score ≥2 at only one visit). Compared with the low irritability group, the high irritability group was younger at the time of MDD diagnosis ($P < 0.001$) and had more frequent lifetime suicidal behavior as quantified by the Columbia-Suicide Severity Rating Scale ($P < 0.05$), longer duration of current episode ($P < 0.05$), more prior AD failures in the current episode ($P < 0.05$), greater anxiety based on the Anxiety factor of the Inventory of Depressive Symptomatology – Clinician Version ($P < 0.05$), more comorbid anxiety disorders at screening ($P < 0.001$), and higher body mass index (BMI; $P < 0.001$).

Patients in the ESK + AD group improved more than patients in the AD + PBO group, and baseline irritability did not significantly moderate this effect. A significant interaction between baseline irritability and treatment group was not observed for change in MADRS total score from baseline to day 28 ($P = 0.925$), treatment response ($P = 0.898$), or remission ($P = 0.411$). In contrast, greater improvement was observed in the ESK + AD group at day 28 compared with AD + PBO regardless of baseline irritability level (change in MADRS score, $P < 0.001$; treatment response, $P < 0.05$; remission, $P < 0.05$). Percentages of patients reporting AEs were similar across the 3 baseline irritability groups.

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

W29. SUSTAINED EFFICACY WITH LONG-TERM TREATMENT WITH AXS-05: RESULTS FROM THE COMET PHASE 3 TRIAL, A LONG-TERM, OPEN-LABEL STUDY EVALUATING THE EFFICACY AND SAFETY OF AXS-05 FOR THE TREATMENT OF MDD

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Abstract: Background: Major depressive disorder (MDD) is a debilitating, chronic, biological disorder. Limitations of current treatments include high rates of inadequate response and suboptimal time to response. Even with treatment, relapse rates remain high. Current oral antidepressants act mainly via monoamine mechanisms. There is an urgent need for novel, faster-acting, more efficacious treatments with durable effects.

AXS-05 (dextromethorphan-bupropion modulated delivery tablet) is a novel, oral, investigational NMDA receptor antagonist with multimodal activity. The dextromethorphan component of AXS-05 is an uncompetitive antagonist of the NMDA receptor, an ionotropic glutamate receptor, and sigma-1 receptor agonist, and the bupropion component serves to increase the bioavailability of dextromethorphan. The efficacy of AXS-05 has been demonstrated in 2 double-blind, randomized, controlled, 6 weeks studies (ASCEND and GEMINI).

Objective: To evaluate the long-term efficacy and safety of AXS-05 in MDD.

Methods: COMET (Clinical Outcomes with NMDA-based Depression Treatment) was a Phase 3, open-label trial to evaluate the long-term efficacy and safety of AXS-05 (45 mg dextromethorphan-105 mg bupropion modulated delivery tablet) in MDD patients treated twice daily for up to 12 months. The study enrolled both de novo (newly enrolled) patients and patients rolling in from prior controlled trials with AXS-05. Here we present the results from the de novo patients. Efficacy outcomes included MADRS total score, remission, response, and functional remission.

Results: A total of 876 patients were enrolled (611 de novo patients who had not previously participated in an AXS-05 trial and 265 patients who rolled over from prior controlled trials with AXS-05). Treatment with AXS-05 resulted in rapid and substantial improvement in depression, demonstrated by mean reductions from baseline in the MADRS total score of 9.1 points at Week 1, 14.0 points at Week 2, and 21.1 points at Week 6. Mean MADRS total score reductions from baseline after 6 and 12 months of treatment were 23.9 points and 23.0 points, respectively. Clinical response on the MADRS (≥50% reduction from baseline) after treatment with AXS-05 was achieved by 18.8% of patients at Week 1, 39.7% at Week 2, and 73.2% at Week 6. Clinical response on the MADRS total score after 6 and 12 months of treatment was achieved by 84.6% and 82.8%, respectively. Remission (MADRS ≤10) after treatment with AXS-05 was achieved by 8.3% of patients at Week 1, 21.5% at Week 2, and 52.5% at Week 6. After 6 and 12 months of treatment, remission was achieved by 68.7% and 69.0%, respectively. Clinical response on the SDS (total score of ≤12) after treatment with AXS-05, was achieved by 42.9% of patients at Week 1, 55.1% at Week 2, and 70.7% at Week 6. Clinical response on the SDS after 6 and 12 months of treatment was achieved by 80.6% and 75.9% of patients, respectively. AXS-05 was well tolerated with a safety profile consistent with that previously reported in short-term controlled trials, with no new safety signals detected. The most commonly reported adverse events were dizziness, nausea, headache, dry mouth, and decreased appetite, which occurred at rates similar to those observed in controlled trials. Discontinuations due to adverse events occurred in 8.4% of patients during the 12-month trial, with no individual event occurring in more than 1.5% of patients.

Conclusion: Patients with MDD treated with AXS-05 experienced rapid, substantial, and durable improvements in depressive symptoms and functional impairment, sustained over 12 months. These data add to the differentiated clinical profile of AXS-05, and are consistent with efficacy and safety results from prior controlled trials.

W30. OPTIMIZING PREDICTION OF RESPONSE TO ANTIDEPRESSANT MEDICATIONS USING MACHINE LEARNING AND INTEGRATED GENETIC, CLINICAL, AND DEMOGRAPHIC DATA

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Abstract: Major depressive disorder (MDD) is a common psychiatric disorder which causes great suffering to patients and their families. Unfortunately, the current clinical practice of trial-and-error to determine optimal treatment for a specific MDD patient lack efficiency. This inefficiency is plausibly caused by the polygenic nature and the phenotypic heterogeneity of MDD. A major gap in the field is therefore the optimization of tailoring the right treatment for the individual MDD patient. Recent technological advancements which are generating large amount of data pave the way for improved understanding of complex clinical challenges, such as optimization of MDD treatment. Machine learning (ML) is an example of an approach to utilize these data to generate new insights. The goal of ML in the context of MDD would be to make predictions about optimal treatment by identifying potentially complex relationships among patients' combinatorial data.
Accordingly, we hypothesized that applying a ML approach on integrated clinical, demographic, and genetic data will enable a more accurate prediction for the treatment of depression. To test this, we used the large patient dataset from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study. We first analyzed the response patterns of patients to antidepressants. We then conducted literature search and applied feature selection algorithms to pinpoint the most relevant components to treatment success. Finally, utilizing these genetic and non-genetic components, we trained ML models which were then compiled to create an ensemble predictive algorithm. Analysis of the algorithm's capacity to predict individualized antidepressants responses on validation and test sets of patients showed average balanced accuracy rate of 71.3% (SD 7.7, $p<0.001$ for all models) across all studied medications, higher than STAR*D's equivalent average response rate of 50.1% (SD 3). Furthermore, the algorithm achieved average positive predictive value of 70.8% (SD 7.5), higher than the average efficacy of antidepressants, which is in the range of 42%-53%. Gene Ontology (GO) enrichment analysis which was performed on of the selected genetic components used by the algorithm revealed an enrichment of neuronal signaling-related terms (4 out of the 10 most significant terms). This reinforces the notion whereby in-depth knowledge of an individual's neurotransmitter circuit connections may lead to better treatment selection. To further validate our design scheme, we obtained data from the Pharmacogenomic Research Network Antidepressant Medication Pharmacogenomic Study (PGRN-AMPS) of patients treated with citalopram, and applied the algorithm's citalopram model. This external validation yielded highly similar results for both STAR*D and PGRN-AMPS test sets, with a balanced accuracy of 60.5% and 61.3%, respectively (both p's<0.01) Altogether, our findings support applying ML to accumulating combinatorial data derived from large studies to achieve a much-needed improvement in the treatment of depression. The algorithm we developed may be used as a tool to aid in the choice of antidepressant medication. Moreover, examination of the genetic factors which we found to improve treatment success will allow further understanding of medications' mechanism of action, and may lead to the development of novel treatments for depressive disorders.

W31. PATIENTS WITH MDD ON ANTIDEPRESSANT TREATMENT (ADT) WHO RECEIVED ADJUNCTIVE THERAPY EXPERIENCED INCREASED HEALTHCARE COSTS

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Abstract: Background: Among patients with major depressive disorder (MDD), inadequate response to antidepressant monotherapy (ADT) is common (Knoth 2010, Gaspar 2019); adjunctive pharmacotherapy or psychotherapy typically follows. (Gelenberg 2010) Little is known about changes in costs following the start of adjunctive therapy.

Purpose: To estimate changes in MDD-specific and all-cause healthcare costs following start of adjunctive therapy.

Methods: From a national sample of medical and pharmacy claims licensed from Decision Resources Group, MDD patients on ADT and added adjunctive therapy between 7/1/2014 and 12/31/2018 were identified. Eligible patients were on ADT for ≥8 weeks preceding and following initiation of adjunctive therapy (index); and were stratified by type of insurance and adjunctive therapy: "pharmacotherapy", "psychotherapy", or both ("dual adjunctive"). Costs were calculated for the 6 months pre- and post-index; cost changes were annualized (PPPY) and standardized to 2019$. Pre-post significance testing was based on non-overlapping 95% confidence intervals.

Results: Among the eligible 156,026 commercially-insured individuals (129,760 pharmacotherapy, 20,037 psychotherapy, 6,229 dual adjunctive), all-cause healthcare costs increased $2,213, $2,002, and $6,171, respectively. Those on adjunctive pharmacotherapy had significant cost increases in pharmacy ($1,129) and outpatient services ($932) but a modest inpatient cost decrease ($231). Those on adjunctive psychotherapy had significant office visit cost increases ($1,832) but decreased inpatient costs ($756). Those on dual adjunctive had no decline in acute care costs but had increased costs for office visits ($2,335), outpatient services ($2,612), and pharmacy ($1,302). For those on adjunctive pharmacotherapy, MDD-specific pharmacy costs increased ($526) while those on adjunctive psychotherapy had increased MDD-specific office visit costs ($1,037). Among each of the 62,166 Medicaid-insured individuals (50,713 pharmacotherapy, 8,097 psychotherapy, and 3,356 dual adjunctive), similar patterns were noted but total healthcare costs increased significantly more with adjunctive treatment: $3,017 (pharmacotherapy); $3,005 (psychotherapy); $8,690 (dual adjunctive).

Importance: Following inadequate response to an ADT, adjunctive therapy was often utilized to resolve MDD symptoms. This analysis found with adjunctive therapy, office visits, outpatient services, and pharmacy costs increased substantially while acute care services costs only decreased modestly. Adjunctive therapy preceded substantial increases in total healthcare costs for all but more so for those who were Medicaid-insured. These results provide information regarding potential cost increases for outpatient and office visits required by patients with MDD requiring adjunctive treatment and suggest the need for alternative therapies.

W32. EFFICACY AND SAFETY OF TNX-102 SL (SUBLINGUAL CYCLOBENZAPRINE) FOR THE TREATMENT OF FIBROMYALGIA IN THE RELIEF STUDY: POSITIVE RESULTS OF A PHASE 3 RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED MULTICENTER TRIAL

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Abstract: Background: Fibromyalgia (FM) is characterized by chronic widespread pain, fatigue, and nonrestorative sleep that is linked to central sensitization, a phenomenon characterized by pathological disturbance in central pain processing. TNX-102 SL* (cyclobenzaprine HCl sublingual tablets, 'TNX') targets improvement in sleep quality to reverse central sensitization. A prior Phase 3 trial of TNX at 2.8 mg showed signals for broad efficacy but missed significance on primary outcome of daily diary pain reduction. This Phase 3 trial ('RELIEF'#) evaluated efficacy and safety of TNX for FM at twice the dose, 5.6 mg.

Methods: 503 patients in the intent-to-treat sample meeting 2016 FM diagnostic criteria were enrolled in a 14-week trial at 39 U.S. sites. Patients received TNX 2.8 mg or placebo for 2 weeks followed by TNX 5.6 mg or placebo for 12 weeks. The primary outcome measure was change from baseline in weekly average of daily diary pain scores (0-10 NRS) at Week 14. The 1st key secondary analysis was proportion of responders (defined as 2, "much improved", or 1, "very much improved") on Patient Global Impression of Change (PGIC). Remaining key secondaries were: Fibromyalgia Impact Questionnaire-Revised (FIQ-R) symptom domain; FIQ-R function domain; Patient Reported Outcomes Measurement Information System (PROMIS) Sleep Disturbance; PROMIS Fatigue; and daily diary NRS of sleep quality. Data were analyzed by mixed model repeated measures with multiple imputation for missing data or by logistic regression for responder analyses.

Results: TNX provided significantly greater decrease in daily diary pain compared to placebo; p=0.010. A ≥30% pain reduction responder analysis also indicated greater pain responders on TNX, at 46.8% compared with 34.9% on placebo (p=0.006). By PGIC, 37.5% on TNX were responders, which was numerically but not significantly greater than 29.4% on placebo (p=0.058). TNX also provided greater separation from placebo on: FIQ-R Symptoms (p=0.007), Function (p=0.009), and Impact (p=0.002); PROMIS Sleep Disturbance (p<0.001); PROMIS Fatigue (p=0.018); and sleep quality by daily diary NRS (p<0.001).

In the TNX group, 82.3% completed vs. 83.5% on placebo. Systemic adverse events (AEs) were infrequent, with somnolence/sedation the only category at a rate of ≥ 5% on TNX (5.6% TNX; 1.2% placebo). The most common (≥ 5% on TNX) local administration site reactions were oral numbness (17.3% TNX; 0.8% placebo), oral pain/discomfort (11.7% TNX; 2.0% placebo), taste impairment (6.5% TNX; 0.4% placebo), and oral tingling (5.6% TNX; 0.4% placebo), which, with the exception of oral pain/discomfort, were nearly always temporally related to dosing and resolved within <60 min in most occurrences. Adverse events led to premature study discontinuation in 8.9% on TNX compared with 3.9% on placebo.

Conclusion: Bedtime TNX at the 5.6 mg dose significantly reduced daily pain and was associated with a higher rate of ≥30% pain responders. This trial demonstrated efficacy for FM pain, and there was also substantial improvement on sleep, fatigue, and other FM symptoms and measures of function. In addition, there was good tolerability of nightly TNX 5.6 mg, a treatment primarily

targeting sleep quality in order to reverse central sensitization, thereby broadly addressing not only pain but also sleep disturbance, fatigue and other disabling symptoms of FM.

*TNX-102 SL is an Investigational New Drug and has not been approved for any indication

#ClinicalTrials.gov Identifier NCT04508621

W33. A MULTICENTER OPEN-LABEL PILOT STUDY EXAMINING NEXT-DOSE TRANSITION FROM ZOLPIDEM TO LEMBOREXANT: RESULTS OF A SUBGROUP ANALYSIS OF OLDER ADULTS

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Abstract: Introduction: Few studies have investigated approaches for switching patients between insomnia medications that differ in drug class. The dual orexin receptor antagonist lemborexant (LEM) (Rosenberg et al, 2019) is approved for the treatment of insomnia in adults in the US, Canada, and Japan. This pilot study was designed to assess pre-planned dosing methods for transitioning subjects directly from zolpidem (ZOL; immediate release [IR]; extended release [ER]) to LEM (5mg [LEM5]; 10mg [LEM10]). As medications commonly prescribed to treat insomnia are associated with safety issues in older adults (Schroeck et al, 2016), outcomes in the subgroup of subjects aged ≥60y were examined post hoc.

Methods: Study E2006-A001-312 (Study 312; NCT04009577) consisted of a 3-wk Screening Period (SCR; subjects stayed on ZOL), 2-wk Titration Period (TITR), a 12-wk Extension Period (EXT), and 4-wk Follow-up Period. Subjects ≥18y with insomnia who used ZOL-IR or ZOL-ER intermittently (INT; 3-4 nights/wk) or frequently (FREQ; ≥5 nights/wk) were enrolled. INT ZOL users and subjects who used INT and FREQ ZOL for 1 wk each entered Cohort 1 and initiated TITR on LEM5. FREQ ZOL users entered Cohort 2 and were randomized 1:1 to LEM5 (Cohort 2A) or LEM10 (Cohort 2B). Subjects who successfully transitioned to LEM could decide to enter EXT. Subjects were able to change LEM dose while in TITR (1 change permitted) and EXT. The proportion of subjects who transitioned from ZOL to LEM after completing TITR was the primary endpoint. Treatment-emergent adverse events (TEAEs) were evaluated based on the dose subjects were on when the TEAE occurred.

Results: A total of 53 subjects were in the Full Analysis Set (Cohort 1, n=10; Cohort 2, n=43); the subgroup of subjects ≥60y included 30 subjects (Cohort 1, n=6; Cohort 2, n=24). The mean (SD) age was 67.5 (4.9)y and 76.7% were female. The chief sleep complaint reported by this subgroup during SCR was waking too early (63.3%), followed by difficulty staying asleep (30.0%), and difficulty falling asleep (6.7%). A total of 23/30 (76.7%) transitioned to LEM following TITR completion. In Cohort 1, 5/6 (83.3%) transitioned to LEM; 3 ended on LEM5, 2 ended on LEM10. In Cohort 2A (LEM5), 7/8 (87.5%) transitioned to LEM; 3 ended on LEM5, 4 ended on LEM10. In Cohort 2B (LEM10), 11/16 (68.8%) transitioned to LEM; 1 ended on LEM5, 10 ended on LEM10. During TITR, 7 subjects discontinued; 1 subject (on LEM5) chose to discontinue and 6 subjects discontinued due to TEAEs (1 each of intentional overdose, nausea, over-sedation,

diarrhea, hemiparalysis, paralysis [hemiparalysis and paralysis were not adjudicated as cataplexy]; 2 were on LEM5 and 4 were on LEM10 at the time of the TEAE). The 23 subjects who transitioned to LEM continued into EXT. One subject discontinued during EXT. Overall, 22/30 (73.3%) subjects completed the study. When examined by modal dose (most frequent dose taken during TITR and EXT combined) groups, median time to first dose change during EXT was 15 days for LEM5 and 55 days for LEM10. TEAEs occurred more often with LEM10 vs LEM5 over TITR and EXT. The TEAEs occurring in ≥2 subjects for LEM5 or LEM10 were abnormal dreams (n=4) and somnolence (n=2). All TEAEs were mild/moderate in severity.

Conclusions: In the subgroup of older subjects (≥60y), the majority successfully transitioned from ZOL to LEM, and reached study completion. The safety profile was consistent with that reported during Phase 3 clinical development studies and, in general, LEM was well tolerated.

Support: Eisai Inc.

W34. VALIDATION OF A COMPUTERIZED ADAPTIVE ASSESSMENT TOOL FOR SEVERITY OF PSYCHOTIC SYMPTOMS AND DIAGNOSTIC PREDICTION

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Abstract: Introduction: Unlike other areas of medicine, psychiatry is highly dependent on patient and family reports to assess the presence and severity of disease. Thus, impairment level is determined by a total score on a rating scale, which requires that the same items of a given assessment tool need to be administered to all respondents, interpreted and coded. Hence, rating scales are time consuming and require trained raters, limiting the widespread use of measurement-based approaches in the routine clinical management of schizophrenia. One alternative to the administration of a full traditional assessment is adaptive testing, in which individuals may receive different scale items that are targeted to their specific impairment level, reducing administration time and increasing measurement efficiency and scalability. When computational algorithms automatically match questionnaire takers with the most relevant questions for them, this is called Computer Adaptive Testing (CAT). This study aimed to test the psychometric properties and predictive power of a self-administered computerized adaptive testing tool for psychosis (CAT-Psychosis).

Methods: Patients from the inpatient and outpatient units at The Zucker Hillside Hospital, New York, rated themselves with the self-administered CAT-Psychosis which yields a current psychotic severity score. The CAT-Psychosis is based on a multidimensional extension of traditional Item Response Theory (IRT)-based CAT that is suitable for complex traits and disorders such as psychosis. The Brief Psychiatric Rating Scale (BPRS) was administered to test convergent validity wit CAT-Psychosis self-report. Subjects were re-tested within 7 days to assess test-retest reliability. Generalized linear mixed models and Pearson product moment correlation coefficients were used to test for correlations between individual ratings and average CAT-Psychosis severity scores respectively and the BPRS. Intraclass correlation coefficients (ICCs) were used to test for

reliability. Generalized linear and non-linear (logistic) mixed models were used to estimate diagnostic discrimination capacity (lifetime ratings) and to estimate diagnostic sensitivity, specificity and area under the ROC curve with 10-fold cross validation.

Results: 200 subjects (160 patients with psychosis and 40 healthy controls) were included in the study. The CAT-Psychosis self-report showed convergent validity against BPRS scores (r=0.690; 95% confidence interval (CI): 0.609-0.756). CAT-Psychosis self-report showed test-retest reliability (ICC=0.815; 95% CI: 0.741-0.871). CAT-Psychosis self-report was able to discriminate psychosis from healthy controls (Area Under the ROC Curve (AUC)= 0.850, 95% CI: 0.807-0.894). Median length of assessment was 1 minute, 20 seconds (interquartile range (IQR): 0:57min-2:09min).

Conclusions: CAT-Psychosis self-report provides valid severity ratings and can reliably discriminate psychotic patients from healthy controls, yielding a dramatic reduction in administration time, while maintaining reliable psychometric properties. The availability of a scalable, valid and reliable self-administered instrument would be of enormous value, both for research and for routine clinical management of psychotic disorders. Independent replication of our findings in other patient populations and in other languages is needed to ensure worldwide scalability.

W35. NATURAL LANGUAGE PROCESSING-BASED QUANTIFICATION OF THE MENTAL STATE OF PSYCHIATRIC PATIENTS

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Abstract: Introduction: Mental health practitioners routinely record behavior and mental state of patients in Electronic Health Records (EHR) using free-text notes. Although this data is invaluable to clinicians for everyday clinical tasks, it is difficult to use for retrospective, prospective, or predictive analytics because of its unstructured format. To tackle this challenge, we have developed natural language processing (NLP) models to convert semi-structured notes into structured psychiatry-specific data labels related to patient symptoms, function, appearance and mood.

Methods: Anonymized semi-structured EHR notes on patient status assessment from a large behavioral health database were used (N>500,000). First, a psychiatry subject matter expert analyzed raw texts, picked 241 elicit data labels (e.g., insomnia, impaired memory, and issue with impulse control) and classified labels into 27 categories (e.g., appearance, functioning, mood). Subsequently, we preprocessed data, designed a multi-component architecture, and created deep-learning based 27 NLP models, one for each category. Each NLP model was trained to map unstructured sentences to corresponding labels in a given category. Performance metrics (e.g., accuracy and Area under the Receiver Operating Curve (AUROC)) were evaluated.

Results and Discussion: The NLP models are able to predict data labels in most of the 27 categories with an accuracy of 0.7 and achieve a median AUROC score of 0.9. The deep-learning models

were also shown to perform better than three traditional models (support vector machine (SVM), K-nearest neighbor (KNN), and Naïve Bayes models). To ascertain the usefulness of these NLP data labels, we investigated three simple use cases. One is to estimate suicidal tendencies of patients diagnosed with Major Depressive Disorder (MDD). We tested the hypothesis that a MDD patient's suicidal tendencies typically increase before hospitalization by using a proxy suicidality score calculated based on suicidality-related NLP data labels. A statistically significant increase was found in suicidality score 1-day before hospitalization ($p<0.05$). Two other simple applications (patient phenotyping, combination with a machine-learning model to predict diagnosis) were detailed in our publication (Mukherjee 2020). These NLP data labels have the potential to be used for downstream analytics for intra- and interpatient clinical insights. Possible future model improvements are needed on both algorithms and utilization in a clinical setting.

Conclusion: We demonstrate that deep-learning based NLP models can convert free text notes to analyzable dimensions of mental function of psychiatric patients. Interested researchers may consider using these NLP models and co-develop custom analytics through collaboration with our data scientists. (contact: enquiry@holmusk.com)

W36. MONITORING MEDICATION ADHERENCE AMONG PATIENTS WITH SERIOUS MENTAL ILLNESSES: CAREGIVER PREFERENCES FOR DIGITAL HEALTH TECHNOLOGY TOOLS

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Abstract: Background: Serious mental illness (SMI) including bipolar disorder, major depression and schizophrenia contribute to significant healthcare and economic burden. In 2018, 4.6% of United States (US) adults were diagnosed with SMI contributing to an estimated $192.3 billion US dollars in lost earnings per year. Poor adherence to antipsychotic medications is a major obstacle to management of SMI patients, and is also associated with poor health outcomes (relapse and recurrence cases) and high direct and indirect medical costs. New technologies such as digital medicine provided prescribers an opportunity to monitor medication adherence and also tailor decision-making while managing their patients diagnosed with SMI. Recent innovations in digital medicine have resulted in emergence of digital tools that track general health along with monitoring adherence to medications. Previous studies have reported prescriber or patient preferences for digital health tools. However, evidence is limited on caregivers who support SMI patients, and their preferences for health technology tools.

Objective: To estimate preferences for digital (ingestible sensor pill, medication containers with electronic monitoring, wearables, mobile apps, smart pill dispensers) and non-digital (medication dairy, simple pill organizer) tools among family caregivers of patients diagnosed with SMI.

Methods: A web-based online survey to collect preferences, sociodemographic, patient clinical characteristics, and knowledge/attitude towards healthcare technologies was administered to family caregivers of adult SMI patients. Caregivers completed 12 discrete choice questions

comparing health technology tools that varied across several attributes including source, access and frequency of medication adherence information, physical activity, mood and rest information, and caregiver out-of-pocket contribution. Preference weights were estimated using random parameter logit models.

Results: A total of 184 family caregivers (42 years mean age, 59% female and 69% Caucasian) of SMI patients were included. Caregivers reported seven times (adjusted Odds Ratio (aOR): 7.34, 95% Confidence Interval (CI): 5.0-10.8) higher preference for a tool that tracked medication adherence using pill with ingestible sensor and collected additional health information about patients' physical activity, mood and quality of rest relative to a non-digital pill organizer. Caregivers also preferred mobile apps (aOR 2.64, 95% CI 1.90-3.70) relative to a pill dispenser, but smart pill dispensers were less preferred (aOR 0.54, 95% CI: 0.40-0.73) compared to non-digital pill organizer.

Conclusion: Family caregivers of SMI patients have a strong preference for digital tools that monitor medication adherence and track patients' general health. As information technology advances, prescribers will need to evaluate how best to integrate these new digital monitoring technologies into daily clinical practice around management of SMI patients.

W37. A PILOT PSYCHEDELIC PSYCHOPHARMACOLOGY ELECTIVE FOR PHARMACY STUDENTS

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Abstract: Background: Psychedelic psychopharmacology represents a niche but growing field of scientific inquiry, generally beyond the scope of traditional psychiatric therapeutics in medical and pharmacy education. As interest in the clinical use of psychedelics grows, future pharmacists, as medication experts, must rise to meet the practice needs of their medical colleagues in psychiatry.

Course Content: The "Psychedelic Psychopharmacology" course at Shenandoah University is a 15-week, pilot elective available for 2nd and 3rd year pharmacy students. The course will discuss the use of psychedelics throughout the world, with an emphasis on modern medicinal use. It will focus on primary literature evaluation of basic, translational, and clinical studies in the field of psychedelic research. Students will also explore ethical topics using a reflective structured dialogue approach. Methods include the pedagogical tool of student-led "journal clubs", discussions on the ritual uses of psychoactive plants (using "Plants of the Gods," by Schultes, Hofmann, and Rätsch), and a term paper representing either a literature review or persuasive essay.

Expected Results: This project is expected to yield a rich, qualitative description of the course, assess the engagement of its students, and provide a roadmap for clinician educators that seek to provide similar didactic learning opportunities.

W38. OPERATIONALIZING EDUCATION ON PSYCHEDELIC COMPOUNDS IN ACADEMIC PSYCHIATRY

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Abstract: Background: Novel therapeutics often take a long time to edge their way into education, as formal didactic and clinical learning is often limited to well-established clinical practices and practice guidelines. The reemerging field of psychedelic medicine and the use of psychedelics in psychiatry is one such area. Discourse in this field is still relatively siloed despite growing acceptance among scholars and practitioners that these compounds have promising therapeutic effects and provide unique options for treatment in modern psychiatry. There is a quickly burgeoning body of research investigating the utility of psychedelic compounds in the last decade, and some treatment modalities are on the path toward FDA approval. Currently, MDMA-assisted psychotherapy and psilocybin-assisted psychotherapy have breakthrough therapy designation by the FDA for the treatment of for post-traumatic stress disorder and major depressive disorder, respectively (1). Likely owing to a number of recent positive trials, publicized decriminalization and notable presence in popular media, an increasing number of individuals in the community, including patients, are trying classical and novel psychedelics for therapeutic or recreational purposes (2). Residents and other trainees are learning about evolving theories and practices involving psychedelic substances and therapies through popular news media and other sources of information such as blogs, but little is available at universities and other training sites across the country in the way of formal education. It is imperative that learners receive evidence-informed instruction in the pharmacology, clinical response, and ongoing research to understand the risks and benefits of psychedelic agents in order to best advice and manage patients who are utilizing these substances.

Objective: We will discuss a training model of expanded education in psychedelic science and medicine we are utilizing. In addition, we will talk about trainee feedback on these scholarly activities and challenges of providing such training. Also discussed are recommendations for incorporating education on psychedelic compounds in residency training curriculum.

Conclusion: The research and use of psychedelics and similar substances in psychiatry represent not only the potential for new pharmacological treatments, but a paradigm shift in psychiatry and medicine. So trainees can gain a foundational understanding of these novel therapies and build a knowledge base rooted in the available evidence, an organized effort is needed to incorporate these teachings into the current construct of medical and pharmacological curricula.

W39. PHARMACOKINETICS OF LOWER-SODIUM OXYBATE IN A PHASE 3, PLACEBO-CONTROLLED, DOUBLE-BLIND, RANDOMIZED WITHDRAWAL STUDY IN ADULT PARTICIPANTS WITH IDIOPATHIC HYPERSOMNIA

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Abstract: Introduction: Idiopathic hypersomnia (IH) is a rare central hypersomnolence disorder characterized by excessive daytime sleepiness (EDS), prolonged nighttime sleep, and sleep inertia. No treatment is currently approved for IH. Lower-sodium oxybate (LXB; Xywav™) is a novel oxybate treatment with 92% less sodium than sodium oxybate (SXB; Xyrem®). LXB and SXB are approved for the treatment of cataplexy or EDS in patients ≥7 years of age with narcolepsy. The pharmacokinetics (PK) of LXB was evaluated in a subset of participants in a phase 3 study (NCT03533114) in adults with IH.

Methods: Eligible participants 18–75 years of age with IH began treatment with LXB, administered once or twice nightly during an open-label treatment titration and optimization period (OLTTOP; 10–14 weeks); dose amount/regimen could be adjusted during this period. Participants next entered a 2-week, open-label, stable-dose period (SDP), then were randomized to placebo or to continue LXB treatment during a 2-week, double-blind, randomized withdrawal period (DBRWP). A 24-week open-label extension period (OLE) followed the DBRWP. Up to 30 participants who were taking a once-nightly or twice-nightly LXB dose were eligible to participate in a single overnight PK evaluation during the OLTTOP or OLE. Administration of LXB for the PK evaluation was per the individual participant's usual regimen (therefore, not standardized for dose, meal intake relative to first dose, or time of second dose [if any]). Blood samples were collected before each dose and sequentially for up to 8 hours. PK results are presented for participants who were taking their effective and tolerable optimized dose of LXB on the night of blood sampling, ie the same dose as during the stable-dose period.

Results: The PK population included 28 participants (mean±SD age: 43.4±14.9 years; 71% female). Median (min, max) LXB total dose in the once-nightly group (n=9) was 4.0 (3, 6) g/night; in the twice-nightly group (n=19), it was 7.5 (5.3, 9) g/night. For the once-nightly stable-dose group (n=7), median (min, max) maximum plasma oxybate concentration (Cmax) was 85.9 (39.7, 110) µg/mL, and area under the plasma concentration versus time curve from time 0 to time t at the last detectable concentration (AUC0-t last) was 229.5 (79.5, 421.8) µg/mL•h. For the twice-nightly stable-dose group (n=13), median (min, max) Cmax was 126 (57.1, 189) µg/mL, and AUC0-t last was 479.3 (190.2, 1033) µg/mL•h. In the overall PK population, the estimate (90% CI) of the dose proportionality constant for AUC0-t last was 1.3128 (0.881, 1.7375), which is considered supra-proportional compared with the reference range (0.7969–1.2031).

Conclusion: The median dosage for the once-nightly LXB regimen was lower than for the twice-nightly regimen. The range of exposure as measured by Cmax and AUC0-t last demonstrated partial overlap between the two regimens. The supra–dose proportionality of LXB observed in participants with IH is consistent with results from other studies of LXB and SXB.

W40. NEUROMELANIN ACCUMULATION IN PATIENTS WITH SCHIZOPHRENIA: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Abstract: Objectives: Neuromelanin (NM) is a by-product of dopamine metabolism that accumulates in the midbrain. However, it is unclear whether patients with schizophrenia demonstrate abnormally increased midbrain NM levels in comparison with healthy controls (HCs). Here, we conducted a systematic review and meta-analysis of in vivo and ex-vivo studies examining NM concentrations between patients with schizophrenia and HCs.
Methods: A systematic literature search was conducted, using PubMed and Embase (from 1947-Jan 2020). The search terms employed were: (neuromelanin or NM) AND (schizophreni* or schizoaffective or psychosis or psychotic). Standard mean differences (SMD) were calculated to assess group differences in MRI-NM levels.

Results: Seven out of 880 articles were deemed relevant. Five in vivo studies were identified which employed NM-MRI while there were two post-mortem studies (1 with immunohistochemistry; 1 with microdensitometer). The most frequently investigated region was the substantia nigra (SN) (7 studies), followed by locus ceruleus (LC) (4 studies), and ventral tegmental area (VTA) (1 study). NM in the SN was higher in patients with schizophrenia compared to HC within 5 NM-MRI studies (SMD=0.50; 95% CI, 0.25 to 0.74; $p<0.001$). No group differences were observed in the SN using ex-vivo methods. Four studies exploring NM in the LC demonstrated no difference in MRI signal or pigmentation levels. In the VTA, decreased signal intensity was observed in 1 study.

Conclusion: Quantitative MRI-NM in the SN could be a potential biomarker in schizophrenia. However, no study has differentiated patients based on treatment response, for which further investigation is warranted.

W41. EXPLORING THE IMPACT OF NEGATIVE SYMPTOMS ON END OF TREATMENT CHANGE IN ACUTE SCHIZOPHRENIA STUDIES

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Abstract: Introduction: There is evidence that subjects entering trials with greater symptom severity show larger drug placebo difference in acute and negative symptom trials (Furukawa, 2015). Anecdotally, there is some evidence that higher severity of negative symptoms at study entry decreases drug placebo difference in acute schizophrenia studies. In the current analysis we wanted to estimate the impact of negative symptom factor score severity on end of treatment change in blinded data in acute schizophrenia trials.
Methods: LOCF data were obtained from 15 acute schizophrenia clinical trials. Change from baseline was estimated for the PANSS total score. We fitted one regression model with study included as a fixed effect as well as individual models for each study. We did not correct for multiple testing.

Results: The dataset included data from 5,052 subjects. The average negative factor score at baseline was 23 points with a standard deviation of 4.8 and ranged from 7 to 42 points. The negative factor severity at baseline significantly increased the end-of-treatment improvement in

the PANSS. Some heterogeneity was observed when data were analyzed on an individual study level.

Discussion: Our analyses on blinded data indicate a possible impact of negative symptom severity on end of treatment change in acute schizophrenia studies in PANSS. As expected, the effect was generally small, only about 3% of the end-of-treatment PANSS change was explained by the baseline negative factor score severity and translated into roughly half-point PANSS improvement for a 1-point increase in the negative factor score. The limitation of our analyses is the fact that it was performed on blinded data and the effect on drug-placebo separation could not be estimated. We plan to expand our analyses in un-blinded datasets as those become available.

W42. FUNCTIONAL TARGETING OF AUDITORY PROCESSING DEFICITS IN SCHIZOPHRENIA USING A MULTIMODAL APPROACH OF TRANSCRANIAL DIRECT CURRENT STIMULATION COMBINED WITH AUDITORY TRAINING

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Abstract: Background: Auditory processing deficits contribute to cognitive impairment and functional deficits in schizophrenia. These processing deficits result in impoverished basic sensory data which limits the fidelity of downstream information available to cortical networks responsible for higher order executive functioning. Improving these auditory processing deficits may result in a cascade effect leading to improved cognitive functioning and patient outcomes. Transcranial direct current stimulation (tDCS) is a non-invasive neuromodulatory technique that has been shown to improve performance on auditory processing measures such as the Tone Matching Task in patients with schizophrenia. Targeting in tDCS can be achieved through electrode placement and current modeling but is limited by individual patient anatomical variation. Functional targeting through state-dependent activation of the auditory processing network may enhance the effects of tDCS on auditory processing. In the current study we examined the effects of integrating tDCS with an auditory training exercise (to activate the auditory system). Outcomes were performance on the Tone Matching Task (a behavioral measure) and mismatch negativity (MMN; a neural measure) in people with schizophrenia (SZ). Methods:Thirty subjects with SZ were randomized to one of three treatment conditions (10 subjects in each study arm) in a single-blind between subject study. Condition TA: cathodal tDCS combined with auditory training. Condition TV: cathodal tDCS combined with visual training. Condition SA: sham tDCS combined with auditory training. Subjects in each study arm received two sessions per day over two days (total of 4 treatments). Primary outcomes were TMT performance and MMN amplitude change from baseline to post-treatment. Cathodal tDCS was delivered bilaterally through two electrodes of the same polarity over the left and right temporal region overlying the auditory cortices for 20 min during each session. Auditory training consisted of the Sound Sweeps module from Brain HQ

delivered when subject were receiving tDCS. Visual training was the Visual Sweeps module from Brain HQ delivered during tDCS stimulation. TMT and MMN data were analyzed using a generalized linear mixed model. Negative symptom severity was assessed at baseline with the Scale for the Assessment of Negative Symptoms (SANS).Results: A significant interaction of treatment condition x time x SANS score ($p < 0.01$) was observed for change in TMT performance from baseline to post-treatment. Condition TA, tDCS + Auditory Training, improved TMT performance under conditions of average and high negative symptom severity. Condition TV, tDCS + visual training, improved TMT performance under low SANS score conditions. For the outcome of MMN amplitude change from baseline to post-treatment, there was a significant interaction of treatment condition x time x SANS score ($p<0.03$). Condition TA decreased MMN magnitude under average and high SANS score conditions, while condition SA decreased MMN magnitude under low SANS score conditions. Conclusions: These results suggest that integrating cathodal tDCS with auditory training result in greater improvements to auditory processing than with either condition alone. This study is the first to employ bilateral tDCS combined with auditory stimulation in a repeated treatment design. Statistically significant changes in both behavioral and neural measures of auditory processing were seen when accounting for negative symptom severity. The interaction of treatment condition with negative symptom severity suggests that patient symptom profiles may be used to individually tailor treatment approaches to provide optimal benefit.

W43. RELATIONSHIP BETWEEN PIMAVANSERIN EXPOSURE AND NEGATIVE SYMPTOMS IN PATIENTS WITH SCHIZOPHRENIA: MODELING ANALYSIS FROM THE PHASE 2 ADVANCE STUDY

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Abstract: Background: Pimavanserin is a selective serotonin 5-HT2A receptor inverse agonist/antagonist and has shown beneficial effects as an adjunctive therapy in patients with schizophrenia, including significant improvement for negative symptoms. This analysis evaluated the relationship between pimavanserin exposure and efficacy endpoints in patients with negative symptoms of schizophrenia.
Methods: Data were from ADVANCE, a phase 2 study evaluating the effects of pimavanserin in patients with negative symptoms of schizophrenia. The study (ClinicalTrials.gov Identifier: NCT02970305) was a 26-week, double-blind, placebo-controlled study conducted in outpatients from centers in Europe and North America. Patients were randomized to pimavanserin or placebo added to background antipsychotic (AP) therapy. The initial dose was 20 mg once daily, and the dose could be adjusted to 34 mg or 10 mg between weeks 2 and 8. The primary endpoint was change from baseline to week 26 on the Negative Symptom Assesment-16 (NSA 16) total score. Secondary endpoints were mean change from baseline to week 26 for the Personal and Social Performance (PSP) scale and the Clinical Global Impression of Schizophrenia Scale – Severity

(CGI-SCH-S). Time-varying exposure measures, including average daily concentration (Cav), peak concentration (Cmax), and area under the concentration time curve from time 0 to 24 hours (AUC0-24), were predicted for each patient based on a population-pharmacokinetic model and individual empiric Bayesian estimates. Exposure-response (ER) models were developed describing the effect of pimavanserin exposure on NSA 16, PSP, and CGI-SCH-S.

Results: ADVANCE randomized 403 patients and 346 (174 placebo and 172 pimavanserin) completed the study. Significant improvement was observed for the NSA-16 total score at week 26 with pimavanserin versus placebo (least squares [LS] mean: -10.4 vs. -8.5, P=0.043, effect size: 0.21). Compared with the 10 mg and 20 mg doses, improvement was greater in patients (n=107) taking pimavanserin 34 mg versus placebo (LS mean: -11.6 vs. -8.5; unadjusted P=0.0065, effect size: 0.34). No significant differences were observed for the PSP or CGI-SCH. The ER model for NSA-16 included 2628 records collected from 396 patients and demonstrated a significant relationship, whereby higher pimavanserin exposure was associated with greater improvement in NSA-16. No tested covariates, including demographics, geographic region, baseline score for NSA-16, or AP medication, had a statistically significant effect on the response observed. Compared with placebo, the model predicted a greater reduction in NSA-16 total score (10.5) with median AUC0-24 of 1465 ng x h/mL for the 34 mg dose and noticeable lesser effect with lower exposures/doses. Similar results were observed with PSP and CGI-SCH but not at the extent as NSA-16; however, higher pimavanserin exposures were still associated with greater improvement in response and with lesser effect with lower exposures/doses. There was no significant ER relationship with relevant adverse events (anxiety, headache, insomnia, somnolence).

Conclusions: Results of this modeling analysis predict higher pimavanserin exposure in patients with negative symptoms of schizophrenia is associated with a greater improvement and suggest the use of pimavanserin 34 mg in this patient population. These results support the further investigation of pimavanserin for the treatment of negative symptoms in schizophrenia.

W44. OPIOID ANTAGONISM AS A TARGET FOR MITIGATION OF ANTIPSYCHOTIC-ASSOCIATED WEIGHT GAIN

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Abstract: Background: Mechanisms underlying antipsychotic-associated weight gain are not well understood. The central and peripheral endogenous opioid system plays a role in weight and metabolic regulation, providing a rationale for targeting this system to attenuate antipsychotic-associated weight-related side effects that may impact treatment outcomes.

Methods: PubMed literature searches using the terms “opioid,” “opioid receptors,” “opioid antagonists,” “antipsychotic,” and “olanzapine” in combination with terms “weight” and “metabolism” were conducted to elucidate the role of the opioid system in the regulation of weight and metabolism, as well as potential for opioid antagonists to mitigate these effects.

Results: Nonclinical models provide evidence that activity at mu, delta, and kappa opioid receptors (MOR, DOR, KOR) mediate aspects of glucose and insulin regulation. Opioid antagonism has been associated with attenuated food consumption, with reduced fat accumulation, and with preventing insulin resistance in rats and nonhuman primates, an effect hypothesized to be mediated through MOR and DOR antagonism. In humans, opioid receptor agonism is associated with increased caloric intake. A new treatment option that combines olanzapine, an antipsychotic associated with weight gain, with the opioid receptor antagonist samidorphan (OLZ/SAM) mitigated olanzapine-associated weight gain in healthy volunteers and mitigated olanzapine-associated weight gain and increases in waist circumference in patients with schizophrenia.

Conclusions: Opioid receptor blockade from samidorphan (in OLZ/SAM) mitigated olanzapine-associated weight gain and may provide additional benefits on other metabolic sequelae. Nonclinical and human data suggest that antagonism of the endogenous opioid system is a potential mechanism to address antipsychotic-associated weight gain and metabolic dysregulation.

W45. IN VIVO CHARACTERIZATION OF THE OPIOID RECEPTOR BINDING PROFILES OF SAMIDORPHAN AND NALTREXONE IN RATS: COMPARISONS AT CLINICALLY RELEVANT CONCENTRATIONS

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Abstract: Background: A combination of olanzapine and the opioid receptor antagonist samidorphan (OLZ/SAM) is under development for the treatment of schizophrenia and bipolar I disorder. Samidorphan is a new molecular entity structurally related to naltrexone, but with differentiated characteristics. OLZ/SAM is intended to provide the efficacy of olanzapine while mitigating olanzapine-associated weight gain. In vitro, samidorphan binds with high affinity to mu (MOR), kappa (KOR), and delta (DOR) opioid receptors and functions as a MOR antagonist with partial agonist activity at KOR and DOR. Samidorphan binds with higher affinity to MOR, KOR, and DOR than naltrexone and functions as a more potent opioid receptor antagonist. The current studies characterize and compare the in vivo binding profiles of samidorphan and naltrexone at clinically relevant concentrations.

Methods: Two cohorts of male Sprague-Dawley rats were injected with 0.03-3 mg/kg SC samidorphan or 0.01-1 mg/kg SC naltrexone. The first cohort of rats was sacrificed to measure plasma and brain uptake. In the second cohort, thirty minutes after receiving samidorphan or naltrexone, rats were IV injected with a triple tracer of NTX-D3, naltriben, and GR103545 to measure MOR, DOR, and KOR occupancy, respectively. Brains were dissected and receptor occupancy of MOR, DOR, and KOR was measured using LC-MS.

Results: At clinically relevant concentrations, samidorphan occupied MOR, DOR, and KOR whereas naltrexone occupied only MOR and KOR. Corrected for free brain concentration, samidorphan also has higher in vivo affinity for MORs, KORs and DORs than naltrexone.

Conclusions: Based on these data, samidorphan has a differentiated binding profile from naltrexone.

W46. RECENT ADVANCES IN TREATING SCHIZOPHRENIA: ASSESSING THE IMPACT OF VIRTUAL MEDICAL EDUCATION

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Abstract: Introduction: There are many unmet needs in the treatment of schizophrenia. Available treatments are not particularly efficacious for negative, cognitive and residual positive symptoms. Besides, EPS and metabolic disturbances persist as side effects in existing drugs. Some new advances have tried to address these unmet needs. This talk addressed the current practice gaps of healthcare providers treating patients with schizophrenia.

Methods: Five virtual broadcasts (Sept-Oct, 2020) consisted of a one-hour, live-streamed discussion from an expert faculty member. Impact of the educational activity was assessed by comparing psychiatrists' responses to four identical questions presented before and directly after activity participation. A follow-up survey was sent to all participants six-weeks post-activity to measure performance in practice changes. A chi-square test was used to identify significant differences between pre- and post-assessment responses. Cohen's d was used to calculate the effect size of the virtual broadcast.

Results: Activity participation resulted in a noticeable educational effect among psychiatrists (n=988; d=4.35, P<.001). The following areas showed significant (P <0.05) pre- vs post-educational improvements: recognition of newly emerging treatment options, side effect management, efficacy of current treatments and cardiometabolic effects of treatment. Additionally, 64% of psychiatrists reported a change in practice performance as a result of the education received in the activity, including developing treatment plans for patients with schizophrenia and educating patients and family members about the potential for adverse effects and how to manage negative symptoms.

Conclusions: The results indicated that a CME-certified one-hour virtual broadcast was effective at improving knowledge among psychiatrists for the recognition and treatment of schizophrenia. This knowledge also resulted in positive changes in practice performance post-activity. Future education should continue to address best practices in the diagnosis, treatment and management of patients with schizophrenia, as there remains an increased need for tailored CME among psychiatrists.

W47. XANOMELINE'S "ANTIPSYCHOTIC ACTIVITY" IS MEDIATED BY CENTRAL MUSCARINIC RECEPTORS AND AUGMENTED BY RISPERIDONE IN RODENT MODELS OF PSYCHOSIS

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Abstract: All approved antipsychotic drugs work primarily by binding to dopamine D2 receptors. Xanomeline, a M1/M4-preferring muscarinic receptor agonist, exhibited antipsychotic activity in schizophrenia as well as Alzheimer's-related psychosis. However, pro-cholinergic adverse events

prevented its further development. KarXT combines xanomeline with the peripheral anticholinergic trospium to improve tolerability, as demonstrated in Phase 1 trials. KarXT was well tolerated and efficacious in a recent Phase 2 trial in patients with schizophrenia experiencing acute psychosis. Here we confirm, using a rodent model of psychosis, that xanomeline's effects are mediated by central muscarinic receptors. Xanomeline and atypical antipsychotics target different receptor families; therefore, there is the potential for greater therapeutic benefit with adjunctive treatment. The administration of xanomeline with the atypical antipsychotic risperidone was investigated in mouse models predictive of antipsychotic activity to determine the potential for greater therapeutic benefit with adjunctive treatment.

Methods: All studies used adult, male C57BL/6J mice. To evaluate the effects of blocking central (with scopolamine) vs. peripheral (with N-methyl-scopolamine; NMS) muscarinic receptors, we used the conditioned avoidance response (CAR) assay in which mice are first trained to avoid a foot-shock to a performance criteria of >85% avoidance responses. Using a repeated-measures, counter-balanced design, a maximally efficacious dose of xanomeline (5.6 mg/kg) was given following scopolamine (0.03-0.3 mg/kg) or NMS (1.0-3.0 mg/kg). Augmentation effects of xanomeline (1.0-5.6 mg/kg dose range) and risperidone (0.001-0.1 mg/kg dose range) were assessed in both CAR and locomotor LMA assays. In the LMA assay, varying doses of xanomeline and risperidone were dosed 30 minutes before a challenge dose of the NMDA receptor antagonist MK-801 (0.3 mg/kg), followed by evaluation of open-field activity for 60 minutes. Plasma was collected for determining drug exposure following the experiment. Data were analyzed by multi-factorial ANOVAs and post -hoc comparisons.

Results: We confirmed that xanomeline's activity in CAR was attributed to activation of central muscarinic receptors. Scopolamine at a dose as low as 0.03 mg/kg significantly reversed xanomeline's efficacy, whereas an NMS dose as high as 3 mg/kg had no effect. In the adjunctive studies, inactive-low doses of either xanomeline or risperidone significantly enhanced efficacy of the other agent, resulting in left-shifted dose response curves. At higher dose combinations of xanomeline and risperidone, maximal efficacy was achieved without inducing escape failures, which are predictive of extrapyramidal motor side-effects. Similar synergistic effects were observed in the LMA tests and analysis of plasma exposures determined that drug-drug PK interactions were not responsible for the larger effect sizes of combined dosing.

Conclusion: Our data confirm that xanomeline's antipsychotic activity in these animal psychosis models is mediated by central muscarinic receptors. Moreover, in both the CAR and MK-801 LMA tests, combined dosing of xanomeline and risperidone significantly augmented the effect sizes over that observed for each agent alone. These data support clinical studies to determine whether the addition of KarXT can improve the therapeutic response to traditional antipsychotic agents.

W48. CHANGES IN CLINICAL MANAGEMENT OF PATIENTS WITH SCHIZOPHRENIA TREATED WITH LONG-ACTING INJECTABLE ANTIPSYCHOTICS (LAIS) SINCE THE ONSET OF THE COVID-19 PANDEMIC, INCLUDING THE ROLE OF TELEPSYCHIATRY

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Abstract: Introduction: In the early period of the SARS-CoV-2 virus (COVID-19) pandemic (i.e., March to April 2020), the number of on-site visits to healthcare providers decreased by almost 60% in the United States (US); however, telemedicine utilization to facilitate patient visits rose to 14% across specialties, and telepsychiatry was utilized in 41-84% of behavioral health visits (1, 2). During this period, psychiatric services remained essential to provide continued support (3), including the prevention/mitigation of exacerbations of schizophrenia. The Observational Study of LAIs in Schizophrenia (OASIS) is an ongoing non-interventional, prospective cohort study (NCT03919994) initiated in March 2019 to collect real-world, longitudinal data on the clinical and socioeconomic characteristics and outcomes among patients with schizophrenia treated with long-acting injectable (LAI) antipsychotics in the US. OASIS was actively recruiting and following patients at the onset of the COVID-19 pandemic in the US. An online survey of clinicians at OASIS sites was conducted (Impacts of COVID-19 Pandemic on Outpatient LAI Management and Use of Telepsychiatry for Patients with Schizophrenia [OASIS-MAPS]) to understand changes in practice since the onset of the COVID-19 pandemic and to examine how sites managed care for patients with schizophrenia treated with atypical LAI antipsychotics, including the role of telepsychiatry, during this period. Analyses of the OASIS-MAPS data are in progress; therefore, this Abstract: is focused on study design and methodology.

Methods: Clinicians at 51 active OASIS sites were invited to participate in this cross-sectional, non-interventional, online survey study. Study participants were either the principal investigator (PI) of an OASIS site, or a PI-appointed designee familiar with operations and with prescribing patterns at the site. One clinician per site was asked to complete the survey. Thirty-eight items were developed to cover six content areas: 1) responder characteristics (5 items), 2) impacts and changes due to the COVID-19 pandemic (11 items), 3) telepsychiatry services and current workflow (10 items), 4) barriers preventing telepsychiatry implementation (3 items), 5) future telepsychiatry considerations (6 items), and 6) global impressions of using telepsychiatry for managing LAI treatment (3 items). Response options included multiple choice selections, Likert-type scale ratings, and open-ended text. The survey was administered to participants October 7th through November 2nd, 2020. Summary descriptive statistics (e.g., frequencies and percentages) will be used to summarize item responses across all participants, as well as by key site characteristics, including US geographic region, urban designation (i.e., urban, suburban, rural), and type of site (i.e., hospital network, independent/private practice, or community mental health clinic). Results will be presented, and are expected to provide information on changes made by health care providers to maintain continuity of care for patients with schizophrenia, including those treated with atypical LAI antipsychotics, during the COVID-19 pandemic.

W49. THE SAFETY PROFILE OF THE TAAR1 AGONIST, SEP-363856, IS DISTINCT FROM ATYPICAL ANTIPSYCHOTICS

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Abstract: Background: The past decade has seen increased utilization of data-mining methods as an adjunct to traditional approaches to pharmacovigilance. The availability of sensitive methods for detecting safety signals is especially important in the development of drugs with a novel mechanism of action. SEP-363856 does not act on dopamine D2 receptors but has agonist activity at trace amine–associated receptor 1 (TAAR1) and 5-hydroxytryptamine type 1A (5-HT1A) receptors. In a double-blind study, SEP-363856 demonstrated significant efficacy in the treatment of an acute exacerbation of schizophrenia. The aim of the current analysis was to identify the adverse event signals of this first agent in a novel drug class that differentiate it from the available class of atypical antipsychotics.

Methods: We performed a disproportionality analysis, calculated using the empirical Bayes geometric mean (EBGM) method, to identify and rank-order preferred terms associated with the 11 most recently approved antipsychotics from the FDA real-world adverse event reporting database (FAERS). We used the results of this analysis to evaluate the frequency and cumulative percentages of drug-associated adverse event (AE) signals in the currently available safety database of SEP-363856, consisting of one placebo-controlled 4 week study (SEP361-201; total N=245 patients) and one 6-month open-label safety study (SEP361-202; total N=157 patients). The results were also compared to the cumulative AE percentages for FAERS-identified, class-related preferred terms for the atypical antipsychotic lurasidone, based on 5 pooled studies (N=1795). A conservative threshold of 3-fold risk in FAERS was used as the criterion level to determine if a class-specific AE was occurring.

Results: In the SEP-363856 safety database, utilizing the 3-fold risk threshold, the cumulative rate of adverse events for preferred terms in FAERS was below 20% for antipsychotic class-specific risks. In contrast, in clinical trials of lurasidone, the cumulative rate of adverse events for preferred terms was approximately 50%, indicating about half of the adverse events reported in clinical trials of lurasidone were antipsychotic class-specific risks.

Discussion: SEP-363856 demonstrated markedly lower cumulative risk for antipsychotic class-related adverse events in comparison with similarly-designed acute schizophrenia trials of the atypical antipsychotic lurasidone. These results support characterization of SEP-363856 as a novel class for the treatment of schizophrenia. This database-driven approach represents a new way to summarize adverse events by cumulative burden of class-specific risks and will serve as a helpful tool to evaluate novel classes of drugs with otherwise uncharacterized safety profiles.

W50. EVALUATION OF TREATMENT FAILURE IN REAL-WORLD MANAGEMENT OF PATIENTS WITH RECENT-ONSET SCHIZOPHRENIA FROM THE DISEASE RECOVERY EVALUATION AND MODIFICATION (DREAM) STUDY

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Abstract: Background: Despite the importance of treatment in early schizophrenia, nonadherence to oral antipsychotics is common during this period and can lead to relapse and hospitalization (1, 2). The DREaM study was conducted to evaluate the effectiveness of paliperidone palmitate (PP) versus oral antipsychotic (OAP) treatment in delaying time to treatment failure (TF) in participants with recent-onset schizophrenia. The primary results, evaluating time to first treatment failure (TtFTF), were not statistically significant but numerically favored PP after 18 months of treatment. The definition of TF used for this analysis was limited in that it did not reflect undesirable real-world treatment outcomes for schizophrenia and the designation of TtFTF was unevenly applied in treatment arms with respect to antipsychotic dose adjustments.

Methods: In the randomized, open-label DREaM (NCT02431702) study, TF after treatment with PP was compared with TF after treatment with OAPs in recent-onset schizophrenia. A 3-part design was employed: Part I, 2-month oral run-in; Part II, 9-month disease progression phase (PP or OAP); Part III, 9 months of additional treatment (PP/PP; OAP rerandomized: OAP/OAP or OAP/PP). PP/PP and OAP/OAP comprised the 18-month extended disease progression (EDP) analysis. This post hoc analysis examined differences in TtFTF between PP and OAP using a modified definition of TF, removing supplementation with another antipsychotic from the TF criteria to consistently exclude antipsychotic dose adjustments in both treatment arms.

Results: In Part II, 21.8% of participants in the PP group and 22.3% in the OAP group experienced TF without demonstrating a statistically significant difference in TtFTF between groups using the revised TF definition. In Part III, 4.1% of participants in the PP/PP group, 14.0% in the OAP/PP group, and 27.0% in the OAP/OAP group experienced TF; the difference in TtFTF among groups was statistically significant (P = 0.002), favoring PP treatment. In the EDP analysis, 14.3% of participants in the PP/PP group and 42.9% in the OAP/OAP group experienced TF; the difference in TtFTF was statistically significant (hazard ratio [PP/PP vs OAP/OAP], 0.28; 95% CI, 0.11 to 0.60; P = 0.001).

Conclusions: Some elements of the original TF definition in the DREaM study were not applied equally across treatment arms and did not reflect outcomes with substantial patient or clinician/public health impact. Dose adjustments and addition of other antipsychotics to patient treatment regimens represent common clinical practices that are recommended by treatment guidelines and do not represent poor real-world outcomes. Another limitation of the DREaM study was a large study participation effect. In the present analysis, a modified definition of TF did not identify differences in TtFTF in Part II, a 9-month treatment phase. However, significant differences between groups in TtFTF favoring PP were identified following a longer period of treatment. These results suggest greater effectiveness of PP compared with OAPs in delaying clinically meaningful treatment failure events in patients with recent onset of schizophrenia.

W51. CHARACTERIZATION AND TREATMENT GOALS OF PATIENTS ON LONG-ACTING INJECTABLE VS ORAL ANTIPSYCHOTICS: RESULTS FROM A PATIENT/CAREGIVER/PSYCHIATRIST SURVEY

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Abstract: Background: Patient preferences in schizophrenia (SCZ), including identification of key goals and outcomes for treatment and relative importance of certain treatment goals to patients, have been assessed by several studies. However, there continues to be a lack of sufficient evidence on US patient attitudes and perceptions towards treatment goals and pharmacotherapy options in SCZ, especially taking into context long-acting injectable antipsychotics (LAIs) in this disease area. This lack of evidence is further pronounced in caregivers of individuals with SCZ. The objective of this analysis was to characterize patients with SCZ on LAIs vs patients on oral antipsychotics (OAPs) and evaluate the treatment goals of patients in each group.

Methods: This was a real-world, cross-sectional survey of US psychiatrists, patients ≥18 years old with a diagnosis of SCZ, and caregivers. Data was collected using the Disease Specific Programme (DSP) methodology, which has been previously published. Psychiatrists (n=120) completed detailed record forms for next 8 consecutive outpatients and 2 inpatients matching inclusion criteria, including non-interventional clinical and subjective assessments. The same patients and their caregivers, if present, were invited by their psychiatrist to voluntarily complete a separate survey.

Results: Of 1135 patients on treatment where the physician provided survey data; 251 were on an LAI, and 884 were on an OAP. Mean (SD) time to SCZ diagnosis for those on an LAI was 10.3 (12.0) years vs 7.8 (10.5) years for those on OAPs. More patients in the LAI vs OAP group were being treated as an inpatient (27.1% vs 15.7%, respectively; $p<0.0001$). Patients on an LAI reported being on their current medication regimen for less time (mean 1.7 years) vs those on OAPs (mean 2.5 years) ($p=0.0093$). More patients on LAIs were unemployed due to disability vs those on OAPs (56.1% vs 39.5%, respectively), and less patients on LAIs were able to work part-time or full-time (21.1% or 4.1%) vs those on OAPs (23.2% or 11.4%). More patients on an LAI had a caregiver vs those on OAPs (37.3% vs 26.1%, respectively; $p=0.0011$). Regarding the most important treatment goals reported by patients, both groups reported similar preferences for decrease in disease symptoms (62% on LAI vs 65% on OAPs) and thinking more clearly (53% on LAI vs 46% on OAPs); however, a numerically higher proportion of LAI patients reported that the current medication helped decrease hospitalizations due to relapse vs those on OAPs (38% vs 32%, respectively).

Discussion: Given the characteristics of patients participating in this real-world survey, those on LAIs exhibited qualities which indicate a higher severity of illness vs those on OAPs. Results suggest that treatment with LAIs is still mainly being provided to patients later in the disease course and/or who have adherence problems, despite a growing body of evidence of utility in younger patients earlier in the course of illness.

W52. DOMESTIC MASS SHOOTERS AND TERRORISTS: PREVALENCE OF UNTREATED PSYCHIATRIC ILLNESS

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Abstract: Objective: Utilizing a standardized interview process of psychiatrists applying the DSM-5, we determined the prevalence of psychiatric diagnosis and whether they had been adequately treated with medication among mass killers and terrorists in the United States. Although many narrative reviews and media reports exist on domestic mass murders and terrorists, there is a dearth of scientific data or studies on the presence of psychiatric disorders and its role in these shootings.

Methods: We used a database compilation of 115 mass shootings with firearms between 1982 and 2019 to study retrospectively 55 shooters in the United States. After developing a psychiatric-assessment questionnaire, psychiatric-interviewers determined diagnosis and existence of medication, by evaluating the clinical evidence obtained by (1) interviewing forensic psychiatrists, who had assessed the assailant and/or (2) reviewing psychiatric court evaluations conducted during the judicial proceedings. We selected all the cases where the assailants survived, which was 35 cases. Then 20 additional cases where the assailant died were randomly selected from the remaining 80, to determine differences in psychiatric diagnosis between such assailants and those who survived.

Results: Of 32 of 35 cases where the assailant survived 87.5 % had the following psychiatric diagnosis: 18 schizophrenia, 4 bipolar I disorders, 2 delusional disorders-persecutory type, 2 personality disorders (1 paranoid and 1 borderline), and 2 substance use disorders. 4 assailants had no psychiatric diagnosis. Of 15 of 20 cases in which the assailant died : 8 had schizophrenia. Combining these two samples, schizophrenia was present in 26 (55 %). None of those diagnosed with psychiatric illness were treated with medication.

Conclusion: A significant proportion of mass shooters and terrorists suffered from untreated severe psychiatric illness, which included: schizophrenia, mood disorder, delusional disorder, personality disorders, and substance abuse disorder.

W53. BUPROPION: MISUNDERSTOOD MEDICATION?

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Abstract: Bupropion, a recognized dopamine and norepinephrine reuptake inhibitor, is a well-known treatment for major depressive disorder and for smoking cessation. Compared to patients with major depressive disorder, patients with bipolar disorder or schizophrenia have higher rates of comorbid tobacco use. Yet, there is limited literature examining the combination of bupropion

and an antipsychotic in the treatment of these illnesses. This is possibly due to the perception that bupropion's direct dopaminergic activity may exacerbate manic or psychotic symptomatology. We discuss bupropion's pharmacological properties and clinical implications, highlighting that this medication undergoes extensive first-pass metabolism and has overall weak dopaminergic activity. We present a retrospective analysis of electronic medical records from 09/01/2016 to 08/31/2018 from ten community mental health centers utilizing the Genoa Healthcare database. The expected prevalence of prescribed medication combinations was compared with the actual prevalence of the prescribed combinations using the test of proportions. Clozapine and the risperidone sprinkle formulation were prescribed concurrently with bupropion significantly less often than chance ($p<0.005$). None of the other antipsychotic medications were prescribed with bupropion significantly differently than chance. Considering the additional impact of smoking on the metabolic profile of patients taking antipsychotic medication, it is important not to discard possible alternatives that may help. We suggest that bupropion should receive more study as a useful augmenting agent in combination with these antipsychotics, to aid with smoking cessation and to target co-morbid mood symptoms.

W54. ADOLESCENT SUICIDAL IDEATION SYMPTOM CLUSTERING: MACHINE LEARNING DRIVEN EXPLORATION

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Abstract: Background: Several lines of research have aimed to identify profiles of suicidal thinking and subtypes of adult individuals at risk of suicide. In line with recent work that has utilized symptom clustering approaches towards understanding adolescent depression, we investigate symptom clusters of adolescent suicidal ideation with a variety of unsupervised machine learning techniques.

Methods: Patient reported data from the Treatment for Adolescents with Depression Study (TADS) (n=439), one of the largest randomized control trials for treating moderate-to-severe adolescent depression, were used to study symptom clusters in suicidal ideation questionnaires. Clusters of symptoms in the Suicidal Ideation Questionnaire Junior (SIQ-JR) were identified with hierarchical clustering, a deterministic data-driven machine learning technique that does not require assumptions about the number of clusters in the data. Agglomerative hierarchical clustering was applied to the SIQ-JR symptom scores from the baseline visit in TADS. To examine internal validity, these results were compared against hierarchical clusters of SIQ-JR symptom scores over two subsequent checkpoints and with varying hyperparameters, clusters established by other unsupervised learning techniques (k-means clustering and NMF [non-negative matrix factorization]), and a variety of clustering metrics.

Results: Agglomerative hierarchical clustering of SIQ-JR symptom scores revealed three clusters of symptoms that persisted across 3 checkpoints (0 weeks, 6 weeks, and 12 weeks) in the TADS study and appeared relatively stable across hyperparameters. These clusters are (items should be read as frequency of thoughts about the specified topic): 1. Death, People dying; 2. Suicide would solve my problems, Wishing to be dead, Better to not be alive, No one cares, Others happy if I'm

dead, Wishing to never been born; 3. Killing myself, When to kill myself, How to kill myself, Suicide note contents, Will contents, Telling people plans for suicide. One symptom, wondering how others would react to [patient's] suicide, showed inconsistent cluster assignment. This clustering solution's Silhouette Score (measure of intercluster vs. intracluster distance that ranges between -1 and 1 where 1 represents highly defined clustering, 0 for complete overlap in clusters, and -1 for incorrect clustering) is 0.280 with a nonparametric 95% CI [0.195, 0.319]. Alternatively, a two cluster solution may also offer a more robust (Silhouette Score 0.362, nonparametric 95%CI [0.312, 0.411]) though less meaningful grouping of SIQ-JR symptoms; the two clusters are: 1. Death, People Dying; 2. all other symptoms listed above. Comparable clustering solutions determined by k-means clustering and NMF demonstrated a high degree of similarity to that found by agglomerative clustering.

Conclusion: Using data from the TADS trial, hierarchical clustering may reveal meaningful groupings of SIQ-JR symptoms which in turn may reflect aspects of adolescent suicidal ideation. The variability in clusters seen across different methods and hyperparameters may be related to the relatively small sample size in this adolescent study (as compared to that of adult studies). Internal validation revealed some similarity in clusters, but further external validation via comparisons to external datasets would be required to draw further conclusions. We plan to further explore if such symptom clusters respond differently to the TADS treatment arms (SSRI, CBT, combination, or placebo). This will also help clarify the relative utility of our clustering solutions.

W55. TARDIVE DYSKINESIA: A PRIMER FOR CLINICIANS – THE ROLE OF CONTINUING MEDICAL EDUCATION

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Abstract: Introduction: Tardive Dyskinesia (TD) refers to abnormal, involuntary, choreoathetoid movements of the tongue, lips, face, trunk, and extremities and is associated with long-term exposure to dopamine-blocking agents, such as antipsychotic medications. The movements are disfiguring and can bring unwanted attention to affected individuals. When severe, especially if the respiratory muscles are affected, the movements can be disabling, limit activity, and reduce quality of life. The prevalence is 7.2% in individuals on newer antipsychotics who have never been exposed to older neuroleptics. Until recently, there were no effective treatments for TD. In recent years, many new treatments have been investigated, including valbenazine, deutetrabenazine, and branched chain amino acids. Virtual broadcasts were developed to assess the ability of continuing medical education (CME) to improve awareness of the recognition and treatment of TD among psychiatrists.

Methods: Five virtual broadcasts (Sept-Oct, 2020) consisted of a one-hour, live-streamed discussion from an expert faculty member. Impact of the educational activity was assessed by comparing psychiatrists' responses to four identical questions presented before and directly after activity participation. A follow-up survey was sent to all participants six-weeks post-activity to measure performance in practice changes. A chi-square test was used to identify significant

differences between pre- and post-assessment responses. Cohen's d was used to calculate the effect size of the virtual broadcast.

Results: Activity participation resulted in a noticeable educational effect among psychiatrists (n=1,320; d=4.71, P<.001). The following areas showed significant (P <0.05) pre- vs post-educational improvements: recognition of movements in patients with TD, differential diagnosis of TD, rate of TD in SGA exposed patients, treatment options for TD (on and off-label), and treatment of TD using VMAT2 inhibitors. Additionally, 64% of psychiatrists reported a change in practice performance as a result of the education received in the activity, including develop treatment plans for patients with TD and educate patients and family members about potential for TD and how to recognize symptoms.

Conclusions: The results indicated that a CME-certified one-hour virtual broadcast was effective at improving knowledge among psychiatrists for the recognition and treatment of TD. This knowledge also resulted in positive changes in practice performance post-activity. Future education should continue to address best practices in the diagnosis, treatment and management of patients with TD, as there remains an increased need for tailored CME among psychiatrists.

W56. TELEPSYCHIATRY FOR ASSESSING AND MANAGING TARDIVE DYSKINESIA: EXPERT INSIGHTS FROM A CROSS-DISCIPLINARY VIRTUAL TREATMENT PANEL

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Abstract: Virtual medical visits in psychiatry (i.e., telepsychiatry) are becoming increasingly useful and will likely continue beyond the current societal circumstances. The diagnosis and assessment of tardive dyskinesia (TD), a persistent and potentially disabling movement disorder associated with antipsychotics and other dopamine receptor blocking agents, can be difficult during in-person visits; assessing TD may be even more challenging in virtual settings. To better understand how telepsychiatry may be applied to TD, insights were solicited from an expert panel of 6 neurologists, 3 psychiatrists, and 3 psychiatric nurse practitioners. In July 2020, these experts participated in individual semi-structured qualitative interviews about how TD is diagnosed and treated in real-world settings. In November 2020, a virtual roundtable was conducted to consolidate findings from the individual interviews. The panel agreed that telepsychiatry offers benefits and opportunities to both patients (e.g., easier access, reduced time/cost) and clinicians (e.g., fewer missed appointments, solicitation of partner/caregiver feedback on quality of life, ability to assess patients in their own environments). The panel also agreed, however, that virtual visits cannot completely replace in-person visits. Given the challenges of differentiating TD from other movement disorders, a new TD evaluation may require an in-person visit. For follow-up, all patients should have an in-office evaluation at least once a year, if possible. The panel agreed that video is preferable and often necessary in this patient population; telephone visits alone may not be sufficient. Key challenges for telepsychiatry include technology issues (e.g., inadequate technology), time constraints (e.g., more time needed for virtual assessments), absence of a

standardized approach, and difficulty observing the patient's whole body for a comprehensive assessment of abnormal movements. For pre-appointment preparation, suggested best practices include ensuring that patients have adequate access/equipment and educating them on how to set up their environments and videos for optimal assessment. During the appointment, medical history and clinical review could be conducted similarly to in-person visits. For an overall assessment of movements (full body including lower extremities), patients can be instructed to walk around with someone else holding the camera. For more specific assessments, clinicians can demonstrate the type of movement that they would like the patient to try in a semi-structured but consistent manner to gauge movements over time. If movements are unclear, a follow-up in-person visit may be required. Clinicians can use telepsychiatry as an opportunity to ask patients and caregivers about bothersome movements and how these movements affect functional ability and quality of life. Telepsychiatry also presents an opportunity to educate both patients and caregivers about TD, including FDA-approved treatment options (e.g., valbenazine) that may improve patient outcomes.

W57. NEUROCOGNITIVE EFFECTS OF INTRAVENOUS KETAMINE TREATMENT IN TREATMENT RESISTANT DEPRESSION

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Abstract: Neurocognitive Effects of Intravenous Ketamine Treatment in Treatment Resistant Depression Cortney E. Sera1, Dan Maixner1, Brendon Watson1, Kelly Ryan1, Eric Achtyes2, Mark Frye3, Jennifer Vande Voort3, Fernando Goes4, Daniela Lopez1, Erica Vest-Wilcox1, LeAnn Smart2, Cindy Stoppell3, Alexis Becerra4, John Greden1, Sagar V. Parikh11Michigan Medicine, University of Michigan Department of Psychiatry and Depression Center, Ann Arbor, MI, USA
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Background: Ketamine is an NMDA receptor antagonist associated with learning and memory. In pre-clinical research, limited evidence suggests neurotoxicity, but there is disagreement over how ketamine treatment for treatment resistant depression (TRD) impacts cognitive function1,2,3,4,. We investigated the possible effects of intra-venous ketamine on cognition using the Repeatable Battery for the Assessment of Neuropsychological Status Update®, (RBANS-Update) a brief, individually administered battery5.

Methods: We conducted a clinical trial to examine biomarkers of remission to ketamine for resistant unipolar or bipolar depression, involving administering 3 IV ketamine infusions over an 11-day period. At baseline and 24 hours after the last infusion, the RBANS-Update was administered. RBANS-Update is a validated and reliable cognitive battery of 12 subtests focused on 5 indexes of cognition: immediate memory, visuospatial/constructional, language, attention,

and delayed memory. Subtest raw scores are converted to standardized index scores by same-age peer groups.

Results: Seventy-five subjects completed the acute phase of infusions and RBANS-Update at across a multi-site study. Twenty-seven of these subjects participated at the University of Michigan and satellite Michigan State University – Pine Rest sites. Preliminary analysis of this subset shows 27 participants, regardless of clinical outcome, had a significant improvement in all five cognitive indexes and by percentile rank. Overall, there was significant improvement from percentile rank by age group at baseline (M=49.67, SD=27.19) to 24 hours post infusion 3 (M=72.14, SD=30.48) conditions; t(26)=-4.898, p = .000. A one-way between subjects ANOVA was conducted to compare the effect of remission on percentile rank. Remission was defined as a score of ≤ 9 on the Montgomery–Åsberg Depression Rating Scale MADRS. There was no significant difference in remitter group at baseline testing on percentile rank (F(1, 25) = .228, p = .638). Because there was no difference between participants that experienced remission and did not experience remission at baseline, baseline differences between groups cannot account for the overall improvement.

Conclusion: These preliminary data provide evidence of cognitive improvement, not decline, following administration of 3 IV ketamine infusions for depression. While cognitive improvement may be mediated by improvement in depression, even individuals not achieving remission demonstrated cognitive improvement. These data are clinically reassuring that low doses of ketamine do not cause neuro-cognitive deficits. Further analysis will be done to explore how depression improvement mediates improved cognition as well as how cognitive performance may be linked to suicidal ideation1.

W58. POOR NEONATAL ADAPTATION SYNDROME (PNAS): RESULTS FROM A PROSPECTIVE PREGNANCY REGISTRY

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Abstract: Background: Use of antidepressants during pregnancy has doubled over the last decade, and with it, a concern about the effects of maternal antidepressant usage on neonatal outcomes. Prior research has estimated the prevalence of poor neonatal adaption syndrome (PNAS) and discontinuation symptoms to be as high as 30% in SSRI-exposed infants. However, to date no consensus definition of PNAS exists. We examined the relationship between prenatal SSRI and SNRI use on symptoms and associated symptoms PNAS within the context of a prospective pregnancy registry using systematic criteria for classification of the syndrome.

Methods: Data were prospectively collected from pregnant women, ages 18-45, enrolled in the Massachusetts General Hospital National Pregnancy Registry for Psychiatric Medications. As part of this study, women complete three phone interviews across pregnancy through 3 months postpartum. Information regarding obstetrical /neonatal outcomes and medication use and dosage across pregnancy are obtained from primary medical record sources. Outcome data are confirmed via abstraction from medical records collected at 6 months postpartum. The exposed group for this

analysis was comprised of women who took an SSRI and/or SNRI at any point during their pregnancy; the control group was comprised of women who took an atypical antipsychotic with no polypharmacy during their pregnancy. In the current analysis , PNAS was defined as including one or more of the following symptoms within the first month after delivery: agitation, sleepiness, difficulty breathing, difficulty feeding, signs of withdrawal noted in the record, or abnormal muscle movements.

Results: Of the 2142 participants enrolled at time of analysis, 384 were eligible for inclusion, having completed all interviews and released medical records (N=191 SSRI/SNRI-exposed, N=193 atypical antipsychotic-exposed). The overall proportion of women for whom medical records were obtained was 81.4%. Among this group, 33.7% of infants presented with one or more symptoms of PNAS, including 34.6% of infants in the SSRI/SNRI-exposed group and 32.7% of infants in the atypical antipsychotic-exposed group. The most commonly observed signs included difficulty breathing and difficulty feeding. Importantly, the majority of infants in each group (65.4% of SSRI/SNRI-exposed infants and 66.8% of atypical antipsychotic-exposed infants) showed no symptoms of PNAS.

Discussion: Among women with psychiatric disorders, there appeared to be no increased risk of PNAS symptomatology between women using a serotonergic antidepressant and women treated with an atypical antipsychotic during the prenatal period. In addition, NICU admission rates and NICU admission duration did not appear to differ significantly between groups. The rates of PNAS observed in this sample were consistent with estimates from prior literature. Clinical implications of these data are also discussed.

W59. INFLAMMATORY CYTOKINE ALTERATIONS IN WOMEN VETERANS FROM PREGNANCY TO POSTPARTUM: EXPLORATORY ANALYSES WITH DEPRESSION

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Abstract: Background: The population of reproductive-age women veterans is growing, and consequently, more women veterans are requiring pregnancy-related healthcare. Pregnant women veterans are at risk of developing mental health symptoms, such as depression and suicidal ideation. Women are known to have significant alterations in inflammatory cytokines to maintain a healthy pregnancy followed by further changes in the postpartum period, together known as the perinatal period. However, investigators also have found associations with specific inflammatory changes and depression. During the 3rd trimester of pregnancy, Leff Gelman et al. determined increased interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-alpha), and interferon-gamma (IFN-gamma) in association with comorbid depression and anxiety when compared with healthy pregnant women (1). In the postpartum period, Achtyes and colleagues found significantly increased IL-6, interleukin-8 (IL-8), and TNF-alpha but no change in interleukin-1beta (IL-1beta) in women with postpartum depressive symptoms in comparison to healthy postpartum women (2). We sought to investigate changes in these inflammatory cytokines in relation to symptoms of depression and suicidal thoughts across the perinatal period.

Methods: We recruited 18 pregnant women veterans to complete a psychological assessment battery including the Edinburgh Postnatal Depression Scale (EPDS) and the Columbia Suicide Severity Rating Scale (C-SSRS). We assessed the women during the 3rd trimester of pregnancy (mean 36.4 weeks gestation, range 31-38 weeks) and in the early postpartum period (mean 6.7 weeks, range 5-8 weeks). We obtained serum for determination of the following inflammatory cytokines by the MesoScale Discovery (MSD) platform: IL-6, IL-8, IL-1beta, TNF-alpha and IFN-gamma. Thirteen women completed the postpartum assessment.

Results: There were no differences from pregnancy to postpartum in the means of IL-1beta (0.0344 pg/mL, versus 0.0424 pg/mL), IL-6 (0.722 pg/mL, versus 0.739 pg/mL), TNF-alpha (1.616 pg/mL, versus 1.783 pg/mL), or IFN-gamma (5.924 pg/mL, versus 7.574 pg/mL). However, IL-8 was significantly increased from pregnancy to postpartum, 2.302 pg/mL and 3.287 pg/mL, respectively ($p = .05$). Elevated IL-1beta was associated with suicidal thoughts during pregnancy as evaluated by the C-SSRS, $r = .529$, $p = .029$. There was a significant negative correlation with IL-8 during pregnancy and postpartum EPDS scores, $r = -.608$, $p = .028$. Larger increases in IL-1beta from pregnancy to postpartum trended towards higher postpartum depression scores, $r = .535$, $p = .09$, large effect size (ES). Similarly, larger increases in TNF-alpha from pregnancy to postpartum trended towards higher postpartum depression scores, $r = .501$, $p = .08$, large ES.

Conclusion: Perinatal women veterans are at higher risk than their civilian counterparts to develop mental health symptoms, including depression and suicidal thoughts. The results presented here add to our currently limited understanding of changes in inflammatory cytokines during these unique reproductive phases. Our findings include: 1) increased IL-8 from pregnancy to postpartum; 2) a positive correlation between IL-1beta and thoughts of suicide during pregnancy; 3) trends of increased IL-1beta and TNF-alpha from pregnancy to postpartum with postpartum depressive symptoms. These results must be interpreted with caution due to the small sample size, but they add to our current understanding of inflammatory changes in relation to depression and thoughts of suicide during the perinatal period. Additional investigation is required to further evaluate these preliminary findings.

W60. THE REAL-WORLD ECONOMIC BURDEN OF MISDIAGNOSING BIPOLAR I DISORDER

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Abstract: Background: Bipolar I disorder (BP-I) is defined by the presence of at least one manic episode with mixed and/or depressive episodes often dominating the longitudinal picture. As the depressive phase is the most enduring and disabling feature of BP-I, patients often seek treatment for depressive symptoms and are often misdiagnosed with major depressive disorder (MDD). Misdiagnosis is common and often leads to ineffective/inappropriate treatments that may adversely affect health outcomes. This study evaluated and compared healthcare resource utilization (HRU)

and costs of patients initially misdiagnosed with MDD who received subsequent BP-I diagnosis versus patients diagnosed with BP-I without any prior MDD diagnosis.
Methods: This retrospective study used data from the IBM® MarketScan® Research Databases (Commercial, 1/2014–6/2019; Medicare, 1/2014–3/2019; Medicaid, 1/2014–12/2018). The index date was the first diagnosis of MDD for the cohort of patients initially diagnosed with MDD and later diagnosed with BP-I (ie, misdiagnosed patients) or the first BP-I diagnosis for the cohort of patients diagnosed with BP-I without any prior MDD diagnosis. Selected adult patients had >=12 months of continuous enrollment pre-index (baseline period) and post-index. The follow-up period spanned from the index date to the earliest of either health plan disenrollment or end of data availability. Outcomes evaluated were all-cause and mental health (MH)-related HRU (hospitalizations, emergency room [ER] visits, and outpatient visits) and costs. Inverse probability of treatment weighting was used to balance demographics and baseline characteristics between cohorts. HRU and costs were reported per patient-year (PPY) and compared between cohorts using rate ratios (RRs; estimated by Poisson regression models) and cost differences, respectively. Confidence intervals and P-values were calculated using non-parametric bootstrap procedures.

Results: A total of 30,560 misdiagnosed patients and 37,221 patients with BP-I without prior MDD diagnosis met selection criteria. After weighting, the median follow-up was 30 and 29 months, respectively, and 44% of patients in the misdiagnosed cohort were still misdiagnosed one year post-index. All demographics and baseline characteristics were well balanced in the weighted cohorts; in both cohorts, the mean age was 40 years old and 66% were female. Misdiagnosed patients used significantly more resources during follow-up compared with patients not misdiagnosed with BP-I, with higher rates of hospitalizations, ER visits, and outpatient visits (all-cause RRs: 1.74, 1.20, and 1.18, respectively, all P<0.01; MH-related RRs: 2.04, 1.39, and 1.32, respectively, all P<0.001). Similarly, misdiagnosed patients incurred significantly higher total healthcare costs PPY (all-cause: $19,509 vs $14,768, cost difference=$4,741; MH-related: $11,881 vs $7,484, cost difference=$4,396; both P<0.001). Cost differences were even higher during the first year of follow-up (all-cause: $5,997; MH-related: $5,106; both P<0.001).

Conclusions: Misdiagnosed patients used significantly more resources and incurred significantly higher costs after their initial MDD diagnosis compared with patients diagnosed with BP-I without prior MDD. These results suggest that the prompt and correct diagnosis of BP-I and use of treatments with activity against MDD and BP-I have the potential to significantly reduce healthcare utilization and costs.

W61. EFFECTS OF SINGLE-DOSE L-THEANINE ON MOTOR CORTEX EXCITABILITY IN HEALTHY SUBJECTS: A DOUBLE-BLINDED, RANDOMIZED ORDER, CROSS-OVER PAIRED-PULSE TMS STUDY

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Abstract: Background: L-theanine (N5-ethyl-L-glutamine) is the primary psychoactive component uniquely in green tea. Epidemiological studies support that green tea consumption is

an independent factor associated with lower prevalence of depression. Preclinical studies have demonstrated anti-depressant effect of L-theanine in rodents and provided evidences for its pharmacological properties of N- methyl-D-aspartate (NMDA) and gamma-aminobutyric acid (GABA) agonism. Yet these effects have not been proven in humans. We propose using pair-pulse transcranial magnetic stimulation (ppTMS) to probe how L-theanine may manipulate the glutamatergic and GABA systems in the frontal region by changing cortical excitability first in healthy subjects. ppTMS is a well-established technique to investigate frontal motor cortical excitability mediated by the inter-neuron NMDA and GABA receptors. Specific changes of ppTMS measures, including impaired short-term and long-term intracortical inhibition (SICI, mediated by GABA-A receptor; LICI, mediated by GABA-B receptor) and intracortical facilitation (ICF, mediated by NMDA receptor), have been demonstrated in MDD. Using this technique, we plan to investigate the neurobiological effects of L-theanine in healthy subjects first. Given the potential NMDA and GABA agonistic effects of L-theanine, we hypothesize that it increases intracortical inhibition and facilitation through enhancement of NMDA- and GABA-receptor mediated neurotransmission, in healthy subjects (N=10 to complete study).
Methods: Double-blinded, Randomized-order, Cross-over placebo-controlled study in 10 healthy subjects. Dose of L-theanine or placebo is 400mg. At baseline, subjects will be randomized to L-theanine or placebo group, then receive ppTMS protocol before drug administration. The ppTMS protocol is repeated after 30min of administration. Then subjects will return to clinic after 1 week free of any medications and repeat the above protocol with the second drug condition. Wilcoxon signed-rank test will be used to compare the baseline-to-post-drug means of SICI, LICI and ICF measures. Two-sided P value < 0.05 is considered statistically significant.

Results: Compared to matching placebo, 400mg single dose L-theanine elicited significantly higher post-pre drug change (D) of ICF (Mean±SE DICFL-theanine=0.073±0.073 vs. DICFPlacebo=-0.341±0.176, p=0.016) and LICI (Mean±SE DLICIL-theanine=0.145±0.100 vs. DLICIPlacebo=-0.068±0.053, p=0.037) within each individual. No significant difference was found for DSICI. No adverse effects from L-theanine were observed.

Conclusion: The results suggest that a single dose of L-theanine may enhance NMDA-R mediated intracortical facilitation and attenuate GABA-B-R mediated intracortical inhibition in the human primary motor cortex.

W62. AN UPDATE AND BASELINE DATA FROM THE PHASE 2/3 GAIN TRIAL OF COR388 (ATUZAGINSTAT) A NOVEL BACTERIAL VIRULENCE FACTOR INHIBITOR FOR THE TREATMENT OF ALZHEIMER'S DISEASE

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Abstract: Introduction: The novel mechanism of action of atuzaginstat is based on the discovery of gingipains, toxic protease virulence factors from the bacterial pathogen Porphyromonas gingivalis (Pg), in >90% of Alzheimer's disease (AD) brains. Gingipain levels correlated with AD

diagnosis and tau and ubiquitin pathology, and oral infection of mice with Pg results in brain colonization, increased Aβ1-42, detrimental effects on tau and loss of hippocampal neurons, effects which are blocked by atuzaginstat, an irreversible lysine-gingipain inhibitor. Pg is best known for its role in periodontal disease. Atuzaginstat was well tolerated in phase 1, including trends of efficacy on clinical scales, and significant improvement on a computerized speech assessment and two relevant biomarkers.

Methods: The Phase 2/3 GAIN trial, designed to be potentially pivotal, completed enrollment in November 2020. 642 subjects (aged 55-80; mild-moderate AD with MMSE 12-24) were randomized to one of two doses of atuzaginstat (40mg or 80mg BID) or placebo. The co-primary endpoints are mean change in ADAS-Cog 11 and ADCS-ADL from baseline to 48 weeks. Additional endpoints include change in CDR-SB, MMSE, NPI, Winterlight Speech Assessment, CSF and oral biomarkers, MRI and other measures.

Results: Baseline data show that the 642 randomized subjects are: 56.9% female, 64.3% ApoE4 positive, 49.5% mild (MMSE = 19-24) and 50.5% moderate (12-18). 73.2% of subjects received symptomatic AD co-medications. New baseline biomarker data from the full set of subjects in the study will be shared, including anti-Pg IgG, amyloid-β peptide ratio 42/40, and phospho tau. 233 GAIN trial patients are also participating in a dental sub-study, and while not selected for periodontal disease, approximately 90% have moderate - severe periodontitis.

Conclusions: Enrollment of the GAIN trial was completed in November 2020, and top-line efficacy data are expected December Q4 2021. An interim analysis in December 2020 indicated that the study should continue as planned without sample size adjustment. Subjects enrolled exhibit baseline characteristics consistent with AD and with Pg infection, indicating an appropriate population to test the efficacy and safety of atuzaginstat in mild-moderate AD. The high correlations of AD, periodontal disease, and Pg infections observed in GAIN replicates findings by others and supports a causal role of Pg in AD.

W63. INJECTABLE WEEKLY AND MONTHLY BUPRENORPHINE IN THE OUTPATIENT TREATMENT OF FENTANYL USERS WITH OUD

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Abstract: Background: The introduction of the very high potency opioid analgesic fentanyl into the illicit heroin supply in the U.S. has compounded the opioid epidemic. Clinical reports suggest substantial proportions of patients seeking treatment for OUD in some regions test positive for fentanyl. Fentanyl and its high potency analogs now account for a majority of overdose deaths, and for the rise in overdose deaths. Few clinical studies conducted to date have tested patients for fentanyl, and data on the effectiveness of buprenorphine (BPN) among fentanyl users is limited.

Methods: This 24-week, randomized, double-blind, double-dummy, active-controlled study, evaluated treatment with weekly and monthly injectable extended-release BPN, CAM2038, compared to daily sublingual BPN/naloxone (SL BPN/NX) for initiation and maintenance treatment of patients with OUD at 35 centers throughout the US. Urine toxicology was evaluated using quantitative LC-MS/MS and GC-MS analytical techniques and included fentanyl and norfentanyl. Post-hoc analyses were conducted in the subgroup of participants with evidence of fentanyl use prior to randomization.

Results: Of the 428 randomized participants, 62 (29.1%) in the CAM2038 group and 49 (22.8%) in the SL BPN/NX group, demonstrated evidence of fentanyl use prior to randomization. Those with evidence of fentanyl use were primarily at sites in Ohio, Missouri, and Florida. Most participants in the fentanyl-positive group (83.8%) identified heroin as their primary opioid, compared to 66.2% in the fentanyl-negative group. There were no difference in intravenous route of use at baseline for both groups (54.1% vs 51.7% for fentanyl-positive and fentanyl-negative groups, respectively). At baseline, the fentanyl-positive group provided higher mean percentage of positive urine samples as compared to the fentanyl-negative group for cocaine (37.8% vs 20.2%) and benzodiazepines (21.6% vs 12.9%). Over the course of the study, mean percentage of opioid-negative urine toxicology results was ~10% higher for fentanyl-negative vs fentanyl-positive group. Within the fentanyl-positive group, mean opioid-negative urine toxicology results was higher for CAM2038 (29.6%) vs SL BPN/NX (20.0%), a difference of 9.6% (95% CI of -3.9%, 23.2%). For fentanyl-negative group, in both cohorts, opioid withdrawal (evaluated by COWS) and cravings (evaluated by Need-To-Use Visual Analog Scale [VAS]), were suppressed from day 1 and throughout the study, including during transitions from weekly to monthly injections, without significant group differences. For fentanyl-positive group, opioid withdrawal and cravings were suppressed in both cohorts, however, COWS and VAS scores were lower for CAM2038 vs SL BPN/NX.

Conclusions: In this sample of participants seeking treatment for OUD, the subgroup with exposure to fentanyl prior to randomization exhibited markers of greater severity of illness at baseline (more heroin use, more co-occurring non-opioid drug use) and fewer opioid negative urine results during treatment. Consistent with previous post-hoc analyses of subgroups reporting heroin or IV drug use at baseline, treatment with CAM2038 resulted in a greater percentage of urine samples negative for illicit opioids in participants with evidence of fentanyl use prior to randomization vs SL BPN/NX. CAM2038 may have an advantage over SL BPN/NX on illicit opioid use outcome among difficult-to-treat patient population, including those who test positive for fentanyl at treatment initiation. As these are post-hoc analyses from a randomized study, results should be interpreted with caution as further studies are needed to confirm the improved effectiveness of CAM2038 in these subgroups.

Thursday, June 3, 2021

Poster Session II

T1. RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, FIXED-DOSE, PARALLEL GROUP STUDY TO EVALUATE THE EFFICACY AND SAFETY OF THE AMPHETAMINE EXTENDED-RELEASE TABLET (AMPH ER TAB) IN ADULTS WITH ADHD

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Abstract: Objectives: To evaluate the efficacy and safety of an Amphetamine Extended-Release Tablet (AMPH ER TAB) in adults with ADHD aged 18 to 60 years.
Methods: In a 5-week forced dose-titration phase, eligible subjects were randomized to either oral double-blind AMPH ER TAB 5 mg starting dose or matching placebo, once daily in the morning beginning the day after the Baseline Visit. Subjects were titrated up (5 mg increments) each week. Safety and efficacy assessments were done weekly. After Visit 3, subjects received 20 mg for 14 (±3) days before Visit 5 (V5). Subjects who could not tolerate study drug discontinued. A Permanent Product Measure of Performance (PERMP) placement test was done at Screening or Baseline. At V5, efficacy assessments included the administration of serial PERMPs predose, 0.5, 1, 2, 4, 8, 10, 12, 13, and 14 hours postdose. The primary efficacy endpoint was the mean PERMP-T score across postdose time points during the Visit 5 serial PERMPs. Safety was monitored by AEs assessed at each visit, C-SSRS, vital signs, weight, and assessment of sleep, appetite, mood, and psychotic AEs.

Results: The mean postdose PERMP-T score over all postdose time points at V5 was statistically significantly higher in the AMPH ER TAB group vs placebo (302.8 vs 279.6; p=0.0043). Common adverse events were decreased appetite, insomnia and dry mouth. The majority of TEAEs were mild to moderate in severity, and no SAEs were reported.

Conclusion: The AMPH ER TAB demonstrated efficacy in treatment of symptoms of ADHD in adults, with an anticipated safety profile.

T2. HOW FREQUENT IS SWITCHING FROM AN INITIAL STIMULANT FAMILY TO THE ALTERNATIVE ONE IN THE CLINICAL SETTING? A PILOT STUDY OF FORTY-NINE CONSECUTIVELY REFERRED MEDICATION NAïVE ADULTS WITH ADHD

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Abstract: Purpose: Due to their well-documented safety and efficacy, the most common treatments for attention-deficit/hyperactivity disorder (ADHD) are psychostimulant medicines, either a short- or long-acting formulation of methylphenidate (MPH) or amphetamine (AMPH). Although both AMPH and MPH products have similar efficacy and tolerability at the group level, data from 54 published clinical trials in adults with ADHD treated with stimulants showed a mean group response rate of 60% (range 42-87%), indicating that a sizeable number of adult ADHD patients will not adequately respond to their initial family of stimulant medications. This study aimed to evaluate the frequency of needing to switch the initial treatment of a stimulant to the alternative family in newly referred, medication naïve adults with ADHD initiating treatment with stimulants.

Methods: Subjects were 49 unmedicated adults (18-45 years old) with a DSM-5 diagnosis of ADHD who initiated treatment with a stimulant. Before the clinical assessment with an expert clinician, participants completed the Adult Self-Report (ASR), Behavior Rating Inventory of Executive Function - Adult Version (BRIEF-A), Emotional Dysregulation subscale of the Barkley Current Behavior Scale – Self-report (CBS DESR), and Mind Wandering Questionnaire (MWQ). The rate switching was examined using information from the electronic medical record for up to three clinical follow-up visits. Patients were considered "switchers" if they required a change of the initially prescribed stimulant family due to poor tolerability. Patients were considered "strugglers" if they required changes in formulation (long- to short-acting and vice versa) or additional antianxiety or antidepressant treatment to remain on their initially prescribed stimulant family. Rates of switching and struggling with initial treatment were compared between patients initially prescribed AMPH and patients initially prescribed MPH. Patients were then re-stratified by those who were switchers and those who were not switchers (i.e. strugglers and patients with no changes or additional psychotropic meds), and compared on demographic and clinical characteristics.

Results: Sixty-seven percent of ADHD patients were initially prescribed a MPH product and 33% an AMPH product. Forty-one percent of ADHD patients needed to switch from their initially prescribed stimulant family within 90 days of initiating treatment due to poor tolerability. While the rate of switching was significantly higher in those initially prescribed MPH (p=0.01; OR=12.83, 95% CI=2.14, 76.99), the rate of patients who required changes in formulation (long- to short-acting and vice versa) or additional antianxiety or antidepressant treatment ("strugglers") was higher in those taking AMPH (p=0.03; OR=7.05, 95% CI=1.19, 41.71).

Importance: Forty-one percent of medication naïve adults with ADHD initiating stimulant treatment required a switch from the initially prescribed stimulant family to the alternative one due to poor tolerability. Switching could not be adequately predicted by baseline demographic or clinical characteristics. These findings call for improved efforts to help identify predictors of response to stimulant treatment in adults with ADHD to avoid unnecessary delays in identifying a safe and effective treatment for these patients.

T3. CAN THE CHILD BEHAVIOR CHECKLIST HELP CHARACTERIZE COMORBID PSYCHOPATHOLOGY IN CLINICALLY REFERRED YOUTH WITH ADHD?

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Abstract: Purpose: While it is well recognized that a major source of morbidity and dysfunction in attention-deficit/hyperactivity disorder (ADHD) is the frequent presence of psychiatric comorbidity, it is unclear how well this information reaches clinical practice and is available for use in the clinical community. Identifying potential comorbid psychopathological conditions affecting a referred youth with suspected ADHD prior to evaluation can help the assessing clinician gain insight into the complexity of the clinical presentation. The Child Behavior Checklist (CBCL) is an easy-to-use assessment tool measuring multiple areas of psychopathology that may provide invaluable information regarding the severity of the presenting complaints. The main aim of this study was to further evaluate the utility of the CBCL to help screen for comorbid psychopathology in youths referred to clinical care for the assessment and management of ADHD symptomatology.

Methods: The sample included 332 youths consecutively referred to an ADHD program for the assessment of suspected ADHD. Before their child's initial evaluation, the parent or guardian completed the CBCL, parent-rated ADHD Self-Report Scale (ASRS), Social Responsiveness Scale (SRS), and Behavior Rating Inventory of Executive Function (BRIEF). The CBCL is an empirically derived 113-item parent-rated assessment of a child's behavior problems and social competence. Raw scores are calculated and used to generate T-scores for eight clinical scales, two composite clinical scales, one total clinical scale, and four competence scales. T-scores ≥70 (2 SDs) are considered to be in the clinical range for the clinical scales, T-scores ≥64 are considered to be in the clinical range for the composite scales and total scale, and T-scores ≤30 are in the clinical range for the competence scales. Because of the established association between the CBCL Attention Problems scale and a structured diagnostic interview of ADHD, all youths analyzed had abnormal Attention Problems T-scores (≥60). Patterns of comorbid psychopathology and dysfunction were assessed in these youths.

Results: Seventy-six percent of youths with elevated Attention Problems T-scores had ≥3 additional abnormal CBCL scales, suggesting they were likely affected with multiple comorbid psychopathological conditions. Moreover, 44% had ≥1 CBCL clinical scale with a T-score more severe than their Attention Problems T-score, suggesting the putative comorbid condition was more severe than the ADHD symptoms. A more detailed look at these more severe scales revealed that 13% of patients had the Anxious/Depressed scale (indexing anxiety and depressive disorders) as their most severe scale, 11% of patients had the Aggressive Behavior scale (indexing ODD) as their most severe scale, and 8% had the Withdrawn/Depressed scale (indexing depression) as their most severe scale. Additional CBCL scale elevations were associated with more severe functional impairments as assessed by the ASRS, SRS, BRIEF, and CBCL competence scales.

Importance: Our CBCL results show that the majority of referred youths with suspected ADHD are affected with high levels of comorbid psychopathology and dysfunction that may affect treatment decisions and outcomes. The presence of multiple CBCL scale elevations should also help clinicians identify ADHD youths who have a complex clinical presentation. Doing so will likely improve the outcomes of the many affected youths with ADHD.

T4. BUPRENORPHINE TREATMENT RETENTION IN INDIVIDUALS WITH OPIOID USE DISORDER: INSIGHTS FROM REAL-WORLD DATASET

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Abstract: Introduction: Opioid Use Disorder (OUD) is a chronic relapsing disorder and a growing cause of overdose deaths in the US. Buprenorphine (BUP) is effective in OUD, but treatment discontinuation represents the greatest obstacle to effective treatment (Brorson 2013). Conversely, treatment retention is associated with higher rates of employment and opioid abstinence, and with lower relapse rates as compared to patients who discontinue treatment [Kleber 2007]. BUP treatment retention in real world settings may be affected by medication dosing patterns and other clinical and sociodemographic patient features, as well as by care settings. Here we systematically analyzed a large longitudinal dataset from electronic health records (EHR) to examine the effects of these factors on treatment retention in adults with OUD.

Methods: Anonymized patient EHR data (2009-2018) for patients with OUD (aged 15 or over) were used in a retrospective study to determine whether certain prescription regimens were more effective than others, along with treatment setting at treatment initiation (i.e., inpatient, intensive outpatient, outpatient), sociodemographic and clinical variables (e.g., psychiatric comorbidities and medications). Dropout from BUP and from SUD treatment overall were based on a data-driven approach, and clinical judgment. Survival analyses of treatment dropouts examined the effect of different clinical, sociodemographic, concurrent SUD conditions and overall disorder severity as measured in the Clinical Global Impression - Severity (CGI-S) scale. We compared dosing trajectories and their relative efficacies.

Results: More than 5,000 patients with comparable numbers of men and women formed the study cohort. Most participants were non-Hispanic/Latino white. Other SUD comorbidities, especially alcohol abuse, were common, and patients had an average CGI-S of 4.8 +- 1.1 at BUP initiation. Overall, patients were more likely to remain in treatment if they were treated in an outpatient facility and had a lower CGI-S value at the start of treatment. Furthermore, people with a comorbidity of cannabis were more likely to drop out of treatment faster than those with no other comorbidities. The effect of having other SUD comorbidities appear to be marginal in terms of dropout. The most common doses for BUP were 16 mg/day, 8 mg/day, 4 mg/day, and 24 mg/day, in that order. Most patients received less than four dose changes within a year. Of Only 10.1% of individuals who began BUP were still on it at a year and 8.5% were still in treatment at that time but not on BUP. The mean number of days in treatment was 65 □ 76 days. It appears that patients who start with an initial dose of 8 mg/day stay in treatment on average longest of 81 days.

Conclusion: Treatment retention is extremely poor with BUP treatment of OUD. Those with greater OUD severity and comorbid cannabis use disorder at treatment initiation have a higher propensity of premature treatment discontinuation. An initial dosing of 8 mg/day appears to be the best course of treatment for patients suffering from OUD.

T5. NATIONAL PRACTICES IN TEACHING PSYCHOPHARMACOLOGY IN PSYCHIATRY RESIDENCY PROGRAMS: RESULTS OF A NATIONWIDE SURVEY

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Abstract: Background: Psychopharmacology is a core educational topic in psychiatry residency programs. Despite this, there is little written on best practices for teaching psychopharmacology. The goal of this study is to survey psychiatry residents throughout the United States to understand program practices for teaching psychopharmacology, including resident perceptions of their program's teaching and potential gaps in curriculum. All results were deidentified.

Methodology: We emailed survey invitations to program directors of every psychiatry residency program in the United States (August 2020). The email instructed program directors to forward their residents the invitation to participate in the survey. REDCap was used to administer the survey, which included an online consent to participate. Survey questions assessed: 1) resident education on psychopharmacology including teaching methods and resources used by programs, 2) perceptions of the quality of psychopharmacology teaching, 3) gaps in curriculum.

Demographics: 201 residents responded to the survey invitation. 144 residents consented, answered survey questions and were included in the analysis. 15.1% of respondents were PGY1 (n = 19), 23.0% PGY2 (n = 29), 28.6% PGY3 (n = 36), 24.6 % PGY4 (n = 31), 7.1% PGY5 (n = 9), 1.6% (n=2) PGY6, and 12.5% did not to identify their year in training (n = 18).

Conclusions: 1) Understanding national trends in teaching methodology and content will be useful for individual programs and educators when evaluating local/personal practices. 2) The results suggest residents prefer more interactive methods of teaching psychopharmacology to be incorporated into their programs such as case-based learning. 3) Notable topics residents felt were not adequately covered in their curriculum include: Clinical trial analysis/design, Cognitive enhancers, Combining psychopharmacology and psychotherapy, Informed consent, Pharmacokinetics/pharmacodynamics, Therapeutic alliance

T6. EVALUATING THE TRANSLATIONAL PROMISE OF COMPUTATIONAL MODELS: RELIABILITY OF REWARD AND PUNISHMENT PROCESSES

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Abstract: Computational psychiatry is an emerging field which aims to better understand psychiatric disorders by deploying mathematical models. Such models offer the advantage of examining behaviorally unobservable, but important latent processes (e.g., reward prediction errors) that may drive cognitive dysfunction associated with mental illness; with the ultimate aim of transforming such knowledge into new treatment strategies. For translational endeavors to be successful, it is imperative that computational measures are able to capture individual characteristics reliably. To date, this issue has received little consideration. Here we examined the reliability of computational parameters derived from two commonly used reward and punishment tasks, which have previously been used to study anxiety disorders. Healthy individuals (n=50) completed a four-armed bandit (reward and punishment learning) and

gambling (decision making) task twice, two weeks apart. For both tasks we derived traditional "model-agnostic" measures (mean probability to stay after losses/rewards, mean probability of gambling) as well as computational parameters. Several different reinforcement learning models were fit to the bandit task, while different versions of a prospect theory model were fit to the gambling task. Models were fit separately for each session with hierarchical Bayesian estimation using the hBayesDM package. Reliability of measures was assessed with intraclass correlation coefficients (ICCs), and by examining the predictive accuracy of the winning models. Model-agnostic outcome measures in the bandit (ICCs=0.60-0.62) and gambling (ICCs=0.60-0.63) task exhibited good reliability (all $p<0.001$). The winning bandit model had separate reward/punishment learning and sensitivity parameters, and a lapse parameter. All but the lapse parameter (ICC=0.02; $p=0.39$) demonstrated fair-to-good reliability (ICCs=0.46-0.64; all $p<0.001$). The parameters from the winning gambling task model showed good-to-excellent reliability (all $p<0.001$), including loss aversion (ICC=0.70), risk aversion (ICC=0.83), and temperature (ICC=0.82). Models estimated from session 1 data predicted session 2 choices above chance at a trial-by-trial level on both the bandit (choices predicted: M=42.09% (chance=25%), SEM=1.9%, $p<0.001$) and gambling task (choices predicted: M=67.70% (chance=50%), SEM=1.46%, $p<0.001$). We provide evidence of stable measurements of computationally-defined parameters derived from two popular reward and punishment tasks. In particular, the model parameters from the gambling task exhibited greater reliability than the model-agnostic measures, suggesting that computational models here may offer advantages in psychometric properties, in addition to their advantage in specifying mechanisms. Interestingly, both models were able to forecast future behavior on the same task two weeks later using a generative model, equivalent to "out-of-sample" validation. These results offer promise for the clinical utility of computational parameters in precision psychiatry.

T7. EFFECT OF BEDTIME SUBLINGUAL CYCLOBENZAPRINE (TNX-102 SL) ON PTSD SLEEP-DEPENDENT EMOTIONAL MEMORY PROCESSING: RETROSPECTIVE ANALYSIS OF PHASE 2 AND 3 TRIAL RESULTS IN MILITARY-RELATED AND CIVILIAN PTSD

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Abstract: Background: PTSD is characterized by memory processing deficits, disturbed sleep, and recurrent intrusion symptoms. Bedtime TNX-102 SL (sublingual cyclobenzaprine) is a functional antagonist at 5-HT2A-serotonergic, α-1-adrenergic, H1-histaminergic and M1-muscarinic receptors that is designed for the treatment of PTSD by targeting sleep disturbance to improve sleep-dependent emotional memory consolidation. Three randomized, placebo-controlled and double-blind clinical trials of TNX-102 SL were performed, a Phase 2 (P201) and a Phase 3 (P301) study in military-related PTSD, and a Phase 3 (P302) study in civilian PTSD. All three trials showed encouraging activity of TNX-102 SL on clinician- and patient-rated global PTSD symptoms (Clinician Global Impression [CGI] and Patient Global Impression of Change [PGIC]) but missed significance on the primary endpoints of total Clinician Administered PTSD Scale for DSM-5 (CAPS-5). The present retrospective analysis examined the activity of TNX-102 SL on select items of the CAPS-5 that reflect its proposed mechanism, specifically PTSD sleep disturbance (B2 [trauma nightmares] and E6 [difficulty sleeping]) and the sequela of chronic dysfunctional extinction consolidation (B1 [unwanted trauma memories], B4 [emotional upset by trauma triggers] and B5 [physical reactions to trauma triggers]).

Methods: P201, P301 and P302 were 12-week, multicenter, randomized, double-blind, placebo-controlled, Phase 2 and 3 studies, testing the efficacy and safety of TNX-102 SL 5.6 mg (2 x 2.8 mg tablets) for PTSD. The primary efficacy endpoint for each was mean change from baseline (MCFB) in total CAPS-5 score at Week 12. Post-hoc analyses included principal component analysis (PCA) and network analysis on the individual CAPS-5 items to illuminate underlying structures in the data, as well as relationships between items; MCFB analysis was performed via mixed-model repeated measures (MMRM) on five individual CAPS-5 items B1, B2, B4, B5 and E6, and on the "5-item total score" to compare treatments.

Results: PCA revealed similar CAPS-5 item loadings for military and civilian PTSD, and network analysis showed grouping of sleep items (B2 and E6) and intrusion items (B1, B4 and B5). TNX-102 SL 5.6 mg treated participants showed a strong trend towards greater improvement in the 5-item total score at Week 12 as compared to placebo using MMRM in P201 (n = 141; p = 0.191; Cohen's d effect size, d = 0.15), P301 (n=252; p = 0.086; d = 0.22) and P302 (n = 163; p = 0.073; d = 0.29). The 5-item total scores in the three studies are more consistent with PGIC and CGI than the total scores of the 20-item CAPS-5. Effect size profiles for the individual CAPS-5 items are illustrated by the P302 data (B1, d = 0.22; B2, d = 0.16; B4, d = 0.22; B5, d = 0.30; and E6, d = 0.28).

Discussion: The 5-item CAPS-5 total score appears useful for measuring the clinical response to drugs that promote recovery from PTSD via a pharmacodynamic mechanism of improving sleep-dependent emotional memory processing. Drug development can provide biological insights via pharmacological dissection of complex syndromes. For example, retrospective analysis revealed that TNX-102 SL impacted select items of CAPS-5 that measure PTSD sleep disturbance and deficient PTSD sleep-dependent emotional memory consolidation. These data are consistent with the proposed mechanism that TNX-102 SL targets PTSD sleep disturbance and thereby facilitates a sleep-dependent healing mechanism.

T8. THE SAFETY AND TOLERABILITY OF LUMATEPERONE 42 MG FOR THE TREATMENT OF BIPOLAR DEPRESSION: A POOLED ANALYSIS OF 2 RANDOMIZED PLACEBO-CONTROLLED TRIALS

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Abstract: Background: Approved treatments for bipolar depression are limited and associated with a spectrum of undesirable side effects. Lumateperone (LUMA), a mechanistically novel antipsychotic that simultaneously modulates serotonin, dopamine, and glutamate neurotransmission, is FDA-approved for the treatment of schizophrenia and is being investigated in bipolar depression. LUMA 42-mg monotherapy was evaluated in 2 randomized, double-blind, placebo (PBO)-controlled studies (Study 401 [NCT02600494]; Study 404 [NCT03249376]) in patients with a major depressive episode (MDE) associated with bipolar I or bipolar II disorder.

A pooled analysis of these studies assessed the safety and tolerability profile of LUMA 42 mg in the treatment of bipolar depression.

Methods: Safety data were pooled from 2 studies that recruited patients aged 18–75 years with a clinical diagnosis of bipolar I or II disorder who were experiencing a MDE and had a Montgomery-Åsberg Depression Rating Scale (MADRS) Total score ≥20 and a Clinical Global Impression Scale-Bipolar Version-Severity (CGI-BP-S) score ≥4. Patients in these studies were randomized to LUMA or PBO and treated for 6 weeks. Safety assessments included adverse events (AEs), laboratory parameters, and vital signs. Additional assessments included changes on extrapyramidal symptom (EPS) scales (Barnes Akathisia Rating Scale [BARS], Abnormal Involuntary Movement Scale [AIMS], and Simpson-Angus Scale [SAS]).

Results: The safety population comprised 746 patients (LUMA, 372; PBO, 374). Treatment-emergent AEs (TEAEs) occurred in 56.2% of LUMA and 47.3% of PBO patients. The only TEAEs that occurred in ≥5% of LUMA patients were headache (LUMA, 14.2%; PBO, 7.8%) and somnolence (LUMA, 13.2%; PBO, 3.2%). Rates of discontinuation due to AEs were 7.0% and 2.1% for LUMA and PBO, respectively. Rates of treatment-emergent events of mania/hypomania were low (LUMA, 1.6%; PBO, 1.3%). Mean change in weight was low and similar between groups (LUMA, +0.06 kg; PBO, +0.19 kg); incidence of potentially significant weight gain (≥7% increase) was low (LUMA, 0%; PBO, 1.4%). Changes in metabolic parameters were low and similar between groups: total cholesterol [mg/dL] (LUMA, −0.6; PBO, −1.1); LDL cholesterol [mg/dL] (LUMA, −0.7; PBO, −0.6). LUMA was not associated with changes in prolactin [µg/L] (LUMA, −0.17; PBO, +1.06).m LUMA was associated with minimal EPS risks as assessed by both TEAEs and mean change in EPS scales: BARS (LUMA, −0.1; PBO, −0.1); AIMS (LUMA, +0.0; PBO, +0.0); SAS (LUMA, +0.0; PBO, +0.0).

Conclusion: In this pooled analysis of 2 randomized, PBO-controlled trials in patients with a MDE associated with bipolar I or bipolar II disorder, LUMA 42 mg showed good tolerability with minimal impact on metabolic parameters, prolactin, and EPS. These results suggest that LUMA may provide benefits over currently available treatments for bipolar depression.

T9. MANAGING BIPOLAR SPECTRUM ACROSS THE LIFECYCLE: A VIRTUAL MEDICAL EDUCATION BROADCAST

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Abstract: Introduction: Bipolar spectrum disorders are frequently misdiagnosed as major depression. Also, there are very few evidence based treatments for bipolar depression. Clinicians often prescribe inefficacious treatments for this disorder. The talk addressed the diagnostic dilemmas and evidence based strategies for bipolar spectrum disorder. Methods Five virtual broadcasts (Sept-Oct, 2020) consisted of a one-hour, live-streamed discussion from an expert key opinion leader. Impact of the educational activity was assessed by comparing psychiatrists' responses to four identical questions presented before and directly after activity participation. A follow-up survey was sent to all participants six-weeks post-activity to measure performance in practice changes. A chi-square test was used to identify significant differences between pre- and post-assessment responses. Cohen's d was used to calculate the effect size of the virtual broadcast.

Results: Activity participation resulted in a noticeable educational effect among psychiatrists (n=1,686; d=5.71, P<.001). The following areas showed significant (P <0.05) pre- vs post-educational improvements: efficacy of newly emerging treatments for bipolar depression,

augmentation therapy, and mechanism of action of antipsychotics. Additionally, 64% of psychiatrists reported a change in practice performance as a result of the education received in the activity, including develop treatment plans for patients with bipolar disorders and educate patients and family members about current treatment options, adverse effects and the importance of adherence to prevent relapse.

Conclusions: The results indicated that a CME-certified one-hour virtual broadcast was effective at improving knowledge among psychiatrists for the recognition and treatment of bipolar depression. This knowledge also resulted in positive changes in practice performance post-activity. Future education should continue to address best practices in the diagnosis, treatment and management of patients with bipolar depression, as there remains an increased need for tailored CME among psychiatrists.

T10. SUBTHRESHOLD MANIC SYMPTOMS (SLEEP DISTURBANCE AND IRRITABILITY) AND RESPONSE TO LURASIDONE IN CHILDREN AND ADOLESCENTS WITH BIPOLAR DEPRESSION

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Abstract: Background: The objective of this post-hoc analysis was to investigate the effect of baseline mixed depression and the specific subthreshold manic symptoms of sleep disturbance and irritability, on the overall response to lurasidone in children and adolescents with bipolar depression in a 6-week acute study followed by a 104-week open-label extension study.

Methods: Patients, 10–17 years of age, with a Diagnostic and Statistical Manual of Mental Disorders, 5th ed. (DSM-5) diagnosis of bipolar I depression were randomized to 6 weeks of double-blind treatment with once-daily flexible doses of lurasidone 20–80 mg or placebo, followed by a 104-week open-label treatment of lurasidone in the extension study. The effects of sleep disturbance (YMRS item 4) and irritability (YMRS item 5) on the overall response to lurasidone treatment were evaluated using MMRM and logistic regression methods.

Results: A total of 182 (53.1%) patients had “decreased need for sleep” (YMRS item 4 > 0) and 288 (84.0%) had “irritability” (YMRS item 5 > 0) at pre-treatment acute study baseline. LS mean changes in sleep disturbance symptoms (YMRS item 4) and depression (CDRS-R item 4, “sleep disturbance”) at week 6 were significantly greater for lurasidone compared with placebo ($P < 0.05$).Moderator analysis showed that the baseline presence or absence of “decreased need for sleep ” alone or combined with “irritability” predicted response to lurasidone (vs. placebo) treatment as assessed by LS change in CDRS-R total score and global functioning (CGAS) at week 6 (all $P<0.05$ for treatment interaction with YMRS items 4 and/or 5). Greater lurasidone (vs. placebo) effect sizes for the reduction in CDRS-R total score (Cohen’s d= 0.64) and CGAS (Cohen’s d = 0.52) score were found in patients with sleep disturbance at baseline, mediated in part by an improvement in sleep disturbance symptoms with treatment. Treatment with lurasidone was associated with continued improvement in “decreased need for sleep” and “irritability” symptoms as well as the overall CDRS-R score and CGAS score over the 104-week open-label extension study. Both “decreased need for sleep” and “irritability” symptoms were found to be significantly correlated with the overall

severity of anxiety as assessed by the pediatric anxiety rating scale (PARS) total score. There was also a significant link between "Irritability" and the overall severity of physical symptoms of anxiety (PARS item 4). The absence of sleep disturbance and irritability symptoms at week 6 (extension study baseline) was associated with higher rates of recovery (symptomatic remission CDRS-R < 28 and functional remission CGAS > 71) (77.4% vs.57.8%, NNT=6, P<0.05) than in the presence of these two specific manic symptoms.

Conclusion: Results from this post-hoc analysis suggest that in children and adolescents with bipolar depression treated with lurasidone, the co-occurrence of specific manic symptoms (sleep disturbance and irritability) at baseline and improvement in these symptoms may be associated with acute-phase treatment response. Absence of these symptoms at week 6 predicted recovery in the long-term treatment.

T11. SUBJECTS PRESENTING AT MULTIPLE SITES DURING THE PANDEMIC: HOW THE CURRENT SHECESSION DIFFERS FROM THE MANCESSION OF A DECADE AGO

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Abstract: Background: Duplicate and professional subjects are a significant problem in clinical trials, particularly in studies with subjective endpoints, such as in CNS or pain. Duplicate subjects can occur, however, in any study where their activity is not monitored across sponsors, even in Alzheimer's Disease, oncology or vaccine studies. Data integrity is compromised when professional subjects purposely deceive with regard to inclusionary symptoms, excluded conditions, adherence to investigational product or previous study participation. CTSdatabase is a subject registry which uses partial identifiers to track duplicate and professional subjects across sites and sponsors.
Following the previous recession, the so called "mancession" of 2008-2009, we noted that the most common professional subject was a man in his 40's, mirroring the group most affected in that recession. We wondered if the current "shecession", which has been widely reported to disproportionally affect women, would be reflected in an increase in women seeking to participate in clinical trials at multiple sites.

Methods: Between Jan 1 2016 and Dec 31 2020, 53,538 subjects were consented and entered into CTSdatabase. 23,709 of these were male and 29,829 were female. The cumulative total of those whose identifiers matched with a subject who presented at another site within the last 30, 60 or 90 days were tracked by quarter of when the entered subject presented to a unique clinical trial site. For example, if Subject A presented at Site A in Q1 2020, how often did that subject also present as Subject B at Site B within the previous 30, 60 or 90 days?

Results: There was a dramatic increase in unemployment for both males and females in Q1 of 2020, with a slightly steeper increase for women (from 3.77% to 14.10%) than men (from 3.80% to 12.10%). There also appears to be a small signal (of unclear significance) for an increase of the number of female subjects who show up at multiple sites in 2020.

Discussion: Professional subjects, by definition, participate in studies to collect stipends. Further research is warranted to discover if, during the course of a recession that disproportionally affects women, there will be an increase in the number of women who

become professional subjects. Sponsors of clinical trials should have even greater vigilance for duplicate and professional subjects during these extreme economic times and in the years that follow.

T12. SEROTONERGIC TOXIDROME FOLLOWING METHYLENE BLUE ADMINISTRATION FOR VASOPLEGIA: BARRIERS IN PREVENTING SEROTONIN SYNDROME AND REVIEW OF THE LITERATURE

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Abstract: Methylene blue is a monoamine oxidase inhibitor that is traditionally known to be used as a procedural dye and historically used for methemoglobinemia. More recently its use for patients who are in shock after cardiac procedures, such as coronary artery bypass (CABG), has grown. Here we present a case of methylene blue use in a 60-year-old male with a past psychiatric history of Major Depressive Disorder and Alcohol Use Disorder, severe (in sustained remission) who presents to the hospital for scheduled three-vessel CABG. He had been stable on mirtazapine 7.5 mg PO daily, duloxetine 120 mg PO daily, and fluoxetine 80 mg PO daily. His surgical course was complex and post-operatively he was ultimately treated with methylene blue for vasoplegia. Following discontinuation of all psychotropic medications, the University of Virginia Medical Center Psychiatry Consultation-Liaison service was consulted for recommendations on the management of Serotonin Syndrome and psychotropic medication management. We discuss the background and relevant literature to this scenario and promote discussion for outpatient and consultation-liaison psychiatrists for medically complex patients at increased risk of Serotonin Syndrome.

T13. SERTRALINE INDUCED SUICIDAL IDEAS AND SELF-INJURIOUS BEHAVIOR IN A CASE OF MAJOR DEPRESSIVE DISORDER AND COMORBID ALCOHOL USE DISORDER

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Abstract: The association between major depressive disorder (MDD) and alcohol use disorder (AUD) has been well studied, the presence of either disorder doubled the risks of the second disorder (1, 2). Several potential developmental pathways have been proposed to explain the high rate of co-occurring AUD and depressive disorders (3). Research showed that for people with co-occurring AUD and depressive disorders, antidepressants are more effective than placebo at reducing symptoms of depression (4, 5). Sertraline was included in multiple clinical trials for treating co-occurring depression and alcohol dependence (6). A debate persists on whether SSRIs might cause the emergence or worsening of suicidal ideas in vulnerable patients (7, 8). Here we present a case of MDD and AUD that exhibited suicidal ideation and self-injurious behavior for the first time after initiation of sertraline treatment.

Mr. K is a 42-year-old man with a history of severe Alcohol use disorder for 8 years, complicated by 3 DUIs and multiple blackouts. No history of psychiatric hospitalization, or treatment for alcohol use or depressive disorder. No history of suicidal ideas/behavior, or any

self-injurious behaviors. After 6 months of sobriety, patient started to develop symptoms consistent with an episode of MDD. He sought psychiatric help and was started on Sertraline by an outpatient psychiatrist, gradually titrated up to 100mg daily over 2 weeks, with no response. Patient binged once on alcohol (1 Liter of Vodka) while still taking Sertraline 100 mg and was hospitalized for the first time the next day for acute suicidal ideation and self-injurious behavior in the form of wrist cutting. His suicidal ideas resolved, and his depressive symptoms partially improved upon discontinuation of Sertraline, starting Remeron 30mg and Naltrexone 50mg. Patient was transferred to inpatient Rehab for 30 days. No reported alcohol binge or self-injurious behaviors on the current regimen for 6 months.

T14. THE EFFECTS OF COVID-19 ON PATIENT POPULATION WITH MENTAL ILLNESS

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Abstract: Introduction: The forthcoming consequences of the COVID-19 pandemic may have a catastrophic effect on mental health and physical well-being, especially in patients currently suffering from mental illness. The pandemic has been associated with increased rates of depression, anxiety, distress, and low self-esteem, with potential increases in substance use disorders and suicide. Persons with mental illness are disproportionately affected by unstable living conditions, complex health problems, and restricted care access – a combination that may promote further viral transmission, yielding an escalated negative societal effect. This study aims to examine the knowledge and impact of COVID-19 among persons with mental illness at the Harris County Psychiatric Center (HCPC).

Methods: A prospective study was conducted involving patients with mental illness at HCPC. Subjects were asked to answer a survey assessing patient demographics, COVID-19 knowledge, and COVID-19 healthcare impact. Data was analyzed with SPSS 20 for Windows (SPSS, Chicago, IL, USA) and statistical significance was set at a p-value less than 0.05. This study was approved by the local institutional review board.

Results: A total of 46 patients were included in the study (Table 1). We found more non-Hispanic (46.4%) than Hispanic (14.3%) patients received a high school degree/GED [p=0.049]. Compared to Native American/Pacific Islander/Asian (APIA/AIAN) patients, fewer Black patients had attained education beyond a high school degree/GED (21% vs. 100%) [p=0.011], had household incomes between 50,000 to 74,999 dollars per year (0% vs 50%) [p=0.005], and were married (14.3% vs. 75.0%) [p=0.044]. Surprisingly we found that patients with mental illness has certain level of knowledge regarding COVID-19 and its prevention measures, although levels are different. To be precise, more women (52.2%) than men (21.7%) learned about COVID-19 through family and friends [p=0.032]. More Hispanic (21.4%) compared to non-Hispanic (0%) patients learned about COVID-19 through the World Health Organization (WHO) [p=0.032]. Fewer Black patients avoided contact with people who were sick (39% vs. 81% White [p=0.01] and 100% APIA/AIAN patients [p=0.04]).

Interestingly we found more non-Hispanic (50.0%) vs. Hispanic (7.1%) patients reported that their personal time was unchanged by COVID-19 [p=0.007]. More Hispanic (57.1%) vs. non-

Hispanic (17.9%) patients reported increased time with family members [p=0.009]. Compared to Hispanic patients, more non-Hispanic patients reported unchanged difficulty scheduling appointments (46.4% vs. 7.1%) [p=0.015], obtaining prescription (71.4% vs. 35.7%) [p=0.045], and finding placement (53.6% vs. 21.4%) [p=0.047]. Furthermore, more White compared to Black patients reported more changes in how they feel (35.7% vs. 76.2%) [p=0.033], anxiety (52.6% vs. 0%) [p=0.002], stress (47.4% vs. 7.7%) [p=0.024], and sadness (30% vs. 0%) [p=0.031]. Finally, more APIA/AIAN (67%) compared to Black patients (0%) reported increased anxiety [p=0.025].

Conclusion: Our findings suggest that Black patients report less knowledge of COVID-19 prevention and less impact on their mental health by the pandemic compared to other racial groups. Across ethnicities, our study suggests that non-Hispanic patients compared to Hispanic patients may have reduced healthcare impact amidst the pandemic. However, further investigation of the impending ramifications of the pandemic is warranted.

T15. NEW EDITION: A MODEL PSYCHOPHARMACOLOGY CURRICULUM FOR TEACHERS OF PSYCHIATRIC RESIDENTS

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Abstract: Started by the ACNP training committee in 1984, the ASCP Psychopharmacology Committee has developed unique and widely disseminated curricula for teaching clinical psychopharmacology to psychiatric residents, medical students and primary care physicians. It has increasingly had global penetration. We present here the 11th edition of the resident curriculum, and the joint 5th edition for medical students and for primary care. The ASCP Curriculum Committee composed of directors of both resident education as well as medical student education educators have developed materials related to the "what, why, and how" to teach and evaluate. In addition for each curriculum, we included both a core series of lectures as well as optional lectures developed by experts in their fields. We have done follow-ups on all three curriculums within the last 2 years. We describe here the process of revising, updating, and moving to a web-based curriculum. We present the content for the three curriculums. Based on the follow up of all three curriculum, we have revised every lecture and updated the pedagogy. Depending on the size/resources of the program, teachers use the curriculum in its entirety or in parts. It works even in non-English speaking countries as committee members work with users to adapt/translate to local conditions and teaching strategies. It has been difficult to connect with primary care training programs. For residents, the curriculum is now in its 10th edition and has 88 lectures and over 4,000 slides. For teaching medical students and primary care physicians, there has never been a generally accepted curriculum or set of teaching materials specifically designed for them. There is a great deal to teach in the four year curriculum and medical students have widely divergent career paths. This curriculum has 22 lectures. Having the curriculum web-based has improved availability although some programs globally still need a hard copy version.

T16. OF MICE AND (WO)MEN: THE SEX-SPECIFIC IMPACT OF ANXIETY ON ALZHEIMER'S DISEASE PROGRESSION

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Abstract: Neuropsychiatric disturbances, such as depression and anxiety, are observed in 90% of Alzheimer's disease (AD) patients and are frequent in those at risk for AD. However, until recently, much of the research narrowly targeted co-morbid depression. Clinical reports have provided evidence that anxiety symptoms predict the conversion to AD, over and beyond the effects of depression, memory loss, and even atrophy. Similarly, epidemiological studies show that neurodegeneration and clinical symptoms occur more rapidly in females once diagnosed. Although most AD studies have been performed using male mice, females represent two-thirds of the AD population and are more susceptible to depression and anxiety. To study how anatomical sex and anxiety impact AD progression, I used our activity-dependent tagging system, the ArcCreERT2 x channelrhodopsin (ChR2)-EYFP x AD (APP/PS1) mice. These mice allow for brain-wide indelible labeling of neurons activated during learning, which then can be compared with secondary neuronal ensembles activated during memory retrieval. The neurons activated at both time points represent a memory trace or engram. Here, we aimed to identify the neural ensembles linking anxiety and memory loss following AD progression by utilizing behavioral studies, calcium imaging and whole-brain microscopy, in female and male mice. We found: 1) Female AD mice exhibited anxiety-like behavior at an earlier age compared to controls and male mice, 2) AD female mice displayed memory deficits as early as 2 months of age, 3) Anxiety-like behavior correlated with memory impairment only in AD female mice, and 4) Unlike their male counterparts, female AD mice showed a decline in memory traces in the CA3 of the hippocampus. We are currently working to translate these findings to humans using the Alzheimer's disease neuroimaging initiative (ADNI) dataset. We have found that in humans, anxiety predicts transition to dementia and that anxiety has a sex-specific effect on brain atrophy. Long-term implications: To use anxiety as a neuropsychiatric biomarker of AD in the human population in combination with current imaging and cognitive testing and to find novel brain areas associated with increased anxiety and memory loss. This could provide new therapeutic targets for 1 2021 ASCP Annual Meeting those at risk for AD.

T17. CO-PRESCRIBED BENZODIAZEPINES IN OLDER ADULTS RECEIVING ANTIDEPRESSANTS FOR ANXIETY AND DEPRESSIVE DISORDERS: ASSOCIATION WITH TREATMENT OUTCOMES

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Abstract: Purpose: The effects of benzodiazepines on treatment response variability and adherence to antidepressant pharmacotherapy for depression and anxiety in late-life is not established. The objective of this large transdiagnostic study was to examine the effect of benzodiazepines on treatment response and medication adherence in older patients with generalized anxiety disorder (GAD) and major depressive disorder (MDD).

Methodology: Participants included 640 adults aged 60+ years with GAD (n=177) or MDD (n=463). Benzodiazepine data was collected prior to treatment allocation. Adherence and treatment response were assessed over 12 weeks. Three questions were asked in this project: 1) Are benzodiazepines related to treatment response, antidepressant medication adherence, and dropout?; 2) Is benzodiazepine use predictive of final dose of antidepressant medication?; and 3) Do patients prescribed benzodiazepines report more antidepressant-related adverse events?

Results: For GAD, we found that patients co-prescribed benzodiazepines were treated with a lower mean dose of escitalopram and were less likely to complete the study. There was no difference in treatment response or adherence. For MDD, we found that patients co-prescribed benzodiazepines were less likely to reach a therapeutic dose of venlafaxine and reported more side effects. For the depressed participants, there was no difference in treatment response, adherence, or dropout.

Significance: Co-prescription of benzodiazepines is associated with inadequate therapeutic dosing of antidepressants, treatment-related side effects, and early attrition. Co-prescription of benzodiazepines may be a marker of a more therapeutically challenging treatment course.

T18. DO SIDE EFFECTS DIFFERENTIATE REMITTERS FROM NON-REMITTERS TO IV KETAMINE FOR DEPRESSION? A BIO-K STUDY ANALYSIS

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Abstract: Introduction: The Bio-K Study is a biomarker development study analyzing response of intravenous racemic ketamine delivered at 100- or 40-minute durations at .5mg/kg for treatment refractory depression across four national sites. Currently, biomarkers are being analyzed to determine why certain participants (n=75) responded to IV-ketamine versus those that did not. Furthermore, while information on ketamine side effects are well-documented there is still little information as to who experiences what type and frequency of side effects.[1,2] As part of a sub-analysis, we wanted to compare whether participants who met study-defined remission status experienced different side effects than those who did not remit as a potential correlate of remission status.

Methods: We looked at the participant MADRS and side effect data to compare whether those individuals who remitted experienced a different amount and frequency of side effects than those that did not met study defined remission criteria. Participants completed three IV-ketamine infusions, at either 100- or 40-min durations, and MADRS scores were collected across all three infusions prior to beginning the infusion, immediately following the infusion, and 24-hours after the infusion. Participants were considered to be "remitters" if their MADRS scores was ≤9 at post 24-hours infusion#3. Side effect data was collected using three different scales, including the Ketamine Side Effects Scale, Young Mania Rating Scale, and an Open-

Ended Treatment Emergent Side Effects questionnaire during several timepoints across infusions.

Results: Of the 75 participants, only 74 completed all 3 infusions, and some, went to complete 4 additional continuation phase infusions. Of those 74, 40 participants (54%) met study-defined remission status at the end of 24-hours post infusion#3. Mean MADRS score for remitters was 4.07 ± 2.76; while non-remitters had a mean score of 19.25± 7.14. All participants experienced some side effects that ranged from very mild to severe during the infusions; however, none required medical intervention or discontinuation of the infusion and all symptoms dissipated 60 min post-infusion. Participants who endorsed marked or higher severity in side effects were equal in number in both remitters and non-remitters (7 in each category). However, non-remitters felt a higher severity of side effects across more domains (i.e. increase in systolic BP, sedation effects, dizziness, vertigo, unusual thought content, visual hallucinations, nystagmus, dissociation) than remitters.

Conclusion: Although the number of participants who achieved remission status did not differ from non-remitters in their experience of side effects, the severity of side effects across domains was different from these two categories. Additionally, the proportion of participants who experienced side effects was higher in non-remitters than remitters. This may suggest that there is not a correlation between antidepressant response and side effect severity, including psychotomimetic effects.

T19. RAPID REDUCTION IN SUICIDAL IDEATION IN PATIENTS TREATED WITH AXS-05, AN ORAL NMDA RECEPTOR ANTAGONIST WITH MULTIMODAL ACTIVITY: RESULTS FROM THE COMET-SI TRIAL

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Abstract: Background: Major depressive disorder (MDD) is a debilitating, chronic, biologically-based disorder and the psychiatric diagnosis most commonly associated with suicide. Suicidal ideation is a major risk factor for suicide in patients.

AXS-05 (dextromethorphan-bupropion modulated delivery tablet) is a novel, oral, investigational NMDA receptor antagonist with multimodal activity. The dextromethorphan component of AXS-05 is an uncompetitive antagonist of the NMDA receptor, an ionotropic glutamate receptor, and sigma-1 receptor agonist. The bupropion component serves to increase the bioavailability of dextromethorphan.

Objective: To evaluate the effect of open-label AXS-05 on suicidal ideation in patients with MDD.

Methods: COMET-SI was a substudy (n=37) of the COMET (Clinical Outcomes with NMDA-based Depression Treatment) Phase 3, open-label trial that evaluated the long-term efficacy and safety of AXS-05 (45 mg dextromethorphan-105 mg bupropion modulated delivery tablet) in MDD patients, treated twice daily for up to 12 months. COMET-SI evaluated those patients with MDD who had suicidal ideation (SI) at study entry, defined as a score of ≥3 on the Suicidality Item (Item 10) of the Montgomery-Åsberg Depression Rating Scale (MADRS-SI). Efficacy measures included the MADRS-SI score, MADRS total score, Clinical Global Impression of Improvement (CGI-I), and Sheehan Disability Scale (SDS).

Results: Treatment with AXS-05 was associated with reductions from baseline in the MADRS-SI score of 2.3 points by Week 1, the earliest time point assessed, 2.5 points by Week 2, and 2.8 by Week 4. Resolution of suicidal ideation, defined as a MADRS-SI score of 0 or 1, after treatment with AXS-05 was achieved by 60.0% of patients by Week 1, 68.8% of patients by Week 2, and 77.8% of patients by Week 4. Functional response on the SDS (defined as a total score of ≤12) after treatment with AXS-05, was achieved by 51.4% of patients at Week 1, 62.5% of patients at Week 2, and 76.9% of patients at Week 6. Marked or moderate improvement in depressive symptoms after treatment with AXS-05, assessed by the CGI-I scale, was achieved by 40.0% of patients at Week 1, 59.4% of patients at Week 2, and 69.2% of patients at Week 6. Treatment with AXS-05 was associated with a mean reduction from baseline in the MADRS total score of 12.9 points at Week 1, 17.8 points at Week 2, and 22.8 points at Week 6. Clinical response on the MADRS (defined as ≥50% reduction from baseline) after treatment with AXS-05 was achieved by 25.7% of patients at Week 1, 46.9% of patients at Week 2, and 69.2% of patients at Week 6. Remission from depression (defined as MADRS ≤10) after treatment with AXS-05 was achieved by 11.4% of patients at Week 1, 28.1% of patients at Week 2, and 50.0% of patients at Week 6. AXS-05 was well tolerated in the COMET trial.

Conclusion: MDD patients with suicidal ideation, when treated with AXS-05, experienced rapid reduction of suicidal ideation, rapid functional improvement, and rapid, substantial, and durable improvements in overall depressive symptoms.

T20. SUSTAINED EFFECTS OF AXS-05, AN ORAL NMDA RECEPTOR ANTAGONIST, IN TREATMENT RESISTANT DEPRESSION PATIENTS: RESULTS FROM THE COMET-TRD TRIAL

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[1]*Axsome Therapeutics Inc.*

Abstract: Background: Major depressive disorder (MDD) is a debilitating, chronic, biological disorder. Limitations of current treatments include high rates of inadequate response and suboptimal time to response. Even with treatment, relapse rates remain high. There is an urgent need for new, effective pharmacotherapies.

AXS-05 (dextromethorphan-bupropion modulated delivery tablet) is a novel, oral, investigational NMDA receptor antagonist with multimodal activity. The dextromethorphan component of AXS-05 is an uncompetitive antagonist of the NMDA receptor, an ionotropic glutamate receptor, and sigma-1 receptor agonist, and the bupropion component serves to increase the bioavailability of dextromethorphan.

Objective: To evaluate the long-term efficacy and safety of open-label AXS-05 treatment in patients with treatment resistant depression.

Methods: COMET-TRD was a substudy (n=70) of the COMET (Clinical Outcomes with NMDA-based Depression Treatment) Phase 3, open-label trial (N=876) that evaluated the long-term efficacy and safety of AXS-05 (45 mg dextromethorphan-105 mg bupropion modulated delivery tablet) in MDD patients, treated twice daily for up to 12 months. COMET-TRD evaluated patients with ongoing depressive symptoms despite treatment with 2 or more antidepressants in the current depressive episode. Efficacy measures included the

Montgomery-Åsberg Depression Rating Scale (MADRS), Clinical Global Impression of Improvement (CGI-I), and Sheehan Disability Scale (SDS).

Results: AXS-05 treatment resulted in rapid and substantial improvement in depression, which was sustained or increased with long-term treatment. AXS-05 treatment was associated with a mean reduction from baseline in the MADRS total score of 10.4 points at Week 1, 14.7 points at Week 2, and 20.6 points at Week 6. Mean MADRS total score reduction from baseline after 6 and 12 months of treatment was 22.9 points and 26.3 points, respectively. Clinical response on the MADRS (≥50% reduction from baseline) after treatment with AXS-05 was achieved by 21.4% of patients at Week 1, 44.1% of patients at Week 2, and 67.2% of patients at Week 6. Clinical response on the MADRS total score after 6 and 12 months of treatment was achieved by 71.7% and 90.9% of patients, respectively. Remission (MADRS ≤10) after treatment with AXS-05 was achieved by 14.3% of patients at Week 1, 19.1% of patients at Week 2, and 43.8% of patients at Week 6. After 6 and 12 months of treatment, remission was achieved by 62.3% and 72.7% of patients, respectively. Marked or moderate improvement in depressive symptoms after treatment with AXS-05, on the CGI-I scale, was achieved by 24.6% of patients at Week 1, 48.5% of patients at Week 2, and 78.1% of patients at Week 6. Marked or moderate improvement after 6 and 12 months of treatment was achieved by 79.2% and 75.0% of patients, respectively. Clinical response on the SDS (total score of ≤12) after treatment with AXS-05, was achieved by 37.1% of patients at Week 1, 52.9% of patients at Week 2, and 64.1% of patients at Week 6. Clinical response on the SDS after 6 and 12 months of treatment was achieved by 69.8% and 91.7% of patients, respectively.

AXS-05 was well tolerated in the COMET trial. The safety profile observed was consistent with what was previously reported in controlled trials in MDD.

Conclusion: Results from the COMET-TRD trial demonstrate rapid and sustained improvement in depressive symptoms accompanied by rapid and clinically meaningful improvement in functioning in patients with TRD. Results from this study add to the differentiated clinical profile of AXS-05, and are consistent with data from prior double-blind efficacy trials.

T21. PREDICTORS OF COMPLETION FOR A CARE MANAGEMENT PROGRAM IN PRIMARY CARE USING A PSYCHOPHARAMACOLOGICAL APPROACH

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Abstract: Introduction: Primary care is the most common setting for individuals to receive mental health treatment, usually through use of psychotropic medication. However, patient adherence to medications is often low. Care management (CM) is an evidence-based protocol for the collaborative treatment of mental health problems in primary care. CM has demonstrated effectiveness in symptom reduction, engagement, adherence, and improvements in patient functioning (1). While CM outcomes are promising, engagement remains a concern. The purpose of this study was to determine which factors predict patient adherence and completion of an antidepressant CM program.

Methods: Data from an existing clinical database was used to review the outcome completion data of patients enrolled in the Antidepressant Monitoring Program (ADM) at the James A.

Haley VAMC. Clinical outcome measures collected to assess predictors of adherence to the program included baseline mood assessments (PHQ-9 and GAD-7), clinical contact with psychology prior to enrollment, class of medication prescribed (SSRI versus non-SSRI), polypharmacy at time of enrollment, and early response (defined as a 20% decrease in PHQ-9 or GAD-7 from enrollment to 3 week follow up).

Results: A total of 791 patients were referred to the ADM program with 254 completers (34.3%). 486 patients did not complete the program (61.4%) and 51 patients (6.4%) were still enrolled and therefore excluded from analyses. Overall mean improvement scores on the PHQ-9 was 5.82 and GAD-7 was 5.41. Completers had greater improvements with mean decreases of 8.31 (SD = 5.40) and 7.62 (SD = 5.27), respectively. Clinically significant improvements in anxiety were noted in 178 (70.1%) of program completers (as indicated by a 5 or more-point decrease on the GAD-7) and clinically significant improvements in depression noted in 190 (74.8%) of completers (50% reduction in PHQ-9 scores). No statistically significant differences were observed in baseline PHQ-9 and GAD-7 mean scores among the completers and non-completers. 486 (65.7%) patients failed to complete the program. The most common reason for non-completion was failure to respond to follow-up or a request for disenrollment (65.2%). 68 patients reported side effects (14.2%) as their reason for not completing the program. 99 patients were never enrolled (20.6%) due to patient declining enrollment or failure to respond to initial contact attempts and were removed from analyses. A binary logistic regression was performed on predictive variables and likelihood of completion. The overall model was significant ($x^2(7) = 44.24$; $p < .00$), explained 14.2% (Nagelkerke R^2) of the variance, and correctly classified 68.5% of the cases. Within the model, only early response on PHQ-9 and GAD-7 were statistically significant. Individuals who showed an early response in depressive symptoms were 3.14 times more likely to complete the program than non-early responders. Individuals who were early responders for anxiety symptoms were 2.10 times more likely to complete the program.

Conclusions: Enrollment in an ADM program is associated with clinically significant improvements in baseline symptomatology. Patients that completed the program had particularly robust improvements. Results suggest that early response on PHQ-9, and GAD-7 were statistically significant predictors of program completion. Future research should continue to determine whether other patient factors may increase likelihood of program completion.

T22. IMPROVEMENT IN ANHEDONIA WITH TRANSCRANIAL MAGNETIC STIMULATION IN A NATURALISTIC CLINICAL SAMPLE OF TREATMENT REFRACTORY DEPRESSION

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Abstract: Background: Anhedonia is one of the hallmark symptoms of Major Depressive Disorder (MDD), yet it remains difficult to target and treat. Transcranial Magnetic Stimulation (TMS) therapy is a proven treatment for MDD; however, its direct effects on anhedonic symptoms are not well known. This study aimed to assess changes in anhedonia with TMS

and explore its potential utility as a clinically relevant predictor of depression treatment outcomes in those with treatment refractory MDD.

Methods: Snaith-Hamilton Pleasure Scale (SHAPS) was administered to patients with treatment-resistant MDD before and after a course of TMS to assess anhedonia. SHAPS score ranges from 0 to 14 with higher scores indicating more severe anhedonia. Inventory of Depressive Symptomatology Self Report (IDS-SR) was used as a measure of clinical response, remission, and depression severity. Stimulation at 120% of motor threshold was administered over the left dorsolateral prefrontal cortex for 3000-4000 pulses/session.

Results: 144 MDD patients receiving TMS at Butler Hospital's TMS clinic were analyzed. At baseline, 7.62% (n=8) of patients were classified as "non-anhedonic," 13.33% (n=14) had mild/moderate and 79.05% (n=83) had severe anhedonia. Post-treatment, 56.19% were "non-anhedonia", 21.90% were mild/moderate and 21.90% were severely anhedonic. There was an overall significant improvement in anhedonia from pre to post TMS (8.10 ± 3.46 vs. 3.06 ± 3.49; a 58.55% improvement, $p < 0.001$). Significant correlations between SHAPS scores and IDS-SR, after correcting for anhedonic items of IDS-SR, at baseline ($r = 0.29$, $p < 0.01$), endpoint ($r = 0.60$, $p < 0.001$), and in overall %change ($r = 0.55$, $p < 0.001$) suggested that anhedonia symptoms were strongly linked to overall depression severity. Logistic regression revealed that baseline SHAPS was not a significant predictor of clinical outcome.

Conclusion: This is the first large, naturalistic study examining effects of standard, non-research TMS on anhedonia and evaluate whether severe anhedonia are good candidates for TMS. Our results indicate that among depressed patients, a course of TMS resulted in a statistically and clinically significant improvement in anhedonia. While the severity of the deficit in experiencing consummatory pleasure prior to treatment did not predict clinical outcome following a standard course of TMS, we found patients with severe baseline anhedonia had an equal chance of achieving clinical response/remission. Patients with marked anhedonia should not be excluded from TMS treatment if they are safe for outpatient care and otherwise appropriate candidates for magnetic stimulation.

T23. THE EFFECTS OF COMP360 (PSILOCYBIN FORMULATION) ON COGNITIVE FUNCTION: RESULTS FROM A RANDOMIZED, PLACEBO-CONTROLLED TRIAL IN HEALTHY PARTICIPANTS

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Abstract: Background: Psilocybin therapy with COMP360 is in clinical development for treatment-resistant depression after promising indications of efficacy in depressive states. Psilocybin's effects on cognitive function have not been widely or systematically studied. Here, we report findings of short- and longer-term effects of COMP360 (COMPASS Pathways' proprietary synthetic psilocybin formulation) on tasks of cognitive function from the largest randomized controlled trial of psilocybin to date.

Method: This was a phase I, placebo-controlled, double-blind trial to evaluate the effects of two doses of COMP360. Healthy volunteers were randomized 1:1:1 to receive either placebo, 10 mg, or 25 mg of COMP360. Prior to dosing, participants took part in a preparatory group session. The drug was administered simultaneously to up to six participants, who received one-to-one psychological support. Participants completed a range of validated measures of cognition from the Cambridge Neuropsychological Test Automated Battery (CANTAB) including Spatial Working Memory, Rapid Visual Information Processing and Paired Associates Learning tasks. These tasks were completed at screening (practice session), baseline (one day prior to dosing), and one- and four-weeks post-dosing (day 8 and day 29, respectively).

Results: 89 participants were recruited (mean age 36.1, standard deviation 9.1 years; 41 females, 48 males) and randomized to placebo (n=29), 10 mg COMP360 (n=30), or 25 mg COMP360 (n=30). For Rapid Visual Information Processing, a measure of sustained attention, there were trends indicating better performance on average for COMP360 10 mg and 25 mg by day 29 compared to baseline, but no difference was observed for COMP360 10 mg and 25 mg when compared to placebo, nor between COMP360 25 mg and 10 mg. For Spatial Working Memory there were trends indicating better performance on average for COMP360 25 mg by day 29 compared to baseline, but no difference was observed for COMP360 10 mg and 25 mg when compared to placebo, nor between COMP360 25 mg and 10 mg. For Paired Associates Learning, a measure of episodic memory, there was no difference for any of the groups at day 29 compared to baseline nor any differences observed between the groups. On a global composite measure of the aforementioned tasks, there was an increasing trend in scores indicating better performance on average for the COMP360 10 mg and 25 mg doses by day 29 compared to baseline. No difference was observed for COMP360 10 mg and 25 mg when compared to placebo, and also between COMP360 25 mg and 10 mg by day 29.

Discussion: Findings suggest that COMP360 does not exert any detrimental effects on the cognitive functions assessed. There were trends on average demonstrating better performance in the COMP360 groups by day 29 compared to baseline. The fact that participants were typically highly educated, and the small sample size, could have limited the generalizability of results. These findings warrant further investigation in clinical populations.

T24. INTERIM DATA FROM THE ONGOING PHASE 3, OPEN-LABEL, LONGITUDINAL SHORELINE STUDY OF ZURANOLONE IN MAJOR DEPRESSIVE DISORDER

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Abstract: Introduction: Zuranolone (ZRN; SAGE-217) is an investigational, oral neuroactive steroid (NAS) ɣ-aminobutyric acid receptor type A (GABAAR) positive allosteric modulator (PAM) being studied as a treatment for patients with Major Depressive Disorder (MDD). ZRN targets both synaptic as well as extra-synaptic GABAAR with a pharmacology distinct from

benzodiazepines, which target only synaptic GABAAR.1 The ongoing open-label, phase 3, 1-year, longitudinal SHORELINE study (NCT03864614) is evaluating the safety, tolerability, and need for retreatment with ZRN in patients with MDD as an "as-needed" 2-week treatment for depression.

Objectives: To present interim ZRN safety, tolerability, and efficacy data from the SHORELINE study.

Methods: An interim analysis from July 2020 evaluated 801 patients with MDD, ages 18-75, with HAMD-17 total score ≥20 and MADRS total score ≥28 at screening, received ZRN 30 mg (ZRN30) or ZRN 50 mg (ZRN50) for 14 days. Patients who achieved a HAMD-17 response (≥50% improvement) at Day 15 were followed for 48 weeks and were eligible to receive re-treatment based on standardized assessments. The primary endpoint was safety and tolerability assessed by adverse events and clinical measures in the interim safety data set of patients starting on ZRN30 (n=725) or ZRN50 (n=76). Secondary endpoints of HAMD-17 response (≥50% improvement) and remission (HAMD-17 total score ≤7) were assessed in the interim ZRN30 efficacy data set (patients who only received ZRN30 and completed the first cycle of treatment; n=640) and rates of re-treatment were calculated in patients who were both responders and completed treatment cycle 1 (n=494).

Results: In the interim safety data set patients who received ZRN30 as a starting dose, most treatment-emergent adverse events (TEAEs) were mild or moderate in severity, with 61.7% (447/725) patients reporting at least 1 TEAE in treatment cycle 1. The most common (≥5%) TEAEs included somnolence (69/725; 9.5%), headache (63/725; 8.7%), and dizziness (39/725; 5.4%), with a study discontinuation rate due to TEAEs of 4.3%. Similar rates and severity of TEAEs were reported in patients who received a starting dose of ZRN50. No events of loss of consciousness and 1 death (unrelated to study drug) were reported. At Day 15 following the first 14-day treatment course, the mean (SD) change from baseline in HAMD-17 total score for patients treated with ZRN30 was -14.9 (7.1; n=640), 71.6% (458/640) of patients achieved a HAMD-17 response and 39.8% (255/640) achieved HAMD-17 remission. The mean number of re-treatments up to 1-year follow-up was 1.7 for patients retreated with ZRN30. Approximately 70.8% (350/494) of patients achieving a HAMD-17 response and completing cycle 1 with ZRN30 used only the single initial or a total of 2 treatment courses.

Conclusions: Interim safety and tolerability data from the SHORELINE study are consistent with prior zuranolone studies. Interim efficacy data from this open-label study suggest potentially sustained responses with nearly half of patients requiring 1 initial treatment course and most requiring 2 or less over a 1-year period. For those who needed re-treatment with ZRN30, safety, tolerability, and efficacy results were similar to those seen in the initial treatment course. These data support continued development of zuranolone for MDD.

T25. ABSENCE OF TREATMENT-RELATED SEXUAL DYSFUNCTION OBSERVED WITH THE CSFQ-14 IN THE PHASE 3, RANDOMIZED, DOUBLE-BLINDED, PLACEBO-CONTROLLED MOUNTAIN STUDY OF ZURANOLONE IN PATIENTS WITH MAJOR DEPRESSIVE DISORDER

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Abstract: Introduction: Sexual dysfunction is a prevalent symptom of major depressive disorder (MDD), as well as a frequent side effect of some commonly prescribed antidepressants, typically emerging 1-3 weeks after treatment initiation1 with an estimated prevalence ranging from 25% to 80%.2 Zuranolone (ZRN) is an investigational, oral neuroactive steroid ɣ-aminobutyric acid receptor type A (GABAAR) positive allosteric modulator with a proposed novel mechanism of action that targets both synaptic and extra-synaptic GABAAR. A multicenter, double-blind, randomized, placebo-controlled Phase 3 MOUNTAIN trial (NCT03672175) evaluated the efficacy and safety of 14-day treatment with ZRN 20 mg (ZRN20) or 30mg (ZRN30) compared with placebo (PBO). The primary endpoint of change from baseline in HAMD-17 total score at Day 15 was not met (p=0.115).

Objectives: To assess the effect of ZRN30 treatment compared with PBO on sexual function using the Changes in Sexual Functioning Questionnaire-14 (CSFQ-14) in the MOUNTAIN trial.

Methods: Adult outpatients (18-65 years) with MDD (HAMD-17 total score ≥22 and MADRS total score ≥32) were randomized 1:1:1 to ZRN20, ZRN30, or PBO, once-nightly for 2 weeks. Standard of care antidepressants that had been taken at the same dose for ≥60 days prior to Day 1 of the trial were permitted. Male and female sexual functioning was evaluated as an exploratory endpoint with the validated, 14-item, patient-reported CSFQ-14 scores at baseline, Day 15, Day 28, and Day 42. It also has 5 sub-scales that measure pleasure, desire/frequency, desire/interest, arousal/excitement, and orgasm/completion. Sexual dysfunction was defined as a CSFQ-14TS of ≤41 for females and ≤47 for males. Mixed model for repeated measure and generalized estimating equation were used for analysis on patients from the ZRN30 and PBO treatment arms with a baseline HAMD-17 total score ≥24 (n=323).

Results: There were 227 females and 96 males included in this analysis. At baseline, the mean CSFQ-14TS for ZRN30 and PBO for female patients was 31.7 (n=121) and 33.7 (n=105), and for male patients was 42.1 (n=45) and 40.9 (n=51), respectively and was similar across treatment arms. There were no significant differences between ZRN30- and PBO-treated patients in least-square mean [SE] change from baseline CSFQ-14TS improvements in females at Day 15 (+4.0 [0.83] and +2.7 [0.74]), Day 28 (+3.3 [0.80] and +3.1 [0.82]) and Day 42 (+3.6 [0.87] and +2.9 [0.88]). No statistically significant differences were observed in males between treatment arms at Day 15 (+1.3 [1.28] and +1.7 [1.23]), Day 28 (+1.7 [1.31] and +2.0 [1.30]) and Day 42 (+2.2 [1.33] and +3.5 [1.54]), respectively. The percentage of all patients with sexual dysfunction as assessed by CSFQ-14TS thresholds decreased from 82.4% (266/323) at baseline to 66.5% (181/272) at Day 42, with no significant difference in the odds ratio for sexual dysfunction between treatment arms. Additionally, there were no significant differences between ZRN30 and PBO in the percentage of patients with sexual dysfunction as assessed in the individual CSFQ-14 subscales.

Conclusions: This post-hoc analysis of CSFQ-14TS in patients with HAMD-17 ≥24 demonstrated similar trends and no differences in sexual functioning between ZRN30 and placebo in female or male patients. These data suggest that treatment with ZRN30 was not associated with treatment-emergent sexual dysfunction.

T26. OVERWEIGHT AS COMPLICATING FACTOR IN TREATMENT RESISTANT DEPRESSION –POORER CLINICAL OUTCOMES OF PATIENTS WITH HIGH BODY MASS INDEX IN AN EUROPEAN MULTI-CENTER DATABASE

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Abstract: Background: Obesity is a risk factor for worse outcomes in cardiovascular diseases, cancer, diabetes or osteoporosis resulting in substantially elevated risks for premature death. Notably, BMI rates are increasing over the last decades at alarming rates in several parts of the world (1). Data from non-depressed subjects indicate that higher BMI is associated with greater suicidal ideation and increased numbers of suicide attempts (1), however, the role of BMI on outcomes in MDD is still understudied.

Methods: Patients were recruited within a multi-center clinical database study by the European Group for the Study of Resistant Depression (GSRD) between 2011 and 2020. Patients, at least 18 years old, had to have MDD with a current severe episode as leading diagnosis, excluding bipolar and schizoaffective depression as assessed with a modified version of the MINI-Interview. All patients were rated with standardized scales (MADRS, YMRS, HAMD) and underwent a list of psychosocial and biometric questions at inclusion. Exclusion criteria were any severe substance abuse disorder or severe comorbid personality disorder. To assess outcomes in MDD we analyzed the clinical phenotypes 'response', and 'treatment resistant'. Response was defined by reaching a MADRS score <22 with at least 4 weeks treatment duration at adequate antidepressant dose. Treatment resistant depression was defined by a failure of response after 2 antidepressant trials of at least 4 weeks at an adequate dose. These phenotypical outcomes, psychosocial variables as well as MADRS items were assessed according to BMI as marker of obesity with ANOVAs, controlled for age, sex and risk of weight gain due to medication.

Results: For this study a sample of 892 patients (580 female, 50.5,□13.6 years) with MDD was available and categorized into responder (n=323) and resistant (n=569). In total, 17% of all patients were obese (BMI>30). There was a trend-wise higher BMI in resistant patients (p=0.085). In the overall sample, higher BMI was significantly associated with higher suicidality (p=0.002), longer hospitalization time (p=0.006) and earlier onset of first episodes (p=0.029). In MADRS subitems, we found that appetite and concentration was significantly reduced with higher BMI irrespective of treatment response, while lassitude (p=0.02) was only reduced at baseline.

Discussion: The results of this study demonstrate that higher BMI is associated with aggravated courses of disease in patients with MDD. There are several lines of evidence explaining close links between weight gain and depression, for example altered stress axis with hypercortisolism, elevated free fatty acids and increases in visceral fat mass (2). Our clinical data add that, patients with obesity demand closer clinical attention for potentially worse outcomes.

T27. CLINICAL UTILITY OF COMBINATORIAL PHARMACOGENETIC TESTING IN DEPRESSION: CANADIAN PATIENT- AND RATER-BLINDED, RANDOMIZED, CONTROLLED TRIAL

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Abstract: Background: Depression treatment consists of stages of trial and error, and remission rates decline with each subsequent stage. Combinatorial pharmacogenetic (PGx) testing, a tool used to help guide the pharmacological treatment of depression, is associated with 50% relative increase in remission compared to treatment-as-usual (TAU), as demonstrated in the largest randomized controlled trial (RCT) (N=1,167) of PGx in psychiatry, the GUIDED trial. Here we present results from the similarly designed Canadian GAPP-MDD trial (Genomic Applications Partnership Program-MDD, ClinicalTrials.gov: NCT02466477), assessing the use of combinatorial PGx testing to guide depression treatment.

Methods: The GAPP-MDD trial was a 52-week, 3-arm, multi-centre, participant- and rater-blinded randomized, controlled trial evaluating clinical outcomes among patients with depression whose treatment guided by combinatorial PGx testing was compared to TAU. The HAM-D17 scale was the primary assessment. Symptom improvement, response, and remission were compared between the combinatorial PGx-guided and TAU arms. The GAPP-MDD study, designed based on effect sizes observed in early open-label studies of PGx testing, was stopped early, prior to meeting target recruitment. During the GAPP-MDD study, the results of the GUIDED study demonstrated a need for a much larger sample size, and GAPP-MDD was thus underpowered to detect statistically significant differences in outcomes between combinatorial PGx and TAU arms. Therefore, considering the similarities in study design between the GAPP-MDD and GUIDED RCTs, patient outcomes observed in GAPP-MDD were compared to those observed in the GUIDED trial. We also conducted meta-analyses of patient outcomes from all 3 RCTs (GAPP-MDD, GUIDED, and Pine Rest (a similar, smaller RCT)) of combinatorial PGx testing.

Results: 276 patients were included at baseline in the GAPP-MDD study. At week 8, patients in the combinatorial PGx-guided arm had greater symptom improvement, response, and remission rates compared to patients in the unguided TAU arm, although this did not reach statistical significance: symptom improvement, PGx-guided 27.60%, TAU 22.68%, $p = 0.274$; response, PGx-guided 30.26%, TAU 22.67%, $p = 0.262$; remission, PGx-guided 15.70%, TAU 8.33%, $p = 0.131$. In the larger GUIDED trial, remission, the target endpoint of acute depression treatment, was significantly improved. When comparing the current study to GUIDED, we observed even greater improvement in remission in the combinatorial PGx-guided arm compared to TAU, with an 88% relative improvement in remission rate, compared to 52% in GUIDED. Across both studies, there was an increase between baseline and week 8 in the proportion of patients in the combinatorial PGx-guided arm, but not the TAU arm, who were taking medications that were consistent with the PGx report guidance (GAPP-MDD, increased 83.4% to 91.1%; GUIDED, increased 79.4% to 91.2%).

A meta-analysis of remission in all 3 RCTs (GAPP-MDD, GUIDED, and Pine Rest) produced an OR of 1.69 (95%CI 1.23-2.32, p=0.001), indicating that combinatorial PGx testing is associated with a 69% higher odds of achieving remission compared to TAU.

Conclusion: The GAPP-MDD RCT demonstrated improvements similar to the GUIDED RCT in clinical outcomes following combinatorial PGx testing in a Canadian population of patients with depression who had failed to respond to at least one previous medication trial. Results from GAPP-MDD, conducted in the context of the Canadian universal health care setting, and the other 2 RCTs, indicate that combinatorial PGx testing can be a useful additional tool to help guide the treatment of depression.

T28. THE IMPACT OF SARS-COVID-2 ON A PSYCHOPHARMACOLOGICAL CARE MANAGEMENT PROGRAM

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Abstract: Introduction: The United States Department of Health and Human Services declared SARS-Covid-2 (Covid) a public health emergency on February 4th, 2020. The resultant global pandemic has had a profound impact on individuals with psychiatric disorders and on the delivery of mental health services. Studies assessing the effects of Covid are complicated by confounders introduced by the abrupt change in the delivery of mental health services including the rapid transition to telehealth. To better ascertain the direct impact of the Covid pandemic, it is prudent to attempt to minimize confounders by examining treatment models which did not require changes to the delivery of services. Telephone based care management (CM) programs are one such model of treatment. One iteration of CM, known as an Antidepressant Monitoring (ADM) program, is a telephone-based intervention for the pharmacological management of depression and anxiety in the primary care setting.1,2. The purpose of this study was to examine Veterans with depression and anxiety managed via the facility's ADM program, to determine the impacts of Covid on this cohort whose mental health treatment services did not require adjustments during the pandemic, as well as, to examine the impacts of the pandemic on the program such as number of referrals and patients treated.

Methods: A longitudinal retrospective cohort analysis was conducted on a sample of Veterans treated in the Tampa VA's ADM program from February 4th, 2020 through December 3rd, 2020 and a control group from February 4th, 2019 through December 3rd 2019. Number of patients referred, and program completion rates were calculated. Symptomatic measurements of depression and anxiety were obtained at baseline and at q3-4 week follow ups. Treatment in the program pre-Covid vs. treatment during the pandemic was compared in relation to baseline symptomatology, improvement in MH symptoms, and program adherence/completion.

Results: 464 Veterans were referred to the ADM program during the 10-month pre-Covid control dates, compared to 351 during the pandemic; a 24.35% reduction in referrals. Further analyses were conducted on Veterans enrolled during the first four months of study data, to allow for a minimum of 6 months of follow up. Veterans who were referred, enrolled, and completed at least 1 ADM follow up during Covid were statistically more likely to complete the ADM program than those in the pre-Covid group; including for those enrolled within the first 2 months (46.99% vs 20.83%, p=0.0009) and the first 4 months (40.87% vs. 19.05%,

p=0.0001). There were no significant differences in baseline depression or anxiety symptoms between the Covid group and the controls (PHQ9=13.24 vs. 13.28, p=0.9542; GAD7=13.06 vs. 12.71, p=0.4071). When examining symptomatic improvement, Veterans receiving care during the pandemic showed a greater reduction in symptoms of depression and anxiety when compared to controls, although depressive symptoms only trended towards significance (PHQ9 -7.07[-57.58%], vs. -5.56 [-41.91%] p=0.0528); GAD7 -7.00 (-52.70%) vs. -5.30 (-41.70%), p=0.0135,].

Conclusions: A notable decrease in the number of individuals referred to the ADM program during the pandemic was observed. However, Veterans receiving care during the pandemic had higher program completion rates and greater improvements in symptoms of depression and anxiety compared to pre-Covid controls.

T29. EXPLORING THE CONCEPT OF LIFE ENGAGEMENT FROM THE PERSPECTIVE OF PATIENTS WITH MAJOR DEPRESSIVE DISORDER: A STUDY USING PATIENT INTERVIEWS

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Abstract: Background: The treatment goals of patients with major depressive disorder (MDD) often differ from those of the clinician, with patients prioritizing outcomes such as meaningfulness of life, life enjoyment, and satisfaction with oneself (1). Expert psychiatrists have defined the concept of 'life engagement', encompassing four domains: emotional, physical, social, and cognitive (2). The aim of the present study was to explore for the first time the concept of life engagement, and its relevance in MDD, from the patients' perspective.
Methods: Semi-structured, 60-minute video interviews were conducted with adults with MDD in the United States. Patients were eligible if, according to their answers in a screening interview, they were aged ≥18 years, had a clinician-provided diagnosis of MDD, had their first depressive symptoms ≥1 year ago, had depressive symptoms within the past 3 months, were currently taking an antidepressant, and did not have another specified diagnosis (Alzheimer's disease, dementia, schizophrenia/schizoaffective disorder, or bipolar disorder). Patients were asked if – on a good day – they ever felt 'engaged with life', and how this affected their feelings, activities, socializing, and thoughts. A handout with illustrative quotations was provided to prompt the discussion. Based on interview transcripts and field notes, qualitative content analysis methods were used to identify, characterize, and summarize themes of the discussion.

Results: Twenty patients were interviewed, with mean age 43 years (range: 20–70 years) and mean duration of diagnosis 14.8 years (range: 2–50 years). The COVID-19 pandemic had a negative impact on the daily life and mood of most patients, but, at the time of the interview, most patients reported having a good or typical day. Overall, patients said that the 'engaged with life' concept was clear, it resonated with them, and they were able to provide related examples from their own lives. When engaged with life, patients reported feeling more energized and motivated, taking greater interest in what they and other people around them

were doing, having a more positive outlook on life, having clearer thinking, finding pleasure in and seeking out enjoyable activities, and increasing their socialization. The most frequently reported thoughts and feelings reflected the physical, social, and emotional aspects of engagement: increased energy/motivation (n=20; 100%); being more social/spending time with others (n=17, 85%); being more communicative (n=16, 80%); and having better mood (n=15; 75%).

Conclusion: Patients found the concept of life engagement to be important and relatable. Patients' definitions and experiences were consistent with the four domains of life engagement previously defined by expert psychiatrists (2).

T30. DIFFERENCES IN COMORBIDITIES AND SERVICE UTILIZATION AMONG PATIENTS WITH MDD ON ADT AND ADJUNCTIVE PHARMACOTHERAPY OR ADJUNCTIVE PSYCHOTHERAPY

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Abstract: Background: Among patients with major depressive disorder (MDD), inadequate response to antidepressant monotherapy (ADT) is common (Knoth 2010). Though adjunctive pharmacotherapy or psychotherapy typically follows, (Gaspar 2019) little is known about factors associated with adjunctive therapy patient and/or provider preference.
Purpose: To describe demographic, comorbidity, and healthcare service utilization differences between individuals who add adjunctive pharmacotherapy versus psychotherapy to ADT.

Methods: Using the Decision Resource Group's (DRG) database of medical and pharmacy claims, a nationally representative sample of commercially-insured MDD patients on ADT who added adjunctive therapy between 7/1/2014 and 12/31/2018 were identified. Eligible patients were on ADT for >8 weeks preceding and >8 weeks following initiation of adjunctive therapy (index); and were stratified by adjunctive therapy type: "pharmacotherapy," or "psychotherapy." Differences in demographics, comorbidities, service utilization, and cost were calculated for the 6 months pre-index, service utilization and cost were annualized (PPPY) and standardized to 2019$.

Results: Among the 149,797 eligible individuals, compared with adjunctive psychotherapy (20,037), those on adjunctive pharmacotherapy (129,650) were older (49.4 vs 43.8 years), more likely to be female (74.1% vs 72.0%), had more medical comorbidities such as hypertension (38.2% vs. 26.4%), hyperlipidemia (34.7% vs. 24.5%), low back pain (31.3% vs. 22.8%), osteoarthritis (17.9% vs. 11.8%), and COPD (19.5% vs. 14.2%). Conversely, those on adjunctive psychotherapy had more psychiatric comorbidities including GAD (33.3% vs. 17.1%), PTSD (9.3% vs. 3.5%), dysthymic disorder (8.2% vs. 4.5%), and alcohol use disorder (8.1% vs. 4.8%).

In the six months preceding index, those on adjunctive psychotherapy were 3.6x, 1.7x, or 1.4x more likely to have an MDD-related office visit, ED visit, or inpatient hospitalization, respectively. Despite higher MDD-related healthcare costs, those on adjunctive psychotherapy had lower all-cause healthcare costs ($11,955 vs. $12,841).

Importance: Compared to MDD patients who added adjunctive pharmacotherapy, those who added psychotherapy differed on demographic, medical and psychiatric comorbidity burden, and healthcare service utilization in the months preceding addition of adjunctive therapy. These results may indicate patient and/or provider treatment preferences associated with specific patient profiles. Further, patient characteristics could be used to identify patients with preferences for specific adjunctive therapeutic options.

T31. EFFICACY AND SAFETY OF ESKETAMINE NASAL SPRAY BY SEX IN PATIENTS WITH TREATMENT-RESISTANT DEPRESSION: FINDINGS FROM SHORT-TERM RANDOMIZED, CONTROLLED TRIALS

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Abstract: Background: Limited data are available on antidepressant efficacy and safety specific to women. The objective of this analysis was to determine if there are sex differences with esketamine for treatment-resistant depression (TRD).

Methods: Post-hoc analyses of three randomized, controlled studies of esketamine in patients with TRD (TRANSFORM-1, TRANSFORM-2 [18-64 years], and TRANSFORM-3 [≥ 65 years]; NCT02417064, NCT02418585, NCT02497287) were performed. In each 4-week study, adults with TRD were randomized to esketamine or placebo nasal spray, each with a newly-initiated oral antidepressant (ESK + AD, AD + placebo). Change from baseline to day 28 in Montgomery Åsberg Depression Rating Scale (MADRS) total score was assessed by sex in pooled data from TRANSFORM-1/TRANSFORM-2 and separately in data from TRANSFORM-3 using a mixed-effects model for repeated measures. Rate of response (defined as ≥50% decrease from baseline MADRS total score) at day 28 was determined by treatment group and sex in all 3 TRANSFORM studies, and by menopausal status among women in TRANSFORM-1/TRANSFORM-2.

Results: Altogether, 702 adults (464 women) received ≥1 dose of intranasal study drug and antidepressant. Mean (SD) MADRS total score at baseline was 37.7 (5.73) for women and 36.8 (5.21) for men in TRANSFORM-1/TRANSFORM-2 and 35.2 (6.41) for women and 35.2 (5.78) for men in TRANSFORM-3. Mean MADRS total score (SD) decreased from baseline to day 28, more so among patients treated with ESK + AD vs. AD + placebo in both women and men: TRANSFORM-1/TRANSFORM-2 women – ESK + AD -20.3 (13.19) vs. AD + placebo -15.8 (14.67), men – ESK + AD -18.3 (14.08) vs. AD + placebo -16.0 (14.30); TRANSFORM-3 women – ESK + AD -9.9 (13.34) vs. AD + placebo -6.9 (9.65), men – ESK + AD -10.3 (11.96) vs. AD + placebo -5.5 (7.64). There was no significant sex effect or treatment-by-sex interaction ($p>0.35$). In the TRANSFORM trials, the proportions of patients who were responders at day 28 were numerically higher among both women and men treated with ESK + AD as compared to AD + placebo: TRANSFORM-1/TRANSFORM-2 women – 60.5% vs. 44.9%, respectively, men – 54.7% vs. vs. 45.7%, respectively; TRANSFORM-3 women – 25.6% vs. 19.4%, respectively, men – 29.2% vs. 4.2%, respectively. In TRANSFORM-1/TRANSFORM-2, pre-menopausal and post-menopausal women treated with

ESK + AD achieved similar response rates (61.0% and 62.1%, respectively). The most common adverse events (incidence >20%) in esketamine-treated patients were nausea, dissociation, dizziness, and vertigo, each reported at a higher rate in women than men.

Conclusions: These post-hoc analyses support the antidepressant efficacy and safety of esketamine nasal spray for women with TRD, with no clinically significant differences observed compared to men. Efficacy results were similar for pre- and post-menopausal women.

T32. PHONE OR VIDEO? FACTORS INFLUENCING PATIENTS' INITIAL DECISIONS REGARDING TELEPSYCHIATRY PARTICIPATION DURING THE COVID-19 PANDEMIC

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Abstract: Background: Telepsychiatry enables patients to establish or maintain psychiatric care during the COVID-19 pandemic.

Objective: This paper seeks to examine factors influencing patients' initial decisions to accept or decline telepsychiatry within the first three weeks of the COVID-19 stay-at-home order in Michigan, their initial choice of virtual care modality (video or telephone), and future participation in telepsychiatry after clinics fully reopen for in-person visits.

Methods: Between June and August 2020, we conducted a telephone-based survey using a questionnaire comprising 14 quantitative and two qualitative items as part of a quality improvement initiative. We used descriptive statistics to report individual survey responses and multivariable logistic regression to assess the association between chosen visit type and patient characteristics.

Results: A total of 244 patients completed the telephone survey. The majority (n=202, 82.8%) initially chose to receive psychiatric care through video visits, while 13.5% (n=33) chose telephone visits and 1.2% (n=3) decided to postpone care until in-person visit availability. Age correlated with chosen visit type (P<.001; 95% CI 0.02-0.06) whereas sex, race, type of insurance, and number of previous visits to the clinic were not statistically relevant. Patients aged ≥44 years were more likely than patients aged 0-44 years to opt for telephone visits (relative risk reduction [RRR] 1.2; 95% CI 1.06-1.35). Half of the respondents stated they were likely to continue with telepsychiatry once clinics fully re-open. Telephone visit users were less likely than video visit users to anticipate future participation in telepsychiatry (RRR 1.08; 95% CI 0.97-1.2). Overall, virtual visits met or exceeded expectations for the majority of users.

Conclusions: In this cohort, patient age correlates with the choice of virtual visit type, with older adults more likely to choose telephone visits over video visits. Understanding challenges to patient-facing technologies can help advance health equity and guide best practices for engaging patients and families through telehealth.

T33. SAFETY, TOLERABILITY, PHARMACOKINETICS, AND SUBJECTIVE EFFECTS OF 50 µG, 75 µG, AND 100 µG LSD IN HEALTHY PARTICIPANTS

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Abstract: Rationale: Emerging clinical evidence suggests that psychedelics hold significant promise in treating a range of psychiatric disorders. Profound perceptual alterations induced by psychedelics require approaches to minimizing potential adverse reactions to enable their use as broad accessible therapeutics.

Objective: This study evaluated a scalable approach to ensuring patient safety, and reports safety assessments, pharmacokinetics, and subjective effects of 50 µg, 75 µg and 100 µg lysergic acid diethylamide (LSD) in healthy adults.

Methods: This was a phase 1, dose-escalation study: one part with an open-label design and another with a double-blind placebo-controlled crossover design. In both parts, participants were supervised by a single attendant and supported by remote monitors.

Results: Thirty-two adults (mean age = 28.8 years) received 50 µg (n=3), 75 µg (n=7), 100 µg (n=3) LSD, 50 µg followed by 75 µg LSD (n=9) one week apart, or placebo followed by a 75 µg LSD (n=10) one week apart. Twenty-eight percent of subjects experienced at least one adverse event, with a single adverse event classified as moderate in severity. Maximum blood plasma levels occurred between 1.2 and 2 hours, with an apparent half-life between 2.8 to 4.3 hours. In most comparisons, doses of LSD induced greater subjective effects ratings relative to placebo.

Conclusions: Our results suggest safety of 50 µg, 75 µg and 100 µg LSD to healthy adults supervised by a single attendant and supported by remote monitors is safe and tolerable. Future research will evaluate a similar care delivery paradigm in clinical populations.

T34. EFFECTS OF BREXPIPRAZOLE ON RDOC NEGATIVE AND POSITIVE VALENCE SYSTEMS: POOLED ANALYSIS OF SHORT-TERM CLINICAL STUDIES ACROSS MENTAL DISORDERS

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Abstract: Background: The National Institute of Mental Health's Research Domain Criteria (RDoC) is a transdiagnostic framework informed by objective behavioral, neurobiological, and genetic measures that may span multiple disorders, rather than using conventional diagnoses as defined in the DSM/ICD (1, 2). Efforts to interpret clinical data within the RDoC framework represent an appealing opportunity for translational research. In a recent study, expert psychiatrists allocated relevant items from validated mental health rating scales, including MADRS, HAM-D17, IDS-SR, HAM-A, and PANSS, to the six RDoC domains of human functioning (negative valence systems, positive valence systems, cognitive systems, social processes, arousal/regulatory systems, and sensorimotor systems). The aim of this post hoc analysis was to determine the effects of the serotonin–dopamine activity modulator,

brexpiprazole, on the proxy scales for negative and positive valence systems, based on pooled data across mental disorders.

Methods: Data were pooled across seven clinical trials in major depressive disorder (MDD) and schizophrenia (SCZ) to determine the effect of brexpiprazole on behavioral manifestations and symptoms aligned within RDoC domains. The MDD studies (ClinicalTrials.gov identifiers: NCT01360645, NCT01360632, NCT02196506, NCT01727726) were randomized, double-blind, placebo-controlled trials of adjunctive brexpiprazole 1–3 mg/day in adult outpatients with MDD (DSM-IV-TR criteria) and inadequate response to 1–3 prior antidepressant treatments (ADTs) plus 1 prospective ADT. The SCZ studies (NCT01396421, NCT01393613, NCT01810380) were randomized, double-blind, placebo-controlled studies of brexpiprazole 2–4 mg/day monotherapy in adult inpatients with an acute exacerbation of SCZ (DSM-IV-TR criteria). Changes from baseline of double-blind treatment were standardized as percentage changes for each item and used to obtain weighted average percentage change in the proxy RDoC related scales, for the brexpiprazole and placebo groups. Least squares (LS) mean estimates were provided for the standardized changes from baseline to Week 6 between brexpiprazole and placebo groups. For each indication separately, and across MDD and SCZ indications, within each RDoC subscale, percent changes for each line item were added and then divided by the total number of line items in the relevant RDoC subscale to create a weighted average. Standardized effect sizes using Cohen's d for the average percent change for each RDoC subscale were calculated.

Results: A total of 2,943 patients were included (brexpiprazole n=770 in MDD, n=868 in SCZ; placebo n=788 in MDD, n=517 in SCZ). For the negative valence system score, the LS mean improvements (brexpiprazole vs placebo) and Cohen's d effect sizes (d=) at Week 6 were: 28.9% vs 23.5% (d=0.17) in MDD (2–3 mg), 48.9% vs 39.4% (d=0.22) in SCZ (2–4 mg), and 37.7% vs 29.3% (d=0.22) in all patients (2–4 mg); all $p<0.01$. For the positive valence system scores, the LS mean changes (brexpiprazole vs placebo) and (d=) were 24.3% vs 15.8% (d=0.24) in MDD (2–3 mg), 21.0% vs 15.2% (d=0.19) in SCZ (2–4 mg), and were 22.7% vs 15.5 (d=0.22) in all patients (2–4 mg); all $p<0.01$.

Conclusion: We believe this is the first attempt to understand existing clinical data within the RDoC framework. In short-term studies, brexpiprazole 2–4 mg showed superiority over placebo in terms of improvement in RDoC negative and positive valence systems, across mental health disorders.

T35. INCLUDING PSYCHIATRIC TRAINEES IN NOVEL TREATMENTS FOR PSYCHIATRIC ILLNESSES DURING TRAINING

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Abstract: Background: With the increasing use of novel therapeutic agents to treat psychiatric illnesses (such as FDA approval of Esketamine and use of IV ketamine for treatment of major depressive disorder, MDD) and the continued expansion of transmagnetic stimulation (TMS) modalities (such as theta burst stimulation protocol, iTBS) it will be important to integrate current novel treatment protocols into trainee education. Many have called for and outlined how to integrate these treatments into a trainee curriculum (1,2,3,4). However, there is little

about how to integrate residents into current treatment protocols. This would include residents understanding the indications for use of these treatments, working with interdisciplinary teams, treatment day protocols, and integrating therapy into treatments.
Objective: Here we propose a framework for including trainees into the evaluation of patients interested in Ketamine, rTMS, and other neuromodulation treatments including both psychiatric suitability and medical evaluation. We will discuss different approaches in providing trainees these experiences, working through potential challenges and exploring the benefits of these strategies. Additionally, we will review how to actively involve trainees on the day of treatment which would provide them with tools to confidently pursue novel therapeutic agents in their own practice. Finally , we will review the feedback from trainees who have participated in these clinical training.

Conclusion: Novel interventional protocols in Psychiatry are exciting treatments for mental illness offering hope for patients with moderate and severe mental illness. As the momentum in the psychiatric community has mounted, it is prudent that trainees are not only exposed to literature but are also participating in the evaluation and treatment of patients with these modalities so that they are prepared upon graduation to use these treatments.

T36. NEUROBLU®: A LONGITUDINAL REAL-WORLD EVIDENCE PLATFORM FOR BEHAVIORAL HEALTH RESEARCH

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Abstract: Introduction: Real-world data from Electronic Health Records (EHR) can be used to derive valuable insights for the healthcare and pharmaceutical industries. However, real-world data in behavioral health is typically free-text, siloed, with limited connectivity and integration. Thus, turning raw data into an analytics-ready format for downstream use is an overwhelming endeavor for most research teams, hindering the development of a learning behavioral healthcare system (Stein 2016).
Methods: We developed NeuroBlu®, a real-world evidence (RWE) platform to drive insight generation in behavioral health. The current built-in database contains longitudinal behavioral health patient records from >25 hospitals that use the MindLinc EHR system across the U.S. (mindlinc.com). In addition, we have enhanced data quality and provide custom analytics tools and applications. Our pipelines cover: (1) data anonymization as per US regulations (2) data aggregation, cleaning, and quality control, (3) transformation of free-text notes into structured labels using proprietary deep-learning models of natural language processing (NLP), and (4) reformatting data into the industry standard for observational data.

Results: NeuroBlu is a web application that allows users to perform custom analyses on a built-in database and save the results for publications/reports. We provide interactive dashboards, in-built R libraries/templates, and guides to help users generate RWE. As of Q4 2020, users can access records of >500,000 patients with >14 million visits over the past 20 years. The dataset covers a wide range of mental disorders, including substance-related disorders, major depressive disorder (MDD), bipolar disorder, etc. Some unique advantages of using NeuroBlu

for RWE include: (1) high availability of outcome measures (e.g., Clinical Global Impression Scores recorded at 77% of all patient visits); (2) linked inpatient and outpatient data records; (3) >500 NLP data labels developed and validated from free-text notes in psychiatric care (e.g., patient symptoms, functions, and stressors) (Mukherjee 2020).

Discussion: Currently, NeuroBlu is used by pharma and healthcare researchers to examine patient phenotypes, identify real-world treatment patterns, and build predictive models to enhance behavioral health care delivery. In the next 1-2 years, we will increase the size of the built-in database, add more NLP data labels through the use of deep learning algorithms, and develop new tools and analytics libraries.

Conclusion: NeuroBlu is a subscription-based commercial product. Researchers can obtain a 14-day free trial before purchasing annual licenses as software-as-a-service contracts (contact: info@neuroblu.ai).

T37. CURRENT AND FUTURE CHALLENGES IN THE DELIVERY OF MENTAL HEALTHCARE DURING COVID-19

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Abstract: The USA is in the midst of the COVID-19 pandemic. We assess the impact of COVID-19 on psychiatric symptoms in healthcare workers, those with psychiatric comorbidities, and the general population. We highlight the challenges ahead and discuss the increased relevance of telepsychiatry. We analyzed all available literature available as of March 25, 2020, on PubMed, Ovid Medline, and PsychInfo. We utilized the MeSH term "covid AND (psychiatry OR mental health)" and included all articles. Duplicates were removed resulting in 32 articles, of which 19 are cited. Four additional references are included to examine suicide data. During the review process, an additional 7 articles were identified which are also included. Frontline healthcare workers are currently experiencing increased psychiatric symptoms and this is more severe in females and nurses. Non-frontline healthcare workers, as well as the general population, are experiencing vicarious traumatization. People with psychiatric comorbidities, and the general population, face increased psychiatric symptom burden. Migrant workers, the elderly, children, and the homeless may be disproportionately impacted. Suicide rates may be impacted. The COVID-19 pandemic has resulted in a severe disruption to the delivery of mental healthcare. Psychiatric facilities are facing unprecedented disruptions in care provision as they struggle to manage an infected population with comorbid psychiatric symptoms. Telepsychiatry is a flawed but reasonable solution to increase the availability of mental healthcare during COVID-19.

T38. PATH ANALYSES TO EXPLORE THE DIRECT AND INDIRECT EFFECTS OF BREXPIPRAZOLE ON LIFE ENGAGEMENT: POST HOC ANALYSIS OF SIX CLINICAL STUDIES IN DEPRESSION AND SCHIZOPHRENIA

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Abstract: Background: Patients with psychiatric disorders often value treatment outcomes that reflect life fulfillment, well-being, and participation in meaningful activities. Expert psychiatrists identified 11 items from the Positive and Negative Syndrome Scale (PANSS) and 10 items from the Inventory of Depressive Symptomatology Self-Report (IDS-SR) that represent patient well-being and life engagement beyond core symptoms, thereby creating the PANSS11 Life Engagement and IDS-SR10 Life Engagement subscales, respectively.1,2 Applying these exploratory subscales to pooled clinical trial data, the serotonin–dopamine activity modulator, brexpiprazole, demonstrated benefits on measures of life engagement in schizophrenia and major depressive disorder (MDD).1,2 The aim of the present study was to explore the extent to which these benefits are a direct treatment effect, or an indirect effect mediated through general improvement of symptoms and functioning.

Methods: Data were pooled from three clinical studies in schizophrenia (ClinicalTrials.gov identifiers: NCT01396421, NCT01393613, NCT01810380) and separately from three clinical studies in MDD (NCT01360645, NCT01360632, NCT02196506). The schizophrenia studies were randomized, double-blind, placebo-controlled studies of brexpiprazole 2–4 mg/day monotherapy in adult inpatients with an acute exacerbation of schizophrenia (DSM-IV-TR criteria). The MDD studies were randomized, double-blind, placebo-controlled trials of brexpiprazole 1–3 mg/day adjunctive to antidepressant treatment (ADT) in adult outpatients with MDD (DSM-IV-TR criteria) and inadequate response to 1–3 prior ADTs plus 1 prospective ADT. Path analyses were performed by fitting analysis of covariance (ANCOVA) models to observed cases data at Week 6 of double-blind treatment to assess, in schizophrenia: the extent to which improvement in PANSS11 Life Engagement score was a direct treatment effect versus an indirect effect mediated through improvement in PANSS Total score and Personal and Social Performance (PSP) Scale Total score, and, in MDD: the extent to which improvement in IDS-SR10 Life Engagement score was a direct treatment effect versus an indirect effect mediated through improvement in Montgomery–Åsberg Depression Rating Scale (MADRS) Total score and Sheehan Disability Scale (SDS) Mean score.

Results: In the schizophrenia studies, 25.9% of the total placebo-subtracted effect of brexpiprazole 2–4 mg on improving life engagement was a direct effect (PANSS11), whereas 74.1% of the total placebo-subtracted effect was an indirect effect mediated via improvement in schizophrenia symptoms (PANSS Total, 77.7%), with minimal impact of social functioning (PSP Total, -3.6%). In the MDD studies, 19.5% of the total placebo-subtracted effect of adjunctive brexpiprazole 2–3 mg on improving life engagement was a direct effect (IDS-SR10), whereas 80.5% of the total placebo-subtracted effect was an indirect effect mediated via improvements in depressive symptoms (MADRS Total, 53.5%) and functioning (SDS Mean, 27.0%).

Conclusion: These analyses of clinical trial data using exploratory subscales suggest that brexpiprazole may have a direct effect on improving life engagement in schizophrenia. In MDD, the benefit might be an indirect treatment effect mediated via improvements in depressive symptoms and functioning. Brexpiprazole may provide a specific benefit on patient life engagement beyond its effect on core symptoms.

T39. BRAIN METABOLITE LEVELS IN PATIENTS WITH REMITTED PSYCHOTIC DEPRESSION WITH AN EXAMINATION OF THE EFFECTS OF ANTIPSYCHOTICS VS. PLACEBO: A PROTON MAGNETIC RESONANCE SPECTROSCOPY STUDY

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Abstract: Background: Psychotic depression is associated with poorer outcomes, however, its neurobiology is not well-understood. Magnetic resonance spectroscopy (MRS) can non-invasively measure brain metabolite levels. A further consideration in neuroimaging studies, particularly in MRS studies, in where the effects of medication may be more notable on neurochemical measures is that participants are almost always medicated.
In the present study, we compared the brain metabolite levels between patients with remitted psychotic depression and healthy controls. Moreover, we examined if the use of olanzapine was related to metabolite level change in comparison with placebo.

Methods: Following the sustained remission after the acute treatment with sertraline (150-200mg/day) and olanzapine (15-20mg/day), patients with psychotic depression were randomly assigned to either continue sertraline plus olanzapine or switch to sertraline plus placebo. Baseline MRS scans were obtained at the time of randomization. Follow-up scans were collected either at the time of relapse or once sustained remission was achieved 36 weeks after their baseline scan. Controls completed one MRS scan. Water-scaled metabolite levels (glutamate + glutamine [Glx], glycerophosphocholine + phosphocholine [Cho], myo-Inositol [mI], N-acetylaspartate + N-acetylaspartylglutamate [NAA], and creatine + phosphocreatine [Cr]) were estimated in the left dorsolateral prefrontal cortex (L-DLPFC) and bilateral supragenual anterior cingulate cortex (SACC), and analyzed data from each site separately then meta-analyzed the effect sizes as a standardized mean difference (SMD).

We performed additional sensitivity analyses: (1) restricted to participants with age of 50 years or older, (2) olanzapine vs. placebo groups only in those who had sustained remission at the time of the second scan, and (3) patients who relapsed or sustained remission at the time of the second scan while receiving placebo.

Results: Patients (N=40) had higher Cho in the L-DLPFC (SMD=0.77; 95%CI=0.26–1.28; p=0.003) and higher mI in L-DLPFC (SMD=0.66; 95%CI=0.20–1.11; p=0.005) and SACC (SMD=0.56; 95%CI=0.12–1.00; p=0.01) compared to controls (N=46) adjusted by age and sex. When the analyses were limited to older participants, the results did not change.

When the time between scans was modelled, a linear mixed-model analysis showed that placebo group (N=16) had a greater change with a decrease in mI (estimate±standard error, 0.00378±0.00165, t(32.9)=2.295, p=0.03) and Cr (0.00461±0.00102, t(29.7)=4.501, p <0.001) compared to olanzapine group (N=15) in the SACC.

In the sensitivity analysis restricted to patients who sustained remission during the follow-up (N=19), the placebo group showed a decrease in Cr level (estimate±standard error, -0.00409±0.00111; t(15.4)=-3.68; p=0.002) in the SACC compared to the olanzapine group. In another sensitivity analysis restricted to the placebo group (N=18), patients who relapsed showed a decrease in Cho levels (-0.00188±0.00067; t(14.3)=-2.80; p=0.01) in the L-DLPFC compared to those who sustained remission. There were no significant correlations between any metabolite level changes and changes in Hamilton Depression Rating Scale (HDRS-17) total score or the Schedule of Affective Disorders and Schizophrenia (SADS) delusion score.

Conclusions: Cho and mI levels in remitted psychotic depression are higher than controls. Cho level decreases are associated with a higher risk of relapse. Olanzapine may maintain mI and Cr levels, a more direct effect of olanzapine on Cr levels. Future placebo-controlled studies with a large sample size are needed to reveal the mechanisms of action of olanzapine.

T40. A PHASE 3B MULTI-CENTER, PROSPECTIVE, OPEN-LABEL TRIAL TO EVALUATE THE EFFECTS OF A DIGITAL MEDICINE SYSTEM ON INPATIENT PSYCHIATRIC HOSPITALIZATION RATES IN ADULTS WITH SCHIZOPHRENIA

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Abstract: Ensuring medication adherence is a major challenge in patients with schizophrenia. The digital medicine system (DMS), comprised of aripiprazole tablets embedded with an ingestible event-marker sensor, wearable sensor skin patches, and a smartphone application, is indicated for the treatment of adults with schizophrenia, bipolar disorder I (with or without lithium or valproate), or as adjunct treatment for adults with major depressive disorder.1 Patients can track their treatment ingestion data via a smartphone application, while investigators, clinicians, and caregivers can track these data using separate Web-based dashboards. In a prior phase 2 study of patients with schizophrenia, most subjects found the DMS to be satisfactory and helpful in managing their condition.2 However, it is not known whether the DMS affects the increased utilization of healthcare frequently observed in patients with schizophrenia. Therefore, we conducted a phase 3b, open-label, prospective, clinical trial in patients with schizophrenia (aged 18–65 years and with at least 1 inpatient psychiatric hospitalization in the past 48 months) to determine if the DMS reduced psychiatric hospitalization rates. Eligible patients had been prescribed oral standard-of-care (SOC) antipsychotics for the previous 6 months (retrospective phase) and then switched to the DMS (months 1–3 of the prospective phase). For prospective months 4–6, patients were maintained on the DMS or reverted to oral SOC antipsychotics for follow-up based on the investigator's discretion. The primary endpoint was the inpatient psychiatric hospitalization rate during prospective months 1–3, when all patients used the DMS, vs retrospective months 1–3, when patients used oral SOC antipsychotics. Among the safety endpoints were adverse events (AEs) related to the medication or patch (e.g., skin irritation), and the Columbia-Suicide Severity Rating Scale was used to assess changes in suicidal ideation from baseline. Of 277 enrolled patients, 113 patients were included in the modified intent-to-treat (mITT) population (median age 49 years; 61.1% male). No patients in the mITT population using the DMS in prospective months 1–3 experienced inpatient psychiatric hospitalization vs 9.7% of patients taking oral SOC antipsychotics in retrospective months 1–3 (difference in hospitalization rate: –9.7%; P=0.001). In the full ITT population (n=277), 1.1% of patients using the DMS in prospective

months 1–3 experienced inpatient psychiatric hospitalization vs 9.4% of patients in the same population taking oral SOC antipsychotics in retrospective months 1–3 (difference in hospitalization rate: –8.3%; P=0.001). The skin patch was well tolerated, with mild skin irritation (the single type of AE recorded) from the adhesive at the patch placement site, impacting 7.6% (21/277) of patients. No patient reported severe skin irritation, other treatment-emergent AEs, or changes in suicide risk. We conclude that, compared with oral SOC antipsychotics, the DMS may reduce inpatient psychiatric hospitalization rates among adults with schizophrenia. By giving providers objective ingestion data to inform timely and appropriate treatment decisions, the DMS may reduce healthcare utilization among patients with schizophrenia.

T41. METFORMIN FOR COMORBID GLUCOSE DYSREGULATION AND SCHIZOPHRENIA SPECTRUM DISORDERS: A PILOT DOUBLE-BLIND RANDOMIZED CONTROL STUDY

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Abstract: Background: Patients with severe mental illness (SMI) loose 15-20 years of life due to cardiovascular disease. Much of the metabolic risk, including high rates of type 2 diabetes (T2D) is accrued early on in the illness, highlighting the need for early intervention strategies to target modifiable cardiovascular risk factors. There is however an astounding paucity of studies in SMI examining interventions outside of weight loss.

Methods: Thirty participants with schizophrenia spectrum disorders and co-morbid prediabetes or T2D were randomly assigned, in a double-blind fashion to 1500mg/d of metformin or placebo (2:1 ratio; n=21 metformin and n=9 placebo). Patients had to be overweight/obese, <40 years old, and receiving a stable dose of antipsychotics. The primary outcome measures were improvements in glycemia (HbA1c, fasting glucose), and insulin sensitivity (Matsuda-derived from glucose tolerance tests and HOMA-IR). Secondary outcomes included changes in weight, fat distribution (MRI quantification of hepatic and visceral fat), cognition, and hippocampal volume (MRI). Data were analyzed using mixed-models methods and intention to treat analysis.

Results: Twenty-two patients (n=14 metformin; n=8 placebo) completed the 4-month trial. The metformin group had a significant decrease in the HOMA-IR (p=0.043), and fasting blood glucose (p=0.007) vs. placebo. There were no differences between treatment groups in the Matsuda index, HBA1c ,or secondary outcome measures. Weight loss among all participants correlated significantly with decreased subcutaneous, but not visceral adipose tissue.

Conclusions: Independently of weight loss, metformin effectively improves dysglycemia and insulin sensitivity in a population at very high risk for early CV mortality.

T42. CHARACTERIZING THE EFFICACY AND SAFETY PROFILE OF THE NOVEL MUSCARINIC AGONIST KARXT (XANOMELINE/TROSPIUM): PRIMARY AND SECONDARY RESULTS FROM A PHASE 2 PLACEBO-CONTROLLED TRIAL IN SCHIZOPHRENIA

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Abstract: Background: Xanomeline is a M1/M4-preferring muscarinic receptor agonist originally developed for Alzheimer's disease, where it was noted to have antipsychotic efficacy. However, procholinergic adverse events (AEs; e.g., nausea and vomiting) contributed to termination of xanomeline development. KarXT (xanomeline + trospium) retains the antipsychotic efficacy of xanomeline while mitigating its associated procholinergic AEs. Trospium is a generic anticholinergic drug that does not cross the blood-brain barrier, and its inclusion in KarXT was shown to reduce rates of procholinergic AEs relative to xanomeline alone in a Phase 1 trial.[1] Here we will review primary results that are currently in press and present additional post hoc analyses from a Phase 2 double-blind, placebo-controlled 5-week trial of KarXT for the treatment of acute psychosis in patients with schizophrenia (EMERGENT-1; NCT03697252).

Methods: EMERGENT-1 was a double-blind, placebo-controlled, 5-week inpatient trial conducted at 12 US sites in patients with schizophrenia who were experiencing acute psychosis. After consent, participants discontinued any prior antipsychotic medication and were then randomized 1:1 to receive KarXT or matched placebo. Flexible BID dosing was utilized beginning with 50mg xanomeline/20mg trospium for two days, then increased to 100mg/20mg for 5 days, followed by an optional increase to 125mg/30mg on day 8 based on tolerability. The primary endpoint was the mean change in PANSS total (PANSST) score from baseline to week 5. Additional post hoc responder analyses evaluated treatment-arm differences in response and number of participants needed to treat (NNTs) to achieve a ≥30% improvement in PANSST, with NNTs calculated as 1/(KarXT responder rate- placebo responder rate). Safety and tolerability assessments included standard AE and SAE rates, labs, and EPS rating scales.

Results: 182 subjects were randomized (KarXT N=90; placebo N=92). At week 5, KarXT was associated with an 11.6-point greater improvement in PANSST scores compared with placebo (-17.4 points vs -5.9 points, $p<0.0001$; Cohen's $d = 0.75$). At week 5, a higher percentage of patients in the KarXT arm showed ≥30% improvement in PANSST score compared with the placebo arm (38.6% vs 11.5%, $p=0.0001$). The NNT (95% CI) for one participant to achieve ≥30% treatment response was 4 (3-7). The most common KarXT-associated treatment-emergent AEs (TEAEs) were constipation, nausea, dry mouth, dyspepsia, and vomiting that were of mild or moderate severity and did not lead to treatment discontinuation. The discontinuation rate for TEAEs was equal in the KarXT and placebo arms (2.2%). The rates of AEs associated with commonly prescribed antipsychotic drugs (e.g., somnolence, weight gain, restlessness, and EPS) were similar in the KarXT and placebo arms.

Conclusion: KarXT treatment, relative to placebo, showed statistically significant antipsychotic efficacy in patients with schizophrenia who were experiencing acute psychosis. In this trial, KarXT showed clinically-meaningful benefit with a Cohen's d effect size of 0.75

on the PANSST compared to a meta-analysis that reported Cohen's d effect size of 0.35 – 0.58 for the most commonly used dopaminergic antipsychotics.[2] In addition, KarXT was associated with substantially higher response rates compared to placebo, and a low NNT to achieve ≥30% treatment response. KarXT treatment was safe and well-tolerated with a low TEAE-related discontinuation rate equal to placebo. These data suggest that M1/M4 agonism may represent a promising new MOA for the treatment of schizophrenia, and Phase 3 trials of KarXT are ongoing.

T43. CLINICAL TRIALS OF ANTIPSYCHOTIC TREATMENT IN SCHIZOPHRENIA PATIENTS WITH CATATONIC SYMPTOMS

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Abstract: Clinical Trials of Antipsychotic Treatment in Schizophrenia Patients with Catatonic Symptoms: Background: There have been numerous attempts to identify markers in schizophrenia predictive of antipsychotic treatment response. One potential marker in the psychomotor dimension may be the presence of catatonic symptoms. Results from observational studies of schizophrenia with catatonic symptoms are inconsistent, with some predicting poor antipsychotic response whilst others caution against antipsychotic treatment in the presence of catatonic symptoms due to risk of serious adverse events (e.g., NMS). Few randomized controlled trials (RCTs) have been conducted in this important area.

Methods: To evaluate the efficacy and safety of antipsychotics for schizophrenia with catatonic symptoms, a systematic search of the Cochrane Schizophrenia Group Trials Study-Based Register was conducted. All RCTs comparing antipsychotic medications with other pharmacological agents, ECT, or placebo for patients who have schizophrenia with catatonic symptoms were extracted. Manually searched reference lists were reviewed and study authors were contacted when relevant. Studies of adults over the age of 16 with the diagnosis of schizophrenia or related disorders who had catatonia listed as a symptom, subtype, modifier, or specifier, were included. Tests of significance included t-tests for continuous data and Chi-square tests for categorical data.

Results: Of 26 studies extracted, 3 RCTs met inclusion criteria. In two studies (n=137), ECT and antipsychotics produced significantly reduced mean ± SD scores at endpoint on the BPRS scale (all $p<0.05$), but ECT showed scores in both trials (27.47±2.90, 19.9± 2.6) that were significantly lower than risperidone (29.80±1.27) or sulpiride (22.9±3.1; both $p<0.05$), respectively. ECT produced significantly higher mean total scores (287.27±3.35) on the NOSIE scale, suggesting improvement in general functioning, compared with risperidone (269.40±3.25; $p<0.05$). In another trial (N=80), schizophrenia patients with stupor improved on amisulpride and aripiprazole ($p<0.01$) with no treatment differences on BPRS and SANS scores or in patients showing ≥50% improvement (70.2% vs. 65.8%; $p>0.05$). Only common side effects were noted across trials (e.g., ECT=headache, memory loss; antipsychotics=extrapyramidal symptoms).

Conclusions: These short-term trials suggest that both ECT and antipsychotics result in clinical improvement among schizophrenia patients with catatonic symptoms without serious adverse

events, but ECT resulted in greater improvement. No difference was found in symptom improvement between antipsychotics. Quality of evidence was limited because of small sample sizes (n=56-81), short duration (2-4 weeks), and unclear randomization and blinding procedures. Further high-quality RCTs are necessary to differentiate treatment response for specific symptoms of catatonia in schizophrenia measured by standardized instruments (e.g., BFCRS). Better understanding of the relative efficacy and safety of antipsychotics and ECT may clarify treatment strategies for the subgroup of schizophrenia patients with catatonic symptoms.

T44. IDENTIFYING PATIENTS WITH TREATMENT-RESISTANT SCHIZOPHRENIA THROUGH ELECTRONIC HEALTH RECORDS: USING A MEASURE OF FUNCTIONING TO VALIDATE

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Abstract: Background: It is estimated that up to one-third of patients with schizophrenia do not respond to antipsychotic medications, excluding clozapine, and are classified as treatment-resistant schizophrenia (TRS). Current treatment guidelines for schizophrenia define TRS as presence of positive symptoms despite being treated by ≥2 trials of different non-clozapine antipsychotic medications at the appropriate dose, duration, and documented adherence. This definition cannot be easily applied to electronic health record (EHR) databases, mostly due to the lack of objective measures of treatment response and documentation of adherence. In contrast, prescription information is readily available in EHRs. Clozapine is the only medication approved for TRS. We identified patients who were prescribed clozapine, as patients with TRS and evaluated their community functioning by an independent measure of functionality, the brief version of UCSD Performance-based Skill Assessment (UPSA-B) to validate the predictability of this method.

Methods: We used a sample of patients with schizophrenia in the Veterans Affairs (VA) Cooperative Studies Program (CSP) #572, who were recruited from January 2011 through June 30,2014. Diagnoses were confirmed by the Structured Clinical Interview for DSM-IV (SCID-IV). Those with other primary psychotic disorders, including schizoaffective disorder, were excluded. We then compared the TRS group with the remaining participants who were not prescribed clozapine (non-TRS). UPSA-B score (range 0 to 20) was measured and compared between the two groups.

Results: As previously reported, the schizophrenia patients had a mean age of 55.3 ± 9.9 (years ± SD); 93% were male. Patients with European and African ancestry constitute 39% and 55% of patients, respectively. A total of 274 patients who received clozapine prior to study recruitment (TRS) was compared to 3470 patients with schizophrenia, labeled as non-TRS. TRS and non-TRS groups had mean UPSA-B score of 14.435 ± 3.63 and 14.85 ± 3.14 respectively. We next performed a linear regression analysis including history of clozapine and self-reported ancestry, age, and gender as moderators. Past clozapine use is significantly associated with lower UPSA-B score (z-score: -3.69, $p<0.01$). Moreover, African ancestry and age were also found to be associated with past clozapine use and lower UPSA-B score ($p<0.01$).

Conclusion: Patients who were prescribed clozapine before enrollment in the study, a potential marker for TRS, had significantly lower functioning, measured by UPSA-B after controlling for ancestry and age. Given that objective measures of treatment adherence and response are usually lacking in EHR, clozapine prescription represents a potential initial surrogate for identifying patients with TRS in studies that do not have clinical ratings. Further work is needed to refine this measure and to identify additional potential indicators of TRS in EHRs.

T45. UTILIZING A STRUCTURED BENEFIT-RISK ASSESSMENT TO EVALUATE A COMBINATION OF OLANZAPINE AND SAMIDORPHAN FOR THE TREATMENT OF SCHIZOPHRENIA AND BIPOLAR I DISORDER

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Abstract: Background: A combination of olanzapine and samidorphan (OLZ/SAM) is being developed for the treatment of schizophrenia and bipolar I disorder to provide the efficacy of olanzapine while mitigating weight gain. To improve communication of the OLZ/SAM benefit-risk profile, a structured framework was utilized.

Methods: The Benefit-Risk Action Team framework was used to evaluate OLZ/SAM with analyses completed for each pivotal study. ENLIGHTEN-1 evaluated antipsychotic efficacy and safety vs placebo. ENLIGHTEN-2 evaluated the weight profile of OLZ/SAM vs olanzapine. Benefit-risk outcomes were selected based on study outcome parameters, known risks of olanzapine and samidorphan, and public health importance. A subset of opioid antagonist risks were not assessed due to clinical trial exclusions; however, they were factored into the overall evaluation. Risk differences and confidence intervals were analyzed.

Results: In ENLIGHTEN-1, OLZ/SAM had a lower risk of psychiatric discontinuation and non-response to treatment compared to placebo; higher risks of hyperprolactinemia, weight gain (≥7%), sedation, and worsening of fasting triglycerides and glucose, and no difference for fasting total and LDL cholesterol, neutropenia, orthostatic hypotension, and movement disorders. In ENLIGHTEN-2, OLZ/SAM had reduced risks of weight gain and waist circumference increase compared to olanzapine along with similar risks of relapse and psychiatric discontinuation and no difference in metabolic worsening, neutropenia, hyperprolactinemia, orthostatic hypotension, sedation, and movement disorders.

Discussion: Based on this assessment, OLZ/SAM has comparable efficacy and a consistent safety profile to olanzapine with reduced weight gain. A structured approach to assessing the benefit-risk profile of a product facilitates transparent evaluation and communication.

T46. OLANZAPINE/SAMIDORPHAN MITIGATES WEIGHT GAIN ACROSS SUBGROUPS OF PATIENTS KNOWN TO BE AT INCREASED RISK FOR WEIGHT GAIN WITH OLANZAPINE TREATMENT

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Abstract: Background: Treatment with olanzapine is associated with clinically significant weight gain. Certain patient characteristics are associated with a greater propensity for olanzapine-associated weight gain, including younger age, being female, being of non-white race, and having a low body mass index (BMI). A combination of olanzapine and samidorphan, an opioid antagonist (OLZ/SAM) has been developed to mitigate weight gain associated with olanzapine treatment while maintaining antipsychotic efficacy. In a phase 3 study in outpatients with schizophrenia (ENLIGHTEN-2), OLZ/SAM treatment significantly mitigated weight gain versus olanzapine over 24 weeks. Here, we present previously unreported prespecified subgroup analyses based on demographics and baseline patient characteristics to determine if any differential treatment effects exist in these subgroups.

Methods: The phase 3 multicenter, randomized, double-blind study enrolled adults (18–55 years) diagnosed with schizophrenia (DSM-5 criteria) who were outpatients, had a BMI of 18–30 kg/m2 and stable body weight (self-reported change ≤ 5% for at least 3 months before study entry). Patients were randomized 1:1 to OLZ/SAM or olanzapine for 24 weeks. Co-primary endpoints were percent change in body weight and proportion of patients with ≥10% weight gain at week 24. In this report, exploratory subgroup analyses were conducted by sex, age, race, and BMI. Percent change in weight from baseline was evaluated by analysis of covariance model, and the proportion of patients with ≥10% weight gain was analyzed by logistic regression model. Missing postbaseline data were imputed by multiple imputation.

Results: A total of 538 patients were included (OLZ/SAM: n=266; olanzapine: n=272). Baseline demographics were similar across treatment groups. OLZ/SAM was associated with a lower percent change in weight vs olanzapine at week 24 across all subgroups evaluated, with least squares mean differences (95% CI) of −2.38% (−3.88%, −0.88%) in the overall population, −2.73% (−4.45%, −1.01%) for males (n=391), −1.53% (−4.43%, 1.38%) for females (n=147), −3.43% (−7.00%, 0.13%) for age <30 years (n=98), −2.14% (−3.78%, −0.51%) for age ≥30 years (n=440), −2.37% (−4.10%, -0.63%) for black patients (n=392), −2.41% (−5.28%, 0.46%) for non-black patients (n=146), −2.17% (−4.10%, −0.24%) with BMI <27 kg/m2 (n=327), and −2.70% (−5.01%, −0.39%) with BMI ≥27 kg/m2 (n=211). The proportion of patients with ≥10% weight gain was smaller in each subgroup treated with OLZ/SAM versus those treated with olanzapine. Relative to olanzapine, the odds ratios (95% CI) for having a ≥10% weight gain from baseline at week 24 with OLZ/SAM treatment were 0.50 (0.31, 0.80) in the overall population, 0.41 (0.23, 0.73) for males, 0.68 (0.30, 1.55) for females, 0.65 (0.25, 1.70) for age <30 years, 0.46 (0.27, 0.78) for age ≥30 years, 0.47 (0.27, 0.82) for black patients, 0.55 (0.24, 1.30) for non-black patients, 0.57 (0.32, 1.00) with BMI <27 kg/m2, and 0.38 (0.16, 0.87) with BMI ≥27 kg/m2.

Discussion: In this exploratory analysis of the 24-week, phase 3 study of patients with schizophrenia, OLZ/SAM treatment mitigated weight gain associated with olanzapine across several patient subgroups, including groups of patients who are known to be at higher risk for weight gain with olanzapine based on sex, race, age, and baseline BMI.

T47. POPULATION PHARMACOKINETIC-PHARMACODYNAMIC ANALYSIS TO EXPLORE THE CONCENTRATION-RESPONSE RELATIONSHIP IN PATIENTS

WITH SCHIZOPHRENIA TREATED WITH OLANZAPINE ALONE OR IN COMBINATION WITH SAMIDORPHAN

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Abstract: Background: A combination of olanzapine and the opioid receptor antagonist samidorphan (OLZ/SAM) is being developed to provide the antipsychotic efficacy of olanzapine while mitigating olanzapine-associated weight gain. An exploratory population pharmacokinetic-pharmacodynamic analysis was conducted to identify potential relationships between drug exposure and treatment effects.

Methods: Positive and Negative Syndrome Scale (PANSS) total score and/or body weight data from efficacy studies were included as pharmacodynamic endpoints. Pharmacokinetic input was provided from predicted plasma drug concentrations using a population pharmacokinetic model for the corresponding studies. Regression and box plots were generated to investigate any potential pharmacokinetic- pharmacodynamic relationships.

Results: PANSS total score and/or body weight records were paired with olanzapine and/or samidorphan concentrations from 1464 patients with schizophrenia. Within the clinical dose range for olanzapine (10─20 mg/d) and samidorphan (5─20 mg/d), no significant correlation was noted between 1) olanzapine concentrations and change in PANSS total score or % change in body weight in patients treated with OLZ/SAM or olanzapine, and 2) samidorphan concentration or samidorphan-to-olanzapine concentration ratio and % change in body weight. There was no meaningful difference in olanzapine and samidorphan concentrations or samidorphan-to-olanzapine concentration ratios between patients who had <10% and ≥10% weight gain.

Conclusions: The antipsychotic efficacy of olanzapine was not affected by the addition of samidorphan at any concentration of olanzapine. Furthermore, olanzapine-associated weight gain did not correlate with olanzapine dose or plasma concentration. Lastly, the effect of OLZ/SAM on mitigation of olanzapine-associated weight gain was not affected by inter-subject variability in olanzapine and/or samidorphan plasma concentrations.

T48. REDUCED RISK ACROSS MULTIPLE CARDIOMETABOLIC RISK FACTORS WITH OLZ/SAM COMPARED WITH OLANZAPINE: RESULTS FROM A 24-WEEK PHASE 3 STUDY

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Abstract: Background: The olanzapine and samidorphan (OLZ/SAM) combination was developed to mitigate olanzapine-associated weight gain while maintaining antipsychotic efficacy. In the phase 3 ENLIGHTEN-2 study, patients gained significantly less weight with OLZ/SAM compared with olanzapine. We present post hoc analyses from ENLIGHTEN-2

assessing the effects of OLZ/SAM versus olanzapine across multiple cardiometabolic risk factors.

Methods: The phase 3, 24-week, randomized, double-blind study enrolled adults with schizophrenia (18–55 years; body mass index [BMI] 18–30 kg/m2). Patients were randomized 1:1 to OLZ/SAM (10/10 or 20/10 mg/day) or olanzapine (10 or 20 mg/day). Post hoc analyses evaluated changes in BMI, risk of obesity (BMI ≥30), changes in blood pressure, and risk of blood pressure shifts from normal to hypertensive (all at week 24), and risk of developing metabolic syndrome (last on-treatment assessment).

Results: OLZ/SAM (n=266) was associated with smaller BMI increases, least squares (LS) mean difference (95% CI): −0.65 kg/m2 (-1.01, -0.28); reduced risk of obesity, odds ratio (95% CI): 0.52 (0.32, 0.82); smaller increases in blood pressure, LS mean difference [95% CI] in systolic (-2.63 mmHg [-4.78, -0.47]) and diastolic (-0.75 mmHg [-2.31, 0.80]) blood pressure; and a reduced risk of blood pressure shifts from normal to hypertensive, (OR [95% CI]: 0.48 [0.24, 0.96]) vs olanzapine (n=272) at week 24. The risk of developing metabolic syndrome per ATP III criteria was also reduced with OLZ/SAM (OR [95% CI]: 0.55 [0.31, 0.99]).

Conclusions: Patients in ENLIGHTEN-2 were less likely to experience worsening of certain clinically relevant cardiometabolic risk factors when treated with OLZ/SAM vs olanzapine.

T49. EXPLORING THE CONCEPT OF LIFE ENGAGEMENT FROM THE PERSPECTIVE OF PATIENTS WITH SCHIZOPHRENIA: A STUDY USING PATIENT INTERVIEWS

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Abstract: Background: The concept of 'life engagement' has recently been described in relation to major depressive disorder (MDD) and is also being explored in schizophrenia. Life engagement has been described by expert psychiatrists as encompassing four domains: emotional, physical, social, and cognitive (1). A group of specialists in the treatment of patients with MDD identified 10 items from the 30-item Inventory of Depressive Symptomatology Self-Report (IDS-SR) anticipated to represent patient well-being and life engagement (2) – the proposed 'IDS-SR10 Life Engagement' subscale. A recent qualitative interview study confirmed that the 10 items resonated with patients with MDD as relevant to the concept of life engagement. Although the IDS-SR was developed for use in depression, the core symptoms of depression were intentionally excluded from the subscale in order to capture concepts related to life engagement not limited to symptoms of depression. Therefore, potentially, the subscale may also be relevant for populations other than MDD. The aim of the present study was to utilize the life engagement model, developed for patients with MDD, to explore the concept of life engagement in individuals with schizophrenia.

Methods: Semi-structured, qualitative interviews were conducted with adults with schizophrenia in the United States of America who were receiving maintenance treatment with an antipsychotic. Patients were asked to describe their spontaneous understanding of life engagement, and then to evaluate the relevance of the four-domain conceptual model of life

engagement and the relevance of the concepts underlying the 10 expert-selected IDS-SR items (as well as the 20 non-selected items of the IDS-SR).

Results: In total, 25 patients were interviewed; the majority were male (n=16), between ages 36–55, and had received their schizophrenia diagnosis 7–30 years previously. The majority of patients (64%) were able to provide a spontaneous definition of life engagement that aligned with the study definition. When presented with the four-domain conceptual model of life engagement, 24 (96%) patients felt that all four domains were important to the concept of life engagement, and 16 (64%) patients suggested additional domains that they perceived to be relevant. Overall, at least 64% of patients considered each of the concepts underlying the 10 expert-selected IDS-SR items to be relevant to the concept of life engagement, with the concept 'Concentration/decision making' considered relevant by all of the patients. When presented with the remaining 20 IDS-SR concepts, albeit with lower proportions, all items were selected by at least one patient and the 'mood quality' concept was selected by 48% of patients as relevant to life engagement.

Conclusion: The four-domain framework of life engagement was relevant to patients with schizophrenia. The concepts underlying the 10 expert-selected IDS-SR items were considered to encompass the concept of life engagement by this sample of stable patients with schizophrenia. These findings suggest that the four-domain model and the proposed IDS-SR10 Life Engagement subscale may be relevant to the concept and measurement of life engagement in patients with schizophrenia.

T50. EFFICACY OF LUMATEPERONE (ITI-007) IN DEPRESSION SYMPTOMS ASSOCIATED WITH SCHIZOPHRENIA

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Abstract: Background: Depression symptoms are commonly associated with schizophrenia and are associated with poorer patient outcomes, including increased risk of relapse and suicidality, worse functioning, and decreased quality of life. Lumateperone (lumateperone tosylate, ITI-007) is a mechanistically novel agent for the treatment of schizophrenia that simultaneously modulates serotonin, dopamine, and glutamate neurotransmission. This mechanism of action may confer beneficial effects in treating depression symptoms associated with schizophrenia. The efficacy, safety, and tolerability of lumateperone in schizophrenia was established in randomized, placebo-controlled studies. An open-label study (Study 303) in stable schizophrenia patients switched from prior antipsychotic treatment to 1 year of lumateperone 42 mg further supported the long-term effectiveness and safety of lumateperone. This post hoc analysis of Study 303 evaluated the effects of lumateperone 42 mg across the range of depression symptoms in stable patients with schizophrenia.

Methods: Depression symptoms were assessed using the Calgary Depression Scale for Schizophrenia (CDSS). This scale comprises 9 items scored 0 (absent) to 3 (severe). Analyses were conducted in patients with moderate-to-severe depression symptoms (CDSS≥6) at baseline. Mean change from baseline was analyzed with a paired t-test. Additional evaluations included subgroup analysis based on concurrent antidepressant use.

Results: The overall population comprised 602 stable schizophrenia patients. Of these, 80 patients had moderate-to-severe depression symptoms (CDSS score≥6) with a mean CDSS score of 7.6 (range 6–16). At the end of treatment (EOT) mean change from baseline was −4.8 (P<.0001); mean CDSS score was 2.4. In patients with CDSS score≥6 at baseline, 50% responded by EOT. Depression (Item 1) and Early Awakening (Item 7) were the most prominent symptoms at baseline (mean scores 1.5 and 1.1, respectively); Suicide (Item 8) was the least severe (0.1). At Day 75 (earliest on-treatment assessment), all CDSS items showed significant improvement (P<.05 to P<.0001) from baseline. The magnitude of improvement for all items increased from Day 75 to EOT (Day 368). The largest improvement was for Item 2 (Hopelessness; change from baseline=−0.8); 5 CDSS items showed marked improvements (−0.6) including Items 1, 3 (Self Depreciation), 5 (Pathological Guilt), 6 (Morning Depression), and 7. Significant and comparable CDSS improvements were seen in patients with and without concomitant antidepressant treatment.

Conclusion: In stable schizophrenia patients with moderate-to-severe depression, lumateperone 42 mg significantly improved a broad range of depression symptoms. Depression symptoms were significantly improved regardless of concurrent antidepressant use. Improvement in depression symptoms supports the benefits of lumateperone, as monotherapy or adjunctive therapy, in treating depression symptoms associated with schizophrenia.

T51. EFFICACY AND SAFETY OF LURASIDONE IN ADOLESCENTS AND YOUNG ADULTS WITH SCHIZOPHRENIA: POOLED ANALYSIS OF DOUBLE-BLIND, PLACEBO-CONTROLLED 6-WEEK STUDIES

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Abstract: Background: Onset of schizophrenia commonly occurs during late adolescence or early adulthood and is often characterized by greater illness severity, chronicity, and functional impairment with a less favorable prognosis than later onset schizophrenia.1,2 The aim of this pooled post-hoc analysis was to evaluate the efficacy and safety of lurasidone in the treatment of an acute exacerbation of schizophrenia in adolescents and young adults.

Methods: The 6 pooled studies in this analysis used similar study designs and outcome measures. Patients (ages 13-25 years) were randomized to 6 weeks of double-blind, placebo-controlled treatment with once-daily lurasidone in fixed doses of 40 mg, 80 mg, 120 mg, or 160 mg. The primary efficacy endpoint was week 6 change in the Positive and Negative Syndrome Scale (PANSS) total score; secondary efficacy endpoints included week 6 change in the Clinical Global Impression, Severity scale (CGI-S), and the PANSS positive and negative subscales; and week 6 responder rates defined as ≥20% reduction in PANSS total score. Change scores were evaluated using mixed-model repeated-measures (MMRM) analysis; responder rates were analyzed using a logistic model.

Results: The safety population consisted of 537 patients (69.8% male; mean age, 18.1 years; mean baseline PANSS total score, 95.75); 82.6% of patients completed the studies. Treatment with lurasidone was significant at all doses (P<0.001) for change in the PANSS total score at

Week 6 endpoint, with higher effect sizes (ES) at higher doses (40 mg, 0.53; 80 mg, 0.57; 120 mg, 0.67; 160 mg, 1.35). Significance was also observed at all doses for change in the CGI-S with medium to large effect sizes (40 mg, 0.51; 80 mg, 0.49; 120 mg, 0.57; 160 mg, 1.75). Treatment with lurasidone was significant at all doses on the PANSS positive subscale ($P<0.001$); and was significant ($P<0.001$) on all but the 120 mg dose on the PANSS negative subscale. Responder rates demonstrated medium-to-large effect sizes for lurasidone 40 mg (NNT=5), 80 mg (NNT=5), 120 mg (NNT=6), and 160 mg (NNT=3). For lurasidone (combined doses), 3 adverse events occurred with a frequency ≥5% (nausea, 13.5%; somnolence, 12.1%; akathisia, 10.1%); 4.8% of patients discontinued due to an adverse event. At LOCF-endpoint, 3.6% of patients had weight gain ≥7%, and 1.5% had weight loss ≥7%. For lurasidone (combined doses), minimal median changes were observed at endpoint in metabolic lab values (cholesterol, -2.0 mg/dL; triglycerides and glucose, 0.0 mg/dL).

Discussion: In adolescents and young adults with schizophrenia, treatment with lurasidone in doses of 40-160 mg/d was a safe, well-tolerated, and effective treatment. Short-term treatment with lurasidone was associated with minimal effects on weight and metabolic parameters.

T52. EFFECTS OF SEP-363856, A NOVEL TAAR1 AGONIST, ON NEGATIVE SYMPTOMS IN SCHIZOPHRENIA: RESULTS ACROSS AN INITIAL DOUBLE-BLIND ACUTE STUDY AND A 6-MONTH, OPEN-LABEL EXTENSION STUDY

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Abstract: Background: SEP-363856 is a novel trace amine-associated receptor 1 (TAAR1) agonist with serotonin 5-HT1A activity that has demonstrated efficacy in animal models of psychosis. In a double-blind, placebo-controlled study, SEP-363856 was efficacious in the treatment of patients with an acute exacerbation of schizophrenia as measured by the Positive and Negative Syndrome Scale (PANSS) total score at Week 4 with a safety and tolerability profile similar to placebo. The current analyses examined the effects of SEP-363856 on negative symptoms in the initial double-blind study, followed by the subsequent 6-month open-label extension study.

Methods: Patients with an acute exacerbation of schizophrenia were randomized, double-blind, to 4 weeks of flexible-dose treatment with SEP-363856 (50 or 75 mg; n=120) or placebo (n=125). Four-week study completers continued into an open-label extension study which involved 26 weeks of treatment with flexible doses (25/50/75 mg/d) of SEP-363856. Prespecified measures evaluating negative symptoms included the Brief Negative Symptom Scale (BNSS) total and factor scores (blunted affect, alogia, avolition, anhedonia, asociality, distress), PANSS negative subscale score, Marder PANSS negative symptom factor, and the Uncorrelated PANSS Score Matrix (UPSM) transformation of the PANSS scale comprising UPSM-PANSS negative-apathy/avolition (UPSM-NAA) and negative-deficit of expression (UPSM-NDE) factors.

Results: In the initial 4-week double-blind study, treatment with SEP-363856 (vs. placebo) showed significant week 4 improvement in negative symptoms as assessed by the BNSS total score (effect size [ES], 0.48), and BNSS subscale scores for blunted affect (ES, 0.51), avolition

(ES, 0.42), anhedonia (ES, 0.39), asociality (ES, 0.47), alogia (ES, 0.32), and distress (ES, 0.13); as well as on the Marder PANSS negative symptom factor (ES, 0.46), and the UPSM-NDE (ES, 0.32) and UPSM-NAA (ES, 0.32) factors. In the open-label extension study, treatment with SEP-363856 was associated with additional mean improvement, from open-label baseline to Week 26 (observed/LOCF), on the BNSS total score (-11.3/-8.0); the PANSS negative subscale score (-5.2/-3.5); the Marder PANSS negative symptom factor (-5.3/-3.5); and the UPSM-NDE (-0.5/-0.3) and UPSM-NAA (-0.4/-0.3) factors.

Discussion: Short-term treatment with SEP-363856 was associated with significant and robust improvement relative to placebo in negative symptoms of schizophrenia as assessed by multiple measures. Continued improvement in negative symptoms was observed during 26 weeks of additional open-label treatment with SEP-363856. These results suggest that agonism at the TAAR1 receptor by SEP-363856 can treat both positive and negative symptoms in schizophrenia without incurring adverse effects on movement, prolactin, weight, and metabolic parameters associated with first- and second-generation antipsychotic drugs. These findings will need to be confirmed in future controlled studies.

T53. FUNCTIONAL CHARACTERISTICS AND LENGTH OF STAY OF WORKING-AGE NURSING HOME RESIDENTS WITH SCHIZOPHRENIA: A LATENT CLASS ANALYSIS

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Abstract: Introduction: There are concerns that working-age adults (22-64 years old) with schizophrenia are being inappropriately placed in nursing homes (NHs), which typically focus on care needs of older adults with chronic medical conditions requiring assistance with activities of daily (ADLs). It is unknown how functional characteristics vary for working-age residents with schizophrenia and how such characteristics influence their NH stays. This study aimed to (1) identify distinct patterns of functioning among these residents, (2) estimate the association between residents' characteristics and these patterns, and (3) examine how these patterns are associated with NH length of stay (LOS).

Methods: We used data from the national Minimum Data Set (MDS) 3.0 to identify working-age adults with schizophrenia who were admitted to a U.S. NH from 2011-2016. MDS 3.0 is a federally required health assessment of residents of all Medicare-/Medicaid-certified NHs. Latent class analysis (LCA) models were built to identify classes representing patterns of hallucinations, delusions, cognitive impairment, and dependency in ADLs at admission. ADL items included bed mobility, transfer from surfaces, walking in room and in corridor, locomotion on and off unit, dressing, eating, toilet use, personal hygiene, and bathing. After the best-fitting LCA model was identified, we examined the associations between: 1) sociodemographic and clinical covariates and the latent classes and 2) the classes and LOS (short: ≤100 days; long >100 day), adjusting for these covariates.

Results: From 2011-2016, 105,271 working-age adults with schizophrenia were admitted to a NH. The majority were men (55.9%), ages 56-64 years (52.1%), and never married (66.6%).

Psychiatric (61.8%) and medical (58.2%) comorbidities were common as was receipt of antipsychotics (88.5%). Four latent classes were identified, distinguished by number of ADL dependencies: Independent (11.4% of residents), Few Dependencies (12.4%), Almost All Dependencies (10.7%), and All Dependencies (65.6%). Having a psychiatric comorbidity was associated with greater odds of being in the Few (adjusted odds ratio (aOR): 1.32, 95% confidence interval (CI): 1.25-1.40), Almost All (aOR: 2.11, 95% CI: 2.00-2.33), and All Dependencies (aOR: 2.63; 95% CI: 2.18-2.37) classes, relative to the Independent class. Antipsychotic receipt was associated with decreased odds of belonging to the Almost All (aOR: 0.58; 95% CI: 0.54-0.63) and All Dependencies classes (aOR: 0.64; 95% CI: 0.60-0.68), compared to the Independent class. Those in the Almost All (aOR: 0.64; 95% CI: 0.61-0.67) and All Dependencies (aOR: 0.56; 95% CI: 0.56-0.60) classes were less likely than those in the Independent class to become a long-stay resident.

Conclusions: Working-age NH residents with schizophrenia can be categorized into four latent classes varying in ADL dependencies. Although receipt of antipsychotics was associated with lower odds of belonging to greater ADL dependency classes, it remains unclear how to successfully manage schizophrenia to prevent NH stays and loss of independence.

T54. ANALYSIS OF TREATMENT GOALS FOR PATIENTS WITH SCHIZOPHRENIA: A US SURVEY OF PSYCHIATRISTS, PATIENTS WITH SCZ AND CAREGIVERS

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Abstract: Objectives: Objectives for this survey are to determine similarities or differences in treatment goals reported by psychiatrists, patients with schizophrenia (SCZ) and caregivers in the US, as well as whether goals differed by patients currently on an oral antipsychotic (OAP) or long-acting injectable (LAI), and whether goals differed by age.

Methods: This was a real-world, cross-sectional survey of US psychiatrists, patients ≥18 years old diagnosed with SCZ, and caregivers. Data was collected using the Disease Specific Programme (DSP) methodology. Psychiatrists (n=120) completed detailed record forms for next 8 outpatients and 2 inpatients matching inclusion criteria. The same patients and their caregivers, if present, were invited by their psychiatrist to voluntarily complete a separate survey.

Results: Responses on treatment goals were collected from psychiatrists for all patients included in the analysis (n=1161), patients (n=542) and caregivers (n=130). Among 3 top goals, psychiatrists, patients and caregivers concurred that "decrease in disease symptoms" is most important (63%, 64%, 68% respectively). For psychiatrists and caregivers, second was "decrease in hospitalization for relapse" (41%, and 38% respectively), whereas for patients, it was "thinking clearly" (47%). Of the 3 least important goals, psychiatrists, patients and caregivers agreed with "sexual problems" (59%, 43%, 44%, respectively) and "weight gain" (38%, 44%, 38%, respectively). When asked which goals were met by current medication, patients responded "decrease in disease symptoms" (68%) and "thinking clearly" (39%). However, caregivers responded "thinking clearly" (30%) was not met by current medication.

Caregivers most important goals, “decrease in disease symptom” (70%) and “decrease in hospitalization for relapse” (41%), were met. Additional analyses of patients on OAPs and LAIs, did not show differences in goals. However, “decrease in disease symptoms” was numerically more important for patients on LAIs vs OAPs according to psychiatrists (68% vs 62%) and caregivers (77% vs 70% respectively). Caregivers responded “decrease in hospitalization for relapse” was met for 63% patients currently on an LAI and 35% OAP. No major differences in treatment goals were observed by patient age (18-35 vs 36-65 vs >65 years).

Discussion: There is consensus among US psychiatrists, patients and caregivers on the most important treatment goal “decrease in disease symptoms”, regardless of patients’ current medication or age. For patients, “thinking more clearly” was second, compared with “decrease in hospitalization due to relapse”, for psychiatrists and caregivers. All agreed that least important treatment goals, related to AEs, were “weight gain” and “sexual problems”. More caregivers agreed “decrease in hospitalization for relapse” was met by patients on LAIs vs OAPs. These findings may help with discussions between psychiatrists, patients and caregivers.

T55. USE OF VITAMIN C, VITAMIN D, ZINC, AND MELATONIN AS SYNERGISTIC ADJUVANT THERAPY IN PATIENTS WITH COVID-19 INFECTION AT A PSYCHIATRIC HOSPITAL: A RETROSPECTIVE STUDY

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Abstract: Purpose: Recent studies have shown that patients with vitamin D deficiency are at increased risk for COVID-19 infection. Both vitamin C and Zinc are essential for immune-cell function and have been used experimentally with some success in patients with COVID-19 infection. Although melatonin is commonly used for insomnia, studies have shown that it can be used as adjuvant therapy for COVID-19 due to its anti-inflammatory effect. The objective of this study is to examine whether this supplemental “cocktail” is associated with decreased duration of illness of COVID-19 infection in patients with comorbid psychiatric disorders.

Method: This retrospective cohort study at a state psychiatric hospital included patients 18 years or older who were found positive for SARS-COV-2 by use of a real-time RT-PCR test approved by the FDA for EUA after routine nasopharyngeal swab done for all patients at the institution. Data was obtained for all patients tested for COVID-19 from April 1st to September 15th, 2020. De-identified EHR data for demographic, psychiatric and medical comorbidity, laboratory values, and medication data within 2 months before the date of their first COVID-19 positive result and 1 month after the date of their second COVID-19 negative result were recorded. Of the 81 patients in three separate psychiatric units tested positive for COVID-19, patients in one unit received the cocktail of vitamin C 500mg twice daily, vitamin D3 5,000 Units daily, Zinc chelated 50mg twice daily, and melatonin 3mg daily and patients in the other two units may receive one component of the cocktails due to different psychiatrists’ decisions on the most effective way to treat COVID-19 infection. The primary endpoint was the average duration of COVID-19 illness in patients receiving the supplemental cocktail compared to the patients who did not. The secondary outcome was the average change in Brief Psychiatric

Rating Score 1-month post recovery in the two groups. The data will be analyzed using Survival Analysis (Time-to event analysis) statistics.

Results: Results is pending and will be presented at the annual meeting.

T56. EFFECTS OF ACUTE ADMINISTRATION OF VMAT2 INHIBITORS ON EXTRACELLULAR LEVELS OF DOPAMINE, NOREPINEPHRINE, 5-HT AND HISTAMINE IN THE STRIATUM AND MEDIAL PREFRONTAL CORTEX: A DUAL-PROBE MICRODIALYSIS STUDY IN AWAKE RATS

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Abstract: Introduction: Austedo (deutetrabenazine) is a selective deuterium-substituted vesicular monoamine transporter -2 (VMAT2) inhibitor, with a similar structure to tetrabenazine. Austedo has been approved for the treatment of chorea in Huntington's disease and tardive dyskinesia in adults. VMAT2 is located within and spanning the membranes of synaptic vesicles in monoaminergic neurons. By inhibiting VMAT2, the uptake of monoamines (dopamine DA; serotonin, 5-HT; norepinephrine, NE and histamine) into the synaptic vesicles is attenuated, which results in decreased monoaminergic neurotransmission and enhanced metabolism. The aim of the present study was to evaluate the effects of reversible VMAT2 inhibitors on extracellular levels of monoamines and their acidic metabolites in rat striatum and medial prefrontal cortex (mPFC).

Methods: Dual-probe in vivo microdialysis and simultaneous blood sampling experiments were carried out in awake rats (n = 7) following a single administration of 5 mg/kg p.o. of each VMAT2 inhibitor (deutetrabenazine, tetrabenazine and valbenazine). The extracellular levels of monoamines and their acidic metabolites DOPAC, HVA and 5-HIAA were quantified by ultra high performance liquid chromatography tandem mass spectrometry (UHPLC-MS/MS) following derivatization with benzoyl chloride. The stereoisomeric pairs of active metabolites of administered parent drugs were separated by chiral column LC-MS/MS and measured both in the brain microdialysates (7 samples for 7 animals per group) and in plasma samples (7 samples for 7 animals per group).

Results: The major finding of the present study is that a single administration of deutetrabenazine, tetrabenazine or valbenazine, each at a dose of 5 mg/kg p.o. in awake rats caused long-lasting decreases (up to 6 h) in levels of DA and 5-HT (but not NE) in the striatum and DA and NE (but not 5-HT) in the mPFC. Specifically, depletion was most profound for DA in the striatum and NE in the mPFC. The time of maximal DA depletion was in correlation with the time of maximal brain concentrations of the active metabolites. On the other hand, the levels of acidic metabolites DOPAC, HVA and, to a lesser extent, 5-HIAA increased in both brain structures indicating an increase in the monoamine turnover. Finally, the VMAT2 inhibitors did not deplete histamine levels.

Conclusions: The results of the present study confirmed the effects of deutetrabenazine on monoamine depletion and metabolism in vivo. Additionally, our results indicate that all VMAT2 inhibitors tested showed a similar depletion profile in both the striatum and the mPFC.

T57. TRANSITION TO INPATIENT TELEPSYCHIATRY SERVICES AND IMPACT ON QUALITY OF CARE

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Abstract: Demands for telepsychiatry have increased due to the challenges of COVID-19. The global pandemic caused a significant increase in anxiety, depression and maladaptive eating disorders while the implementation of social distancing both exacerbated these mental health issues and disrupted in-person delivery of mental health services. Rapid adaptation of telepsychiatry in the acute inpatient setting has been reported with favorable outcome of patient experience. Here we reported our experience of a telepsychiatry transition on an acute eating disorder unit and the impact on quality of care. Out of 1,288 telepsychiatry encounters completed since the transition, over 230 surveys were completed by patients at an inpatient eating disorders unit to evaluate patient satisfaction. Simultaneously, physician surveys were distributed to identify technical and connectivity issues. Our experience showed that patients were very satisfied with the telepsychiatry on an eating disorder unit with an average length of stay of 21.95 days, with few technical or safety issues.

T58. THE IMPACT OF THE COVID-19 PANDEMIC ON PSYCHIATRIC SYMPTOMS IN HEALTH CARE WORKERS AND FIRST RESPONDERS OVER TIME: IMPLICATIONS FOR WELLBEING, WORKPLACE FUNCTIONING AND RETENTION, AND THE RELATIONSHIP OF ACUTE STRESS DISORDER TO PTSD

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Abstract: Elevated rates of psychiatric symptoms in health care workers working during the Covid-19 pandemic have been identified in multiple contexts. Less is known about what aspects of Covid-19 related occupational stressors are generating these psychiatric symptoms; the impacts on workplace functional impairment or retention or suicidality; and about first responders. Here, we report results from an ongoing longitudinal study of health care workers and first responders working during the Covid-19 pandemic (current N=456). Among all respondents, a majority report psychiatric symptoms in the clinical range (37% for PTSD, 74% for depression, 75% for anxiety, 34% for insomnia). Symptom burden is strongly associated with intensity of exposure to covid-19 related occupational stressors (Pearson's R=.54, p<2.2e-16 for PTSD; R=.44, p=4.2e-15 for depression; R=.43, p=1.1e-14 for anxiety; R=.40, p=1e-15 for insomnia). 53% of health care workers and 39% of first responders report that their likelihood of remaining in their current field has been somewhat or significantly decreased by their experiences working during the pandemic. 22% of health care workers and 14% of first responders report trouble completing work-related tasks, while 12% of health care workers and 19% of first responders reported thoughts of being better off dead or of hurting themselves in the past 2 weeks; ratings in both areas were significantly related to intensity of exposure to covid-19 related stressors (Spearman's R=.27 p=2.8e-7 and R=.21, p=.0004, respectively). A factor analysis of our 13-item rating scale of exposure to Covid-19 related occupational

stressors identified 3 factors, which weighted items assessing (1) total volume of covid-19 related care delivered ("volume" factor), (2) being asked to take unnecessary risks or being unsupported by one's workplace, or care delivered being futile or inadequate ("demoralization" factor) and (3) perceived risk of one's self or family contracting Covid-19 ("risk" factor). The demoralization factor was the most strongly related to all symptom clusters and functional outcome measures, followed by the volume factor. Hyperarousal and intrusive symptom clusters at the time of baseline assessment were the strongest predictors of elevated PTSD symptoms 2-3 months later.

T59. THE NATIONAL PREGNANCY REGISTRY FOR PSYCHIATRIC MEDICATIONS: EFFECTS OF FETAL EXPOSURE TO ATYPICAL ANTIPSYCHOTICS ON RISK FOR MAJOR MALFORMATIONS

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Abstract: Background: The National Pregnancy Registry for Psychiatric Medications (NPRPM) is used to systematically collect prospective pharmacovigilance data in order to inform the care of reproductive age women with psychiatric disorders.

Methods: Prospective data are collected from pregnant women, ages 18-45 years, with three phone interviews conducted at time of enrollment, 7 months gestation, and 3 months postpartum. The exposed groups are composed of women who have taken an atypical antipsychotic during the first trimester of pregnancy, with subgroups of women who have taken specific atypical antipsychotics of interest in these analyses, while the comparison group consists of women with psychiatric disorders who have not taken atypical antipsychotics during pregnancy. Data regarding the presence of neonatal major malformations identified in the first 6 months of life are abstracted from medical records. Identified cases of major malformations are adjudicated by an expert dysmorphologist blinded to drug exposure and psychiatric diagnoses.

Results: As of April 9th, 2020, 1906 women had enrolled (n=889 exposures, n= 1017 controls). Medical records were obtained for 81.2% of participants. N=1363 women were eligible for inclusion in the analysis. There were 620 live births in the group exposed to atypical antipsychotics, and 16 confirmed major malformations were identified. Of 691 live births in the control group, 14 major malformations were reported. No consistent pattern of malformations was noted in any group. The absolute risk of neonatal major malformations was 2.58% in the exposed group and 2.03% in the comparison group, and the relative risk (RR) comparing exposures to controls was 1.48 (95% CI: 0.63-3.52). In assessing specific medications, the following rates of major malformations were observed: aripiprazole (n=7 malformations/167; RR=2.10; 95% CI=0.82-5.21), lurasidone (n=3/125; RR=1.18; 95% CI=0.34-4.18), and quetiapine (3/247; RR=0.60; 95% CI=0.17-2.10). Out of 47 pregnancies with exposure to olanzapine, there were no major malformations.

Conclusion: The NPRPM utilizes a systematic approach for the collection of prospective reproductive safety information to inform the care of women using psychiatric medications during pregnancy. Greater numbers of participants are needed to refine the risk estimates associated with exposure to individual atypical antipsychotics . CDC national data report a major malformation prevalence of 3% among all live births in the United States. In these analyses, the absolute risk of major malformations was similar (2.58%) in the exposed group and lower (2.03%) in the unexposed group. These new estimates are consistent with earlier preliminary results from the NPRPM indicating that atypical antipsychotics as a group and select individual atypicals do not present major teratogens.

T60. ZYN002 CANNABIDIOL (CBD) TRANSDERMAL GEL: EFFICACY AND SAFETY FINDINGS IN CHILDREN AND ADOLESCENTS WITH AUTISM SPECTRUM DISORDER (ASD) AND RELATED DISORDERS

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Abstract: Objective: ZYN002 is a pharmaceutically manufactured transdermal CBD gel in development for ASD, Fragile X syndrome (FXS), and Developmental Epileptic Encephalopathies (DEE). ASD may be comorbid with FXS and DEE. Select efficacy assessments and safety of ZYN002 in patients aged 3-17 years are presented from two open-label studies [BRIGHT (ASD) and BELIEVE (DEE)] and a double-blind, placebo-controlled study [CONNECT-FX (FXS)].

Methods: BRIGHT and CONNECT-FX assessed behavioral symptoms (i.e., irritability) of ASD and FXS. Patients received ZYN002 250 or 500 mg/day for up to 14 weeks added to standard of care. BELIEVE assessed seizure frequency and other measures including impact on sleep using the caregiver-rated Sleep Disturbance Scale for Children (SDSC). Patients received ZYN002 titrated up to 750 or 1000 mg/day for up to 72 weeks (data presented through Week 26). Safety assessments included adverse events (AEs), laboratory tests, skin assessments and electrocardiograms (ECGs).

Results: BRIGHT: 37 patients with ASD, mean age 9.2 years, 94% had moderate/severe symptoms of ASD and a mean baseline Aberrant Behavior Checklist-Community (ABC-C) Irritability score of 30.3. Significant improvement from baseline was observed for each ABC-C subscale. Patients also experienced mean improvements of 46% in Parent-Rated Anxiety Scale-ASD score ($p<0.0001$) and 39% in Autism Parenting Stress Index ($p<0.0001$) and significant improvements in all domains of the Autism Impact Measure; 57% were "very much/much improved" on CGI-Improvement. CONNECT-FX: 212 patients with FXS were randomized, mean age 9.7 years, 180 (85%) had symptoms of ASD. Improvements in the primary endpoint, ABC-CFXS Social Avoidance, was not significant in the full population. A pre-specified, ad hoc analyses was conducted in patients with ≥90% FMR1 methylation (n=169; 80%) of whom 146 (86%) had symptoms of ASD. A significant improvement in ABC-CFXS Social Avoidance ($p=0.020$) occurred in these patients and significantly more patients had a clinically meaningful change in Social Avoidance ($p =0.031$) and Irritability ($p =0.036$). Believe: 48 patients with DEE, mean age 10.5 years; 14 had comorbid ASD diagnosed by investigators. Over the first 6 months of treatment, median reduction from baseline in monthly

frequency of focal impaired awareness seizures and tonic-clonic seizures ranged from 45% at Month 3 to 59% at Month 6 in patients with ASD, which was similar to all patients. Nine of 14 patients had clinically significant sleep disturbance at baseline, defined as a SDSC Total score ≥52 (t-score >70). In this cohort, significant improvements in mean t-scores from baseline were reported for Sleep Breathing Disorders (p=0.018) and Sleep Wake Transition Disorders (p=0.006) and Total score (p=0.024) at week 26. ZYN002 was well tolerated. BRIGHT and CONNECT-FX: AEs were mild to moderate in severity and no serious or severe events occurred. No other clinically relevant abnormalities occurred, including changes in liver function. BELIEVE- In DEE patients with ASD, most AEs were mild or moderate. In this medically complex population, 5 serious AEs were reported in 3 patients, none were considered drug related. There were no clinically significant changes in vital signs, ECGs, or labs.

Conclusion: ZYN002 demonstrated a positive benefit-risk profile across a spectrum of endpoints including behavior, seizure reduction and sleep, when added to standard of care in children and adolescents with ASD and related disorders. Further studies are warranted to confirm these finding in ASD.

T61. POPULATION PHARMACOKINETIC MODELING AND SIMULATION TO GUIDE DOSE SELECTION FOR TV-46000, A NEW LONG ACTING FORMULATION OF RISPERIDONE FOR SUBCUTANEOUS INJECTION

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Abstract: Introduction: Patient adherence is a major challenge and an important factor for treatment success and relapse prevention of patients with schizophrenia. TV-46000 is a risperidone extended-release suspension for subcutaneous (sc) injection allowing multiple dose-exposure levels and flexible dosing regimens over an extended period of time. The objective was to determine potentially clinically effective dosing regimens of TV-46000 based on population PK (popPK) modeling and simulations of data obtained in a Phase 1 study in patients, to support further clinical development. To this end, a popPK model for the Total Active Moiety (TAM) comprised of risperidone + 9-OH risperidone (equipotent metabolite) concentrations, was developed to describe the population exposure following TV-46000 sc administration. Simulations of the TAM plasma levels for a range of TV-46000 doses and dose intervals were compared to published data of oral risperidone. Using published data, the dopamine D2 receptor occupancy (D2RO) values were derived from the simulated TAM plasma concentrations. PopPK modeling and simulations were then utilized to identify dosing regimens of TV-46000 that would provide 60-80% D2RO, considered as the therapeutic window for optimal antipsychotic effect with minimal side effects (Eerdekens M, et al. Schizophrenia Research 2004;70:91-100).

Methods: The popPK model was generated by applying pharmacokinetic data from the phase 1 study in patients (n = 97) with a diagnosis of schizophrenia or schizoaffective disorder who received single doses of TV-46000 (between 50-225mg) or three consecutive monthly doses of 75mg and 150mg. TV-46000 pharmacokinetic profile was found to be best described by a double Weibull function of the in-vivo release rate and by a two-compartment disposition and

elimination model. Simulations were performed to determine TV-46000 dose levels and intervals that maintained median TAM concentrations within the 60-80% D2RO over the dosing interval.

Results: The popPK model-based simulations indicated that TV-46000 is expected to successfully deliver therapeutic levels of the TAM over dosing intervals of one month (q1m) or two months (q2m). Four dose strengths of TV-46000 were identified for each dosing interval to deliver the required D2RO: 50mg, 75mg, 100mg and 125mg for the q1m dosing regimens, and 100mg, 150mg, 200mg and 250mg for the q2m dosing regimens.

Conclusion: PopPK modeling and simulations identified TV-46000 dosing regimens that would provide therapeutic exposure levels of TAM to treat patients with schizophrenia. These dosing regimens will be further assessed for safety and efficacy in a phase 3 program. The flexibility of the q1m and q2m sc dosing regimens has the potential to significantly improve patient compliance and acceptance of risperidone treatment, both of which are essential for the treatment of schizophrenia.

T62. SEP-363856: A COMPOUND WITH A NON-D2 RECEPTOR MECHANISM OF ACTION FOR THE TREATMENT OF SCHIZOPHRENIA: UPDATE

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Abstract: SEP-363856, the first of a new class of CNS-active compounds, is a full agonist at trace amine-associated receptor 1 (TAAR1) and 5-HT1A receptors. SEP-363856 does not act on dopamine D2 or 5-HT2A receptors which are known to mediate the effects of currently approved first- and second-generation antipsychotics. SEP-363856 has been shown to reduce ketamine-induced increases in striatal dopamine synthesis capacity in mice, suggesting it can provide inhibitory modulation of the presynaptic dopamine dysfunction observed in patients with schizophrenia. Consistent with its mixed TAAR1/5-HT1A pharmacology, SEP-363856 has demonstrated antipsychotic-like activity in preclinical models of schizophrenia, including prepulse inhibition, and cocaine- and PCP-induced hyperactivity models. In a 4-week, double-blind, placebo-controlled study, SEP-363856 demonstrated significant efficacy in the short-term treatment of adults with an acute exacerbation of schizophrenia. The incidence of adverse events (AEs) was generally similar in the SEP-363856 and placebo groups, with a difference of 2.5% or less for each event. Groups were also similar with respect to the percentage of patients who reported extrapyramidal symptoms (3.3% vs. 3.2%) and findings on movement disorder scales. In addition, minimal effects on prolactin and other metabolic values were observed. These findings are consistent with the absence of D2-receptor binding for SEP-363856. These results were maintained in a subsequent open-label extension study (26 weeks) with continued improvement in various efficacy measures. Phase 3 studies are ongoing to confirm these results. Here, we provide an update on clinical research that further demonstrates the therapeutic characteristics of this compound.

Pharmacokinetic (PK) analyses across multiple Phase 1 and Phase 2 studies showed that SEP-363856 was well-absorbed and exhibited dose-proportionality in doses ranging from 10-100 mg. Moderate inter-individual variability was observed in concentration-time profiles. The estimated median time to maximal concentration (Tmax) was 2.8 hours and the median effective half-life was 7 hours, corresponding to an exposure accumulation ratio of 1.10 at

steady-state with daily dosing. No clinically meaningful effects on SEP-363856 PK parameters were observed based on race, age, sex, or clinical status (healthy volunteer vs. patient with schizophrenia); body weight was the only meaningful covariate.

In secondary analyses of the completed Phase 2 studies SEP-363856 demonstrated significant and robust improvement relative to placebo in negative symptoms of schizophrenia as assessed by multiple measures, and continued improvement during 6-months of extension phase treatment. Notably, improvement in negative symptoms on SEP-363856 was observed in the Uncorrelated PANSS Matrix (UPSM) negative symptom factors, a measure of negative symptoms that has been shown to have minimal correlation with improvement in traditional PANSS subscales.

Lastly, we summarize the results of a disproportionality analysis used to identify and rank-order AE preferred terms associated with the 11 most recently approved antipsychotics from the FDA Real-world Adverse Event Reporting (FAERS) database. We used the results of this analysis to evaluate the frequency and cumulative percentages of drug-associated AE signals in the currently available safety database of SEP-363856. SEP-363856 demonstrated markedly lower cumulative risk for antipsychotic class-related AEs in comparison with other atypical antipsychotic, providing confirmation of the non-D2 safety profile of the drug.

T63. ASSOCIATION BETWEEN PSYCHIATRIC DIAGNOSES, SUBSTANCE USE DISORDERS, AND COVID-19 OUTCOMES: A RETROSPECTIVE COHORT STUDY

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Abstract: Introduction: There is increasing evidence that COVID-19 risk and mortality are associated with psychiatric comorbidities. While studies have examined the relationship between psychiatric diagnosis and COVID-19 mortality (Nemani et al. 2021; Wang et al. 2021), the association between substance use disorder and COVID-19 outcomes has not been systematically examined.

Methods: In this retrospective cohort study of 6,291 COVID-19 patients seen at the Yale New Haven Health (YNHH) hospital system from January 1 to December 31, 2020, we examined the association of major psychiatric disorders (anxiety disorders, mood disorders, and schizophrenia/non-affective psychotic disorders) and substance use disorders (SUD) (alcohol use disorder, opioid use disorder, benzodiazepine use disorder, cannabis use disorder, cocaine use disorder, PCP use disorder) with COVID-19 outcomes. Data was analyzed using multivariable logistic regression in SAS. All analyses controlled for smoking status, age, sex, race and medical comorbidity (Charlson Comorbidity Index).

Results: Among patients with COVID-19, those with major psychiatric disorders had longer duration of hospitalization ($P < 0.001$). This was driven by patients with schizophrenia/non-affective psychotic disorder, anxiety disorder, and mood disorder. Similarly, patients with SUD were found to be more likely to need ventilatory support (OR = 1.49 [1.09-2.03], P =

0.01). Post-hoc analysis revealed that this was driven by significantly greater risk among those with opioid use disorder and alcohol use disorder. Patients with SUD also had longer duration of hospitalization ($P < 0.001$). This was driven by patients with opioid use disorder and alcohol use disorder. There was no significant association between either major psychiatric diagnosis or SUD with total length of ICU stay.

Conclusion: Our analysis shows that both psychiatric disorders and SUD were significantly associated with longer duration of hospitalization for COVID-19 patients, even after adjusting for medical comorbidity. SUD was significantly associated with increased likelihood of needing ventilatory support. Schizophrenia/non-affective psychotic disorders, mood disorders, and opioid use disorder were consistently associated with worse outcomes. These results indicate a need for early identification of psychiatric and substance use comorbidities in COVID-19 patients in order to optimize their treatment.