

# **NNDC 2022 ANNUAL CONFERENCE POSTER LIST**

#	First Name	Last Name	Institution	Poster Title
1	Sai Sruthi	Amirtha Ganesh	Penn State Milton S. Hershey Medical Center	The Relationship between Biological Rhythms and Mitochondrial Dysfunction in Bipolar I Disorder
2	Sarah	Andrews	University of Florida	Predictors of Early Dropout from Residential Substance Use Treatment: Evaluating Relationships with Depression, Pain and Age
3	Emily	Beydler	University of Florida	Legislative Barriers to Electroconvulsive Therapy
4	Abigail	Biehl	University of Michigan	Evaluating Uptake e-Mental Health Tools in a Primary Care Collaborative Care Program
5	Scott	Breitingner	Mayo Clinic	Implementation of a Digital Tool for Monitoring Depressive Symptoms: A Case Series
6	Mason	Breitzig	Penn State Milton S. Hershey Medical Center	A metric of pharmacotherapy guideline concordance and its association with major depressive disorder symptom severity and patient functioning.
7	Claire	Cohen	Penn State Milton S. Hershey Medical Center	Zebrafish as a Model for Studying Embryonic Development and Behavior in Bipolar Disorder
8	Samuel	Cooper	University of Texas at Austin	Latent Depression and Anxiety Symptom Dimensions Predict Biased Acquisition and Extinction Learning in a Web-Based Causal Learning Task
9	Zachary	Cordner	Johns Hopkins University	Psilocybin reverses stress-induced depression and anxiety-like behaviors and also promotes stress resilience in a wild type mouse model by mechanisms that are independent of 5HT2A and 5HT2C receptors
10	Chesika	Crump	University of Louisville	Pimavanserin for Bipolar Disorder
11	Joshua	Cunningham	Michigan State University & Pine Rest Christian Mental Health Services	Psychiatric Electroceutical Interventions (PEIs) and Clinical Treatment Guidelines: Results from a National Survey of Board-Certified Psychiatrists
12	Radha	Dhingra	Penn State Milton S. Hershey Medical Center	Cardiovascular Disease Burden is Associated with Worsening Depression Trajectory
13	Omar	Elsayed	University of Louisville	Use of KIOS Smartphone App for Bipolar Patients in a General Medical Clinic
14	Mete	Ercis	Mayo Clinic	Assessment Tools Used in Bipolar and Related Disorders Research: A Systematic Review of Studies from Turkey
15	David	Farris	Michigan State University & Pine Rest Christian Mental Health Services	Lumateperone as a treatment for bipolar depression: a scoping review
16	Brian	Farstead	University of Utah	SafeUT: Short-Term Effectiveness of Mobile Crisis App Utilization in Adolescents
17	Gabriel	Fries	University of Texas Health Science Center at Houston	Epigenetic GrimAge Acceleration and History of Suicide Attempt in Bipolar Disorder
18	Mark	Frye	Mayo Clinic	Public Health Emergency-related Access to Telemedicine: A Bridge To Rural Mental Health?
19	Manuel	Fuentes Salgado	Mayo Clinic	Race Mediates Healthcare Utilization During the Period Before the First Episode Mania and Schizophrenia
20	Manuel	Gardea Resendez	Mayo Clinic	Antidepressants that Increase Mitochondrial Energetics Elevate Risk of Treatment-Emergent Mania
21	Jody	Greaney	The University of Texas at Arlington	Negative Affective Responsivity to Daily Stress is Exaggerated in College-Aged Adults with Depression
22	Christopher	Hammond	Johns Hopkins University	Similarities and differences in cannabis and cannabidiol related attitudes and behaviors between adolescents receiving mood disorder treatment in the US and their parents
23	Ethan	Holland	University of Florida	Maintenance ECT Considerations in a Post Covid-Induced Catatonia
24	Duncan	Honeycutt	University of Cincinnati & Lindner Center of HOPE	Do pharmacogenetics factors influence escitalopram-induced adverse events or treatment failure in youth at high-risk for bipolar disorder?
25	Rebekah	Huber	University of Utah	Cortical Thickness in the Right Anterior Cingulate Cortex and Non-Suicidal Self-Injury in Youth with Mood Disorders
26	Mbemba	Jabbi	University of Texas at Austin	Insula-cingulate brain network transcriptomes for lifetime mood disorders and longevity

# **NNDC 2022 ANNUAL CONFERENCE POSTER LIST**

#	First Name	Last Name	Institution	Poster Title
27	Dora	Juhasz	Michigan State University & Pine Rest Christian Mental Health Services	The Influences of COVID-19 as a Risk Factor for Admissions to An Inpatient Geriatric Psychiatry Unit
28	Lauren	Katzell	University of Florida	Electroconvulsive Therapy Treatment Trial in Super Refractory Status Epilepticus: A Case Study
29	Amanda	Keeler	Penn State Milton S. Hershey Medical Center	Can an online mental-contrasting and implementation-intentions intervention increase help seeking initiation for individuals with depression?
30	Rakesh	Kumar	Mayo Clinic	Association Between Thyroid Stimulating Hormone And Depression: A Historical Cohort Study
31	Sophie	Lazarus	The Ohio State University	Ohio State University Comprehensive Psychotherapy Pathway for Depression: Implementation of a stepped-care model guided by patient-reported outcomes in an academic medical center
32	Steven	Levine	Compass Pathways, Inc	COMP360 Psilocybin Therapy in Treatment-Resistant Depression: Results of a Large Randomized Controlled Phase IIb Monotherapy Study and an Exploratory Uncontrolled Adjunctive Therapy Study
33	Tenzin	Lhaksampa	Johns Hopkins University	The Use of Electronic Communication-based Automated Language Technologies to Augment Traditional Mental Health Care
34	Kevin	Li	Johns Hopkins University	Racial Differences in the Major Clinical Symptom Domains of Bipolar Disorder
35	Zehan	Li	University of Texas Health Science Center at Houston	No Association between Neutrophil-to-Lymphocyte Ratio and Suicidality: A study from large sample size
36	Brian	Mickey	University of Utah	Treatment-Resistant Mood Disorders Among LGBTQ People: Clinical Features and Response to ECT
37	James	Moley	The Ohio State University	Treating Attention and Mood Disorders in Collegiate Athletes: Developing a Best Practices Framework for Sports Psychiatrists
38	Débora	Moreira	University of Texas Health Science Center at Houston	Efficacy and adverse effects of ketamine versus electroconvulsive therapy for major depressive disorder: a systematic review and meta-analysis
39	Alyssa	Nielsen	University of Florida	Comorbid Conditions and Caution: A Case of Phentermine-Induced Mania with Psychotic Features
40	Zachary	Nitsch	Penn State Milton S. Hershey Medical Center	Delineating Anhedonia from Depressed Mood and Apathy: The Relationship Between Anhedonia, Cognition, Activity, and Social Support
41	Lauren	Oberlin	Weill Cornell Medical College	Functional and Structural Network Features of Apathy in Late-life Depression and Associations with Response to Escitalopram Treatment
42	Carolina	Olmos	University of Texas Health Science Center at Houston	Is there an impact of race on lifetime medication history of patients with bipolar disorder?
43	Alexander	Osborn	Cincinnati Children's Hospital Medical Center	Using Natural Language Processing and Machine Learning to Predict School Violence
44	Mehak	Pahwa	University of Louisville	KIOS: A Smart Phone App for Self-Monitoring for Patients with Bipolar Disorder
45	Sagar	Parikh	University of Michigan	Depression Management in Psychiatry and Primary Care: The Impact of Online CME on Physician Knowledge, Competence, and Confidence Related to Pharmacogenetics
46	Michelle	Ptak	University of Michigan	Prevalence of Workplace Trauma and PTSD Symptoms Among Intern Physicians Training Before and During the COVID-19 Pandemic: A Repeated Annual Cohort Study
47	Boyu	Ren	McLean Hospital	Personalized characterization of the evolution of cognitive function in older adults with mood disorders
48	Perry	Renshaw	University of Utah	Housing rats at moderate altitude increases depressive symptoms, causes systemic inflammation and alters cognitive behavior
49	Salih	Selek	University of Texas Health Science Center at Houston	Surge protected portable Ear EEG for Electroconvulsive Therapy
50	Cortney	Sera	University of Michigan	Neurocognitive Effects of Intravenous Ketamine Treatment in Treatment Resistant Depression
51	Pravesh	Sharma	Mayo Clinic	Female Sex and Pre-COVID Depressive Symptoms Associated with COVID-19 Binge Drinking
52	Priyanka	Sheth	University of Louisville	Impact of the National Suicide Hotline Number on Care of Outpatient Psychiatric Patients

# **NNDC 2022 ANNUAL CONFERENCE POSTER LIST**

#	First Name	Last Name	Institution	Poster Title
53	Balwinder	Singh	Mayo Clinic	Comparative Effectiveness Of Intravenous Ketamine And Intranasal Esketamine In Clinical Practice Among Patients With Treatment-Refractory Depression: An Observational Study
54	Alyssa	Smith	Indiana University	Depression Treatment for Children and Adolescents: Promising Results from a Collaborative Care Program
55	Nathen	Spitz	University of Iowa	The temporal association and differential decrease of depression symptomatology between 10 Hz repetitive transcranial magnetic stimulation (rTMS) and intermittent theta burst stimulation (iTBS)
56	David	Steinberger	McLean Hospital	Examining Mental Health Links to Group-Based Multi-Trajectory Models of Stress Experience and Physiology in Current and Remitted Depression
57	Jason	Straub	Johns Hopkins University	NNDC Mood Outcomes program: Where we are and where we are going.
58	Laura	Suarez	Mayo Clinic	Characterizing Depression and Psychological Constructs Associated with Cardiovascular Disease: A Qualitative Analysis of the Literature from the Last Sixty Years
59	Elizabeth	Sullivan	The Nathan Kline Institute and NYU Langone	Empathic Concern and Personal Distress: Exploring the Intricacies of Self and Other Oriented Empathy in Depression
60	Perry	Tsai	University of Illinois at Chicago	Affective neural circuits and inflammatory markers linked to depression and anxiety symptoms in patients with comorbid obesity
61	Erica	Vest	University of Michigan	Clinical Outcomes in the Biomarkers of Ketamine (Bio-K) Study of Open-Label IV Ketamine for Refractory Depression
62	Ekaterina	Vlasova	University of Florida	A Case Study of Asymptomatic Hyperprolactinemia Secondary to Risperidone
63	Yuji	Wakimoto	University of Utah	Outcomes and Predictors of Response to Maintenance Ketamine in a Large Outpatient Cohort with Treatment-Resistant Depression
64	Alex	Walker	Johns Hopkins University	Feasibility of Smartphone App MindLAMP in Developing Digital Phenotypes in Depression
65	Krista	Wartchow	University of Texas Health Science Center at Houston	Higher Lactate and Pyruvate Levels and Lactate-to-Pyruvate Ratio Patients with Treatment Resistant Depression
66	Addie	Weaver	University of Michigan	Moms & Babies Feeling Better Together: Open Pilot Results of a Technology-Assisted, Entertaining Cognitive Behavioral Therapy Tailored for Rural WIC Clients with Perinatal Depression
67	Bennett	Wechsler	University of Massachusetts	Antecedent symptoms associated with onset of major depressive episode in pregnancy
68	Anastasia	Yocum	University of Michigan	The Heinz C. Prechter Bipolar Research Program: A Snapshot of Longitudinal Data
69	Gary	Zammit	Clinilabs Drug Development Corporation	A Randomized, Double-Blind, Placebo-Controlled Study of the Safety, Tolerability, and Efficacy of Zuranolone in Adults With Comorbid Major Depressive Disorder and Insomnia

# 1. The Relationship between Biological Rhythms and Mitochondrial Dysfunction in Bipolar I Disorder

Sai Sruthi Amirtha Ganesh<sup>1</sup>; Vinashya Venkatasubramani, M.Sc.<sup>2</sup>; Nuno Raimundo, PhD<sup>3</sup>; Robert Gonzalez, MD<sup>2</sup>; Suzanne Gonzalez, PhD<sup>2</sup>

## Institutions:

1. Bioinformatics and Genomics, Huck Institutes of the Life Sciences, Penn State University
2. Department of Cellular and Molecular Physiology, Penn State College of Medicine
3. Department of Psychiatry and Behavioral Health, Penn State College of Medicine

## Presenters:

underlined submitting presenter

**Background:** Bipolar disorder (BD) is a severe psychiatric disorder that ranks among the highest causes of functional impairment, disability, and death worldwide. Circadian rhythm disturbances are a fundamental characteristic of BD and meet the criteria for potential phenotypes in the illness. Emerging evidence suggests circadian control of mitochondrial rhythmicity in cellular respiration, with major implications on mitochondrial function. Our previous research demonstrated that individuals diagnosed with bipolar I disorder (BDI) could be meaningfully classified into homogeneous sub-groups according to circadian rhythm characteristics - a High Chronobiological Disturbance group (HCD) and a Low Chronobiological Disturbance group (LCD). We propose that there are fundamental cellular and molecular differences between HCD and LCD BDI groups that lead to differences in mitochondria functioning and dynamics.

**Methods:** Gene expression profiles of 98 mitochondrial-related genes were compared between HCD and LCD groups using a predesigned QIAseq Targeted RNA Panel Kit (Qiagen) via RNA-seq. The abundance of transcripts was quantified with respect to the reference transcriptome (hg38) using Bowtie2. The differential expression analysis was conducted using DESeq2 adjusting for sex, age, and ethnicity. Transcripts differentially expressed at  $p \leq 0.05$  were considered nominally significant and  $FDR \leq 0.05$  was considered statistically significant. Mitochondrial respiratory function and oxidative phosphorylation of lymphoblastoid cell lines (LCLs) were compared between HCD and LCD groups using the Seahorse XFp Cell Mito Stress Test Kit (Agilent) via the XFp Extracellular Flux analyzer (Seahorse Bioscience). Briefly, cells were seeded at  $4.4 \times 10^5$  cells per well and cultured overnight under standard conditions. Mitochondrial oxygen consumption rate (OCR) and extracellular acidification rate (ECAR) were measured following baseline and time course sequential injections of 1  $\mu$ M Oligomycin, 2  $\mu$ M FCCP, and 1  $\mu$ M Rotenone/Antimycin. Results were analyzed by the WAVE desktop software (Agilent) and normalized to compare basal respiration, ATP-linked respiration,  $H^+$  (proton) leak, maximal respiration, spare respiratory capacity, and non-mitochondrial respiration between groups. Statistical significance was set at  $p \leq 0.05$  based on t-test (two-tailed, unequal variance).

**Results:** Seven nominally significant genes in mitochondrial Complexes I, III, and V were differentially expressed between HCD and LCD groups; however, none of the genes reached statistical significance after FDR adjustment. Bioenergetic analysis revealed a general increase in mitochondrial respiratory function in the HCD group, with significantly higher mitochondrial maximal respiration and spare respiratory capacity compared to the LCD group.

**Conclusion:** The expression of genes encoding key ETC proteins within the mitochondrial matrix (Complex I- NDUFV1, Complex III- UQCRC1, and Complex V- ATP5F1B) were nominally downregulated, and genes encoding ETC proteins within the mitochondrial membrane were upregulated (Complex I- NDUF11 and NDUF8; Complex V- ATP5MC1 and ATP5PB) in HCD compared to LCD groups. Mitochondrial bioenergetic results suggest that BDI subjects with greater circadian disturbance exhibit a more robust response to increased energy demand or under stress. The interaction between circadian rhythms and mitochondrial functioning needs to be further explored in relation to BD and BD phenotypes.

## 2. Predictors of Early Dropout from Residential Substance Use Treatment: Evaluating Relationships with Depression, Pain and Age

Sarah Andrews, MD<sup>1</sup>; Hugh N. Farrior, Jr. BA<sup>2</sup>; Scott Teitelbaum, MD<sup>1</sup>; Ben Lewis, PhD<sup>3</sup>

### Institutions:

1. Department of Psychiatry
2. Department of Psychology
3. Department of Neuroscience – University of Florida College of Medicine, Gainesville, FL

### Presenters:

submitting presenter

**Background:** Despite the demonstrated efficacy of psychosocial treatment for substance use disorders, the rate at which individuals leave treatment early, against medical advice, remains high. Across various settings (e.g. outpatient, residential, inpatient), dropout rates are commonly estimated at between 40-70%. Among identified risk factors, younger age, depressive symptomatology, and pain endorsement appear particularly impactful, although their interactive effects remain poorly understood. The current analysis included all three. We expected each would be predictive, but speculated that their combined effects might be multiplicative.

**Methods:** Participants included 1,095 individuals in treatment for substance use disorders. Pain endorsement was queried via the NIH PROMIS. Depressive symptomatology was indexed with the depression module of the Patient Health Questionnaire-9 (PHQ-9). Treatment dropout was defined as discharge from treatment against medical recommendations or a removal from treatment due to positive results on a urine or blood screen for recent substance use. Analyses were conducted using logistic regressions in R.

**Results:** Age, depressive symptoms, and pain were significant predictors of dropout ( $p$ s < .01). Effects were in the expected directions, with higher dropout among individuals with more depressive symptoms, higher pain, and younger ages. Two interactions with depression were observed: One suggested that older age may be particularly protective among individuals with higher depression; younger individuals with high symptomatology were at substantially greater dropout risk, and effect that was attenuated at older ages. In contrast, the interaction with pain suggested that while depressive symptomatology was positively associated with dropout among individuals without pain, individuals with high levels chronic pain were at an elevated dropout risk, regardless of depressive symptomatology.

**Conclusions:** These data highlight dropout risks associated with younger age, higher depression, and greater pain. Notably, they suggest age effects may be particularly impactful in the presence of other risk factors. Additionally, although the depression-pain interaction did not support our hypotheses, the relationship was consistent with observations that negative affect is a core component of both depression and pain. Thus, the presence of either individually, or both in combination, appears sufficient for elevated dropout risk. Taken together, this work informs prevention and treatment efforts, emphasizing the importance of pain and depression as critical targets in treatment of substance use disorders.

### 3. Legislative Barriers to Electroconvulsive Therapy

Emily Beydler, BS\*; Ryan Joy, DO; Brent Carr, MD\*

#### Institutions:

Department of Psychiatry, University of Florida College of Medicine, 1149 Newell Drive, Suite L4-100

#### Presenters:

underlined submitting presenter

\* co-presenters

**Background:** Electroconvulsive therapy (ECT) has the highest rates of response and remission of any antidepressant treatment, with 70%–90% of those treated showing improvement (APA, 2010). Despite this, various state laws in place to protect vulnerable patients delay patient care, which can prolong and worsen suicidality, treatment-resistant affective disorders, and catatonia (Kim, 2018).

**Methods:** A literature search using LexisNexis and PubMed was performed, and bibliographies were manually searched. The Florida state legislative website, state statutes, and Florida Mental Health Act “Baker Act Benchguide” were searched in July 2022. All sections of state law pertaining to ECT were reviewed, and pertinent data regarding consent, age restrictions, treatment limitations, and other information were extracted. Search terms included the constructs “electroconvulsive therapy,” “law,” “informed consent,” “extraordinary treatment,” “guardian,” and appropriate synonyms.

**Results:** Despite the proven efficacy of ECT, a significant barrier to access is individual states’ well-intentioned, yet archaic, legislative barriers. These include the requirement for informed consent from a guardian of an adjudicated incapacitated patient to first go through a court hearing. For example, in Florida, a guardian advocate must be granted authority to consent for ECT as the state has ruled ECT an “extraordinary” procedure from the era of “psychosurgery”. This necessitates a second court hearing despite the limited availability of judges and magistrates. Patients with illnesses that preclude capacity, such as catatonia, acute mania, and psychotic depression, often experience a significant delay in urgent treatment due to the lengthy process of guardian appointment. This holds for individuals who are receiving outpatient ECT consistently but require admission for worsening disease. Additional state restrictions include arbitrary limitations on diagnoses, ages, approval by up to five clinicians, fees, and the number of ECT sessions that can be performed. This disrupts the continuity of the Index Series of ECT and conflicts with APA guidelines. Overall, legislation on ECT treatment is increasing in the US, and previous studies have shown a correlation between restrictive laws and diminished access to ECT (Livingston, 2018).

**Conclusions:** Our review suggests that restrictive state ECT laws, particularly regarding guardianship for incapacitated patients, can limit access to life-saving treatment in patients with acute psychiatric illness. Future systematic investigation of morbidity and mortality in patients awaiting ECT should be performed, particularly in Florida, given its large ECT provider and patient population.

#### References:

1. American Psychiatric Association. Practice Guidelines for the Treatment of Patients With Major Depressive Disorder. 3rd ed. 2010.
2. Kim H-H. Electroconvulsive therapy: A historical and legal perspective. *American Journal of Psychiatry Residents' Journal*. 2018 Mar;13(3):10–1.
3. Livingston R, Wu C, Mu K, Coffey MJ. Regulation of electroconvulsive therapy: A systematic review of US state laws. *J ECT*. 2018 Mar;34(1):60–8

## 4. Evaluating Uptake e-Mental Health Tools in a Primary Care Collaborative Care Program

Abigail Biehl

**Institution:**

University of Michigan

**Presenters:**

underlined submitting presenter

**Background:** Electronic mental health (e-MH) tools, such as internet or smartphone-based applications or programs, are high- impact, low-cost, and low-risk evidence-based interventions to treat depression. This study sought to evaluate the uptake of e-MH tools among depressed individuals receiving mental health care in a primary care clinic through a Collaborative Care model.

**Methods:** Participants were recruited from one of Michigan underserved county with a high need for mental health services, a higher suicide rate than Michigan on average, and a higher rate of unemployment than Michigan overall. Thirty- two patients entering a primary care clinic Collaborative Care program and who screened positive for depression on the Patient Health Questionnaire 9 (PHQ-9), were recruited to a 10-week study. The Sheehan Disability Scale (SDS) was administered to assess patient level of disability and impairment in functioning. Participants were introduced to a cognitive behavioral therapy (CBT)-based online depression program (moodgym), a mobile CBT- based app (MoodKit), and an informational University of Michigan-developed website (Depression Center Toolkit; [depressioncenter.org/toolkit](http://depressioncenter.org/toolkit)), and asked to choose one tool to use throughout the duration of the study for approximately 15 minutes at a time, 3 times a week. Following enrollment, each participant received six, once- weekly phone calls from the Collaborative Care Manager (CM) providing low intensity coaching to participants. These calls aligned with the CM's regular clinical calls as part of the Collaborative Care model and were intended to reduce attrition. Patient satisfaction and utilization of the selected e-MH tool were assessed through self-reports and tool use metrics at baseline, post-intervention, and 1-month follow-up.

**Results:** Of the 32 participants, the majority were female (84%, n=27) and mostly younger adults (50%, n=16). At the time of their enrollment, 78% of the participants screened positive for moderate to moderately severe depression, and 19% for severe depression and reported various levels of impairment in work, school, social and family life. About 19% of the participants were Non-Hispanic Caucasian. Moodkit was the most desired tool, chosen by 53% of participants, followed by 25% choosing Moodgym, and 22% the Depression Center Toolkit. Participants' reasons for selecting their chosen tool were primarily organization, convenience, accessibility, privacy policies, and ease. For the 23 participants who have completed the 10-week study, adherence to the chosen tool was 91% as measured by use of the tool for 11-20 minutes at a time for an average of 3.31 times per week. Satisfaction with the chosen tool increased with progressive use of the tool with 37.5% extremely satisfied at week 1 and 66.7% extremely satisfied by week 6. Of those 23 participants, 68% reported continuous use of their selected tool after study participation ended. Five participants dropped out and four have yet to complete the study.

**Conclusion:** Preliminary results demonstrate that combining e-MH tools within an existing primary care Collaborative Care program in an underserved population can be beneficial for those experiencing depression. Additionally, harmonizing the CM regular clinical calls with a low intensity coaching reduced attrition. Future research should continue to explore the implementation of e-MH tools in underserved primary care settings.

## 5. Implementation of a Digital Tool for Monitoring Depressive Symptoms: A Case Series

Scott A. Breiting, M.D.

**Institution:**

Mayo Clinic

**Presenters:**

underlined submitting presenter

**Background:** Over the past decade, there has been a rapidly developing field of mental health research focusing on leveraging digital hardware like smartphones and wearables as aides in the diagnosis and monitoring of psychiatric disorders, including mood disorders. Identifying a digital phenotype of depression can potentially translate in the integration of mobile devices for monitoring mood symptoms as part of the routine clinical care.

**Methods/Intervention:** In this case series, we present two patients with depressive symptoms and a control enrolled in a 12-week study to create a digital phenotype of depression through active and passive data collection from a smartphone and a wearable device combined with their routine clinical care for mood disorders.

**Results:** Interindividual differences in levels of engagement and acceptability of active and passive data collection (self-reported, behavioral, cognitive, and physiological data) was seen in two treatment-seeking depressed patients and the healthy control, in particular with data obtained through patients-app interaction and consistency in use of wearable devices.

**Conclusion:** Within patient-generated data, passive data collection could potentially offer higher reliability and, in consequence, more clinical utility for clinical care in depression. Analysis of larger samples are required to enable the digital phenotyping of depression.



## 6. A metric of pharmacotherapy guideline concordance and its association with major depressive disorder symptom severity and patient functioning.

Mason T. Breitzig<sup>1</sup>, Fan He<sup>1</sup>; Lan Kong<sup>1</sup>, Guodong Liu<sup>1,2</sup>, Daniel A. Waschbusch<sup>2</sup>, Jeff D. Yanosky<sup>1</sup>, Erika F. H. Saunders<sup>2</sup>, Duanping Liao<sup>1</sup>

### Institutions:

1. Department of Public Health Sciences, Penn State College of Medicine, Hershey, PA
2. Department of Psychiatry and Behavioral Health, Penn State College of Medicine and Penn State Milton S. Hershey Medical Center, Hershey, PA

### Presenters:

underlined submitting presenter

**Background:** Previous studies estimate that fewer than 70% of patients with major depressive disorder (MDD) receive guideline-concordant care. However, these estimates rely upon disparate and often oversimplified definitions of concordance that are also rarely examined with respect to patient outcomes. To address this issue, we developed a multifaceted scoring framework for MDD pharmacotherapy guideline concordance and assessed its association with MDD symptom severity (PHQ-9) and functioning (WHODAS 2.0).

**Methods:** This analysis involved 1,452 adults (68% female; mean age of 43 years) with MDD from the Penn State Psychiatry Clinical Assessment and Rating Evaluation System (PCARES) psychiatric outpatient registry. Patients with psychotic features or a diagnosis of bipolar disorder were excluded. At baseline, patients started with a perfect concordance score (9 points; 1 point per criterion). Point deductions were made for each criterion failed within a 1-year window. Since fewer criteria apply to those with recurrent depression, point deductions were weighted by baseline diagnosis (non-recurrent: -1.00; recurrent: -1.285). Out of the nine criteria, four focus on treatment sequence, two on treatment dose and duration, two on interactions and regulations, and one assesses visit frequency. Linear associations between concordance scores and 1-year PHQ-9/WHODAS scores were evaluated using naïve Spearman's rank correlation coefficients ( $\rho$ ) and multivariable-adjusted general linear models.

**Results:** Twenty-seven percent of patients received a perfect concordance score of 9, 18% scored 8-8.9, 32% scored 7-7.9, and 23% scored below a 7. The concordance score and raw (all repeated measures a 1-year window) PHQ-9 and WHODAS visit scores demonstrated significant inverse rank correlations (PHQ-9:  $\rho = -0.18$ ,  $p < 0.0001$ ; WHODAS:  $\rho = -0.11$ ,  $p < 0.0001$ ). After adjustment for sociodemographic variables and co-morbidities, higher guideline-concordance was associated with better mean (average of all visit scores in a 1-year window) symptom scores (PHQ-9:  $\beta = -0.29$ ,  $p = 0.0002$ ) and functioning (WHODAS:  $\beta = -0.54$ ,  $p = 0.0127$ ). The most frequently failed criterion was reaching the maximum recommended dose before switching to a different medication, which 55% of patients failed at least once.

**Conclusions:** This study demonstrates a significant association between the degree of pharmacotherapy guideline-concordance and measures of MDD response. Future longitudinal work with this pharmacotherapy guideline concordance metric will help identify gaps in guideline application and provide strategies to improve pharmacotherapy effectiveness.

## 7. Zebrafish as a Model for Studying Embryonic Development and Behavior in Bipolar Disorder

Claire Cohen, B.S.<sup>1</sup>; Vinashya Venkatasubramani, M.Sc.<sup>1</sup>; Robert Gonzalez, M.D.<sup>1</sup>; Colleen A. McClung, Ph.D.<sup>2</sup>; George-Lucian Moldovan, Ph.D.<sup>1</sup>; Khai Chung Ang, Ph.D.<sup>1</sup>; Keith Cheng, M.D., Ph.D.<sup>1</sup>; Suzanne Gonzalez, Ph.D.<sup>1</sup>

### Institutions:

1. Penn State Milton S. Hershey Medical Center, Hershey, PA.; 2 University of Pittsburgh, Pittsburgh, PA.

### Presenters:

underlined submitting presenter

**Background:** Bipolar disorder (BD) is defined primarily by recurrent manic and depressive episodes. Fluctuations in energy levels and locomotor activity as well as circadian rhythm disturbances are hallmarks of the disorder. Models based on clinical characteristics of the disease may provide great insight into shared and distinct disease-related mechanisms. We created a BD zebrafish animal model by morpholino (MO) knockdown of the core circadian gene *-clock-* that regulates biological rhythms. We hypothesize that knockdown of *clocka* and *clockb* genes in zebrafish affects embryonic development and behavior similar to the previously described BD mania mouse model (mClock $\Delta$ 19).

**Methods:** Embryonic image comparisons between *clocka* MO, *clockb* MO, *clocka/b* MO, and WT(TU) zebrafish were performed using ZEISS Axio Zoom Imaging System. DanioVision Observation Chamber and EthoVision tracking software were used to compare behavior patterns of WT Tübingen (TU) versus *clock* MO morphant zebrafish. Statistical analyses were performed using JMP v16.2.0. Results: WT(TU) *clock* morphants exhibit embryonic developmental delay in gastrula (5 hr.), segmentation (10 hr.), and pharyngula (24 hr.) phases.

**Results:** Locomotor activity differed significantly between groups, as *clock* morphants exhibited increased movement, swim speed, and exploration of the center zone compared to the control group. Significant group differences were also detected in response to the Light-Dark Challenge Test. The greatest differences were detected in fish injected with both *clocka* MO (4.5ng) and *clockb* MO (1.5ng) compared to uninjected WT(TU).

**Conclusions:** Future studies using CRISPR-Cas9-mediated techniques to knockout exon regions in zebrafish genes *clocka* $\Delta$ 20 and *clockb* $\Delta$ 17, homologous to mClock $\Delta$ 19, will enable us to examine the role of the circadian timing system in the developmental, anatomical, and behavioral mechanisms that underlie BD and allow for high-throughput therapeutic screenings for the treatment of BD.

## 8. Latent Depression and Anxiety Symptom Dimensions Predict Biased Acquisition and Extinction Learning in a Web-Based Causal Learning Task

Samuel E Cooper, Nicole E Keller, Mason McClay, Joseph E Dunsmoor

### Presenters:

underlined submitting presenter

Causal learning is a form of conditioning whereby behavior can be learned based on acquired stimulus-outcome pairings. Pairings are then modified through extinction learning, in which an expected outcome is violated due to the omission of the outcome during stimulus presentation. These tasks have been proposed as simple and cost-effective tests of learning deficits with relevance to anxiety-related psychopathology (e.g., impaired safety learning and threat extinction). However, relations between causal learning tasks and depression and anxiety symptoms have yet to be empirically tested. We address this gap by using anxiety symptom measures and an online within-subjects “allergy task”. Participants monitored the intake and reactions of a fictional food allergy patient. Consumed food served as conditioned threat (CS+) and safe (CS-) stimuli, allergic reactions were negatively-valenced outcomes, and predicted allergy severity was the dependent variable. During extinction, a CS- continued to be presented while two different CS+s were extinguished either through omission of the allergic outcome (CSext) or the outcome was replaced with a pleasant image (i.e., counter-conditioned, CScc). Reversal learning was also tested, as an original CS- during acquisition was paired with the allergic outcome during extinction (CSrev). Participants (N=314) completed this task and dimensional measures related to depression and anxiety (IDAS-II). Structural equation modeling was used to construct latent depression and anxiety factors, which were then related to learning indices. During acquisition, higher depression predicted lower expected CS- severity, whereas higher anxiety predicted increased severity. During extinction, higher depression predicted lower expected severity to the CScc and CS-, but not to the CSext or CSrev. Higher anxiety predicted higher expected severity across all stimuli except the CSrev, which had the inverse relation of lower anxiety predicting higher expected severity. Our results provide evidence for the validity of simplified associative learning tasks as probes of depression and anxiety-related psychopathology in larger online samples, and are discussed in the context of strategies for behavioral activation and extinction-based treatments.

**9. Psilocybin reverses stress-induced depression and anxiety-like behaviors and also promotes stress resilience in a wild type mouse model by mechanisms that are independent of 5HT2A and 5HT2C receptors.**

Megan Pedicini\*, Lindsey Macias, Kellie L.K. Tamashiro, Zachary A. Corder\*

**Institution:**

The Johns Hopkins University School of Medicine, Department of Psychiatry & Behavioral Sciences, Baltimore, MD 21287

**Presenters:**

underlined submitting presenter

\* co-presenters

**Background:** Much enthusiasm has emerged for the therapeutic potential of psilocybin, with growing evidence of remarkable benefit for depression as well as several other psychiatric disorders. However, despite promising clinical data, our understanding of psilocybin's therapeutic mechanisms remains remarkably limited. The lack of mechanistic studies appears to be due, in part, to the assumption that psilocybin's agonism of serotonin receptors in the brain – known to be responsible for the drug's psychedelic effects – also explains its diverse therapeutic benefits.

Here, we begin to systematically test the serotonergic hypothesis of psilocybin's therapeutic effects while also establishing the feasibility of such studies in preclinical models.

**Methods:** In the first study, adult male and female C57BL/6J mice were exposed to a single intraperitoneal dose of saline, psilocybin (1 mg/kg), the 5HT2A and 5HT2C receptor antagonist ketanserin (2 mg/kg), or psilocybin co-administered with ketanserin. The head twitch response, a validated behavioral measure of central 5HTR agonism, was measured 30 minutes after treatment. Behaviors relevant to depression and anxiety were measured between 3 and 6 days after treatment. In a second cohort, the behavioral effects following a single dose of psilocybin were monitored out to 35 days post-treatment. In a third cohort, mice were exposed to control conditions or two weeks of chronic variable stress. After chronic stress exposure, mice were treated with a single intraperitoneal dose of saline, psilocybin, ketanserin, or psilocybin co-administered with ketanserin followed by behavioral testing. In a fourth cohort, mice were treated with saline, psilocybin, ketanserin, or psilocybin co-administered with ketanserin 1 week prior to two weeks of chronic variable stress exposure.

**Results:** We found that psilocybin induces a robust head twitch response, suggesting the drug is engaging serotonin receptors in the CNS of both male and female mice. Psilocybin also increases exploratory behavior in the elevated plus maze, increases social behavior in the social interaction test, and decreases immobility in the forced swim test. Coadministration of ketanserin fully blocks the head twitch response without significantly altering psilocybin's effects on other behavioral outcomes. When the durability of these behavioral responses to a single dose of psilocybin were assessed, we found that effects persist for at least 35 days. In a stress-treatment study, we found that a single dose of psilocybin fully reverses stress-induced behavioral changes in the elevated plus maze and sucrose preference test, and increases social interaction above the level of unstressed controls.

Coadministration of ketanserin fully blocks the head twitch response without significantly altering psilocybin's effects on other stress-related behavioral outcomes. In a resilience study, we found that pre-treatment with psilocybin prevents the emergence of chronic stress-induced behavioral changes. Again, these effects of psilocybin are largely unaffected by coadministration of ketanserin.

**Conclusions:** Our data suggest that preclinical studies of psilocybin's effects and mechanisms are both feasible and potentially informative. We have also demonstrated that a single dose of psilocybin leads to long-lasting behavioral changes in male and female mice, these behavioral changes are relevant for studies of affective disorders, and the behaviors are not fully dependent on psilocybin's agonism of 5HT2A and 5HT2C receptors. In particular, we have found that psilocybin can both reverse the effects of chronic variable stress, and promote resilience against chronic stress effects.

## 10. Pimavanserin for Bipolar Disorder

Chesika Judyth Crump, MD, Carleigh A Litteral, Rif S. El-Mallakh, MD

**Institution:**

Mood Disorders Research Program, Depression Center Department of Psychiatry and Behavioral Sciences University of Louisville School of Medicine Louisville Kentucky

**Presenters:**

underlined submitting presenter

**Background:** Patients with bipolar disorder (BD) have an increased risk of developing PD (OR, 3.35; 95% CI, 2.00- 5.60;  $I^2 = 92\%$ ). This is important because antipsychotics are now commonly used in the treatment of BD due, in part, to extensive efficacy data. From 1997 through 2016, there has been a greater than fourfold increase in the use of antipsychotics in the management of bipolar disorder (BD). In patients with BD who ultimately develop PD, continued administration of atypical antipsychotics can be potentially problematic. No previous work has discussed the use of pimavanserin in bipolar disorder.

**Methods:** This report presents three cases of longstanding bipolar disorder in whom PD developed in later life and in whom replacement of an augmenting antipsychotic with pimavanserin was associated with maintained mood stability. Table 1 summarizes the key characteristics of the three patients with bipolar illness. All had developed type I bipolar illness in their twenties and had experienced at least one hospitalization for mania during their lifetime. All had developed disability after a lifelong history of productive, high level employment function (patient 1: social worker; patient 2: business manager; patient 3: pharmacist). Antipsychotic was added predominantly for mood stabilization (patients 1 and 3) and treatment of depressive symptoms (patients 1 and 2). Discontinuation of previous antipsychotic was required due to significant worsening of parkinsonian symptoms.

**Results:** Replacement with pimavanserin resulted in motor function stabilization, and either stable (patient 1), or improved (patient 2) mood state. Patient 3 developed hypomania after reduction of oxcarbazepine dose due to hyponatremia, which responded to increase of oxcarbazepine dose.

**Conclusions:** In addition to its effect in PDP, pimavanserin has also demonstrated efficacy in schizophrenia and dementia-related psychosis. This is the first demonstration of potential augmentative efficacy in bipolar disorder.

## 11. Psychiatric Electroceutical Interventions (PEIs) and Clinical Treatment Guidelines: Results from a National Survey of Board-Certified Psychiatrists

Joshua E. Cunningham, Eric D. Achtyes, Aaron M. McCright, Robyn Bluhm, Laura Y. Cabrera

### Presenters:

underlined submitting presenter

**Background:** Psychiatric electroceutical interventions (PEIs) are treatments that use electrical or magnetic stimuli to treat psychiatric conditions [1]. Clinical practice guidelines are systemically developed to assist practitioners in making appropriate clinical decisions and may inform psychiatrists' knowledge and familiarity with PEIs [2,3,4]. As new knowledge emerges, guidelines for the utilization of PEIs may quickly become outdated and require updating [3,4]. Little is known about how psychiatrists' prior knowledge of and experience with PEIs may shape their views about specific treatment guidelines for using these modalities.

**Methods:** We administered a survey with an embedded experiment to a national sample of psychiatrists (n=505). We randomly assigned respondents to one of 8 conditions using a full factorial experimental design: 4 PEI modalities [ECT, rTMS, DBS, or adaptive brain implants (ABIs)] by 2 depression severity levels [moderate or severe]. We analyzed the survey data with ANOVA and logistic regression.

**Objectives:** To examine how psychiatrists' main consideration when developing practical guidelines for PEIs varies with PEI familiarity.

**Results:** Overall, 46.8% of psychiatrists reported that the main consideration when developing practical guidelines should be "providing evidence of the safety and efficacy of these interventions." Yet, such aggregation conceals substantial variation across modalities. For instance, much greater percentages of psychiatrists assigned to non-FDA-approved PEIs (61.6% for DBS and 72.4% for ABIs) than those assigned to FDA-approved PEIs (20.8% for ECT and 31.4% for rTMS) reported this as their main consideration. Similar percentages of psychiatrists assigned to FDA-approved PEIs reported their main consideration to be "selecting patients who would be good candidates for the intervention" (28.8% for ECT and 24.8% for rTMS). Each different PEI that psychiatrists either administered or referred patients for increased their likelihood of choosing "selecting patients who would be good candidates for the intervention" rather than "providing evidence of safety and effectiveness" by 30% and their likelihood of choosing "establishing treatment approaches for subgroups" rather than "providing evidence of safety and effectiveness" by 150%.

**Conclusions:** Our results show that several factors influence psychiatrists' considerations when developing PEI guidelines. PEI modalities matter, especially the distinction between FDA-approved PEIs and non-FDA-approved PEIs. Further, greater professional experience with PEIs leads psychiatrists to shift their main considerations from safety and efficacy to patient selection and treatment optimization.

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## 12. Cardiovascular Disease Burden is Associated with Worsening Depression Trajectory

Radha Dhingra, MBBS, MPH; Fan He, PhD, MS<sup>1</sup>; Erika F.H. Saunders, MD<sup>2</sup>; Daniel A. Waschbusch, PhD<sup>2</sup>; Amanda M. Pearl, PhD<sup>2</sup>; Edward O. Bixler, PhD<sup>2</sup>; Jody L. Greaney, PhD<sup>3</sup>; Laila Al-Shaar, PhD, MS, MPH<sup>1</sup>; Vernon M. Chinchilli, PhD<sup>1</sup>; Jeff D. Yanosky, ScD, MS<sup>1</sup>; Duanping Liao, MD, PhD<sup>1</sup>

### Institutions:

1. Department of Public Health Sciences, Penn State College of Medicine, Hershey, Pennsylvania
2. Department of Psychiatry and Behavioral Health, Penn State College of Medicine and Penn State Milton S. Hershey Medical Center, Hershey, Pennsylvania
3. Department of Kinesiology, The University of Texas at Arlington, Arlington, Texas

### Presenters:

underlined submitting presenter

**Background:** Cardiovascular disease (CVD) and depression are the leading causes of disability worldwide and in the U.S.<sup>1</sup> CVD is also the leading cause of premature mortality among persons with depression<sup>2</sup> and depression is a leading contributor to healthcare costs associated with CVD.<sup>3</sup> We examined the impact of prevalent CVD conditions/risk factors on depression symptom trajectory using electronic health record (EHR) data from a mid- Atlantic registry of persons with mental illness.

**Methods:** The Penn State Psychiatry Clinical Assessment and Rating Evaluation System (PCARES) Registry is a measurement-based care system and data registry which merges EHR data with patient-reported data. Persons who sought mental healthcare services at a mid-Atlantic clinic between 2015 and 2020 were included. The Patient Health Questionnaire (PHQ-9) depression scale was obtained at each visit. For this study, persons with at least two PHQ-9 measurements over one year from the index psychiatry visit were included, thus providing a sample size of 2110. Socio-demographics, body mass index (BMI), and diagnoses of major CVD conditions (coronary heart disease, stroke, congestive heart failure, and transient ischemic attack) and CVD risk factors (hypertension, diabetes, and dyslipidemia) were extracted from the EHR. For analyses, the first step involved group-based trajectory modeling that divided the study sample into five mutually exclusive longitudinal trajectory groups, called depression severity groups, based on intra-individual PHQ-9 score trajectories over the study period. The second step involved using a proportional odds model to calculate odds ratios (95% CI) for the association between baseline CVD status and the likelihood of belonging to the group with more severe depression symptoms.

**Results:** Our sample included 2110 individuals and had a mean (SD) age, BMI, and PHQ-9 score of 43.04 (16.87) years, 30.63 (7.99) kg/m<sup>2</sup> and 10.80 (7.06), respectively. The sample comprised of 65.12% females, 85.69% Non- Hispanic Caucasians, 42.84% married individuals, and 56.55% individuals with commercial health insurance. Depression severity groups included lowest (5.32%), lower (35.31%), middle (29.14%), higher (21.19%), and highest (9.04%), with the majority study sample being in the lower to higher severity groups, with PHQ-9 scores ranging between 5 and 15. Persons with at least one major CVD at baseline had 1.18 (0.87–1.61) times higher odds of more severe depression symptoms and persons with at least one CVD risk factor at baseline were at 1.33 (1.10–1.61) times higher odds of more severe depression symptoms after adjusting for age, race, sex, marital status, insurance type, and BMI.

**Conclusions:** Presence of CVD risk factors at baseline was associated with worsened depression trajectory among persons with mental illness. Integrated healthcare services, routine depression screening among persons with CVD, special attention to persons with mental illness in CVD health improvement programs, and research bridging the pathways between depression and CVD could allow timelier depression diagnoses/treatment, thereby reducing disability, premature mortality, and associated healthcare costs.

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### 13. Use of KIOS Smartphone App for Bipolar Patients in a General Medical Clinic

Omar Elsayed, MD<sup>1</sup>, John Cecil, MD<sup>2</sup>, Richard Priesmeyer, PhD<sup>3</sup>, Gregg Siegel, MS<sup>4</sup>, Phyllis Siegel, JD<sup>4</sup>, Rif S. El-Mallakh, MD<sup>1</sup>

#### Institutions:

1. Department of Psychiatry and Behavioral Sciences, University of Louisville School of Medicine, Louisville, Kentucky
2. Cecil Clinic, Paducah, Kentucky,
3. Jurica Professor of Management, Department of Management and Marketing, St Mary's University, San Antonio, Texas
4. Biomedical Development Corporation, San Antonio, Texas

#### Presenters:

underlined submitting presenter

**Background:** Bipolar Disorder (BD) is a relatively common, chronic, and debilitating illness. Psychoeducation and early recognition of symptoms is therefore important for the long-term monitoring and management of BD. Mental health software applications (apps) had been gaining traction as a solution to address this issue. These apps have, however, not been adequately studied and there is an unmet need for evidence-based apps. This study examined the use of a self-monitoring/self-management smart phone app in a general practice setting on patients with bipolar disorder (KIOS-Bipolar). The app was specifically designed with patient-centered computational software system based on concepts from nonlinear systems (chaos) theory.

**Methods:** This was an open-label 12-week beta test of KIOS-Bipolar assessing usability and acceptability of the app in a general medical clinic (Cecil Clinic, Paducah, KY) utilizing the Bipolar Inventory of Symptoms Schedule (BISS). A total of 12 patients were enrolled and completed an online assessment two times per week. Average scores were compiled and compared to baseline at day 7, 14, 30 and 60. Primary outcome measure was percentage reduction in patient reported composite score for depression, mania, and instability. Participant usability scores through a satisfaction survey post-study were presented.

**Results:** 12 patients met criteria and were enrolled in the study. 100% of participants completed the study. All BISS symptoms showed a reduction after 1 week and after 60 days. Composite depression scale showed a reduction of 31% at the end of the first week and 41% at day 60. Mania composite symptoms displayed a decrease of 17% after 1 week and 46% at day 60. Instability composite score showed a 24% reduction after one week and 39% after 60 days. Mean usability rating was 80.76 (95% CI: 71.2 to 90.3). Usability score over 68 is considered above average.

**Conclusion:** KIOS-Bipolar could potentially be a useful tool in assessing and controlling symptoms of bipolar illness in primary care. KIOS-Bipolar was favorably received in terms of usability by the participants.

## 14. Assessment Tools Used in Bipolar and Related Disorders Research: A Systematic Review of Studies from Turkey

Mete Ercis MD<sup>1</sup>; Ilayda Arjen Kara MD<sup>2</sup>; Abdullah Fenercioglu MD<sup>2</sup>; Furkan Durmus MD<sup>2</sup>; Doruk Uludag MD<sup>2</sup>; Aysegul Ozerdem, MD, PhD<sup>1</sup>

### Institutions:

1. Department of Psychiatry & Psychology, Mayo Clinic, Rochester, MN, 55901, USA
2. Department of Psychiatry, Istanbul Medical Faculty, Istanbul University, Istanbul, Turkey

### Presenters:

underlined submitting presenter

**Background:** There are numerous studies conducted on bipolar disorders (BD) in Turkey, and a substantial amount of them are undertaken in various mood disorders centers (MDCs). However, since different clinical assessment tools (CATs) are used, it is not usually possible to combine the data from different MDCs at a national level. There has been ongoing efforts to establish large, multicenter longitudinal BD cohorts<sup>1</sup> The aim of this review is to summarize the methods used in BD studies conducted in Turkey in the last 20 years.

**Methods:** A systematic search of studies including patients with BD in Turkey was conducted using Medline/PubMed database. We limited our search to Turkish and English language and publication date to between January 1, 2000 and November 23, 2021. The search terms used were 'bipolar disorder\*' and 'Turkey'. Our inclusion criteria were for participants to be BD, prodromal BD, and probands of BD without age restriction, that all or part of the data was collected in Turkey and the study was published in a peer-reviewed journal.

**Results:** Our search revealed 353 original articles. Majority of them used data from patients attending to state university hospitals (58.9%). The most common study design was case-control (63.7%), followed by analytical cross-sectional design (24.6%). Twenty-nine (8.2%) of the articles included familial high-risk groups and three (0.8%) included clinical high-risk groups. BD type II was included only in 50 (14.2%) of the studies. Adolescent and pediatric patients were included in 25 (7.1%) of the articles. In 160 of 327 articles that had adult patients, a structured clinical interview was conducted, Structured Clinical Interview for DSM Disorders (SCID) being the most common (n=153, 95.6%). Hamilton Depression Rating Scale (HDRS-17; n=167, 91.9%) and Young Mania Rating Scale (YMRS; n=190, 92.3%) were the most common depressive and manic symptom assessment tools used, respectively. About one third of the articles used cut-off scores in CATs to define euthymia. Median (min-max) cut off scores was < 8 (1-13) for HDRS-17 and < 7 (1-13) for YMRS. Most commonly used CATs for psychosis, anxiety, attention-deficit-and-hyperactivity, personality, trauma were Positive and Negative Syndrome Scale (n=12, 40%), Hamilton Anxiety Rating Scale (n=4, 33.3%), Wender Utah Rating Scale (n=7, 77.8%), Temperament Evaluation of Memphis, Pisa, Paris, and San Diego Autoquestionnaire (n=18, 48.7%) and Childhood Trauma Questionnaire (n=9, 90%), respectively.

**Conclusion:** Most of the studies were conducted in university hospitals which might reduce the generalizability of the results. The majority had a cross-sectional design that does not reveal much about the disease course. This may be because fundings are often very limited while there is rapid publishing pressure. This approach favors quantity over quality and has little to contribute to the existing literature. Furthermore, the CATs used varied widely. Even for the most commonly used depression (HDRS-17) and mania (YMRS) scales, the cut-off scores for euthymia differed significantly across studies. These factors make it difficult to combine data from different centers even at a national level. We would like to call for action to plan for long- term multicenter follow-up studies to understand the risk factors and clinical course in BD and improve treatment outcomes. Our findings may guide researchers in this regard.

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## 15. Lumateperone as a treatment for bipolar depression: a scoping review

David Farris, BS<sup>1</sup>; Joshua Hales<sup>1,2</sup>, MD; Christopher Gideon<sup>1,2</sup>, MD; Carol A Janney<sup>1,2</sup>, PhD; Eric D. Achtyes<sup>1,2</sup>, MD

### Institutions:

1. Pine Rest Christian Mental Health Services
2. Michigan State University College of Human Medicine

### Presenters:

underlined submitting presenter

**Background:** Bipolar disorder is a chronic illness which is commonly characterized by extended periods of depression with intermittent manic-hypomanic episodes<sup>1</sup>. These periods of depression constitute the primary mood state over the course of illness<sup>2</sup>. Lumateperone is a recently FDA-approved atypical antipsychotic for the treatment of depressive episodes associated with bipolar I/II disorder<sup>3</sup>. Lumateperone has a unique mechanism of action characterized by indirect modulation of glutamatergic neurotransmission, potent 5-HT<sub>2A</sub> receptor antagonism ( $K_i = 0.5$  nM), D<sub>2</sub> receptor antagonism comparable to current atypical antipsychotics ( $K_i = 32$  nM); serotonin transporter (SERT) antagonism ( $K_i = 62$  nM); lower binding to  $\alpha_1$  adrenergic receptors ( $K_i = 73$  nM) associated with adverse side effect orthostatic hypotension; and no significant binding to muscarinic cholinergic receptors, 5-HT<sub>2c</sub> receptors, or histamine H<sub>1</sub> receptors associated with adverse cardiometabolic and sedating side effects of current atypical antipsychotics<sup>8</sup>.

**Objective:** The objective is to review current literature on lumateperone as a treatment for bipolar depression.

**Methods:** A PubMed search was performed utilizing the following terms: "ITI-007", "ITI-722", "lumateperone", "Caplyta", "bipolar", and "depression". A total of 31 articles were identified meeting these criteria. Of those 31 articles, 5 have been chosen. The criteria for selection of these articles are as follows: does the article display information relevant to studies involving the effects of lumateperone on bipolar depression and does it report the safety and/or efficacy of the studies identified. In total, 3 of the studies met the review criteria. Two studies used lumateperone as monotherapy in bipolar depression and one study used it as adjunctive therapy with lithium or sodium valproate. However, one of these monotherapy studies reported only the safety and tolerability profile of lumateperone which was combined with the other monotherapy study to yield pooled results.

**Results:** Lumateperone 42 mg (N=188) in comparison to placebo (N=189) showed significant improvement in the Montgomery-Åsberg Depression Rating Scale (MADRS) (least squares mean difference [LSMD], -4.6; 95% confidence interval [CI], -6.34 to -2.83; effect size vs placebo [ES], -0.56;  $p < 0.0001$ ) and the Clinical Global Impressions Scale-Bipolar Version severity scale (CGI-BP-S) (LSMD, -0.9; 95% CI, -1.37 to -0.51; ES, -0.46;  $p < 0.001$ ).<sup>3,5,6</sup> Furthermore, the efficacy of lumateperone 42 mg in conjunction with lithium or valproate (N=176) in comparison to placebo (N=176) was significant for both the MADRS [LSMD] = -2.4; 95% CI = -4.42 to -0.37;  $p < 0.05$ ) and the CGI-BP-S (LSMD = -0.3; 95% CI = -0.59 to -0.09;  $p < 0.01$ )<sup>3,7</sup>.

Lumateperone has shown a favorable safety and tolerability profile with bipolar depression in comparison to placebo, with treatment emergent adverse events (TEAE) such as headaches (Lumateperone = 17.6% vs placebo = 10.1%), somnolence (8.5% vs 1.1%), and nausea (6.4% vs 2.1%) being the most common TEAEs among patients receiving lumateperone<sup>5,6</sup>. Pooled results (N=746) show somnolence (13.2% vs 3.2%) and headaches (14.2% vs 7.8%) are the most prevalent TEAEs<sup>3,4</sup>.

**Conclusion:** In patients with bipolar depression, treatment with lumateperone has resulted in improvement in depression symptoms in comparison with placebo, both as monotherapy and adjunctive therapy. In addition, the rates of commonly reported issues with antipsychotic medication such as extrapyramidal symptoms (EPS), weight gain, changes in prolactin, and changes in cholesterol were similar to placebo<sup>3,4,5,6</sup>. However, the literature is very limited with little research on important factors such as quality-of-life indicators, long-term effects, and youth and elderly population effectiveness. In conclusion, current data indicates that lumateperone shows promise for the treatment of bipolar depression.

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## 16. SafeUT: Short-Term Effectiveness of Mobile Crisis App Utilization in Adolescents

Brian W. Farstead<sup>1</sup>; Daniel A. Feldman<sup>1</sup>; Alina K. Dillahun<sup>1</sup>; Somi Lee<sup>1</sup>; Scott A. Langenecker, PhD<sup>1</sup>; Mindy Westlund Schreiner, PhD<sup>1</sup>

### Institutions:

1. University of Utah, Department of Psychiatry

### Presenters:

underlined submitting presenter

**Background:** Access to convenient, effective mental health care for teens and adolescents is a complex issue, particularly for those experiencing crises, due to availability of and attitudes toward certain resources. We examined the influence of mental health service utilization (including SafeUT) on the most common presenting problems among users by assessing depressive symptoms and self-injurious thoughts and behaviors (SITBs).

**Methods:** SafeUT is a text-based app developed by the University of Utah that anonymously connects students to master's level counselors for real-time crisis intervention.

The sample included 188 adolescents (118 female, mean age[SD] = age 14.7[2]) who were recruited through the SafeUT app after chatting with a crisis worker. Participants completed surveys assessed engagement in mental health services in the past and at the time of SafeUT contact, motivation to seek treatment, depressive symptoms, and any self-injurious thoughts or behaviors (SITBs).

**Results:** The most commonly reported barriers to getting help were reluctance to tell their parents (16%), cost/insurance (12.2%), and seeming too overwhelming (12%). Paired-samples t- tests were conducted to compare intensity of depressive symptoms and SITBs before and after using the SafeUT app. Before engaging with the crisis counselor, 137 users were experiencing depressive symptoms and 65 were exhibiting SITB's. Intensity of these problems were significantly reduced by the end of their chat;  $t(136)=19.24$  ( $p<.01$ ) and  $t(64)=9.74$  ( $p<.01$ ).

**Conclusion:** Observations in pre-post crisis intervention show that the SafeUT app can be a successful tool in mitigating serious mental health symptoms. Motivation and likelihood to pursue mental-health services may be associated with specific barriers perceived by the adolescent.

## MAIN STAGE PRESENTATION

### 17. Epigenetic GrimAge Acceleration and History of Suicide Attempt in Bipolar Disorder

Camila N. de Carvalho Lima<sup>1</sup>, Emese H. C. Kovács<sup>2</sup>, Alexandra Del Favero-Campbell<sup>1</sup>, Alexandre Paim Diaz<sup>1,3</sup>, Salahudeen Mirza<sup>1</sup>, Consuelo Walss-Bass<sup>1</sup>, Joao Quevedo<sup>1,3</sup>, Jair C. Soares<sup>1,3</sup>, Benney M. R. Argue<sup>4</sup>, Marie E. Gaine<sup>4,5</sup>, Gabriel R. Fries<sup>1,3</sup>

#### Institutions:

1. Translational Psychiatry Program, Faillace Department of Psychiatry and Behavioral Sciences, The University of Texas Health Science Center at Houston, Houston, TX
2. Department of Neuroscience and Pharmacology, Carver College of Medicine, The University of Iowa, Iowa City, IA 3. Center of Excellence in Mood Disorders, Faillace Department of Psychiatry and Behavioral Sciences, The University of Texas Health Science Center at Houston, Houston, TX
3. Pharmaceutical Sciences and Experimental Therapeutics, College of Pharmacy, The University of Iowa, Iowa City, IA;
4. Iowa Neuroscience Institute, The University of Iowa, Iowa City, IA.

#### Presenters:

underlined submitting presenter

**Background:** Bipolar disorder (BD) has been previously associated with premature mortality and aging, including an acceleration of biomarkers of aging predicted based on DNA methylation levels (“epigenetic clock”) in blood and brain. Suicide is a major cause of mortality in BD, and a previous history of suicide attempt has been associated with decreased lifespan and worse clinical outcomes. In this study, we investigated the acceleration of GrimAge, a novel epigenetic clock trained on time-to-death data and uniquely associated with mortality and lifespan, in patients with BD with and without a lifetime history of suicide attempt.

**Methods:** Study participants from a discovery cohort (Houston) included BD patients with no history of suicide attempt (BD/non-SA, n = 66), BD patients with a lifetime history of suicide attempt (BD/SA, n = 77), and healthy controls (HC, n = 51) matched for age, sex, and race. An index of GrimAge acceleration (AgeAccelGrim) was computed based on peripheral blood genome-wide DNA methylation levels and chronological age for all participants. Linear models were used to compare groups for AgeAccelGrim as well as DNA methylation-based smoking pack-years and seven age-related plasma proteins (adrenomedullin, beta-2-microglobulin, cystatin C, growth differentiation factor 15, leptin, plasminogen activation inhibitor 1 (PAI-1), and tissue inhibitor metalloproteinases 1). Results from the patient-specific comparisons were independently validated in a replication cohort (Iowa) including BD/non-SA (n = 47) and BD/SA (n = 47).

**Results:** In the discovery cohort, controls, BD/non-SA, and BD/SA significantly differed for AgeAccelGrim after controlling for age, sex, population genetic stratification, years of education, body mass index, smoking status, and blood cell counts ( $F(2,175) = 6.598$ ,  $p < 0.001$ ), with the highest AgeAccelGrim found in BD/SA ( $p = 0.004$ , compared to HC). BD/SA also showed a significantly higher AgeAccelGrim compared to BD/non-SA after adjusting for covariates in the discovery ( $p = 0.027$ ) and replication cohorts ( $p < 0.001$ ). Finally, BD/SA showed significantly higher PAI-1 levels than controls ( $p < 0.001$ ), with no differences found for the other proteins or DNA methylation-based smoking pack-years.

**Conclusions:** Epigenetic GrimAge acceleration may contribute to premature morbidity and mortality in BD patients with a lifetime history of suicide attempt. These findings pair with existing evidence that not only BD, but also suicide attempt may be associated with an acceleration of biological aging, and provide putative biological mechanisms for premature mortality in these conditions (for example, through the actions of PAI-1). Future studies are warranted to explore the role of epigenetic aging and PAI-1 in the pathophysiology of BD and suicidal behavior, as well as to dissect their shared and unique biological underpinnings.

## 18. Public Health Emergency-related Access to Telemedicine: A Bridge To Rural Mental Health?

Mark A. Frye, MD<sup>1</sup>; Scott A. Breiting, MD; Melanie T. Gentry<sup>1</sup>, MD; Monica Taylor Desir, MD; Christi A. Patten, Ph.D<sup>1</sup>; Pravesh Sharma, MD<sup>1</sup>

### Institutions:

1. Department of Psychiatry and Psychology, Mayo Clinic, Rochester, MN

### Presenters:

underlined submitting presenter

**Background:** Due to the ongoing COVID-19 pandemic and public health emergency declaration, now extended to October 2022, insurance restrictions on telemedicine visits are temporarily lifted. This has led to improved access to health care for many, that otherwise would not have been possible. It is increasingly recognized that rural America has limited access to high-speed broadband internet service and smart devices, and poor digital health literacy increasing the possibility that access to digital care has emerged as a social determinant of health (SDoH)<sup>1,2</sup>. This case highlights how digital health during COVID-19 provided access to subspecialty care and greater evidence-based care.

**Methods:** We describe the case of Mr. A, a 19-year-old Caucasian male who presented to his primary care physician (PCP) with depressive symptoms. Suspicious of a bipolar diathesis because of “mood swings and irritability”, the PCP was reluctant to prescribe medication and wanted to refer to a psychiatrist. The distance to travel to the closest psychiatrist was more than 120 miles round trip. For many months, the young man did not schedule an appointment given the travel commitment, the lost hourly wage, time off work, and uncertainty about medical insurance coverage. Symptoms of depression worsened which contributed to a commensurate increase in alcohol and electronic nicotine use and strain on his significant other relationship. Ultimately, his PCP referred him to a psychiatrist during the pandemic. Various regulatory barriers limiting reimbursement for telemedicine were lifted by the Centers for Medicare & Medicaid Services to reduce the spread of the virus and increase consumer and provider willingness to use telehealth, consequently improving Mr. X's access to a psychiatrist.

**Results:** Mr. A was seen for an outpatient telemedicine visit for evaluation of depression with an index episode now 7 months in duration. Symptoms included a sleep cycle shift (staying up at night watching TV and waking up in the afternoon), anhedonia, decreased energy, limited attention span, poor self-esteem because of being overweight, and increased irritability. He tolerated the initiation and titration of escitalopram and trazodone without side effects. Four weeks after the 2<sup>nd</sup> appointment, Mr. A's symptoms improved significantly, and he was referred back to his PCP for the continuation of care.

**Conclusion:** Directly related to the pandemic, integrated psychiatric care with primary care medicine has opened a channel of depression care not otherwise accessible to many patients. Immediate federal and state policy changes are required to facilitate easy access to digital health care services. Health systems could consider screening patients for digital access, digital literacy, and digital support so that more focused solutions can be applied.

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## 19. Race Mediates Healthcare Utilization During the Period Before the First Episode Mania and Schizophrenia

Manuel Fuentes Salgado, MD; Javier Ortiz Orendain, MD; Manuel Gardea Resendez, MD; Mark A. Frye, MD; Monica Taylor-Desir, MD

### Institution:

Department of Psychiatry and Psychology, Mayo Clinic, Rochester, MN, USA.

### Presenters:

underlined submitting presenter

**Background:** Mental illness morbidity and mortality are magnified by racial disparities in access to, or provision of healthcare. Bipolar persons of African Ancestry compared with bipolar persons of non-African Ancestry are more often misdiagnosed with schizophrenia. Prior to the first episode of mania, there is a period of deterioration characterized by non-specific psychiatric symptoms. This investigation was conducted to evaluate the illness trajectory preceding incident case mania with a schizophrenia comparison group. A secondary analysis was specifically focused on racial disparities.

**Method:** Using the Rochester Epidemiology Project (REP), a unique record linkage database in the upper midwest of the USA, we searched for subjects born after 1985 that had been diagnosed with bipolar disorder (BD) or schizophrenia (SZ). Case ascertainment, based on DSM criteria was completed by two psychiatrists (JOO, MGR) supervised by a senior panel of psychiatrists including a data comparison of white (W) patient's vs non-white (NW) patients.

**Results:** 205 incident cases of BD (n=74) and SZ (n=131) were identified. The proportion of white patients was significantly higher ( $p = 0.048$ ) in the BD group (76%) compared to the SZ group (61%). White patients had a longer illness trajectory prior to the first episode ( $W = 8.55$  (SD 6.02) years vs  $NW = 6.06$  (SD 5.63) years;  $p = < 0.05$ ). Non-white patients had less use of mental health services, diagnosis, and pharmacological treatments ( $p = < 0.05$ ) compared to white patients before the first episode. Substance use history was similar between the two groups.

**Conclusion:** Race seems to mediate the healthcare utilization patterns prior to the first episode of BD and SZ. Non-white patients tend to have less service utilization in most metrics compared to white patients. Interventions to increase access and awareness to specific populations can help reduce the racial disparities in people with SZ and BD.



## 20. Antidepressants that Increase Mitochondrial Energetics Elevate Risk of Treatment-Emergent Mania

Manuel Gardea Resendez

**Institution:**

Mayo Clinic

**Presenters:**

underlined submitting presenter

**Background:** Preclinical evidence suggests that antidepressants (ADs) differentially influence electron transport chain complex activity by increasing (Mito+) or decreasing (Mito-) mitochondrial energetics. This study was conducted to investigate the relationship between mitochondrial function and illness vulnerability in bipolar disorder (BD), specifically risk of treatment emergent mania (TEM+).

**Methods:** Participants with BD already clinically phenotyped as TEM+ (n=176) or TEM- (n=519) were further classified whether the TEM associated AD, based on preclinical studies, increased (Mito+, n= 600) or decreased (Mito-, n=289) mitochondrial activity. Comparison of TEM+ rates between Mito+ and Mito- ADs was performed using generalized estimating equations to account for participants exposed to multiple ADs.

**Results:** Adjusting for sex and BD subtype, TEM+ was more frequent in antidepressants that increased (24.7%), in comparison, to decreased mitochondrial energetics (13.5%, OR= 2.12, p= 0.00002).

**Conclusions:** Our preliminary retrospective data suggests there may be merit in reconceptualizing AD classification, not solely based on monoaminergic conventional drug mechanism of action, but additionally based on mitochondrial energetics. Recognizing pharmacogenomic investigation of drug response may extend or overlap to genomics of disease risk, future prospective larger clinical studies should investigate potential interactions between mitochondrial mechanisms of disease risk and adverse drug response.

## 21. Negative Affective Responsivity to Daily Stress is Exaggerated in College-Aged Adults with Depression

Ashley M. Darling<sup>1</sup>, Jacqueline Mogle<sup>2</sup>, Joanna H. Hong<sup>3</sup>, Erika F.H. Saunders<sup>4</sup>, David M. Almeida<sup>3</sup>, Jody L. Greaney<sup>1</sup>

### Institutions:

1. Department of Kinesiology, The University of Texas at Arlington, Arlington, TX
2. Department of Psychology, Clemson University, Clemson, SC
3. Department of Human Development and Family Studies, The Pennsylvania State University, University Park, PA
4. Department of Psychiatry and Behavioral Health, Penn State College of Medicine, Hershey, PA

### Presenters:

underlined submitting presenter

**Introduction:** Affective dysregulation is a core pathophysiological characteristic of major depressive disorder (MDD) influencing emotional health; however, surprisingly few studies have examined emotional responsiveness (i.e., affective responsivity) in the context of daily stress. As a unique and ubiquitous domain of psychosocial stress, daily stress is defined as the routine challenges and concerns of day-to-day and the unexpected and episodic hassles that disrupt everyday life. Increased affective responsivity to daily stress is associated with heightened risk of future chronic disease. The aim of this study was to characterize affective responsivity to daily stress in young adults with MDD. We hypothesized that both negative and positive affective responsivity to daily stress would be exaggerated in young adults with MDD compared to healthy young non-depressed adults (HA).

**Methods:** Twenty-nine HA (17 females, 22±3 yrs) and twenty-eight adults with MDD (24 females, 20±2 yrs, PHQ-9: 9±5 a.u., 8 in remission) completed the Daily Inventory of Stressful Events (DISE) interview for 8 consecutive days to assess objective (e.g., frequency) and subjective appraisal characteristics (e.g., affective response) of daily stressors. The DISE consists of stem questions asking whether any of seven types of naturally occurring psychosocial stressors occurred in the past 24-hours: argument, argument avoidance, stressful event at work or school, stressful event at home, stressful event related to racial/ethnic/sexual discrimination, network stress, or any other stressful event. Affective responsivity to daily stressors was quantified as the magnitude of the change (i.e., slope) in positive and negative affect between days on which at least one stressor was reported and stressor-free days.

**Results:** The total number of daily stressor events across the 8-day sampling timeframe was not different between HA and adults with MDD (3±2.4 HA vs. 4±3.4 a.u. MDD;  $p=0.12$ ). In both groups, negative affect was greater on stressor days compared to stressor-free days (HA: 0.3±0.21 stressor-free days vs 0.5±0.25 stressor days; MDD: 0.6±0.37 stressor-free days vs 0.9±0.48 stressor days; main effect:  $p<0.01$ ) and positive affect was reduced (HA: 2.2±0.91 no stress days vs 1.8±0.80 stress days; MDD: 1.6±0.93 no stress days vs 1.4±0.86 stress days; main effect:  $p<0.01$ ). There were no differences in positive affective responsivity between groups (HA: -0.35±0.11 vs MDD: -0.32±0.09;  $p=0.29$ ). However, negative affective responsivity was greater in adults with MDD (HA: 0.27±0.08 vs MDD: 0.41±0.16 a.u.,  $p<0.01$ ).

**Conclusion:** These preliminary data demonstrate that daily stressor exposure elicits alterations in affect in young adults and further suggest that negative emotional consequences of daily stress are amplified in young adults with MDD.

## 22. Similarities and differences in cannabis and cannabidiol related attitudes and behaviors between adolescents receiving mood disorder treatment in the US and their parents

Christopher J. Hammond<sup>1\*</sup>, Yoon Ji Moon<sup>1</sup>, Mary A. Fristad<sup>2</sup>, Christopher D. Schneck<sup>3</sup>, Aimee E. Sullivan<sup>3</sup>, Melissa M. Batt<sup>3</sup>, Neera Ghaziuddin<sup>4</sup>, Richard Dopp<sup>4</sup>, Jarrod M. Leffler<sup>5</sup>, Manpreet K. Singh<sup>6</sup>, Sally Weinstein<sup>7</sup>, Leslie Hulvershorn<sup>8</sup>, Leslie Miller<sup>1\*</sup>

### Institutions:

1. Department of Psychiatry, Johns Hopkins University, Baltimore, MD
2. Division of Child & Family Psychiatry, Nationwide Children's Hospital, Columbus, OH
3. Department of Psychiatry, University of Colorado Anschutz Medical Campus, Aurora, CO
4. Department of Psychiatry, University of Michigan, Ann Arbor, MI
5. Department of Psychiatry Virginia Commonwealth University, Richmond, VA
6. Department of Psychiatry, Stanford University, Palo Alto, CA
7. Department of Psychiatry University of Illinois at Chicago, Chicago, IL
8. Department of Psychiatry, Indiana University School of Medicine, Indianapolis, IN

### Presenters:

underlined submitting presenter

\* co-presenters

**Background:** Widespread changes in cannabis legislation (CL) over the past 20 years have resulted in increased availability and use of medical cannabis (CAN) and cannabidiol (CBD) supplements throughout the US with unknown implications for American youth. In the present study, we examined attitudes, perceptions, and behaviors related to CAN and CBD use among youth receiving mood disorder treatment in the US and their parents.

**Methods:** An anonymous survey querying CAN and CBD related attitudes and behaviors (including beliefs about medical benefits, harms, and impact of use on different psychiatric symptoms) was administered to 68 youth with mood disorders (mean age=17.2, 66% female) and 56 parents/caregivers. All youth participants were receiving mood disorder treatment at the time of the study, and were recruited in tandem with parents/caregivers from five NNDC-affiliate child mood programs. Participants were from nine US states with variable CL (1 state w/ recreational, 5 states w/ medical, and 3 states w/ no CL). Comparative analyses and regressions were used to examine group differences and investigate relationships between perceptions, behaviors, and state CL status.

**Results:** The majority (>70%) of youth and parents/caregivers endorsed believing that CAN and CBD are safe and effective treatments for mental health conditions. Approx. half and a third of both groups reported believing that regular use of CAN and CBD reduces depression/anxiety and suicidal behaviors, respectively. Compared to parents/caregivers, youth were more approving of adolescent CAN use, and more likely to believe that medical CAN is beneficial for mental health conditions and endorse plans to use CAN and/or CBD products in the next 6 months. No group differences in general CAN expectancies were observed, but youth and parents/caregivers differed in CAN expectancies related to specific psychiatric symptom categories (e.g., depression/anxiety vs. drug problems vs. psychosis). Some CAN expectancies were influenced by CL status.

**Conclusions:** Results from this multisite study show that US youth receiving mood disorder treatment and their parents perceive CAN and CBD to be safe and effective for mental health problems, including youth depression and anxiety. Further, they identify intergenerational differences in attitudes and expectancies, with youth generally having more favorable attitudes and expectancies related to CAN compared to parents/caregivers, who underestimate the likelihood of their offspring using CAN in the future. State CL status was shown to influence some of these attitudes and expectancies. Given these findings, separate public health messaging campaigns targeting youth and parents are warranted to increase awareness and monitoring with the goal of mitigating risk for adverse outcomes related to CAN and CBD use in vulnerable youth populations.

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## 23. Maintenance ECT Considerations in a Post Covid-Induced Catatonia

Ethan Holland<sup>1</sup>; Nafisa Choudhury MD<sup>2</sup>; Brent Carr MD<sup>2</sup>

### Institutions:

1. University of Florida, College of Medicine, Gainesville, FL
2. University of Florida, Department of Psychiatry, Gainesville, FL

### Presenters:

underlined submitting presenter

**Introduction:** Electroconvulsive therapy (ECT) has been shown to be highly effective in treatment of multiple psychiatric disorders, including acute catatonia. In other disorders, such as major depressive disorder, the relapse rate post Index Series of ECT without Maintenance ECT treatment is high. However, there is sparse information on the relapse and recurrence of catatonia that remits after an Index Series of ECT. Here we review the one-year post ECT clinical outcome of a female whose acute onset Covid induced catatonia remitted with a full series of ECT and discuss case conceptualization and current literature of catatonia relapse post ECT.

**Objectives:** Assess the clinical outcome for this specific patient. Discuss theoretical expectations for relapse using the better studied ECT response and relapse rates using MDD, chronic recurrent as a surrogate in decision making process. And discuss relapse prevalence in ECT for catatonia discussing its potential impact on long term treatment decisions such as Continuation Phase ECT and Maintenance ECT.

**Methods:** Here a case study will be discussed for a 15-year-old female with no previous psychiatric history nor prodromal symptomatology who was hospitalized for acute psychosis and catatonia secondary to post Covid-19 symptoms. The patient responded robustly to an initial index series of ECT and was given a Continuation taper of ECT over 4 months. Post Index Series she was also started on Risperidone 2 mg qhs. The decision to forgo Maintenance ECT was based on full remitted status at 4 months, this being her sole episode of catatonia, high premorbid functioning, no past psychiatric history, and desire to return to high school to stay on academic pace with her current high school peers. Consideration will be discussed that COVID induced catatonia may suggest a resolved organic etiology may have lower relapse risk with resolution of COVID symptomatology. Given these factors, decision was made to closely monitor patient instead of Maintenance ECT. Currently there is no standard guideline for how long to continue ECT treatment for prevention of relapse in patients with catatonia. A literature review of relapse in patients who were treated with ECT for catatonia was done. The review focused its search on articles that included the key terms "ECT," "catatonia," and "relapse."

**Results:** In the 6 months since finishing ECT, patient has been in remission with no relapse of psychosis or catatonia. She has resumed school and sports activities with no setbacks. The results showed two articles that had prevalence of catatonia relapse percentages after ECT treatment. One article was related to treatment with catatonic schizophrenia and had a relapse rate of 63.6% (7/11 patients) at one year status post acute-ECT treatment. The second article looked at catatonia cases over ten years via a chart search of a mental health care provider service and a showed catatonia relapse rate of 25% (out of 1456 patients reviewed) for any treatment. All other articles that met search criteria did not provide a numerical value for prevalence or incidence of relapse after ECT beyond individual cases.

**Conclusions:** There is little research on the prevalence of relapse for patients that have had their catatonia treated with ECT. Providers must rely on the patient's past history and global assessment of morbidity and functioning, and any breakthrough symptoms as to whether maintenance ECT is indicated. For now in this patient, given her continued remission, the psychosis being likely due to COVID etiology versus a psychiatric disorder, high baseline functioning status and lack of risk factors, the decision to have held Maintenance ECT seems to have been the correct path for this patient. We will continue to monitor. More cases reporting various outcomes for post ECT catatonic patients may help better delineate relapse risk, decision tree planning, and expectations for families.

## 24. Do pharmacogenetics factors influence escitalopram-induced adverse events or treatment failure in youth at high-risk for bipolar disorder?

Duncan C. Honeycutt, MS<sup>1</sup>; Laura B. Ramsey, PhD<sup>2</sup>; Jeffrey A. Welge, PhD<sup>1</sup>; Thomas J. Blom, MS<sup>1</sup>; Kaitlyn M. Bruns, MA<sup>1</sup>; Luis R. Patino, MD<sup>1</sup>; Manpreet Singh, MD, MS<sup>3</sup>; Melissa P. DelBello, MD, MS<sup>1</sup>

### Institutions:

1. University of Cincinnati College of Medicine,
2. Cincinnati Children's Hospital Medical Center
3. Stanford University School of Medicine

### Presenters:

underlined submitting presenter

Selective serotonin reuptake inhibitors (SSRIs), such as escitalopram, are effective and well-tolerated treatments for depression and anxiety symptoms in children and adolescents. In patients with bipolar disorder, however, antidepressants can induce manic symptoms. Bipolar disorder is highly heritable, and the children of parents with bipolar disorder have an elevated risk for a "hyperarousal event," during which they may exhibit irritability, restlessness, insomnia, and impulsivity. The risk of such events may be influenced by genetic factors including polymorphisms in genes encoding cytochrome P450 enzymes which metabolize antidepressants (CYP2C19 or CYP2D6 in the case of escitalopram), and polymorphisms in the genes for the serotonin transporter (SLC6A4) and the serotonin receptor 2A subtype (HTR2A). Our study will examine whether these genetic factors influence the emergence of hyperarousal in depressed or anxious youth with a family history of bipolar disorder (NCT02553161).

Children and adolescents aged 12 to 18 with a first-degree relative with confirmed bipolar I were randomly assigned to receive escitalopram (n=66) or placebo (n=37) and monitored for symptoms of a hyperarousal event. At 8 weeks or early termination of the study, subjects provided a blood sample to determine serum escitalopram concentrations and a cheekswab for pharmacogenetic testing. All study participants provided samples for genetic testing (mean age: 14.9±1.65 years, 57.7% female), and most participants in the treatment group also provided samples for serum escitalopram levels (n=49, mean age: 14.9±1.68 years, 57.1% female). Subjects who provided samples for genetic testing were of Caucasian non-Hispanic (n=67), Caucasian Hispanic (n=8), African (n=9), and mixed or other ancestry (n=19). We used Clinical Pharmacogenetic Implementation Consortium guidelines to determine CYP2C19 and CYP2D6 metabolizer phenotypes.

Our preliminary analysis of participants' serum escitalopram levels and CYP2C19 metabolizer phenotype shows that CYP2C19 metabolizer phenotype significantly influences escitalopram pharmacokinetics. Among participants who received escitalopram and from whom serum and genetic test results were collected, there were intermediate (n=10), normal (n=24), rapid (n=14), and ultrarapid (n=1) metabolizers. CYP2C19 metabolizer phenotype had a significant effect on the maximum concentration (C<sub>max</sub>; p=0.0478), 24-hour area under the curve (AUC<sub>24</sub>; p=0.021), trough concentration (C<sub>trough</sub>; p=0.0116), and elimination half-life (t<sub>1/2</sub>; p=0.0008), but not the clearance (CL; p=0.22) of escitalopram. Further analysis of these data will help us determine the influence of other additional variables, especially participants' CYP2D6 metabolizer phenotype.

Our team is analyzing participants' clinical data to determine the significance of other alleles, especially polymorphisms in SLC6A4 and HTR2A. The "short" or "S" allele of SLC6A4 has previously been reported to diminish the efficacy of antidepressants relative to the "long" or "L" allele, and high-risk youth were found to have S/S (n=24), L/S (n=59), and L/L (n=20) genotypes. Previous studies have also implicated a SNP near the HTR2A gene (rs6313, -1438G>A), which may increase the risk of adverse events; high-risk youth were found to have G/G (n=39), G/A (n=51), and A/A (n=13) genotypes. Further analysis will attempt to correlate genetic findings with clinical outcomes such as risk of hyperarousal and other adverse drug events, as well as clinical response to escitalopram.

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## 25. Cortical Thickness in the Right Anterior Cingulate Cortex and Non-Suicidal Self-Injury in Youth with Mood Disorders

Rebekah S. Huber<sup>1</sup>, Danielle Boxer<sup>1</sup>, Xianfeng Shi<sup>1</sup>, Punitha Subramaniam<sup>1</sup>, Perry F. Renshaw<sup>1,2</sup>, Deborah A. Yurgelun-Todd<sup>1,2</sup>, Douglas G. Kondo<sup>1,2</sup>

### Institutions:

1. Department of Psychiatry, Huntsman Mental Health Institute, University of Utah School of Medicine
2. Mental Illness Research, Education & Clinical Care Center (MIRECC), Veterans Affairs, Salt Lake City, UT

### Presenters:

underlined submitting presenter

**Background:** Non-suicidal self-injury (NSSI) is highly prevalent in patients with mood disorders and has been associated with increased suicide risk, particularly during adolescence<sup>1</sup>. Understanding the neurobiological mechanisms underlying NSSI may guide the development of treatments and aid in suicide prevention. Structural alterations in cortical regions involved in emotional processing<sup>2</sup> including the anterior cingulate cortex (ACC) have been reported in youth with NSSI<sup>3</sup> and is associated with suicide risk in adults with mood disorders<sup>4,5</sup>. Few studies have examined cortical thickness associated with NSSI in youth. Furthermore, most of these studies have combined patients with mood disorders and not compared youth with bipolar disorder (BD) to youth with major depressive disorder (MDD). The aim of the present study was to investigate the relationship between cortical thickness of the ACC and NSSI in youth with MDD compared to BD.

**Methods:** One-hundred thirty-seven youth (86 with MDD and 51 with BD), ages 13 to 21, completed a diagnostic interview, clinical assessments, and underwent 3T magnetic resonance imaging. Morphometric analysis of brain images was performed using FreeSurfer to evaluate differences in cortical thickness in cingulate regions of interest. Lifetime symptoms of suicidal thoughts and behaviors and NSSI were assessed using the Columbia Suicide Severity Rating Scale. Chi-square was used to examine the relationship between type of mood disorder and NSSI. A two-way analysis of covariance (ANCOVA) was used to evaluate differences in cingulate thickness between youth with NSSI and no-NSSI and youth with MDD and BD, controlling for age and sex.

**Results:** Seventy-five youth (55% of the sample; 40 with MDD and 35 with BD) reported a history of NSSI and 62 youth (46 with MDD and 16 with BD) did not have a history of NSSI. Chi-square test found that youth with BD were more likely to report NSSI than youth with MDD,  $\chi^2(1) = 6.32$ ,  $p = 0.012$ . Two-way ANCOVA revealed that youth with BD and NSSI had significantly lower cortical thickness in the right rostral ( $p = .033$ ,  $\eta^2 = .03$ ) and caudal ACC ( $p = .028$ ,  $\eta^2 = .04$ ) than youth with MDD and NSSI. There were no main effects or significant differences in ACC cortical thickness between youth with BD and MDD or between youth with NSSI and no- NSSI.

**Conclusions:** These findings demonstrate that youth with BD were more likely to report NSSI than youth with MDD. In addition, we found reduced cortical thickness in the right rostral and caudal ACC in youth with BD and NSSI compared to youth with MDD and NSSI. The ACC is involved in emotional regulation and processing of pain. Therefore, these structural alterations may be related to increased suicide risk that has been reported in youth with BD compared to MDD.

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## 26. Insula-cingulate brain network transcriptomes for lifetime mood disorders and longevity

Dhivya Arasappan<sup>1</sup>, Abby Spears<sup>1,3</sup>, Simran Shah<sup>1,3</sup>, Zo-Ann Lee<sup>1</sup>, Ericka Salas<sup>1</sup>, Nirmala Akula<sup>2</sup>, Francis McMahon<sup>2\*</sup>, Mbemba Jabbi<sup>3,4,5,7\*</sup>

### Institutions:

1. Center for Biomedical Research Support, the University of Texas at Austin
2. Human Genetics Branch, National Institute of Mental Health, NIMH
3. Department of Psychiatry and Behavioral Sciences, Dell Medical School, UT Austin
4. Mulva Clinics for the Neurosciences, Dell Medical School, UT Austin
5. Department of Psychology, UT Austin
6. Institute for Early Life Trauma, Dell Medical School, UT Austin
7. Center for Learning & Memory & Institute for Neuroscience, UT Austin

### Presenters:

underlined submitting presenter

\* co-presenters

Several brain changes are present in major depression (MD) and bipolar disorder (BD), including a reduction in cortical anatomical and physiological integrity. Brain RNA-sequencing studies have identified transcriptomic changes in mood disorders. Given that not all brain regions across the cortical and subcortical mantle are equally involved in mediating mood functions and related feeling states, studies of brain regions with no direct regulatory involvement in mood and affective states are unlikely to identify the molecular pathologies underlying mood disorders. To address this problem, we applied postmortem RNA-sequencing to study gene expression change (GEC) in the anterior insula (Ant-Ins) and subgenual anterior cingulate (S-ACC) brain cortical regions in mood disorders and unaffected controls. We targeted the Ant-Ins and S-ACC based on their integral roles in sensing and regulating mood and affective feeling states. Combining gene coexpression, differential expression, and pathway-enrichment analyses, we found GECs for mood disorder-related phenotypic variability. With factor-analytic data reduction, we identified *psychiatric morbidity*-associated innate immune and inflammatory GECs in the Ant-Ins in mood disorders. In contrast, longevity-associated metabolic and biosynthesis GECs were identified in the S-ACC, whereas *suicide*-associated inflammatory, metabolic, and cellular developmental GECs were recapitulated in the S-ACC. Together, our results reveal brain region-specific and regionally overlapping gene expression repertoires and provide a valuable framework for defining molecular mechanisms underlying pathological and mortality risks for mood disorders.



## 27. The Influences of COVID-19 as a Risk Factor for Admissions to An Inpatient Geriatric Psychiatry Unit

Jaylyn Kelly MD<sup>1</sup>; Dora Juhasz BS<sup>1</sup>, Carol Janney PhD<sup>1,2</sup>; Swapnil R Rath MD<sup>2</sup>

### Institutions:

1. Michigan State University College of Human Medicine
2. Pine Rest Christian Mental Health Services

### Presenters:

underlined submitting presenter

**Background:** The COVID-19 pandemic has introduced new and difficult obstacles for vulnerable populations in the United States. In particular, the geriatric population may be at a greater risk of negative mental health outcomes due to the COVID-19 pandemic, as they may be more vulnerable to the effects of social distancing and isolation. Given the known adverse effects of loneliness and social isolation on mental health, we hypothesized that the majority of inpatients in the geriatric unit at a local psychiatric hospital implicated COVID-19 as a negatively contributing reason for admission. Specifically, we investigated the number of admissions that were reportedly due to the effects of lifestyle changes as a result of the pandemic and not necessarily due to the COVID-19 illness itself.

**Methods:** We studied all patients ages 60 and over admitted to the older adult unit in a local psychiatric hospital at the height of the COVID pandemic between July 1st, 2020 through September 30th, 2020 via retrospective chart review. Our main outcome was looking at the number of patients admitted for COVID-19- related causes. Exploratory analyses between the two groups included differences in demographics, psychiatric histories, and reasons cited for admission using a chi-square analysis with p-values of 0.05.

**Results:** The study population revealed that 48% of patients were perceived to be admitted due to circumstances of COVID-19. To date, there were no significant differences between the two groups of patients in age, gender, or length of stay.

**Conclusions:** COVID-19 has had a substantial impact on the mental health of the older adult population. In addition to the normal stressors faced by older adults, nearly half of all patients reported the effects of COVID- 19 contributing to their inpatient psychiatric admission. While there were no factors from our study that could give insight on what pre-disposes some patients to psychiatric emergencies in light of social isolation, our results are still notable for highlighting the impact that COVID-19 has had on the older adult population's psychiatric health.

## 28. Electroconvulsive Therapy Treatment Trial in Super Refractory Status Epilepticus: A Case Study

Lauren Katzell<sup>1</sup>, Gerald Richardson MD<sup>2</sup>, Kevin Putinta MD<sup>2</sup>, Brent Carr MD<sup>2</sup>

### Institutions:

1. University of Florida, College of Medicine, Gainesville, FL
2. University of Florida, Department of Psychiatry, Gainesville, FL

### Presenters:

underlined submitting presenter

**Background:** Status epilepticus (SE) has a mortality rate purported to be 20-50%, with acute symptomatic SE having a higher risk compared to chronic SE.<sup>1</sup> Electroconvulsive therapy (ECT) has been utilized for treatment of SE when traditional therapies fail, however success rates of ECT in cases of super refractory SE (SRSE) have not been well-documented. In 2012, the success rate of ECT in treatment of SE was said to be 80%, however an analysis in 2016 demonstrated the rate to be 57.9%.<sup>2,3</sup> While the mechanism behind ECT treatment in SE remains unclear, proposed mechanisms include release of inhibitory transmitters, such as GABA; prolongation of the refractory period; elevation of the seizure threshold, which has been demonstrated in patients receiving ECT for treatment of mood disorders; and, induction of endogenous seizure termination mechanisms.<sup>1,4</sup>

**Methods:** HM is a 44yo female with a history of developmental delay and localization-related epilepsy diagnosed at age 16 with vagal nerve stimulator placement at age 38 following a traumatic brain injury at age 43 and craniotomy who presents with prolonged periods of generalized seizures lasting up to 20 minutes, which is increased from her baseline of one seizure per day controlled with home regimen of topiramate 200mg TID and lamotrigine 400mg BID, progressive aphasia, and declining mental status.

Lumbar puncture revealed HHV-6 encephalitis. As HM continued to decline, she was intubated, weaned off of prior Versed and Midazolam drips, and started on Lamictal, Keppra, Topiramate, Perampanel, Onfi, Lyrica, Epidiolex, Phenobarbital, Propofol drip, and Ketamine drip. Patient was determined to not be a candidate for a ketogenic diet. Thus, the multidisciplinary team decided to attempt ECT to induce burst suppression and increase seizure threshold. Due to patient's prior right craniotomy and subsequent right hygroma, initial ECT sessions were performed with a right anterior, left temporal lead placement using a MECTA spECTrum 5000Q ECT Device. ECT session 1 was performed on day 17 with propofol and ketamine drips paused 30 minutes prior to treatment. Session 1 consisted of treatment 1 at 2.0ms, 3 sec, 120 Hz, 800mA in an attempt to depolarize neurons to break the SE; treatments 2 and 3 used a longer stimulus train in an attempt to induce a seizure (0.37 ms, 6 sec, 120 Hz, 800mA). ECT session 2 was performed on day 18 with ketamine and propofol infusions paused 2 hours prior to session and consisted of 2 treatments at 1ms, 6 sec, 60Hz, 800 sec and 2 treatments at 2ms, 3 sec, 60Hz, 800 sec. ECT session 3 was performed on day 19 with ketamine and propofol infusions paused 3 hours prior to session and consisted of 1 treatment at 1ms, 3 sec, 60 Hz, 800mA with a 3 minute hiatus followed by 1ms, 3sec, 60Hz, 800mA in a bitemporal lead configuration.

**Results:** ECT session 1 was unable to induce seizures nor change baseline, and seizure burden continued to increase from 11% prior to session to 20% burden over the next 24 hours. ECT session 2 did induce epileptiform activity with suppression but was followed by an almost immediate return to baseline.

Seizure burden continued to increase to 30% despite a combination of treatments. ECT session 3 induced mild epileptiform activity with return to baseline followed by no significant change in seizure burden following the procedure. In discussion with the epileptologist and neuro critical care team, as seizure burden had continued to steadily worsen over the course of the patient's illness with only mild transient EEG changes from ECT treatment, the decision was made to discontinue ECT treatment. The patient's family opted for comfort care measures and HM passed away on day 24.

**Conclusions:** The wide variability in efficacy rates of ECT in treatment of SE in the literature may be due to publication bias, as ineffective cases are unlikely to be published. Or, successful cases offer limited information on ECT total charge dose and parameters that yielded them, as well as the ECT lead placement. This case is presented to demonstrate an instance of inefficacy of ECT treatment in the setting of SRSE. There exists a need for

prospective studies testing efficacy in this area to minimize publication bias and a need for guidelines for treatment protocols.

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## 29. Can an online mental-contrasting and implementation-intentions intervention increase help seeking initiation for individuals with depression?

Amanda R. Keeler, PhD<sup>1</sup>; Liesl A. Nydegger, PhD, MPH<sup>2</sup>; William D. Crano, PhD<sup>3</sup>

### Institutions:

1. Department of Psychiatry/ Department of Family and Community Medicine, Penn State College of Medicine, Hershey, PA
2. Department of Kinesiology and Health Education, University of Texas, Austin TX
3. Division of Behavioral and Organizational Sciences, Claremont Graduate University, Claremont, CA.

### Presenters:

underlined submitting presenter

**Background:** There are multiple reasons why individuals with depression may fail to seek help. Among individuals with elevated depressive symptomatology, some previous interventions aimed at increasing helping seeking have unintentionally led to a decrease help seeking intentions. Beck's cognitive theory of depression describes how individuals with elevated depressive symptomatology process information differently than those without depression (i.e., increased cognitive load and negative bias), which may explain the iatrogenic results of previous interventions. Implementation intentions and mental contrasting (MCII) interventions have successfully been used for increasing health behaviors—especially among populations experiencing high cognitive load—including mental health. However, it has not been used specifically for initiating help seeking for depression. The goal of this research was to ascertain whether an online MCII intervention could increase *actual* help seeking or the *intention* to seek help for depression.

**Method:** All 228 participants had Beck Depression Inventory (BDI-II) scores of 14 or above (indicating mild depressive symptomatology) and were not currently seeking professional help at Time 1. Participants completed measures on help seeking intentions, were provided with resources for formal and informal help seeking for depression before being randomized to either the control group ("C";  $n = 124$ ) or the MCII intervention group ("HS";  $n = 105$ ). The only difference between groups was that the HS group completed the process of designing an advanced situation-based "if-then" plan to seek help for depression. All participants were then asked specific questions about the strength of their plans and intentions to seek help for depression if the need occurs via a strength of implementation intention scale (SIIS HS). At Time 2, participants were asked to complete all the same questions and whether they sought help for depression in the past two weeks.

**Results:** The HS group reported greater *intentions to seek help* ( $F[1,226] = 11.468, p = .001$ , partial  $\eta^2 = .048$ ) as well as *actual help-seeking* ( $t[202] = 2.509, p = .013$ , CI: .103,.860) two weeks post intervention. Proportionally, help-seeking was more likely for individuals who received the HS intervention and either did not *perceive* themselves as depressed at Time 2 ( $X^2[1] = 8.387, p = .004$ , Odds Ratio = 3.741) or individuals whose *actual* BDI-II scores at Time 2 fell below 14 indicating that they reported no or minimal depressive symptoms at Time 2 ( $X^2[1] = 6.844, p = .009$ , Odds Ratio = 10.626).

**Conclusion:** At a time when depression rates are increasing due to the COVID-19 pandemic it is vital to develop remote, affordable, scalable, and effective interventions to encourage help-seeking. This study offers support that a novel online MCII intervention to seek help is feasible, but determining whether actual help seeking success is based solely on the intervention requires replication. The discussion offers several ways that future research can modify and expand this line of research utilizing MCII for help-seeking for depression to include addition of complementary models, addition of features such as ecological momentary assessment, as well as targeting loved ones to recognize warning signs and plan a strategy intervening with a loved one with depression.

### 30. Association Between Thyroid Stimulating Hormone And Depression: A Historical Cohort Study

Rakesh Kumar<sup>1</sup>, Allison LeMahieu<sup>2</sup>, Marius N. Stan<sup>3</sup>, Ashok Seshadri<sup>1</sup>, Vanessa M. Pazdernik<sup>2</sup>, Tara L. Haynes<sup>4</sup>, David H. Daugherty, III<sup>4</sup>, Marin Veldic<sup>1</sup>, Aysegul Ozerdem<sup>1</sup>, Paul E Croarkin<sup>1</sup>, Mark A. Frye<sup>1</sup>, Balwinder Singh<sup>1</sup>

#### Institutions:

1. Department of Psychiatry & Psychology, Mayo Clinic, Rochester, MN, USA
2. Department of Quantitative Health Sciences, Mayo Clinic, Rochester, MN, USA
3. Division of Endocrinology, Diabetes, Metabolism, Nutrition, Department of Internal Medicine, Mayo Clinic, Rochester, MN, USA
4. IT Executive Administration and Data Solution Services, Mayo Clinic, Rochester, MN, USA

#### Presenters:

underlined submitting presenter

**Objective:** To investigate the association between thyroid-stimulating hormone (TSH) and clinically relevant depression (CRD) in a population-based study.

**Methods:** We included adult patients ( $\geq 18$  years) who received care at the Mayo Clinic in Rochester, Minnesota, and completed TSH and PHQ-9 within six months of each other, between 1/1/2000 and 8/31/2021. Demographics, medical comorbidities (Charlson comorbidity index [CCI]), thyroid function laboratory data, psychotropic medications (SSRIs, SNRIs, TCAs, MAOIs, benzodiazepines, stimulants, and antipsychotics), and thyroid hormone replacement (T3, T4) were extracted electronically. Mood disorders and thyroid disorders diagnoses were identified using ICD-10/10-CM codes. Our primary outcome was CRD, *defined as a PHQ-9 score  $\geq 10$* . Logistic regression analysis was conducted to assess the association between TSH categories (*low TSH  $\leq 0.3$ ; normal/reference TSH group  $>0.3-4.2$ ; high TSH  $>4.2$  mIU/L*) and CRD, adjusting for covariates (age, sex, CCI, thyroid disorders, mood disorders diagnoses, BMI, thyroid hormone replacement, and psychotropic medications). Sub-group analysis was also conducted between males and females.

**Results:** The cohort included 29,034 patients, mean age 51.4 years, 65.0% female, 89.9% Caucasian, mean BMI 29.9, and mean CCI score 3.3 (moderate, with CCI scores of 3–4) The mean $\pm$ standard deviation (SD) for TSH (n=29,034) was  $3.0 \pm 8.5$ , and mean PHQ-9 (n=29,034) score was  $6.3 \pm 6.2$ . After adjustment, the odds of CRD were significantly higher among the low TSH (TSH  $\leq 0.3$ ) category (OR=1.37, 95% CI=1.18-1.57,  $p < 0.001$ ) compared to the normal TSH category. The odds of CRD were not significantly different between the high TSH (TSH  $>4.2$  mIU/L) category (OR=0.92; 95% CI=0.81-1.04;  $p=0.181$ ) and the normal TSH category. Conducting a sensitivity analysis with index date within one-month (n=17,115), higher odds of CRD in the low TSH category compared to the normal TSH category remained significant (OR=1.36; 95% CI=1.12-1.66;  $p=0.002$ ). On subgroup analyses, low TSH was significantly associated with CRD in female patients ( $p < 0.001$ ) but not in male patients ( $p=0.104$ ). Specifically, female patients with low TSH had higher odds of CRD compared to those with normal TSH (OR=1.39; 95% CI=1.19-1.63;  $p < 0.001$ ). Free-T4 levels were available for 15% of the cohort (n=4372). The odds of CRD among patients with subclinical/overt hypothyroidism/hyperthyroidism (after adjusting for covariates) were not significantly different compared to the euthyroid patients.

**Limitations:** Our major limitation is the cross-sectional study design; thus, we were not able to investigate the time-dependent relationship between TSH and depression. The retrospective nature of the study raises the possibility of unmeasured bias and confounding. The thyroid laboratory assessments were conducted randomly and not at a fixed time, thus, could not account for circadian fluctuations in the TSH concentrations.

**Conclusion:** In this large population-based cross-sectional study, we report that low TSH was associated with a higher odds of depression. Longitudinal studies in population-based cohorts are needed to further investigate the relationship between alteration in thyroid hormones and depression as well as sex differences.

### 31. Ohio State University Comprehensive Psychotherapy Pathway for Depression: Implementation of a stepped-care model guided by patient-reported outcomes in an academic medical center

Sophie A Lazarus<sup>\*</sup>, Kristen M Carpenter, Jay C Fournier<sup>\*</sup>

#### Institution:

Department of Psychiatry and Behavioral Health, The Ohio State University Wexner Medical Center, Columbus, OH 43210

#### Presenters:

underlined submitting presenter

<sup>\*</sup> co-presenters

**Background:** Major depressive disorder is a serious illness characterized by significant impairment for individuals and costs to society<sup>1</sup>. Analyses of data from the National Survey on Drug use and Health revealed that substantial unmet treatment needs remain in the MDD population. While the number of individuals with MDD has increased, the proportion receiving treatment has not<sup>1</sup>. Further, depression is highly recurrent and depressive relapse is related to disproportionate healthcare burden<sup>2</sup>. Both stepped-care models of treatment<sup>3</sup> and an emphasis on evidence-based approaches to relapse prevention<sup>4</sup> have the potential to address these problems. Despite this, there are few real-world investigations on how to implement these models.

**Methods:** In July of 2021 we secured funding via an internal medical center mechanism to implement a stepped care and relapse prevention pathway for the treatment of depression. The aim of the project is to build upon our existing resources for outpatient individual psychotherapy for depression to 1) initiate an entry-level behavioral activation group for mild to moderate depression, 2) increase capacity to provide MBCT groups for relapse prevention once patients complete standard acute treatments, 3) and enhance utilization of patient-reported outcomes (PROs) to inform treatment assignment and progression.

**Results:** In year 1 of the project, we have successfully 1) initiated a group behavioral activation therapy offering (23 patients enrolled to date), 2) increased capacity to provide MBCT groups for relapse prevention (44 patients to date), and 3) enhanced provider education and outreach to increase utilization of group resources and PROs. Obstacles identified include the creation of a new referral workflow for the BA group offering, provider education and uptake of PROs and the stepped-care model, and patient compliance with PROs. Preliminary data on depressive outcomes and psychosocial outcomes will be presented.

**Conclusions:** With the availability of effective treatments for depression, increasing access to high quality care informed by PROs is critical. The initial phase of this project is complete, and we continue to increase the frequency of group offerings and refine the use of PROs throughout the pathway. Longer term goals for the program are to augment PROs with objective measures to support treatment assignment, to assess progress, and to better integrate medication management and interventional psychiatry services into treatment decision-making algorithms.

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### 32. COMP360 Psilocybin Therapy in Treatment-Resistant Depression: Results of a Large Randomized Controlled Phase IIb Monotherapy Study and an Exploratory Uncontrolled Adjunctive Therapy Study

Guy M. Goodwin, Lindsey Marwood, Sunil Mistry, Claudia Sisa, Susan C. Stansfield, Joyce Tsai, Sam Williams, Steve Levine, Ekaterina Malievskaia

**Institution:**

COMPASS Pathfinder Ltd, London, United Kingdom (UK)

**Presenters:**

underlined submitting presenter

**Background:** COMP360 is a synthetic, purified form of psilocybin in development for treatment of patients with treatment-resistant depression (TRD). COMP360 psilocybin therapy is an integrated therapy that combines oral COMP360 administration with psychological support. It has received FDA designation as a breakthrough therapy. Here, we report on the efficacy and safety results from two clinical studies of COMP360 psilocybin therapy in adults with TRD.

**Methods:** The COMP001 monotherapy study (N=233) was a randomized double-blind controlled study evaluating the efficacy and safety of COMP360 psilocybin therapy at doses of 25mg (n=79), 10 mg (n=75) and 1 mg (n=79) of COMP360. Participants were required to discontinue any antidepressant treatments prior to randomization. Participants were evaluated the day after the study drug session (Day 2) and at Weeks 1, 3, 6, 9, and 12. The COMP003 study (N=19) was an open-label trial that explored the effect of COMP360 (25 mg) psilocybin therapy as an adjunct to an ongoing serotonergic antidepressant. Participants were evaluated at Day 2 and Weeks 1, 2, and 3. In both studies, the primary endpoint was change in Montgomery-Asberg Depression Rating Scale (MADRS) total score from Baseline to Week 3.

**Results:** In the COMP001 monotherapy study, dose-related improvements in MADRS were evident at Day 2 and persisted at Week 3 primary endpoint, where mean changes from Baseline in the primary endpoint (standard deviation [SD]) were -12.0 (12.98), -8.9 (10.94), and -6.8 (11.10) in the 25 mg, 10 mg, and 1 mg groups, respectively. The least-squares mean difference between 25 mg and 1 mg was statistically significant (LSMD=-6.6,  $p<0.001$ ); the difference between 10 mg and 1 mg was not. Rates of response ( $>50\%$  reduction in MADRS) and remission (MADRS  $\geq 10$ ) at Week 3 were higher for COMP360 25 mg (36.7% and 29.1%) than for 1 mg (17.7% and 7.6%), and sustained response at Week 12 was higher for 25 mg (24.1%) than for 1 mg (10.1%). In the COMP003 (25 mg) adjunctive therapy study, improvement in depressive symptoms was observed beginning at Day 2. At Week 3 endpoint, participants had a mean change from Baseline of -14.9 (SD=11.97) points in MADRS, and 42.1% of participants met criteria for remission. COMP360 25 mg was generally well-tolerated in both studies. In COMP001, treatment-emergent adverse event (TEAE) rates were 83.5% (n=66), 74.7% (n=56), and 72.2% (n=57) in the 25 mg, 10 mg, and 1mg groups, respectively. Over 90% of TEAEs were mild or moderate in severity. Treatment-emergent serious adverse event (TESAE) rates were 6.3% (n=5), 8.0% (n=6), and 1.3% (n=1) in the 25 mg, 10 mg, and 1 mg groups, respectively. In the adjunctive therapy study, the TEAE rate was 57.9% (n=11); and 82% of TEAEs were mild. No TESAEs were reported.

**Conclusions:** A single administration of COMP360 25 mg in combination with psychological support appears to be a rapid, efficacious, and well-tolerated treatment in patients with TRD, and may provide additional benefit as an adjunctive therapy to common antidepressant treatments. The efficacy and safety of COMP360 25 mg should be further evaluated in large, controlled, confirmatory studies.

### 33. The Use of Electronic Communication-based Automated Language Technologies to Augment Traditional Mental Health Care

Tenzin Lhaksampa, MHS<sup>1</sup>, Alex Walker, MHS<sup>1</sup>, Leslie Miller, MD<sup>1</sup>, Mark Dredze, PhD<sup>2</sup>, Carlos Aguirre<sup>2</sup>, Keith Harrigian<sup>2</sup>, Ayah Zirikly, PhD<sup>2</sup>, Margaret Chisolm, MD<sup>1</sup>, Peter Zandi, PhD<sup>1</sup>

#### Institutions:

1. Department of Psychiatry & Behavioral Sciences, Johns Hopkins University, Baltimore, MD 21224
2. Department of Computer Science, Whiting School of Engineering, Johns Hopkins University, Baltimore, MD 21224

#### Presenters:

underlined submitting presenter

**Background:** Mood and anxiety disorders are highly prevalent and significantly decrease the quality of life over the lifespan. Adolescence and young adulthood are critical times to intervene in the onset and course of common psychiatric disorders. Electronic communication such as text messaging, social media, and email are ubiquitous and often the predominant form of communication in adolescents and young adults. Research on individual-level electronic communication data and mental health is an emerging area of inquiry in clinical care and research. In the present study, we examine the feasibility and acceptability of incorporating patient electronic communication data into routine clinical care through a dashboard accessible by both the patient and clinician.

**Methods:** We invited all mental health providers who provide treatment to English-speaking patients ages 12 and older with a diagnosis of a mood or anxiety disorder at outpatient psychiatric clinics at Johns Hopkins Medicine to participate in the study. The research team partnered with Bark ([www.bark.us](http://www.bark.us)), a commercially available application (app), to collect participant electronic communication data. Patients were randomly assigned to the Intervention or Treatment as Usual (TAU) arm; providers were not randomized. For patients in the Intervention arm, the research team developed a participant-specific dashboard using information gathered via Bark from participants. Additionally, the provider shared the dashboard with the patient, and they collaboratively decided on whether or not to discuss the dashboard in detail in session. For participants in the TAU arm, the providers did not receive a clinical dashboard for review. Patients and providers completed a set of measures at baseline (first study visit after randomization), at each regularly scheduled clinic visit, every 3 months, every 6 months, and at the end of the study.

**Results:** A total of 67 patients and 31 providers enrolled in the study. We had a patient retention rate of 79.1% and a provider retention rate of 93.5%. Patients were between 12-63 years old (M=24.4, SD=11.7), 80.6% female (n=54), 73.1% White (n=49), 16.4% Black or African American (n=11), 7.5% Hispanic or Latino (n=5), and 3.0% other race (n=2). We will report on data to show patient and provider feedback on using the study dashboard in clinical sessions.

**Discussion:** We will discuss this novel approach to augment clinical care and how acceptable and feasible it is to patients and providers given the concerns around privacy.



### 34. Racial Differences in the Major Clinical Symptom Domains of Bipolar Disorder

Kevin Li, MD; Fernando Goes, MD

Presenters:

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**Background:** While most epidemiological studies show few differences in rates across race and ethnicities, Black individuals are routinely less likely to receive a diagnosis of Bipolar Disorder (BD) and more likely to be diagnosed with Schizophrenia, a traditionally more severe and chronic disorder with more limited expectations for remission. Prior studies have noted a greater preponderance of specific psychotic symptoms (such as persecutory delusions and hallucinations) and a dysphoric/mixed presentation in mania, but have been limited by the lack of systematic phenotypic assessment and small sample sizes. In the current report, we have combined data from two large multi-ethnic studies of BD with comparable semi-structured interviews to investigate differences in symptoms presentation across the major clinical domains of BD.

**Methods:** We combined two studies with comparable interview questions assessing mood and psychotic symptoms: the National Institute Mental Health Genetics Initiative (NIMH) Sample and the Genomic Psychiatry Cohort (GPC). Harmonization of both interviews were performed by extracting questions that specifically inquired about DSM-IV criteria for depressive, manic Episodes and lifetime psychotic symptoms.

**Results:** In the NIMH and GPC studies, there were 4823 patients diagnosed with BD1, including 856 of self-reported black ancestry. Both studies showed slight differences in sex distribution, but no difference in history of alcohol or drug use in Black subjects. Black subjects were less likely to endorse elevated mood (meta-OR=0.45[95% CI= 0.33-0.61]), pressured speech (meta-OR=0.58[0.45-0.74]), increase activity (meta-OR=0.7[0.5-0.97], and decreased need for sleep (meta-OR=0.78[0.61-0.98]). Depressive symptoms showed more heterogeneity across the two samples, but there were nevertheless robust differences in all aspects related to disturbed sleep, which were found to be more commonly endorsed in Black subjects. Psychotic symptoms showed a slight increase in prevalence in Black compared to White subjects (meta OR=1.27[1.07-1.5]). As consistent with the prior literature, we found prominent over-representation of hallucinations and both delusions and hallucinations of persecutory content in Black subjects.

**Discussion:** In a substantially larger sample compared to the prior literature, we find difference in symptom profiles in Black subjects may lead to presentations that can differ from the “prototypical” ideal of BD and provide impetus to ongoing efforts to better define the central manifestations and boundaries of psychiatric disorders across diverse populations.

### 35. No Association between Neutrophil-to-Lymphocyte Ratio and Suicidality: A study from large sample size

Zehan Li, M.S<sup>1</sup>; Salih, Selek, M.D<sup>2</sup>; Hua, Xu, Ph.D<sup>1</sup>

#### Institutions:

1. UTHHealth School of Biomedical Informatics, Houston, Tx
2. UTHHealth McGovern Medical School, Houston, Tx

#### Presenters:

underlined submitting presenter

**Background:** Indicators of chronic low-grade systemic inflammation have shown possible association with suicide ideation and behaviors among patients with bipolar disorder. Neutrophil to lymphocyte ratio (NLR), a systemic inflammation indicator, has shown promising linkage between low-grade inflammation and suicide among psychiatric patients. Prior study has investigated the interaction between NLR and stress-diathesis factors to suicidal risk in bipolar patients. This proposed study aims to continue research on the existing idea and to improve study design as well as statistical analysis by leveraging a larger sample from a local SafetyNet psychiatric hospital.

**Methods:** The proposed study adopts a case-control design to assess the association between NLR and suicide risk among bipolar patients from a large hospital database. Suicide risks were assessed using Columbia-Suicide Severity Rating Scale (C-SSRS) and blood sample were collected at the beginning of each visit for all patients. On the other hand, patients were selected as control if the suicide risk is low. Both groups are compared with their NLR value as the exposure. F-values were the main measurement to determine the effect of suicide risk level on NLR.

**Results:** A total of 2,618 patients are selected into the study. Analysis was done on descriptive statistics to characterize the study groups using Pearson's correlation, independent samples t-test, one-way ANOVA, and three-way ANOVA controlling for confounding factors such as age, gender, and suicide risk level. Correlation tests and ANOVA revealed that there was not a significant effect of suicide risk level on NLR ( $r = -0.03$ ;  $F = 1.42$ ,  $P = 0.24$ ).

**Conclusion:** This study is among the first to explore the association between NLR as an inflammation biomarker and suicide risk among bipolar disorder. However, the results contradict with the prior studies and pose questions to association between NLR and suicide risk. This study is limited to the cross-sectional nature of method. Future studies should investigate the dynamics between NLR and suicide risk through repeated measures to further validate their underlining association.

### 36. Treatment-Resistant Mood Disorders Among LGBTQ People Clinical Features and Response to ECT

Fumie Oka, MD; Kamile Weischedel, MD; Amanda Bakian, PhD; Brian J. Mickey, MD, PhD

**Institution:**

Huntsman Mental Health Institute and Department of Psychiatry University of Utah, Salt Lake City

**Presenters:**

underlined submitting presenter

**Background:** Individuals who identify as lesbian, gay, bisexual, transgender, or queer (LGBTQ) experience greater social exclusion and discrimination and higher rates of depression. Little is known about the clinical characteristics or treatment outcomes of LGBTQ people who have severe mood disorders. We hypothesized that LGBTQ patients would present with distinct clinical features and that they may not respond as favorably to electroconvulsive therapy (ECT).

**Methods:** A retrospective chart review (2018–2020) compared 59 LGBTQ patients and 441 non-LGBTQ patients who received an acute ECT series for treatment-resistant illness. Ninety-five percent were treated for a depressive episode. Clinical response was evaluated with the Clinical Global Impression Improvement (CGI-I) scale, self-rated Quick Inventory of Depressive Symptomatology (QIDS-SR), and QIDS-SR suicide item. ECT-related adverse effects were collected in six categories. Inverse probability of treatment weights were applied to regression models to balance baseline confounders.

**Results:** At baseline, LGBTQ status was associated with younger age, greater current suicide ideation, history of suicide attempt, self-injurious behavior, posttraumatic stress disorder, personality disorder, tobacco smoking, past substance use disorder, and history of sexual abuse (all  $P < 0.05$ ). With ECT treatment, LGBTQ and non-LGBTQ groups did not differ with respect to CGI-I score (odds ratio = 0.82, 95% CI = 0.48–1.40,  $P = 0.47$ ), change in QIDS-SR total score (least-squares mean =  $-9.2$  vs  $-8.1$ ;  $F_{1,408} = 1.42$ ;  $P = 0.24$ ), or change in QIDS-SR suicide item (odds ratio = 1.83, 95% CI = 0.91–3.68,  $P = 0.09$ ). Self-reported adverse effects did not differ between LGBTQ and non-LGBTQ patients (all  $P > 0.05$ ). Exploratory analyses of LGBTQ sub-groups showed that improvement in the QIDS-SR total score was greater for transgender than for cisgender patients ( $-11.5$  vs  $-7.5$ ;  $P = 0.02$ ).

**Conclusions:** LGBTQ people with treatment-resistant mood disorders presented with distinct clinical features. Some characteristics such as trauma, personality disorder, and substance use have been previously linked with less favorable treatment outcomes. Despite these differences, LGBTQ and non-LGBTQ patients experienced similar therapeutic and adverse effects with an acute ECT series. Patients with treatment-resistant depression should be offered timely access to ECT regardless of sexual orientation and gender identity.

### 37. Treating Attention and Mood Disorders in Collegiate Athletes: Developing a Best Practices Framework for Sports Psychiatrists

James Moley

**Institution:**

The Ohio State University

**Presenters:**

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**Background:** Attention-deficit hyperactivity disorder (ADHD) is commonly associated with depressive disorders with evidence suggesting a 6.5-fold increased risk for depression within the first year following ADHD diagnosis. Multiple possible explanations have been described regarding this relationship, including causal links of ADHD genetic liability on subsequent depression. To highlight the importance of adequate treatment and unique challenges associated with treating student-athletes, we present the case of a 20-year-old Caucasian male student-athlete who presented to the outpatient clinic with uncontrolled hyperactive and inattentive symptoms consistent with his history of ADHD, combined type. He endorsed difficulty concentrating on tasks, avoidance of tasks that require attention, distractibility, inability to sit still, forgetting items, and intermittent difficulty with mood and lack of frustration tolerance. Despite taking maximum doses of methylphenidate and lisdexamphetamine daily for the past several months, he was at risk to fail multiple classes and lose NCAA eligibility. Past medication trials include maximum doses of amphetamine/dextroamphetamine salts, dexamethylphenidate, guanfacine, and atomoxetine; all of which were helpful but waned in efficacy with time. He was interested in trying new medication but expressed concern related to compliance with NCAA guidelines as well as what information would be released to his training staff. After consultation with the patient and his family, pharmacy, and a child/adolescent psychiatrist the decision was made to initiate treatment with dextroamphetamine at the maximum dose. He was briefed about compliance with NCAA prescribing guidelines and provided consent for the treating physician to speak with his training staff about the generic risks of stimulant use in athletes. He returned to clinic in four weeks and reported significant improvement in his attention and mood symptoms. He was better able to focus and complete assignments and was now on pace to complete the coursework required to remain eligible and graduate.

**Discussion:** This case illustrates the link between ADHD and depressive symptoms as well as unique challenges associated with prescribing stimulant medication in a population under strict regulatory guidelines. Adequate assessment and treatment of ADHD symptoms is critical to identifying and preventing depressive disorder co morbidities, as evidence by this patient's reported mood symptoms and considering significant evidence demonstrating the link between these disorders. In addition, the use of stimulant medication in high performance athletes is controversial and necessitates consideration of many factors including the likelihood of performance enhancement, regulatory guidelines, and risks associated with use. While NCAA guidelines mandate consideration of non-stimulant options prior to use, this patient's past medication trials and level of impairment drove the decision to prescribe dextroamphetamine. Further, this case highlights unique challenges faced when consulting for college athletes, namely potential pitfalls around boundaries and communication with the patient, family, and athletic training staff. Best practice guidelines should focus on multidisciplinary engagement, incorporate institutional and NCAA regulations, and be framed to emphasize efficacy, privacy, and psychoeducational aspects of treatment.

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### 38. Efficacy and adverse effects of ketamine versus electroconvulsive therapy for major depressive disorder: a systematic review and meta-analysis

Débora Moreira, MD<sup>1</sup>; Luís Eduardo Gauer, MS<sup>2</sup>; Guilherme Teixeira, MS<sup>3</sup>; Amanda Silva, MS<sup>4</sup>; Stefanie Cavalcanti, MD<sup>1,5</sup>; João de Quevedo, MD, PhD<sup>1,5</sup>

#### Institutions:

1. Faculdade de Ciências Médicas de Santos, Fundação Lusíada (UNILUS), Santos, SP, Brazil
2. Universidade Federal do Paraná (UFPR), Curitiba, PR, Brazil
3. Universidade de Pernambuco (UPE), Recife, PE, Brazil
4. Universidade Federal de Santa Catarina (UFSC), Florianópolis, SC, Brazil
5. The University of Texas Health Science Center at Houston, McGovern Medical School Houston, Texas, USA

#### Presenters:

underlined submitting presenter

**Background:** Major depressive disorder is one of the most prevalent (16%–20%) psychiatric disorders worldwide (1). Unfortunately, approximately one-third of patients that receives standard pharmacotherapy treatment fail to achieve functional recovery (2). The gold standard treatment for TRD is ECT, which has a faster therapeutic onset than antidepressant drugs. However, it requires multiple sessions, may have cognitive side effects, and carries a well-known stigma among patients and their families. (3) Clinical studies involving ketamine have shown its rapid-onset antidepressant effects and impact on suicidal thoughts, which seems to be an attractive alternative for TRD (4-6).

We performed an updated meta-analysis, including Randomized controlled trials and observational studies evaluating the efficacy and side effects they presented. No studies have yet achieved a statistical analysis comparing the latest published studies about ECT and sub-anesthetic doses of ketamine.

**Methods:** We searched the bibliographic databases MEDLINE, Web of Science, Embase, PsycInfo, and Google Scholar without restrictions on publication date. We also searched trial registers, which were the Cochrane Register of Controlled Trials, ClinicalTrials.gov, and the World Health Organization's International Clinical Trials Registry Platform (WHO-ICTPR), to identify any unpublished or ongoing trials.

This study was conducted following the Cochrane Handbook and registered with PROSPERO (registration number CRD42022349220). All reports were consistent with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

**Results:** A total of 2876 articles were retrieved. After a full-text screening of 15 studies, six (involving 327 patients) met the inclusion criteria.

Effect estimates and standard errors were used to perform a random effects meta-analysis of the comparison between intervention groups at the end of the treatment. The pooled estimate of the Hedges' g in depression scores between the ketamine and electroconvulsive therapy arms was 0.05 (95%CI: -0.62 to 0.72), where positive values suggest electroconvulsive therapy was superior to ketamine in reducing depressive symptoms. The between-study heterogeneity variance was estimated at  $\tau^2$ -estimate = 0.24 (95%CI: 0.01 to 2.61), with an  $I^2$  value of 66% (95%CI: 19.1 to 85.8%).

**Conclusion:** The analysis's results could not generate robust evidence to support the superiority of any of the interventions studied. Further research is needed to establish whether ketamine is equivalent, superior, or inferior to ECT in treating depressive patients.

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### 39. Comorbid Conditions and Caution: A Case of Phentermine-Induced Mania with Psychotic Features

Alyssa Nielsen, BS<sup>1</sup>; Lymaries Velez, MD<sup>2</sup>; Steven Toffel, MD<sup>2</sup>; Brent Carr, MD<sup>2</sup>

#### Institutions:

1. College of Medicine, University of Florida, Gainesville, FL 32610
2. Department of Psychiatry, University of Florida, Gainesville, FL 32608

#### Presenters:

underlined submitting presenter

**Background:** Stimulants such as methamphetamine and cocaine have well documented histories of inducing mania, psychosis, and other mental health pathology.<sup>1</sup> Phentermine, a sympathomimetic amine, has properties akin to d-amphetamine. Tolerance, psychosis, and mania have even appeared in patients taking prescribed, therapeutic doses.<sup>2,3</sup> Proper screening and monitoring are critical for safe prescribing of this medication and its abuse potential must not be underestimated.

**Methods:** Here we review this medication's potential pitfalls and report a case of a patient vulnerable to problematic outcome. Ms. D is a 45-year-old Caucasian female attorney with a documented psychiatric history of "bipolar affective disorder", alcohol use disorder, and stimulant use disorder (phentermine) who presented voluntarily to an inpatient substance use treatment facility for alcohol and phentermine use. The patient reported "occasional" use of "6 or more" phentermine tablets, 2-3 binge drinking episodes per week, and daily use of CBD gummies. The online drug monitoring system confirmed a phentermine prescription. Past psychiatric history was positive for a previous inpatient hospitalization 15 years prior secondary to an episode concerning for mania with psychotic features in the context of phentermine use. She has not had any other psychiatric hospitalizations until her current admission.

Collateral from coworkers during the current admission revealed recent separation from her husband, abrupt departure from work, and her being found wandering barefoot and confused in her neighborhood. During admission, she was noted to be paranoid, responding to internal stimuli, and displayed guarded and uncooperative behavior with mood lability, which led to involuntary transfer to an inpatient psychiatric facility. Laboratory tests were initially refused by the patient, but UDS performed two days following admission was positive for cannabis.

**Results:** After transfer to an inpatient psychiatric facility, she was managed for 5 days without psychotropic medications under involuntary status. A legal proxy was identified and the patient was stabilized with 4 days of risperidone 2mg qhs. Given the history of bipolar affective disorder per records and presenting symptoms of mania with psychosis lasting 5 days after admission, the differential diagnosis included bipolar 1 disorder currently manic with psychosis versus substance induced mania versus substance induced psychotic disorder. As proxy had ongoing concerns for poor medication adherence and symptom relapse, the decision was made to initiate monthly paliperidone 156mg injections.

**Conclusions:** This case highlights the importance of screening patients for illicit substance use and reviewing use of prescribed medication. The use of an LAI in this case could be up for debate as the patient's symptoms may have been substance induced and remitted with time. Final points for consideration are the areas for improvement in the medical management of this patient, including delayed time to identification of legal proxy and medication initiation, sparse collection of collateral information, and prescription of phentermine with potential for inducing psychosis or mania especially for a patient with bipolar disorder.

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#### 40. Delineating Anhedonia from Depressed Mood and Apathy: The Relationship Between Anhedonia, Cognition, Activity, and Social Support

Zachary Nitsch, B.S.<sup>1</sup>; Natalie S. Marr, B.S.<sup>1</sup>; Erika F.H Saunders<sup>1</sup>, MD; Dahlia Mukherjee, PhD<sup>1</sup>

##### Institution:

1. Department of Psychiatry and Behavioral Health, Penn State Milton S. Hershey Medical Center, Hershey PA

##### Presenters:

underlined submitting presenter

**Objective:** Anhedonia, defined as a loss of interest or pleasure in activities that were once pleasurable, is a key symptom of Major Depressive Disorder (MDD). Interventions primarily focus on reducing depressed mood, and anhedonia is often missed as a treatment target. Cognitive behavioral therapy (CBT) of MDD reduces depressed mood by targeting cognitions, behavior and interpersonal relationships. Additionally, apathy, which indicates lack of motivation or energy, is considered a distinct construct from anhedonia. In this study, we examined the relationship between anhedonia and cognitions, physical activity, and perceived social support controlling for depressed mood and apathy. We hypothesized that there would be significant positive correlations between anhedonia and negative thoughts, suicidal thoughts, and sedentary behavior, and a significant negative correlation between anhedonia and perceived social support and thoughts related to self-esteem.

**Methods:** The sample consisted of 17 participants diagnosed with MDD and 13 healthy controls recruited from the central Pennsylvania area. Participants were part of a larger study and filled out self-reported questionnaires, measuring perceived social support (the Multidimensional Scale of Perceived Social Support (MSPSS)), apathy (the Apathy Motivation Index Scale (AMIS)), depressed mood (item 2), suicidal thoughts (item 9) and negative thoughts (items 6 and 7) from the Patient Health Questionnaire (PHQ9), thoughts on self-esteem (the Rosenberg Self-Esteem Scale (RSES)), sedentary behavior (the International Physical Activity Scale (IPAQ)), and anhedonia with the Snaith-Hamilton Pleasure Scale (SHAPS). Pearson product moment bivariate and partial correlations were calculated.

**Results:** Anhedonia was positively correlated with sedentary behavior ( $r=.44$ ,  $p=.02$ ), negative thoughts ( $r=.73$ ,  $p<.001$ ), and suicidal thoughts ( $r=.67$ ,  $p<.001$ ) and negatively correlated with self-esteem ( $r=-.83$ ,  $p<.001$ ) and marginally significant with perceived social support ( $r=-.35$ ,  $p=.056$ ). When controlling for apathy and depressed mood, anhedonia remained positively correlated with sedentary behavior ( $r=.38$ ,  $p=.046$ ) and suicidal thoughts ( $r=.51$ ,  $p=.006$ ) and negatively correlated with self-esteem ( $r=-.55$ ,  $p=.003$ ).

**Conclusion:** Anhedonia is specifically associated with cognitions and activity levels. This may have treatment implications suggesting management of anhedonia by focusing on thoughts and physical activity during CBT.



## 41. Functional and Structural Network Features of Apathy in Late-life Depression and Associations with Response to Escitalopram Treatment

Lauren E. Oberlin, PhD<sup>1,2</sup>; Lindsay W. Victoria, PhD<sup>1,2</sup>; Irena Ilieva, PhD<sup>1</sup>; Katharine Dunlop, PhD<sup>1</sup>; Matthew J. Hoptman, PhD<sup>3,4</sup>; Jimmy Avari, MD<sup>1,2</sup>; George S. Alexopoulos, MD<sup>1,2</sup>; Faith M. Gunning, PhD<sup>1,2</sup>

### Institutions:

1. Department of Psychiatry, Weill Cornell Medicine, 525 E 68th St, New York, NY 10065, USA
2. Weill Cornell Institute of Geriatric Psychiatry, 21 Bloomingdale Road, White Plains, NY 10605, USA
3. Clinical Research Division, Nathan S. Kline Institute for Psychiatric Research, Orangeburg, NY 10962, USA
4. Department of Psychiatry, NYU Grossman School of Medicine, New York, NY 10016, USA

### Presenters:

underlined submitting presenter

**Background:** Apathy is a disorder of motivation common in late-life depression with substantial clinical implications including poor response to pharmacotherapy and higher rates of chronicity, disability, and functional decline. Effective treatments are scarce, and the brain network mechanisms underlying apathy are poorly understood. This study combined functional and diffusion-weighted imaging to assess the network mechanisms of apathy in major depression and identify brain network features that predict response to antidepressant treatment.

**Methods:** Structural and functional magnetic resonance imaging (MRI) data were collected from 40 non-demented older adults (age 59-85 years; Mean: 70.02) with nonpsychotic major depressive disorder. We used resting state MRI to evaluate whether resting state functional connectivity (rsFC) of the salience network distinguished apathetic from nonapathetic depressed older adults. Diffusion MRI connectometry was similarly used to evaluate differences in structural connectivity. We further examined whether apathy-associated variability in rsFC at baseline mediated the relationship between presence of apathy and treatment response following a 12-week single-arm escitalopram trial (NCT01728194).

**Results:** Forty participants (mean age 70.02 years, SD: 6.6) with major depression were studied. Of these, 20 (50%) also had apathy. Relative to nonapathetic depressed participants, apathetic depressed participants had lower rsFC of salience network seeds with the dorsolateral prefrontal cortex (DLPFC), premotor cortex, midcingulate cortex (MCC) and paracentral lobule, and greater rsFC with the lateral temporal gyrus and temporal pole. Reduced anisotropy was observed among participants with apathy in the corpus callosum, cingulum, and the left frontooccipital fasciculus. Lower insula-DLPFC/MCC rsFC was associated with lesser symptomatic improvement ( $\beta(df) = 0.588(26)$ ;  $p=0.001$ ) and decreased likelihood of remission (OR (95% CI)=1.041 (1.003, 1.081)  $p=0.036$ ) posttreatment. In regression models, insula-DLPFC/MCC rsFC was a mediator of the relationship between apathy at baseline and persistence of depression (indirect effect  $\beta = -0.586$ ; bootstrapped 95% CI: -1.477, -0.072).

**Conclusions:** Motivational disturbances in depression may arise from alterations in functional connectivity among the salience, default mode, and executive control networks, along with compromised structural connectivity in a core set of brain circuits. Network abnormalities associated with apathy also predicted persistent depression following selective serotonin reuptake inhibitor treatment. These findings demonstrate the importance of salience network disruptions to the behavioral manifestations of apathy and the persistence of clinical symptoms following pharmacologic treatment, and highlight potential brain network targets for novel interventions.

## 42. Is there an impact of race on lifetime medication history of patients with bipolar disorder?

Carolina Olmos, MD<sup>1,2</sup>; Sudhakar Selvaraj, MD, PhD<sup>1</sup>; Vineeth John, MD, MBA<sup>1</sup>; Marsal Sanches, MD, PhD<sup>3,4</sup>; Jair C. Soares, MD, PhD<sup>1,2</sup>

### Institutions:

1. UT Center of Excellence on Mood Disorders, Department of Psychiatry and Behavioral Sciences, UT Health McGovern Medical School, Houston, TX
2. UT Harris County Psychiatric Center, Department of Psychiatry and Behavioral Sciences, UT Health McGovern Medical School, Houston, TX
3. Department of Psychiatry and Behavioral Sciences, Baylor College of Medicine, Houston, TX
4. The Menninger Clinic, Houston, TX

### Presenters:

underlined submitting presenter

**Background:** Several studies suggest that there are differences in the way diagnoses of affective disorders and schizophrenia are made across different racial groups. In particular, previous research suggests that African American patients are less likely to be diagnosed with bipolar disorder (BD) and more likely to receive a diagnosis of schizophrenia when compared with individuals from other racial groups. Notably, such differences in the diagnoses suggested to contribute to the racial inequalities in the treatment of BD in that there are differences in the lifetime use of mood stabilizers according to race. We assessed the differences in treatment history among outpatients with BD from different racial backgrounds.

**Methods:** The sample consisted of 293 outpatients with BD (194 Bipolar I, 77 Bipolar II, and 22 Bipolar NOS). Patients were classified according to race: 200 Caucasians (66 males, 134 females, mean age = 38.71 +- 12.94), 70 Hispanics/Latinos (22 males, 48 females, mean age = 34.83 +- 10.88), and 23 African Americans (10 males, 13 females, mean age = 31.10 +- 8.02). Data about lifetime treatment/medication history was collected. The diagnosis of BD and the patient's lifetime history of psychotic symptoms was established by administering the Structured Clinical Interview for DSM-IV (SCID-IV). The statistical analysis was performed using the chi-square test, and a 0.05 significance level was adopted.

**Results:** Based on lifetime treatment history, there were no statistically significant differences across groups regarding the use of mood stabilizers (Whites/Caucasians: 61%; Hispanics/Latinos: 57%; African Americans: 61%). Lifetime use of antipsychotics was remarkably higher among African American patients (78%, against 35% of White/Caucasian patients and 45% of Hispanic/Latino patients,  $X^2 = 16.96$ ;  $df=2$ ;  $p<0.05$ ). However, these differences were not related to the presence of psychotic symptoms, as the rates of lifetime psychosis were similar across the three groups (Whites/Caucasians: 27%; Hispanics/Latinos: 30%; African Americans: 30%).

**Conclusions:** Our results point to critical differences in antipsychotics medication use/prescription among patients with BD from different racial backgrounds. African American patients showed higher rates of antipsychotic treatment use than the two other groups analyzed despite the similar rates of lifetime psychosis history. These findings raise concerns about possible influences of the racial/ethnic background on the decision- making process during the treatment of patients with BD.

**Key words:** bipolar disorder, health/racial disparities, antipsychotics, mood stabilizers

### 43. Using Natural Language Processing and Machine Learning to Predict School Violence in Youth

Alexander Osborn, M.S.<sup>1</sup>; Blessing Fanegan<sup>1,2</sup>; Andrew Cifuentes<sup>1</sup>; Reine Decker<sup>1</sup>; Rosalie Hemphill<sup>1</sup>; Patrick Kennedy<sup>1</sup>; Jennifer Combs, L.I.S.W.<sup>1</sup>; Michael Sorter, M.D.<sup>1</sup>; Judith Dexheimer, Ph.D.<sup>1</sup>; and Drew Barzman, M.D.<sup>1</sup>

**Institution:**

1. Division of Child and Adolescent Psychiatry, Cincinnati Children's Hospital Medical Center
2. College of Arts and Sciences, University of Cincinnati

**Presenters:**

underlined submitting presenter

School Violence involves all violence that occurs in a school setting, It includes bullying, weapon use, fighting, and sexual violence. In recent years, there has been an uptake in a more extreme forms of school violence: school shooting. An AI using natural language processing and machine learning has been built to predict the risk of school violence in children and adolescents between the ages of 10 to 18. The study recruited, enrolled, and tracked outcomes for 682 patients admitted to College Hill. After being enrolled in the study, participants were interviewed and their data was uploaded to the AI. The study found that AI was good at detecting risk of school violence. The study also found that scores on the BRACHA were the best predictor of school violence. The study intends to continue to expand their number of participants to improve the effectiveness of the risk assessment program.

#### 44. KIOS: A Smart Phone App for Self-Monitoring for Patients with Bipolar Disorder

Mehak Pahwa, MD<sup>1</sup>; Susan L. McElroy, MD<sup>2</sup>; Richard Priesmeyer, PhD<sup>3</sup>; Gregg Siegle, MS<sup>4</sup>; Phyllis Siegle, JD<sup>4</sup>; Sharon, Nuss, MS<sup>1</sup>; Omar H Elsayed<sup>1</sup>; Rif S. El-Mallakh, MD<sup>1</sup>

##### Institutions:

1. Department of Psychiatry and Behavioral Sciences, University of Louisville School of Medicine, Louisville, Kentucky
2. Department of Psychiatry and Behavioral Neuroscience, University of Cincinnati, Cincinnati, Ohio
3. Jurica Professor of Management, Department of Management and Marketing, St Mary's University, San Antonio, Texas
4. Biomedical Development Corporation, San Antonio, Texas

##### Presenters:

underlined submitting presenter

**Background:** Bipolar Disorder (BD) is a recurrent, life-long, and often chronic psychiatric illness with episodic course and relapses despite treatment making the course of the illness more challenging.<sup>1</sup> Mental health applications (apps) offers opportunities to address some of these challenges through self-monitoring and self-management,<sup>1</sup> and have the potential to individualize treatment by collecting daily data for symptom pattern and can well complement clinical practice.<sup>2</sup> This study examined the use of a self-monitoring/self-management smart phone application (app) for patients with bipolar disorder. The app was specifically designed with patient-centered computational software system based on concepts from nonlinear systems (chaos) theory.

**Methods:** This was a randomized, active comparator study of use of the KIOS app compared to an existing free app that has high utilization rates known as eMoods, over 52 weeks, and performed in three academic centers. Patients were evaluated monthly utilizing the Bipolar Inventory of Symptoms Schedule (BISS). The primary outcome measure was persistence of using the app over the year of the study.

**Results:** Patients assigned to KIOS persisted in the study longer than those assigned to eMoods; 57 patients (87.70%) in the KIOS group versus 42 (73.69%) in the eMoods group completed the study ( $P = 0.03$ ). By 52 weeks, significantly more of KIOS group (84.4%) versus eMoods group (54%) entered data into their programs ( $\chi^2=14.2$ ,  $df=1$ ,  $P = 0.0002$ ). Patient satisfaction for KIOS was greater ( $F = 5.21$ ,  $df = 1, 108$ ,  $P = 0.025$ ) with a standardized effect size (Cohen's  $d$ ) of 0.41. There was no difference in clinical outcome at the end of the study between the two groups.

**Conclusions:** This is the first randomized comparison study comparing two apps for the self-monitoring/self-management of bipolar disorder. While no clinical superiority was demonstrated, the study revealed greater patient satisfaction and greater adherence to a patient centered software program (KIOS) than a monitoring program that does not provide feedback (eMoods). Future studies need to examine acutely symptomatic patients to determine the role of apps in contributing to recovery. This was a first of its kind randomized trial in the field of mental health apps with an active comparator and gives some valuable findings which can be used for developing further studies to study more specific role of apps in the management of bipolar disorder.

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#### 45. Depression Management in Psychiatry and Primary Care: The Impact of Online CME on Physician Knowledge, Competence, and Confidence Related to Pharmacogenetics

Natalie Guevara, DVM, MPH; Clinton Wright, PharmD, BCPP; Jovana Lubarda, PhD; Sagar Parikh, MD, FRCPC

##### Presenters:

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**Background:** Major depressive disorder (MDD) is the most common mental disorder in the United States. It accounts for an average of 8 million ambulatory care visits per year and is the leading cause of disability worldwide. Despite the morbidity and mortality associated with MDD and the considerable toll on productivity and quality of life, many patients do not receive adequate treatment. Pharmacogenomic testing, and particularly combinatorial pharmacogenomics testing, represents a potential means for delivering personalized treatment selection or treatment adjustments for patients with MDD. This study examined whether online continuing medical education (CME) could improve the knowledge, competence, and confidence of psychiatrists and primary care providers (PCPs) regarding the role of pharmacogenetic testing in the management of MDD.

**Methods:** Clinicians participated in a 30-minute online video-based roundtable discussion led by 3 expert faculty members. A multi-perspective, video format was chosen as the educational format based on the objectives of the program. A repeated-pair design was used to assess educational effectiveness. Three multiple choice questions assessed knowledge, and 1 question rated on a Likert-type scale assessed confidence. A paired samples t-test was conducted for significance testing on overall average number of correct responses and for confidence rating, and a McNemar's test was conducted at the question level (5% significance level,  $P < .05$ ). Data were collected from 10/15/2021 to 6/6/2022.

**Results:** A total of 195 PCPs and 1,250 psychiatrists completed both the pre- and post- assessments. The results demonstrated a high baseline of knowledge/competence among psychiatrists and a significant improvement in knowledge, competence, and confidence related to the role of pharmacogenetic testing in depression management among PCPs. Among PCPs, there was a 60% relative increase ( $P < 0.001$ ) in knowledge regarding the clinical data on the genetic variants that may affect clinical response to antidepressant therapy (pre 35%, post 56%). Psychiatrists had a 4% relative increase ( $P < 0.01$ ) in knowledge with this learning objective and demonstrated a high level of baseline knowledge, with a pre-education mean correct response of 80% (post 83%). Among PCPs, there was an 8% relative increase ( $P < 0.05$ ) in competence related to the selection of antidepressant therapies based on the results of PGx testing in patients with depression (pre 71%, post 77%).

Psychiatrists showed a 3% relative increase in competence and demonstrated a high baseline in competence, with a pre-education mean correct response of 86% (post 89%). Psychiatrists were 13% more likely and PCPs were 110% more likely to answer all questions correctly at post versus pre ( $P < 0.05$ ). 45% of PCPs and 46% of psychiatrists increased ( $P < 0.001$ ) their confidence in their ability to identify patients with depression who may benefit from pharmacogenomic testing resulting in 16% of PCPs and 33% of psychiatrists being "mostly confident" or "very confident" post-education (PCPs: pre 6%, psychiatrists: pre 18%).

**Conclusions:** This study demonstrated the success of online, video-based panel discussion CME on improving knowledge, competence, and confidence related to the role of pharmacogenomics in the management of MDD. Additionally, the results revealed a higher level of knowledge and competence among psychiatrists regarding pharmacogenomics in depression care. These findings suggest that future educational programs should tailor education to these physician learner groups to address their different needs along the adult learning continuum.

## 46. Prevalence of Workplace Trauma and PTSD Symptoms Among Intern Physicians Training Before and During the COVID-19 Pandemic: A Repeated Annual Cohort Study

Michelle Ptak; Karina Pereira-Lima, PhD, MSc; Elena Frank, PhD; Srijan Sen, MD, PhD

### Presenters:

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**Background:** Medical internship has been shown to be a time of high stress, during which intern physicians experience high rates of mental health problems, including symptoms of post-traumatic stress disorder (PTSD)<sup>1</sup>. The COVID-19 pandemic posed an unprecedented global health crisis that resulted in relevant changes to the work environment of intern physicians. In response to the anticipated negative consequences of the pandemic on physicians' mental health, an enhanced focus on the wellbeing of training physicians was adopted by several residency programs nationwide. While previous studies suggest a high prevalence of PTSD symptoms among healthcare professionals working during the COVID-19 pandemic<sup>2</sup>, to our knowledge, no studies assessed whether the prevalence of PTSD symptoms among intern physicians training during the pandemic differs from pre-pandemic levels. Here, we leveraged data from a repeated annual cohort study of intern physicians to assess differences in the prevalence of workplace trauma exposure and PTSD symptoms among interns training in the 2018 (pre-COVID) and 2019 (during COVID) academic years.

**Methods:** We analyzed data from two cohorts (2018 and 2019) of the Intern Health Study<sup>3</sup>, a repeated annual cohort study of intern physicians. Data included demographic characteristics collected two months prior to commencing internship and the Primary Care PTSD Screen for DSM-5 (PC-PTSD-5) collected at the 12<sup>th</sup> month of internship (June 2019 [for the 2018 cohort] and June 2020 [for the 2019 cohort]). The PC-PTSD-5 begins with a screen for trauma exposure, which was adapted to specify physician-specific exposures: *"Sometimes things happen to physicians that are unusually or especially frightening, horrible, or traumatic. For example: sudden patient deaths, serious medical errors, workplace violence, hazardous exposure, or repeated or extreme exposure to the details of traumatic events. Have you ever experienced this kind of event as a physician?"* A score of 3 or greater on the PC-PTSD-5 is considered a positive screen for PTSD. Differences in the prevalence of medical trauma exposure and PTSD symptoms were assessed using  $\chi^2$  tests. A 2-sided  $P < .05$  was considered statistically significant.

**Results:** A total of 3,812 interns enrolled in the Intern Health Study in 2018 (N=2,127) and 2019 (N=1,685). Of those, 1,958 (51.4%) completed the PC-PTSD-5 at the 12<sup>th</sup> month of internship and were included in the present study (2018 cohort, 1,138 [58.1%]; 2019 cohort, 820 [41.9%]; women, 1116 [57.0%]; mean age, 27.5 years [SD=2.9]). Compared to medical interns who worked prior to the pandemic (2018 cohort), those who worked during Wave 1 of the pandemic (2019 cohort) were significantly less likely to report medical trauma exposure (644 [56.6%] vs. 424 [51.7%],  $\chi^2 = 4.6$ ,  $p = .03$ ) and to screen positive for PTSD (124 [10.8%] vs. 61 [7.4%],  $\chi^2 = 6.7$ ,  $p < .01$ ). A secondary analysis including only interns who reported workplace trauma exposure also demonstrated a significantly higher prevalence of PTSD symptoms among interns working prior to the pandemic in comparison to those working during the pandemic (128 [19.2%] vs. 61 [14.4%],  $\chi^2 = 4.2$ ,  $p = .04$ ).

**Conclusions:** Our results suggest that the prevalence of workplace trauma exposure and PTSD symptoms among medical interns working during the onset of the COVID-19 pandemic was lower than that of medical interns working prior to the pandemic. Future analyses should investigate the potential impact that experiences with one's residency program may have on the likelihood of screening positive for PTSD, as well as potential drivers of the lowered prevalence of PTSD symptoms among intern physicians working during the pandemic.

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## 47. Personalized characterization of the evolution of cognitive function in older adults with mood disorders

Boyu Ren<sup>1</sup>; Regan Patrick<sup>2</sup>; Brent Forester<sup>2</sup>

### Institutions:

1. Laboratory for Psychiatric Biostatistics, McLean Hospital, Belmont, MA 02478
2. Geriatric Psychiatry Research Program, McLean Hospital, Belmont, MA 02478

### Presenters:

underlined submitting presenter

**Background:** Individuals with mood disorders (MDs), such as depression and bipolar disorder, have been observed to have distinct changes in cognition with advancing age compared to healthy controls. However, the temporal evolution of these cognitive changes, especially amongst an older population, has not been well characterized at the individual level due to the limitations of sample sizes and analytic approaches that are insufficient to capture the complex relationship between mood disorders and cognitive impairment with advancing age.

**Methods:** The association between baseline MDs and rate of decline in cognitive function were examined using longitudinal data from a combination of the McLean Geriatric Mood Disorders Database (GMDD; 47 major depression, 43 bipolar disorder and 25 controls) and the Alzheimer's Disease Neuroimaging Initiative (ADNI; 100 controls). A two-level hierarchical spline model was applied to model the potentially non-linear subject-level relationship between time and three measures of cognitive function, include the Mini-Mental State Examination (MMSE) score and times to complete Trail Make Test (TMT) A and B. Baseline MD status (major depression, bipolar disorder and control) and demographic information as well as spline basis of time since enrollment were included as covariates in the model. An interaction between baseline MDs and time was used to explicitly capture the association between MD status and the rate of change in cognitive function. Study-specific (GMDD vs. ADNI) and subject-specific random intercepts and slopes were included to account for the nesting structure of the data. Statistical tests were performed at two time points (12 months and 24 months) to compare the differences in rate of change between different patient groups.

**Results:** A significant decline in the baseline MMSE scores was observed in both major depression (MDD; - 0.69, 95% CI: [-1.04, -0.33]) group and bipolar disorder (BD; -1.17, 95% CI: [-1.54, -0.79]) group compared to healthy controls. However, the interaction between MD status and time were not significant (F-statistic = 0.98, df = 3, p-value = 0.40). A similar set of results was observed for time to complete TMT A: significant increases in time to complete at baseline for MDD (26.27, 95% CI: [14.66, 37.88]) and BD (23.9, 95% CI: [11.52, 36.28]) groups compared to healthy controls while the interaction between MD status and time was not significant (F- statistic = 1.11, df = 3, p-value = 0.35). For time to complete TMT B, the baseline significant association with MD status was again detected. But there was also a significant increase in the rate of change at month 24 (2.71, 95% CI: [0.46, 4.97]).

**Conclusion:** Our results suggest that there is a consistent cross-sectional association between MD status and cognitive function while the rate of change of cognitive function is only significantly different between MDD and healthy control in TMT B. This implies that the MD-related accelerated cognitive decline might be most pronounced in executive functions.

## 48. Housing rats at moderate altitude increases depressive symptoms, causes systemic inflammation and alters cognitive behavior.

P.F. Renshaw<sup>1,2</sup>, R. Ettaro<sup>1</sup>, S. Kanekar<sup>1,2</sup>

### Institutions:

1. Dept of Psychiatry, University of Utah, Salt Lake City, UT
2. VISN19 Rocky Mountain MIRECC & US Dept of Veterans Affairs, Salt Lake City, UT

### Presenters:

underlined submitting presenter

**Background:** Risk for major depressive disorder (MDD) increases with living at altitude, and hypobaric hypoxia may play a role. Residents at 4,500ft exhibit low arterial blood oxygen levels and MDD-linked deficits in fore- brain energetics vs. those at sea level. We developed a sex-based animal model to study depression at altitude. Rats housed at moderate altitude (4,500ft, 10,000ft) exhibit behavioral and molecular biomarkers for depression vs those at sea level: increased depressive symptoms, and reduced energetic markers and monoamines in MDD-linked brain regions <sup>1,2</sup>. MDD is linked to issues in decision-making, problem-solving and cognitive control, and both MDD and hypoxia are linked to inflammation. In this study, we asked whether housing at altitude may alter cognitive function and inflammatory status.

**Methods:** Male (M) and female (F) rats were housed for 2wks at sea level conditions (in a hyperbaric chamber) or at 4,500ft (local conditions, Salt Lake City, UT). Rats were tested for cognitive behavior in the novel object recognition test. On day 1, rats are habituated to the novel field. On day 2, a rat is placed in the box with 2 identical objects at 2 corners (sample trial). On day 3, the rat is placed in box with a novel object replacing one of the original (familiar) objects for the choice trial. Time spent with each object, number of contacts made and latency to first contact are measured. Rodent serum was tested by ELISA for the inflammatory cytokine, interleukin 6 (IL6), a biomarker of systemic inflammation.

**Results:** Cognitive Function: In sample trial, rats did not differ with altitude in exploration, latency to first contact or frequency of contact with either object. In the choice trial, rats at sea level spent more time with the novel object (F-96sec, M-83sec) vs. the familiar one (F-88sec, M-63sec), as expected. However, rats at altitude spent less time exploring the novel object (F-54sec, M-31sec) vs. the familiar one (F-93sec, M-52sec). Time spent with the novel object was significantly lower in males at altitude vs. sea level (Student's t-test,  $p=0.03$ ,  $n=5ea$ ), and shows a trend to be lower in females at altitude ( $p=0.06$ ). Rats at sea level show much shorter latency to first contact of novel object (M, F-2sec) vs. the familiar one (F-11sec, M-37sec). In contrast, rats at altitude show longer latency to first contact of both the novel (F-11sec, M-17sec) and familiar objects (F-17sec, M-22sec). Altitude groups do not differ in motor function and do not show signs of neophobia (all rats approach the novel object before the familiar one). Inflammation: Serum IL6 was significantly higher at altitude vs. at sea level in females (Student's t-test,  $p=0.04$ ,  $n=6ea$ ) and shows a similar trend in males ( $p=0.07$ ).

**Conclusions:** These data indicate that hypobaric hypoxia exposure at moderate altitude may increase systemic inflammation and cause cognitive dysfunction. Cognitive dysfunction and systemic inflammation are linked to MDD, and may be involved in altitude-related depression.

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## 49. Surge protected portable Ear EEG for Electroconvulsive Therapy

Alexandra Bailey<sup>1</sup>, John Craig<sup>1</sup>, Collin McCloskey<sup>1</sup>, Shreya Ramesh<sup>1</sup>, Andrew Stowers<sup>1</sup>, Nicola Polizotto<sup>2</sup>, Salih Selek<sup>2</sup>

### References:

1. Department of Biomedical Engineering, University of Texas at Austin
2. Department of Psychiatry, UTHealth McGovern Medical School

### Presenters:

underlined submitting presenter

**Background:** there are limited options for monitoring neural activity following the delivery of stimulus during ECT. In order to fully capture all brain states included before and after procedures without losing valuable data during stimulus delivery, a new mechanism is needed. Ear EEG, specifically, might be ideal for ECT to explore temporal lobe activity.

**Methods:** A portable Bluetooth interfaced, 10 channel, real time data processing Ear EEG that will be a more convenient way to monitor electrical activity in a patient's brain continuously before, during, and after ECT.

**Results:** The device has the ability to withstand shock independent of the ECT machine through the implementation of diodes in the instrumentation. Because of its Bluetooth capabilities and minimal design, the device is portable and allows for continuous recording of electrical activity in the brain. Hardware testing results yielded qualitative data to confirm comfort and stability of the headset. All amplifier currents were measured and confirmed to be significantly below the maximum output current for the AD620 and OP07 respectively.

**Conclusion:** Overall, our EEG device successfully embodies the three main goals we were trying to achieve: portability, surge protection capabilities, and an ear design. Furthermore, with our interface we were able to achieve real-time data processing and filtering functionality.

## 50. Neurocognitive Effects of Intravenous Ketamine Treatment in Treatment Resistant Depression

Cortney E. Sera<sup>1</sup>, Sophia Wolk<sup>1</sup>, Abigail Biehl<sup>1</sup>, Erica Vest-Wilcox<sup>1</sup>, Kelly Ryan<sup>1</sup>, Eric Achtyes<sup>2</sup>, Mark Frye<sup>3</sup>, William V. Bobo<sup>3</sup>, Jennifer Vande Voort<sup>3</sup>, Fernando Goes<sup>4</sup>, John Greden<sup>1</sup>, Sagar V. Parikh<sup>1</sup>

### Institutions:

1. Michigan Medicine, University of Michigan Department of Psychiatry and Depression Center, Ann Arbor, MI, USA
2. Pine Rest Christian Mental Health Services, Grand Rapids, MI USA
3. Mayo Clinic, Rochester, MN USA
4. Johns Hopkins University, Baltimore, MD USA

### Presenters:

underlined submitting presenter

**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 function<sup>1,2,3,4</sup>. We investigated the possible effects of intravenous ketamine on cognition using the Repeatable Battery for the Assessment of Neuropsychological Status Update®, (RBANS-Update) a brief, individually administered battery<sup>5</sup>.

**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 (the University of Michigan (UM), Mayo Clinic, Johns Hopkins University, and Pine Rest). Twenty-seven of these subjects participated at the UM 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  $\leq 9$  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. Analysis of the full dataset from all sites to be presented.

**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 ideation<sup>1</sup>.

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## 51. Female Sex and Pre-COVID Depressive Symptoms Associated with COVID-19 Binge Drinking

Pravesh Sharma, M.D.<sup>1</sup>; Ashley Holland D.O.<sup>1</sup>; Vanessa Pazdernik, M.S.<sup>1</sup>; Jennifer Geske, M.S.<sup>1</sup>; Christi A. Patten, Ph. D<sup>1</sup>; Douglas Mathew, Ph. D<sup>2</sup>; Shweta Sharma, M.P.H.<sup>3</sup>; Gillian Rossmann<sup>2</sup>; Bhanuprakash Kolla<sup>1</sup>, M.D; Scott A. Breiting M.D.<sup>1</sup>; Mark A. Frye, M.D.<sup>1</sup>; Aysegul Ozerdem, M.D., Ph. D<sup>1</sup>

### Institutions:

1. Department of Psychiatry and Psychology, Mayo Clinic, Rochester, MN
2. Department of Psychology, University of Wisconsin, Eau Claire WI
3. Department of Epidemiology, University of Minnesota, Minneapolis, MN

### Presenters:

underlined submitting presenter

**Background:** A large body of evidence suggests stress and negative affective states increase vulnerability to alcohol use initiation, escalation, and relapse. While the association between COVID-19-associated stress and change in patterns of alcohol use is well studied<sup>1</sup>, little is known about how symptoms of depression and sex differentially impacted alcohol use during COVID-19. Our aim was to assess sex differences in pre-COVID symptoms of depression on subsequent COVID-19 binge alcohol consumption.

**Methods:** The Mayo Clinic Electronic Medical Record (EMR) was the data source for this analysis. Mayo Clinic consists of 3 academic medical centers and associated health care systems spanning five states (MN, WI, IA, FL, AZ). A total of 265,568 patients aged 21 or older, as of March 30<sup>th</sup>, 2019 were identified from the EMR. Pre-COVID data collection was defined as one year before March 31<sup>st</sup>, 2020, with COVID data collection between April 1<sup>st</sup>, 2020 and March 30<sup>th</sup>, 2021. Groups based on PHQ9 included: no pre-COVID PHQ9, PHQ9<10, and PHQ9 ≥10. Based on the NIAA criteria, binge drinking during COVID-19 was defined categorically as at least 3-4 drinks or 5-6 drinks per day for women and men, respectively. Chi-square test was used to study the association between sex and COVID binge drinking. A logistic regression model was utilized to examine the effects of pre-COVID symptoms of depression, age, and sex on binge drinking.

**Results:** In the sample with no recorded pre-COVID PHQ-9 score (n=138,651), 9.7% of females endorsed binge drinking during COVID in comparison to 3.5% of males (p<0.0001). In the pre-COVID sample with a PHQ-9 <10 (n=25,901), 16.1% of females reported binge drinking compared to 6.3% of males; with PHQ9 ≥10 (n=4,912), 23.2% of females reported binge drinking compared to 12.3% of males (all p<0.0001). In the logistic regression model, there was a three-way interaction between age, sex and pre-COVID PHQ-9 (p=0.023). Among females, the effect of a 1-unit increase in pre-COVID PHQ-9 score increased the odds of binge drinking but to a lesser extent with increasing age (1.035 -1.021, 25- 75 years of age), while, among males, the odds of binge drinking also increased but with a stronger effect with increased age (1.029-1.084, 25 -85 years of age). At a common age of 50 and PHQ-9 of 10, the odds of binge drinking for females was 2.1 (95% CI, 1.9 to 2.3) times the odds for males.

**Conclusion:** Our study marks an important contribution to the literature identifying females endorsing higher rates of binge drinking, vs. males, during COVID-19 regardless of depression status. The effect of severity of depressive symptoms on risk for binge drinking seems to be more highlighted at younger ages in women as opposed to older ages in men. Our findings have both research and clinical implications. Clinicians should regularly screen for depression among patients as it could be a risk factor for binge alcohol drinking, especially in young women. Additional research with representative samples is required to assess psychosocial constructs associated with increased binge drinking among females.

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## 52. Impact of the National Suicide Hotline Number on Care of Outpatient Psychiatric Patients

Priyanka Sheth (priyanka.sheth@louisville.edu), Oladele D. Osisami (oladele.osisami@louisville.edu), Rif S. El-Mallakh (rselmal01@louisville.edu)

### Institution:

Department of Psychiatry, University of Louisville Louisville, Kentucky

### Presenters:

underlined submitting presenter

**Background:** The Federal Government has approved implementation of a single national suicide prevention hotline number. The Federal Communications Commission had already picked 988 as the number for this hotline and it came into effect in July 2022. It is not clear how aware psychiatric patients are of this event, and how much impact this will have on outpatient psychiatric care.

**Methods:** Prior to the introduction of 988, we performed a study of patients attending the outpatient psychiatric clinic at the department of psychiatry's outpatient services. The study comprised of a one-page questionnaire to acquire qualitative and quantitative data on patients' knowledge and acceptance of the change in the access of the suicide prevention number.

**Results:** A total of 74 outpatient psychiatric patients were surveyed during the course of the study. 78.4% (58) self-reported a mood disorder diagnosis, 18.9% (14) schizophrenia or schizoaffective disorder, and 12.2% (9) anxiety disorder. ADHD, PTSD, dementia, Parkinson's, panic attacks, and borderline personality disorder were also represented in a smaller number.

87.8% (65) of all surveyed individuals denied memorization of their local mental health crisis or suicide prevention hotline number. Of the 24 individuals who reported previously having called a crisis hotline, over one-third (37.5%) reported difficulty remembering or finding the number.

In response to the potential introduction of a 3-digit crisis hotline number, 63.5% (47) of surveyed individuals reported both increased confidence in receiving prompt, effective psychiatric care, and greater likelihood of seeking help if a 3-digit number were available. Finally, 77.0% (57) stated that a 3-digit number would be more easily remembered than current options.

Prior to this study, 89% (66) of survey responders were not aware of the new federally approved 988 hotline number. At completion, 100% of participants both reported that 988 is an easy number to remember and approved of its choice for the national crisis line.

**Conclusion:** Patients believe the 988 number will be a helpful tool in their care.

### 53. Comparative Effectiveness Of Intravenous Ketamine And Intranasal Esketamine In Clinical Practice Among Patients With Treatment-Refractory Depression: An Observational Study

Balwinder Singh, MD, MS<sup>1</sup>; Simon Kung, MD<sup>1</sup>; Vanessa Pazdernik, MS<sup>2</sup>; Jennifer Geske, M.S.<sup>2</sup>; Kathryn M. Schak, MD<sup>1</sup>; Phillip J. Schulte, PhD<sup>2</sup>; Mark A. Frye, MD<sup>1</sup>; Jennifer L. Vande Voort, MD<sup>1</sup>

#### Institutions:

1. Department of Psychiatry and Psychology, Mayo Clinic Depression Center, Mayo Clinic College of Medicine, Rochester, Minnesota, USA
2. Department of Quantitative Health Sciences, Mayo Clinic, Rochester, Minnesota, USA

#### Presenters:

underlined submitting presenter

**Background:** Ketamine has been redeveloped as a rapid-acting antidepressant for treatment-resistant depression (TRD). There is a paucity of literature comparing subanesthetic intravenous (IV) ketamine and FDA approved intranasal (IN) esketamine for TRD in real-world clinical settings. We compared the efficacy and time to achieve remission/response with repeated ketamine/esketamine.

**Methods:** An observational study of adults with TRD received up to 6 IV ketamine (0.5 mg/kg over 40 minutes) or up to 8 IN esketamine (56/84 mg) treatments. Depressive symptoms were measured utilizing the 16-Item Quick Inventory of Depressive Symptomatology self-report (QIDS-SR) before and 24 hours after treatment. Cox proportional hazard models were used to evaluate associations between time to response ( $\geq 50\%$  change in QIDS-SR score) and remission ( $\text{QIDS-SR} \leq 5$ ).

**Results:** Sixty-two adults (median age 50 years, 64% female) received IV ketamine (76%,  $n=47$ ) or IN esketamine (24%,  $n=15$ ). Response (57.4 vs 60.0%) and remission rates (42.6 vs 26.7%) were similar among patients who received IV ketamine or IN esketamine, respectively ( $p>0.05$ ). Unadjusted analyses of percent change (*decrease*) from baseline to lowest QIDS-SR score after their last treatment was not significantly different between the two treatment groups (IV ketamine=53% versus IN esketamine=55%,  $p=0.65$ ). The median (IQR) number of treatments received to achieve response (2.0 [1.0-3.0] vs 4 [3.0-6.0]) and remission (2.0 [1.75-3.0] vs 7.0 [5.3- 8.0]) were significantly lower among patients who received IV ketamine vs IN esketamine, respectively ( $p<0.01$ ). After adjusting for age, sex, BMI, and baseline QIDS-SR, defining time as the treatment number, the time to response is suggestively faster for IV (HR = 2.61, 95% CI: 1.0-7.1;  $p=0.05$ ) and time to remission is faster for IV (HR = 5.0, 95% CI: 1.0-24.3;  $p=0.02$ ).

**Limitation:** Our major limitation is the small sample size, especially with the IN group, which can affect the statistical analysis. This was an observational study, thus, predisposed to a higher risk of bias.

**Conclusion:** Intravenous ketamine and intranasal esketamine showed similar rates of response/remission in TRD patients but the number of treatments required to achieve remission was significantly lower with IV ketamine compared to IN esketamine. These findings need to be investigated in a randomized control trial comparing these two treatment interventions.

## 54. Depression Treatment for Children and Adolescents: Promising Results from a Collaborative Care Program

Alyssa C. Smith MD\*; Kyle Webster DO PhD\*; Krystal Salazar MD\*; Jenifer L. Vohs PhD; Emily G. Holmes MD

### Institution:

Indiana University School of Medicine, Department of Psychiatry, Indianapolis, Indiana

### Presenters:

underlined submitting presenter

\* co-presenters

**Background:** In the United States in 2020, the one-year prevalence of depression in adolescents aged 12-17 was 17%. Despite this, only 40% of these teens received treatment.<sup>1</sup> One important treatment barrier is lack of access to specialty mental health services. Other postulated barriers are not well understood, but include lack of engagement in health care systems and diminished access to services due to affordability and lack of coordinated infrastructure.

Collaborative care has a strong evidence base for adults and an emerging evidence base for pediatric patient for treatment of depression.<sup>2,3</sup> In the collaborative care model, primary care providers (PCPs) identify patients with a mental health condition and refer them to an integrated care manager who provides evidence-based short term behavioral interventions or therapy. The care manager also staffs cases with a consulting psychiatrist who can proactively provide medication recommendations to the PCP. Here, we present the results for patients treated for depression in a pediatric population in a real-world collaborative care program.

**Methods:** Pediatric patients (age <18 years old) seen in the university's collaborative care program were tracked using a program registry. Demographic data, presenting complaint, and symptom monitoring scales were recorded as part of routine clinical care. The primary monitoring and screening scale used in the clinic was the Pediatric Symptom Checklist-17 (PSC-17). For patients who presented primarily with depression, the PHQ-9 adolescent form was used.

**Results:** Between July 2019 and December 2021, 463 unique patients were seen for a total of 2281 visits. Of the 463 patients evaluated, 27 (6%) met criteria for adjustment disorder and 86 (18%) for depression (MDD or unspecified depression). Of the patients with repeated PHQ-9 testing, 41% had at least a 50% reduction in their score after engagement in the collaborative care program. Of those with a mood disorder with repeated PSC testing (but not repeated PHQ testing), 53% had at least a 50% improvement in symptoms.

**Conclusions:** In the pediatric collaborative care program, 113 patients were seen between 2019-2021 who met criteria for either adjustment disorder or depression. Of these, a substantial amount showed improvement in symptomatology with therapy and/or medications delivered in the primary care setting. Collaborative care is a promising model for improving access to effective depression care for children and adolescents.

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## 55. The temporal association and differential decrease of depression symptomatology between 10 Hz repetitive transcranial magnetic stimulation (rTMS) and intermittent theta burst stimulation (iTBS)

Nathen A. Spitz<sup>1</sup>, Benjamin D. Pace<sup>1</sup>, Patrick Ten Eyck<sup>2</sup>, Nicholas T. Trapp<sup>1,3</sup>

### Institutions:

1. Department of Psychiatry, University of Iowa, Iowa City, IA, United States.
2. Institute for Clinical and Translational Science, University of Iowa, Iowa City, IA, United States.
3. Iowa Neuroscience Institute, University of Iowa, Iowa City, IA, United States

### Presenters:

underlined submitting presenter

**Background:** Transcranial magnetic stimulation (TMS) is a novel, FDA-cleared neuromodulation treatment for major depressive disorder, which has demonstrated an overall improvement in depressive symptom burden during a standard 30-session treatment course. TMS can be delivered to the prefrontal cortex using different parameters including the standard 10 Hz repetitive TMS (rTMS) and a newer modality, intermittent theta burst (iTBS). Although iTBS has demonstrated non-inferiority to 10 Hz rTMS in terms of overall depression symptomatology and time to treatment response, few studies to date have examined the trajectory of symptom-specific responses to TMS treatment or differences in symptom-specific changes between these two TMS treatment modalities. Our study sought to explore if certain depression symptoms improved more rapidly than others to TMS treatment, and to examine differences between trajectories of symptom improvement with iTBS and 10 Hz rTMS treatment.

**Methods:** Retrospective analyses of participants with MDD that received open-label TMS treatment at the left dorsolateral prefrontal cortex (DLPFC) to examine clinical response to treatment using weekly Patient Health Questionnaire 9 (PHQ-9) scores [10 Hz rTMS (n=68) and iTBS (n=37)] and pre-, mid-, and post-treatment Montgomery-Åsberg Depression Rating Scale (MADRS) scores [10 Hz rTMS (n=65) and iTBS (n=28)]. Using the cumulative logistic regression framework, as well as pairwise odd ratio point and interval estimates, interaction effects between treatment group and treatment number at weekly intervals were used to investigate if specific depression symptoms had differential responses to TMS treatment modalities.

**Results:** When baseline interactions were accounted for, PHQ-9 scores amongst all TMS responders (>50% improvement on PHQ-9, n=41) showed rapid and statistically significant improvement in most individual items within one week of treatment, but a slower improvement on item #6 “feeling bad about yourself” (significance realized at week 3,  $p = 0.046$ ) and on item #8 psychomotor changes (significance realized at week 5,  $p = 0.0031$ ). When investigating differences on the PHQ-9 between 10 Hz rTMS and iTBS, we found that 10 Hz rTMS showed greater treatment response for item #2 “feeling down, depressed, or hopeless” at week 6 of treatment ( $p = 0.045$ ); in addition, we discovered a significant difference from the first to second week of treatment for item #4 “feeling tired or having little energy”, with 10 Hz rTMS having a significantly greater reduction from baseline, compared to iTBS ( $p = 0.027$ ). MADRS scores between 10 Hz and iTBS responders showed faster response in the 10 Hz rTMS group on symptoms of “reported sadness” (item #2) and “lassitude” (item #7) from baseline to the mid-treatment time interval ( $p = 0.0320$  and  $p = 0.0060$ , respectively). There were no other depression symptoms that had a significantly different response pattern between the two modalities.

**Conclusion:** Using patient self-report (PHQ-9) and clinician-administered (MADRS) depression rating scales, we found that TMS treatment responders demonstrated more gradual improvements in pessimistic thinking and psychomotor abnormalities compared to other depressive symptoms. When comparing treatment responders who received either 10 Hz rTMS or iTBS, 10 Hz showed faster response in symptoms of reported sadness and lassitude, as well as trended towards a faster response in other symptom categories. Importantly, there does not appear to be a significance difference between 10 Hz rTMS and iTBS in overall response rates at completion of treatment. Delineating the temporal trajectory of depression symptom improvement and identifying differences between TMS modalities may enable clinicians to tailor their treatment strategies and further guide patient expectations in relation to specific symptoms of depression.



## 56. Mental Health Links to Group-Based Trajectories of Stress Experience and Physiology in Current and Remitted Depression

Steinberger, D.C.<sup>1,#</sup>, Blank, J.M.<sup>1,#</sup>, Kuhn, M.<sup>1,2</sup>, Ironside, M.A.<sup>1,2,3</sup>, Kang, M.S.<sup>1</sup>, Brunner, D.L.<sup>1</sup>, Null, K.E.<sup>1</sup>, Pizzagalli, D.A.<sup>1,2</sup>

### Institutions:

1. Center for Depression, Anxiety, and Stress Research, McLean Hospital
2. Department of Psychiatry, Harvard Medical School
3. Laureate Institute for Brain Research

### Presenters:

underlined submitting presenter

# Denotes equal contribution and co-presentation

**Introduction:** Correspondence between subjective and physiological stress responses is assumed. However, prior work suggests that not all individuals exhibit stress response correspondence and that such discordance may be implicated in internalizing disorders. Here, we examined stress response profiles in adults with major depressive disorder (MDD), remitted MDD (rMDD), and healthy controls (HCs). Follow-up analyses examined putative relations between these profiles and various clinical variables. We predicted that at least one stress response profile would show high discordance and that those with this profile would be more likely to (1) have a history of depression and (2) report higher levels of mental health problems.

**Methods:** Unmedicated adults with MDD ( $N = 42$ ), rMDD ( $N = 33$ ), and HCs ( $N = 44$ ) participated in a study examining reward processing. All participants ( $M_{age} = 26.43$ , 75.60% female) completed the Maastricht Acute Stress Test (MAST), which elicits physical and psychological stress responses (Smeets et al., 2012). Participants rated their subjective stress on a sliding scale from 0 ("Relaxed") to 100 ("Tense") (Visual Analogue Mood Scale; VAMS) and provided saliva samples for cortisol assays. The VAMS was administered immediately pre- and post-MAST, and 50 minutes post-MAST. Cortisol was collected immediately pre- and post-MAST, as well as 30-, 50- and 75-minutes post-MAST. To test hypotheses, we generated group-based multi-trajectory models (Nagin et al., 2018) of VAMS score and cortisol. Multinomial logistic regressions then included stress response subgroup as the dependent variable and clinical status, sex, depression (Beck Depression Inventory; BDI), trait anxiety (State-Trait Anxiety Inventory; STAI), and childhood trauma (Childhood Trauma Questionnaire; CTQ) as predictors.

**Results:** The best-fitting model consisted of three subgroups. Group 1 exhibited high subjective stress-high physiology ( $N = 48$ ), Group 2 exhibited moderate subjective stress-moderate physiology ( $N = 38$ ), and Group 3 exhibited low subjective stress-low physiology ( $N = 33$ ). We did not identify a stress response profile with clear discordance. Follow-up multinomial logistic regressions revealed that Groups 1 and 3 were significantly more likely to have higher childhood trauma exposure than Group 2. BDI, STAI, and sex were not significant predictors of subgroup membership. A chi-square test confirmed that subgroups were independent of clinical group.

**Conclusion:** Stress response discordance did not appear in this sample of adults with or without a history depression. Additionally, while three distinct subgroups of subjective and physiological stress responses emerged, they were not related to diagnostic status (i.e., MDD, rMDD, HC) nor to our other clinical variables (except childhood trauma). Our findings contrast with those of Bendezu and colleagues (2022), who found a highly discordant stress response profile in adolescents that was linked to depression severity.

## 57. NNDC Mood Outcomes program: Where we are and where we are going.

**Authors:** Jason Straub, LCSW-C, MPH, Peter P. Zandi, PhD, Paresh Patel, MD, David Katzelnick, MD, Carolyn Turvey, PhD, Jesse H Wright, MD, PhD, Olu Aijilore, MD, PhD, William Coryell, MD, Christopher D. Schneck, MD, Constance Guille, MD, Erika Saunders, MD, Kathy Dougherty, MD, Sophie Lazarus, PhD, Jay Fournier, PhD, Valeria Cuellar, MD, Sudhaker Selvaraj, MD, Heather Flynn, PhD, Amanda Tan, BS, Taya Prince, BS, Dana Steidtmann, PhD, Jorge Almeida, MD, PhD, Wade Weber, MS, Michael Morreale, MPH, Mark Williams, MD, Joseph Gage, MA, LPN, LLP, Patricia Dill Rinvelt, MBA, Dane Larsen, BA, Rachelle May-Maki, MPA, Ryan M. Callahan, BS, John Greden, MD, J. Raymond DePaulo, MD

**Author Affiliations:** Johns Hopkins University, Baltimore, MD (Straub, Zandi, Morreale, DePaulo); University of Michigan, Ann Arbor, MI (Patel, Greden); Mayo Clinic, Rochester, MN (Katzelnick, Williams); University of Iowa Healthcare, Iowa City, IA (Turvey, Coryell); University of Louisville, Louisville, KY (Wright); University of Illinois at Chicago, Chicago, IL (Aijilore); University of Colorado, Denver, CO (Schneck, Steidtmann); Medical University of South Carolina, Charleston, SC (Guille); Penn State Hershey Medical Center, Hershey, PA (Saunders, Dougherty); Ohio State University, Columbus, OH (Fournier, Lazarus); University of Texas Health Science Center, Houston, TX (Cuellar, Selvaraj, Prince); Florida State University (Flynn); Emory University (Tan); University of Texas at Austin (Almeida, Weber), Pine Rest Christian Mental Health Services (Gage), National Network of Depression Center, Ann Arbor, MI (Rinvelt, Larsen), Altarum, Ann Arbor, MI (May-Maki, Callahan)

### Presenters:

underlined submitting presenter

**Background:** Mood disorders are among the most burdensome public health concerns. The National Network of Depression Centers (NNDC) is a non-profit consortium of 30 leading clinical and academic member centers around the U.S. providing care for patients with mood disorders, including depression and bipolar disorder. The NNDC has established a measurement-based care program called the Mood Outcomes Program whereby participating sites follow a standard protocol to electronically collect patient reported outcome assessments on depression, anxiety and suicidality in routine clinical care. The purpose of this poster is to provide an update on the Mood Outcomes program development, recruitment, and initial observations.

**Methods:** To date, 15 centers have collected assessments from more than 40,000 unique patients (31,824 included in this analysis). Standard assessments included the 9-item Patient Health Questionnaire, the 7-item Generalized Anxiety Disorder Questionnaire, and the Columbia Suicide Severity Rating Scale plus basic demographic and diagnosis information.

**Results:** By collecting this data as a part of the standard of care, researchers have access to longitudinal patient records from real world settings that forms the basis of a Learning Health System, providing insights into patient outcomes over time. Updated longitudinal data will be presented.

**Conclusion:** The Mood Outcomes program demonstrates that large scale standard collection of patient-reported outcomes is possible with current health information technology. It also demonstrated the need for a more robust set of data to better characterize the patient experience. Based on these findings, a new version of Mood Outcomes that captures additional patient information from the electronic health record based on the PCORnet data model has been developed and is currently being piloted. It is expected to be made available to all NNDC sites in 2023.

## 58. Characterizing Depression and Psychological Constructs Associated with Cardiovascular Disease: A Qualitative Analysis of the Literature from the Last Sixty Years

Laura Suarez M.D.; Jeffrey P. Staab, M.D., M.S.

### Institution:

Mayo Clinic Department of Psychiatry and Psychology

### Presenters:

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**Background and Aims:** The association of psychological distress and cardiovascular disease (CVD) has been widely studied over the years with most of the literature focusing on depression and coronary artery disease. Although this research has led to important advancements, like the recognition that depression can be considered a risk factor for CVD, it has not progressed to the point of systematic characterization of psychological symptoms that affect different subpopulations of patients with cardiovascular diseases or to repeatable results from therapeutic interventions. One problem may be the lack of universal and consistent language to identify and characterize symptoms and track their responses to treatment. Therefore, the aim of this qualitative study was to identify thematic constructs used to describe psychological variables associated with CVD from 1960 to 2021.

**Methods:** We searched for all types of publications from 1960 – 2021 that included the words cardiac disease, heart disease, myocardial infarction, ischemic heart disease, coronary heart/artery disease, acute coronary syndrome, coronary events, psychological, depression, depressive disorders/states/symptoms, somatic, cognitive-affective, melancholia/melancholic, heart-brain, distress, or stress in their titles. All references were imported into NVivo software (Version 12, QRS International), to identify common themes related to psychological/psychiatric constructs via auto coding. Themes were further organized into 5 temporal groups based on the year of publication to identify commonalities and differences that developed over the last sixty-one years.

**Results:** 213 references were found and 211 were used for analysis; 52% of references were published from 2000-2010. Eleven thematic categories were identified: adjustment, affect, anxiety, depression, distress, exhaustion, loss/grief, other psych/comorbidity, personality, somatic manifestations, and stress. The largest category was depression with over 150 references that included “depressive symptoms” and “major depression” as the most common terms. The second largest category was other psych with “mental disorders” being the most common term. The third largest category was somatic manifestations with “somatic symptoms” as the most common term. By epoch, the most common terms were: “acute stress” in the years 1960-79; “psychiatric illness” in the years 1980-89; “major and minor depression” in the years 1990-99; and “depressive symptoms” in the years 2000-2021.

**Discussion and Conclusion:** Research on potential associations of psychological variables and CVD has included a wide variety of terms for symptoms and syndromes throughout time. Some of these changes reflected updates to official nomenclature including the Diagnostic and Statistical Manual of Mental Disorders and the International Classification of Diseases, but that alone cannot explain the variability. Curiously, some of the vaguest terminology was used in studies published during the last 20 years. The evolution from acute stress in the 1960-70s to more distinct diagnostic terminology in the 1980-90s back to vaguer language in recent years may reflect changing conceptualizations about psychological variables in patients with CVD from acute stress reactions to distinct psychiatric disorders to less certainty about the nature of psychological morbidity.

Variability also may be due to differences in the psychological factors of most importance for different subpopulations of patients with CVD. Regardless, inconsistency in language is a barrier to precisely and accurately identifying the most important psychological processes that affect patients with CVD and developing effective interventions to improve cardiovascular and psychiatric outcomes. As research within cardiac psychiatry and psychology continues to grow, clinicians and investigators face the important task of precisely and consistently defining terms to convey evolving concepts that can be shared and tested in clinics and research laboratories throughout the world.

## 59. Empathic Concern and Personal Distress: Exploring the Intricacies of Self and Other Oriented Empathy in Depression

Elizabeth F. Sullivan, Allison M. Sparpana, Zamfira Parincu, Molly K. Irvin, Matthew J. Hoptman, Katherine A. Collins, Dan V. Iosifescu

### Presenters:

underlined submitting presenter

**Background:** Empathy, the ability to relate to and feel for another person, is a multifaceted phenomenon of human emotion and behavior. Capturing its psychological complexities, the Interpersonal Reactivity Index (IRI) measures four empathy constructs: Perspective Taking, Fantasy, Empathic Concern, and Personal Distress. Previous research has shown that empathy is crucial for friendship development and maintenance, making it a key factor in social wellness. Social connectivity and friendship correlate with lower levels of depression and suicide attempts. Thus, capacity for empathy should be considered while clinically assessing one's risk for both. Personal Distress (PD), defined as self-oriented feelings of anxiety while someone else is in distress, and Empathic Concern (EC), defined as other-oriented feelings of sympathy for those in distress, may be of particular interest, as they measure both the inward and outward emotions related to interpersonal interaction. Here, we hypothesize that depression may be associated with lower EC and higher PD. Additionally, we examine potential symptom clusters related to EC and PD.

**Methods:** We analyzed the data of 792 individuals (age=41.54  $\pm$  15.27, sex=64% female) from the Nathan Kline Institute Rockland Sample. The IRI and the Beck Depression Inventory (BDI) were administered to all subjects. We conducted a correlational analysis comparing EC and PD scores to depression severity (BDI). A forward stepwise linear regression was also performed to identify any significant relationships between clusters of depressive symptoms and either EC or PD.

**Results:** Depression severity was positively correlated with PD ( $r=.32$ ,  $p=0.01$ ), but not with EC ( $r=.03$ ,  $p=0.37$ ). A model including increased sadness, guilt, concentration difficulty, indecisiveness, changes in appetite, decreased suicidal thoughts and irritability significantly predicted higher PD [ $F(7, 784)=22.74$ ,  $p<.001$ , adj.  $R^2=0.16$ ]. A model including increased guilt, indecisiveness, anhedonia, loss of interest in sex, and decreased suicidal thoughts significantly predicted higher EC [ $F(5, 792)=6.78$ ,  $p<.001$ , adj.  $R^2=0.035$ ]

**Conclusion:** These results suggest that depression severity may be associated with PD, but not directly associated with EC. This could indicate that higher levels of depression increase self-oriented feelings of empathy, whereas other-oriented empathy remains normal. Therefore, this could imply that depressed individuals are more likely to take emotional ownership of other's burdens in an anxiogenic manner.

Additionally, specific depression symptoms such as indecision, guilt, and concentration difficulty are associated with higher anxious PD. Although total depression severity is not correlated with EC, our results indicate that symptoms like guilt and anhedonia are related to EC. Of interest, suicidal thoughts were inversely related to EC. These results offer insight into the relationship between depression and empathy and may provide foundation for future interventions that target social wellness and depression.

## 60. Affective neural circuits and inflammatory markers linked to depression and anxiety symptoms in patients with comorbid obesity

Perry Tsai, MD, PhD

**Institution:**

University of Illinois at Chicago

**Presenters:**

underlined submitting presenter

**Background:** Although we have effective treatments for depression as a broad diagnostic group and for anxiety often associated, we lack evidence-based strategies to tailor these treatments in the context of major comorbidities such as obesity. We also lack a mechanistic understanding of which patients respond to treatment and why. The current feasibility study uses functional neuroimaging and biospecimen data to determine if changes in plasma inflammatory markers, fecal short-chain fatty acids, and neural circuit-based targets can predict depression and anxiety outcomes among participants with comorbid obesity.

**Methods:** Blood and stool samples and functional magnetic resonance imaging (fMRI) data were obtained at baseline and 2 months, during the parent ENGAGE-2 trial which was designed to test the neural target effects of the Integrated Coaching for Better Mood and Weight version 2 (I-CARE2) behavioral intervention for comorbid depression and obesity. From 30 participants with both biospecimen and fMRI data, this subsample study extended the goal to explore the relationship among changes in plasma inflammatory markers and fecal short-chain fatty acids and changes in neural targets, and their joint relationship with depression and anxiety symptoms. Bivariate and partial correlation, canonical correlation, and partial least squares analyses were conducted, with adjustments for age, sex, and treatment group.

**Results:** The subsample of 30 participants were mean age 45.7 years (SD 10.8), mostly female (66.7%) and African American (56.7%), with 16.7% non-Hispanic white, 16.7% Hispanic, and 10% other. Most had at least some college education (86.7%), and more than half reported annual income <\$55,000 (56.7%). At baseline, they reported a mean Patient Health Questionnaire-9 score of 12.1 (SD 2.3), 20-item Depression Symptom Checklist score of 1.0 (SD 0.7), 7-item Generalized Anxiety Disorder score of 4.9 (SD 3.8), and body mass index of 35.9 kg/m<sup>2</sup> (SD 5.7). Initial bivariate and canonical correlation analyses revealed three inflammatory markers (IL-1RA, IL-6, and TNF- $\alpha$ ) and five neural targets (in Negative Affect, Positive Affect, and Default Mode Circuits) with significantly associated changes at 2 months (canonical correlation coefficient 0.95). Partial least squares analyses then showed that changes in IL-1RA and TNF- $\alpha$  and changes in three neural targets (in Negative Affect and Positive Affect Circuits) at 2 months were associated with changes in depression and anxiety symptoms at 6 months.

**Conclusion:** This study sheds light on the plausibility of incorporation of inflammatory and gastrointestinal biomarkers with neural targets as predictors of depression and comorbid anxiety outcomes among patients with obesity.

## 61. Clinical Outcomes in the Biomarkers of Ketamine (Bio-K) Study of Open-Label IV Ketamine for Refractory Depression

Parikh, S, Vande Voort, J, Bobo, W, Yocum, A, Goes, F, Achtyes, E, Frye, M, Greden, J, Sera, C, Vest, E on behalf of Bio-K team

**Presenters:**

underlined submitting presenter

**Background:** Globally, it is estimated by WHO that 5% of adults suffer from major depressive disorder (MDD) annually, while the United States alone has a prevalence of 8.1% in 2020. The impact of depression has lasting effects including impaired functioning that may result in disability and increased rates of suicide. This is also true in bipolar disorder (BPD). In some cases, depression has proven to be difficult to treat with conventional and serial therapeutic antidepressants, and the response may take several months or longer. Previous controlled trials of single and multiple infusions of ketamine have shown to be fast acting and improve overall symptoms of depression including a reduction in suicidal ideation in patients with MDD and BPD. We report here the design, baseline characteristics, and clinical outcomes of multi-site, open label, single-arm trial designed to identify preliminary blood-based biomarkers of ketamine response in patients with treatment-resistant, non- psychotic, unipolar major depression (MDD) or bipolar I or II depression (BPD).

**Methods:** Across 4 US sites, 75 patients ages 18 – 65 with treatment-refractory unipolar or bipolar depression received 3 IV ketamine infusions over an 11-day period. Key exclusion criteria were psychotic symptoms, significant substance abuse, unstable medical conditions, and any use of cannabis. Pre-existing antidepressant medication was maintained. Primary outcome was remission as measured by Montgomery-Asberg Depression Rating Scale (MADRS), with secondary outcome of 50% reduction in Beck Suicide Scale score. Safety monitoring and varying durations of infusions were also key parameters.

**Results:** Using remission as MADRS score less than 9, after 3 infusions 52% achieved remission, with 67% achieving response. Of those achieving response after a single infusion, 22 of 33 (66%) reached remission after 3 infusions, while 16 of 40 (40%) non-responders after the first infusion went on to achieve remission after 3 infusions. Only 20% of non-responders after 2 infusions achieved remission. Most participants had significant suicidal ideation at baseline; of these, two-thirds (67%) experienced at least a 50% reduction in suicidality. Side effects were minimal. Uniquely, we had three different types of infusion categories, with individuals receiving: (1) slow (100-minute) infusions only or (2) regular (40-minute) infusions only or (3) a mix of infusion durations. These three infusion groups showed comparable safety and efficacy. Exploration of clinical factors revealed no link between BMI, age, or gender to remission.

**Conclusions:** The consistency of outcomes across 4 clinical sites and across multiple instruments, suggests high efficacy and safety of IV ketamine for serious depressive episodes. Duration of infusion did not alter outcomes. Meaningfully, 40% of non-responders after a single infusion did reach remission subsequently, while only 20% of non-responders after 2 infusions achieved remission, suggesting early response is suggestive for eventual remission. Our data on varying ketamine infusion duration adds novel insights into the clinical administration of this new treatment for refractory and severe patients. Our limitations included a lack of a control group, necessitating caution about conclusions of efficacy balanced by the utility of reporting “real-world” outcomes across multiple clinical sites. We could also not separately analyze results for bipolar disorder due to small numbers. Together, the Bio-K clinical results are promising and provides significant sample sizes for forthcoming biological markers analyses.

## 62. A Case Study of Asymptomatic Hyperprolactinemia Secondary to Risperidone

Ekaterina Vlasova<sup>1</sup>, Brent Carr MD<sup>2</sup>

### Institutions:

1. Thomas Jefferson University, Sidney Kimmel Medical College, Philadelphia, PA
2. University of Florida, Department of Psychiatry, Gainesville, FL

### Presenters:

underlined submitting presenter

**Background:** Antipsychotics have been commonly shown to induce side effects arising from the infundibular pathway and its effects on prolactin (PRL). Here we present a case report of a gentleman who voiced a fear to his outpatient psychiatrist that he was developing gynecomastia. MW is a 36-year-old man with medication resistant schizoaffective disorder with comorbid alcohol use disorder and significant baseline anxiety. After multiple medication trials he had finally been stabilized with Risperdal 9mg. Upon voicing his concern a PRL level was ordered revealing an elevation at 41.7 ng/ml (male nl < less than 17 ng/ml). His provider decreased Risperdal from 9mg to 6mg, but patient elected to self-taper to 3mg. This led to subsequent relapse such that he presented to the emergency department with worsening symptoms of paranoia, anxiety, depressed mood, auditory hallucinations, and suicidal ideation.

**Methods:** The patient was admitted to the psychiatric unit. Given his response to Risperdal and previous monotherapy failures, the primary team decided to resume Risperdal. In order to alleviate the potential for a repeat in elevation in PRL levels his regimen was augmented with aripiprazole 5 mg. During his hospital course the dose of risperidone was gradually titrated up to 8 mg. Aripiprazole is a unique antipsychotic that has partial dopamine agonist properties, which could potentially provide sufficient negative feedback for inhibition of the tuberoinfundibular prolactin pathway. This could potentially buffer the proclivity for a PRL elevation at higher Risperdal doses, or allow for small Risperdal doses to work synergistically with aripiprazole.

**Results:** The Risperdal again stabilized his symptoms including paranoia and persecutory delusions involving the police. And, he reported no sign or symptoms of hyperprolactinemia such as gynecomastia or galactorrhea. He was lost to follow up to the authors after discharge. The patient's prolactin was not rechecked immediately prior to discharge but planned for as a repeat during outpatient follow up after discharge.

**Conclusions:** It is unclear if this strategy had been successful for this patient long term, but this poster will explore antipsychotics effects on PRL and the theoretical strategy employed by his inpatient team.

### 63. Outcomes and Predictors of Response to Maintenance Ketamine in a Large Outpatient Cohort with Treatment-Resistant Depression

Tyler Durns, M.D.<sup>1,2,3\*</sup>; Tatyana V. Kuzmenko, Ph.D.<sup>1,2</sup>; Yuji Wakimoto, M.D.<sup>1,2,4^</sup>; Paul Carlson, M.D.<sup>1,2</sup>; Andrey A. Shabalin, Ph.D.<sup>1,2</sup>; Emily DiBlasi, Ph. D.<sup>1,2</sup>; Jeremy Kendrick, M.D.<sup>1,2‡^</sup>; Anna R. Docherty, Ph.D.<sup>1,2,5‡</sup>

#### Institutions:

1. Huntsman Mental Health Institute, Salt Lake City, UT USA
2. Department of Psychiatry, University of Utah School of Medicine, Salt Lake City, UT USA
3. Division of Psychiatry and the Law, University of California Davis, Sacramento, CA USA
4. Department of Pediatrics, University of Utah School of Medicine, Salt Lake City, UT USA
5. Department of Psychiatry, Virginia Commonwealth University, Richmond, VA USA

#### Authors:

underlined submitting presenter

\*Corresponding author

‡Senior authors

^ Presenting authors

**Background:** Short-term administration of ketamine reduces depressive symptoms, but the effects of ketamine are short-lived. To date, response to long-term ketamine is understudied, and the patient and treatment characteristics moderating response to long-term ketamine remain unknown. This study examined a large outpatient cohort at the Huntsman Mental Health Institute to examine the long-term effects of intravenous ketamine on depressive symptoms, and to identify significant predictors of ketamine response.

**Methods:** Treatment-resistant depression outpatients (N = 203) were provided with ketamine infusions, monitored for depressive symptoms at each infusion, and characterized via retrospective chart review. Depression symptom severity was measured using the PROM-Dep and QIDS-SR. Joint statistical modeling techniques examined moderators of response by longitudinal and time-to-event data. Hypothesized moderators of response included treatment duration, age, sex, BMI, prior history of neuromodulation, and concomitant medications at the initiation of treatment. Initial(N=50), acute(N=55), and maintenance(N=98) phases were examined to evaluate long-term benefit.

**Results:** Per clinical protocol, rapid response to ketamine within the first 6-8 infusions was followed by gradual spacing between infusions, in which depression severity continued to improve. 48.3% of outpatients continued maintenance treatments, responding at higher rates. Increased response was associated with male sex and concomitant oral antidepressants and psychostimulants. Decreased response was associated with concomitant mood stabilizers, antipsychotics, alpha-antagonists/inverse agonists, and a history of prior neuromodulation.

**Conclusions:** In this retrospective analysis, serial intravenous ketamine was observed to offer continued benefits with ongoing maintenance treatments for most outpatients, but with some exceptions. Important moderators of long-term response to ketamine including sex, specific concomitant medications, and history of neuromodulation may inform clinical decision-making.



## 64. Feasibility of Smartphone App MindLAMP in Developing Digital Phenotypes in Depression

Alex Walker MHS<sup>1</sup>; Manuel Gardea-Resendez MD<sup>2</sup>; Scott Breiting MD<sup>2</sup>; Joe Laivell BAS<sup>2</sup>; Cynthia Stoppel<sup>2</sup>; Laura Harper<sup>2</sup>; Tenzin Lhaksampa MHS<sup>1</sup>; John Torous MD<sup>3</sup>; Fernando Goes MD<sup>1</sup>; Peter Zandi PhD<sup>1</sup>; Mark Frye MD<sup>2</sup>

### Institutions:

Department of Psychiatry & Behavioral Sciences, Johns Hopkins University, Baltimore, Maryland, USA

Department of Psychiatry & Psychology, Mayo Clinic, Rochester, Minnesota, USA

Department of Psychiatry, Beth Israel Deaconess Medical Center, Boston, Massachusetts, USA

### Presenters:

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**Background:** There is increasing recognition of the potential to integrate HIPAA compliant technologies, such as smartphone apps and sensors, directly into current care models to provide greater access or augment conventional mental health care. Out of clinic measurement of patient's lived experiences is critical to improved understanding of the course of illness and potentially new opportunities for more timely interventions. We aim to investigate whether digital phenotypes collected from the smartphone and a wearable device can be used to track and predict mood outcomes as the basis for such interventions in patients with mood disorders.

**Methods:** We are conducting a two-site digital phenotyping pilot study of patients with major depressive disorder (MDD), bipolar disorder (BP), and healthy controls at Johns Hopkins University and the Mayo Clinic. Treatment seeking depressed patients who are English-speaking, ages 18 and older, and not currently suicidal are eligible. Patients are given either an Oura smart ring (<https://ouraring.com/>) or Willful & Letscom Smartwatch, if they do not already own a wearable device, to collect passive sensor data on activity, heart rate, and sleep quality. In addition, they download the MindLAMP app onto their smartphones, which pushes out surveys on mood and sleep during the week and gathers the passive sensor data for analysis. Participants also complete self-report measures about sleep, satisfaction/enjoyment of life, mental alertness, anxiety, and stress at baseline and three follow-up visits a month apart for three months.

**Results:** We report here interim results on 40 case participants ([n=28 MDD, 12 BP], mean age=35.9, 30% male) and 35 controls (mean age=30, 47.6% male). Study discontinuation rates were 4.1%. Participants that finished the 12-week trial had a 51.3% average survey completion rate and 68.1 % average smart ring adherence. Main factors that influenced data completion included forgetting to complete surveys or charge the device, traveling, and technical issues.

**Conclusion:** We seek to leverage our experience with developing a pilot feasibility study in real world clinical settings to help academic and industry researchers to better conceptualize and operationalize current and future digital phenotyping investigations in the study and treatment of mood disorders.

## 65. Higher Lactate and Pyruvate Levels and Lactate-to-Pyruvate Ratio Patients with Treatment Resistant Depression

Krista M. Wartchow<sup>1\*</sup>, Tina Li<sup>1</sup>, Bashar Asir<sup>2</sup>, Giovana Zunta-Soares<sup>2</sup>, Albert J. Fenoy<sup>3</sup>, Jair C. Soares<sup>2</sup>, João Quevedo<sup>1,2</sup>, Giselli Scaini<sup>1,2</sup>

### Institutions:

1. Translational Psychiatry Program, Faillace Department of Psychiatry and Behavioral Sciences at McGovern Medical School, UTHealth Science Center at Houston, TX, USA
2. Center of Excellence on Mood Disorders, Faillace Department of Psychiatry and Behavioral Sciences at McGovern Medical School, UTHealth Science Center at Houston, TX, USA
3. Department of Neurology, McGovern Medical School, UTHealth Science Center at Houston, TX, USA

### Presenters:

underlined submitting presenter

**Background:** Major Depressive Disorder (MDD) affects roughly 264 million people worldwide, which translates to approximately 4.5% of the global population, being recognized by the World Health Organization (WHO) as one of the major causes of disability worldwide. Antidepressant medication or psychotherapy are common treatments for MDD; however, not all patients respond to treatment. Treatment-resistant depression (TRD) is a form of depression where standard medications tend to provide little to no relief. Mitochondria are organelles responsible, both directly and indirectly, for multiple cellular functions and signaling cascades, being considered a central platform in the execution of diverse cellular events. In this framework, it is particularly intriguing to think of the mitochondria as an active regulator of many of the biological phenomena involved in depression and the efficacy of or resistance to the most widely used pharmacological treatments. This study aims to evaluate biochemical markers associated with mitochondrial function in patients with MDD and TRD.

**Methods:** In this interim analysis of an ongoing pilot study, we included 17 healthy controls, 11 patients with MDD, and 14 patients with TRD. All subjects underwent a comprehensive clinical interview and diagnosis of MDD and TRD according to the DSM-IV-TR. Mood symptoms were assessed with the Montgomery Asberg Depression Scale (MADRS). Quantitative analysis of lactate and pyruvate plasma levels was performed using commercial kits.

**Results:** One-Way ANCOVA after controlling for age, gender, and length of disease showed that TRD patients had higher levels of lactate and pyruvate when compared to healthy controls and MDD patients. Moreover, the lactate to pyruvate ratio was significantly different between TRD patients and healthy controls but not between TRD and MDD patients. Additionally, we evaluated the lactate to pyruvate ratio in a mitochondrial disease cohort for comparison/validation purposes. Our results showed that the lactate to pyruvate ratio is higher in patients with mitochondrial diseases than in other groups. Another notable finding was that subjects with higher lactate to pyruvate ratio had higher MADRS scores and worse functional status.

**Conclusion:** In summary, our findings corroborate previous studies and support the notion that mitochondrial dysfunction is integral to the pathogenesis of MDD and may play a role in clinical and functional outcomes. Although preliminary, our results highlight the importance of identifying potential biomarkers when assessing TRD patients.

## 66. Moms & Babies Feeling Better Together: Open Pilot Results of a Technology-Assisted, Entertaining Cognitive Behavioral Therapy Tailored for Rural WIC Clients with Perinatal Depression

Addie Weaver<sup>1</sup>, Caroline Landry<sup>1</sup>, Rachael Whitted<sup>2</sup>, Danae Ross<sup>1</sup>, Isabella Ginsberg<sup>1</sup>, Ajsa Jasarevic<sup>1</sup>, Tahani Al-Shamari<sup>1</sup>, Anusha Chudhry<sup>1</sup>, Joseph Himle<sup>1,3</sup>

### Institutions:

1. University of Michigan School of Social Work, Ann Arbor, MI, USA
2. Lenawee County WIC Program, Community Action Agency, Adrian, MI, USA
3. University of Michigan Department of Psychiatry, Ann Arbor, MI, US

### Presenters:

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**Background:** Systematic reviews suggest between 22-33% of women living in rural areas of the U.S. experience perinatal depression;<sup>1,2</sup> yet, rural women are less likely to receive any treatment for their perinatal depression compared to non-rural residents. Barriers related to the availability of providers, access to care, and acceptability of mental health treatment all impact this treatment access disparity.<sup>3-10</sup> It is imperative to build capacity for perinatal depression treatment within rural community settings. The Special Supplemental Nutrition Program for Women, Infants, and Children (WIC) serves low-income pregnant and breastfeeding women, and women with children between the ages of zero and five, providing nutrition education and food assistance. Women prioritize attending WIC appointments, given WIC resources support their children's basic needs and are often viewed as non-stigmatizing. This study reports results of open pilot research testing the impact of an 8-session technology-assisted, entertaining, cognitive-behavioral therapy-based depression treatment tailored for WIC clients in the perinatal period, called Moms and Babies Feeling Better Together (MBFBT), on depressive symptoms.

**Methods:** A one-group pre-/post- test design was used to assess the association between participation in the MBFBT program and symptoms of depression and anxiety over time. Symptom measures included the Edinburgh Postnatal Depression Scale and Generalized Anxiety Scale-7. Assessments were conducted pre- treatment, post-treatment, and at a 3-month follow-up. Dependent samples t-tests and Repeated Measures ANOVA were used to assess mean differences in symptom scores over time.

**Results:** 23 women enrolled in the program between March and December 2021. Twelve were lost to follow- up; one was triaged to a higher level of care before starting the program. Nine women completed all 8-sessions MBFBT and comprise the analytic sample. All nine participants identified as female (100%), and about three- quarters identified as non-Hispanic white (n=7; 77.8%). Participants' average age was 30.6 years old ( $SD=8.06$ ). Participants experienced a clinically and statistically significant decrease in depressive symptoms between pre-treatment ( $M=15.56$   $SD=4.25$ ) and post-treatment assessment ( $M=8.11$   $SD=6.72$ ;  $t(8)=$   $p=.014$ ). Repeated measures ANOVA indicated a significant pattern of difference in depressive ( $F(2)=40.52$  ;  $p=.001$ ) symptoms across the three time points. A similar pattern was found for anxiety symptoms.

**Conclusions:** Pilot findings indicate the MBFBT program may be a promising way to increase access to perinatal depression treatment for some women in rural communities and that WIC clinics are likely feasible, acceptable settings for delivering MBFBT. Participants who completed the 8-week depression treatment experienced a decrease in symptoms of both depression and anxiety. Additional research on the program with larger samples and more rigorous study designs are needed, with specific attention to understanding factors impacting withdraws.

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## 67. Antecedent symptoms associated with onset of major depressive episode in pregnancy

Bennett Wechsler

**Institution:**

University of Massachusetts

**Presenters:**

underlined submitting presenter

**Background:** About 20% of women may develop depression during pregnancy.<sup>1</sup> Due to this elevated incidence and the increased morbidity and mortality associated with the disorder<sup>2</sup>, early detection and treatment of major depression in pregnant women is critical for at risk mothers. Our analysis examined a pregnant population and retrospectively assessed the symptoms of depression associated with subsequent major depressive episode (MDE).

**Methods:** This is a secondary analysis from a prospective cohort study on the relationship between an MDE, antidepressant treatment and birth outcomes. Pregnant individuals were eligible to participate if they were at least 18 years of age, less than 17 weeks gestation, and were willing to provide informed consent. The original cohort included 2,654 participants; the current analysis included 2,594 participants who were at risk of an MDE because they did not have an MDE in the first month of pregnancy. We used The World Mental Health Composite International Diagnostic Interview v2.1 WMH-CIDI (CIDI) (Kessler, 2004) to determine a likely diagnosis of, and symptoms of depression for each month of pregnancy. We applied generalized linear mixed models with a random intercept to examine the association of MDE at each month of pregnancy with individual symptoms from the previous month, adjusted for month of pregnancy, age, race/ethnicity, education, history of MDE prior to pregnancy, and prior MDE at any previous month during pregnancy. Symptoms of depression (N=13) were entered into separate models along with adjusting variables. Symptoms that were statically significantly associated ( $p < 0.05$ ) with MDE were then entered into a single, multivariable model concurrently.

**Results:** Roughly 6% (N=162) of participants likely had an onset of an MDE during pregnancy after the first month of pregnancy. In bivariate models, MDE was not associated with confused thoughts, increased energy, and increased appetite in the previous month, independent of demographic variables and history of MDE. Results from the multivariable model that included the remaining ten symptoms showed that the odds of MDE were greater among participants who endorsed trouble concentrating [OR (95% CI) = 2.6 (1.5-4.6)], feeling guilty [OR (95% CI) = 3.4 (1.7-7.1)], feeling jittery [OR (95% CI) = 4.8 (2.1-10.7)], low appetite [OR (95% CI) = 2.3 (1.5-3.5)], and low energy [OR (95% CI) = 2.9 (1.8-4.7)] (all  $p < 0.002$ ) compared to those without these symptoms in the previous month, independent of other symptoms and other adjusting variables. Inability to decide, racing thoughts, trouble sleeping, sleeping more than usual, and moving/talking slowly were not associated with subsequent MDE in the multivariable model.

**Conclusions:** Our results indicate that the likelihood of developing MDE was increased in pregnant individuals reporting difficulties concentrating, feelings of guilt, feeling jittery, having low appetite, or low energy, during the prior month. These findings may lead to the development of tools to identify individuals at risk for subsequent MDE, and to develop targeted interventions that strengthen resilience against depression.

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## 68. The Heinz C. Prechter Bipolar Research Program: A Snapshot of Longitudinal Data

Yocum AK, Abu-Mohammad AS, Ahearn E, Anderau S, Bertrum H, Burgess HJ, Carley I, Diaz-Byrd C, Grimm C, Jenkins P, Kaur R, Marshall DF, Mower-Provost E, K. Sue O'Shea, Kelly A. Ryan, Sperry SH, Smith SN, Tso IF, Vest E, Williams S, Wright BM, Zöllner S, McInnis MG

### Presenters:

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The Heinz C Prechter Bipolar Research Program (PrBP) at the University of Michigan is a collaborative network of research projects focused the discovery of mechanisms underlying the etiology of bipolar disorder (BD) as well as the study of predictive patterns of outcomes of disease. The study has been ongoing for 16 years; the core features of the program include deep phenotyping and ongoing (every 2 months) longitudinal collection of clinical data. The data are organized into 7 ontological platforms: 1) disease states; 2) neurocognitive functioning; 3) personality, 4) motivated behaviors; 5) sleep and circadian patterns; 6) life story and experiences; 7) treatment and outcomes patterns.

Deep clinical phenotyping gathers clinical data across each of the ontological platforms. Biological modelling of disease states uses induced pluripotent stem cell (iPSC) methods. Blood is sampled for genetic analysis.

Clinical disease states are assessed using standardized interviews and are categorized according to the DSM IV criteria. Neurocognitive assessments evaluate a range of cognitive functions including memory and executive functioning. Personality and other measures of temperament are assessed along with motivated behaviors including alcohol and substance use. Sleep, circadian patterns as well as life story events are recorded in standardized survey instruments. Treatment and outcomes patterns include the documentation of medication and symptom severity, assessed bimonthly using self-report measures, as well as quantifying number and type of episodes, hospitalizations, and employment are assessed via bi-yearly standardized clinical interviews.

There are currently 1,357 participants in the PrBP. This includes 574 BD I, 32 SA-BD, 163 BD II, and 77 BD NOS as well as 282 unaffected controls and the balance representing other psychiatric diagnoses (e.g., MDD, anxiety). Herein, descriptive statistics are presented to describe the baseline features along with clinical correlations of features with outcomes measures. Analysis based in each of the ontological platforms will be featured in addition to longitudinal outcomes patterns.

For instance, there are approximately 40,000 PHQ9 measures in the total sample. The average PHQ9 at entry into the study is 6.8, participants have on average approximately 30 measures, the variance in the measures is highly variable (range 0 - 155 , median = 9.5). The descriptive data from each of the ontological classes and longitudinal outcomes patterns show a wide range of variability in the cohort which provides opportunities for stratification that will be highlighted in the presentation. Instruction to obtain this data set for research are also provided.

## 69. A Randomized, Double-Blind, Placebo-Controlled Study of the Safety, Tolerability, and Efficacy of Zuranolone in Adults With Comorbid Major Depressive Disorder and Insomnia

Andrew D. Krystal, MD<sup>1</sup>; Gary K. Zammit, PhD<sup>2</sup>; Eric M. Chavez, MD, MS<sup>3</sup>; Robert Lasser, MD, MBA<sup>4</sup>; Sigui Li, MS<sup>4</sup>; Fiona Forrestal, MS<sup>5</sup>; Maxwell Adams, PharmD<sup>5</sup>; Sean Knox, MD<sup>5</sup>; Amy Bullock, PhD<sup>4</sup>

### Institutions:

1. Weill Institute for Neurosciences, University of California, San Francisco, CA, USA
2. Clinilabs Drug Development Corporation, New York, NY, USA
3. Artemis Institute for Clinical Research, San Diego, CA, USA
4. Sage Therapeutics, Inc., Cambridge, MA, USA
5. Biogen Inc., Cambridge, MA, USA

### Presenters:

underlined submitting presenter

**Background:** Major depressive disorder (MDD) is a serious medical condition, and one of the most common and disruptive symptoms associated with MDD is insomnia. Improving sleep in MDD is associated with improved outcomes. Zuranolone (ZRN), an investigational neuroactive steroid, positive allosteric modulator of both synaptic and extrasynaptic GABA<sub>A</sub> receptors, is in clinical development as an oral, once-daily, 14-day course for the treatment of adults with MDD.

**Methods:** RAINFOREST (NCT03771664) was a Phase 3, randomized, double-blind, placebo (PBO)-controlled trial of the efficacy, safety, and tolerability of ZRN 30 mg compared with PBO in patients with comorbid MDD and insomnia. Patients were aged 18-64 years, with Montgomery-Åsberg Depression Rating Scale total score (MADRS)  $\geq 28$ , 17-item Hamilton Rating Scale for Depression total score (HAM-D-17)  $\geq 20$ , and an Insomnia Severity Index (ISI) score  $\geq 15$ . Primary endpoint: change from baseline (CFB) in % sleep efficiency (%SE) as assessed by 8-hour overnight polysomnography (PSG) performed at baseline (Days -2 and -1), prior to randomization, and at the end of double-blind treatment (EODBT; Days 13 and 14). Secondary endpoints included CFB at EODBT in other PSG-derived endpoints (ie, wake after sleep onset [WASO], number of awakenings [NAW], total sleep time [TST], latency to persistent sleep [LPS], mean duration of awakenings [mDURAW], and Rapid Eye Movement [REM] sleep endpoints).

**Results:** After the WATERFALL Study (NCT04442490; ZRN 50 mg) met its primary endpoint (CFB in HAM-D-17 at Day 15), RAINFOREST was terminated early for reasons not related to safety (prior to reaching planned sample size [n=102]). In total, 87 patients were randomized (ZRN, 44; PBO, 43) and 86 (ZRN, 43; PBO, 43) received  $\geq 1$  dose of double-blinded drug and had valid baseline and  $\geq 1$  postbaseline efficacy evaluation. Baseline demographics and characteristics were generally balanced between treatment groups. Mean (SD) baseline HAM-D-17 (ZRN vs PBO) was 25.9 (3.5) vs 25.5 (3.4); mean (SD) baseline ISI score was 21.6 (3.6) vs 21.8 (3.2); and mean (SD) baseline %SE (average from 2 nights of PSG) was 73.67% (9.81) vs 67.70% (14.94). At EODBT, the model-based ZRN vs PBO treatment difference (95% CI) was 3.2% (-1.2, 7.7) (p=0.1537). An ad hoc analysis, intended to eliminate the potential impact of the "first night effect" using only second night PSG data as baseline %SE, showed significant improvement in %SE (treatment difference [95% CI]: 6.0 [0.7, 11.2]; p=0.0266). ZRN led to numerical improvement compared with PBO (p>0.05) in other objective measures of sleep (WASO, TST, LPS, NAW, and mDURAW) from 2 nights of PSG. However, nominally significant differences favoring ZRN over PBO were observed in REM sleep endpoints at EODBT (latency [p=0.0313], duration [p=0.0320], percent [p=0.006], density [p=0.0004], and activity [p<0.0001]). ZRN was generally well tolerated. The most common treatment-emergent adverse events (>5% incidence; ZRN vs PBO) were somnolence (14.0% vs 7.0%), headache (11.6% vs 2.3%), dizziness (9.3% vs 0%), upper respiratory tract infection (7.0% vs 20.9%), diarrhea (7.0% vs 7.0%), nasopharyngitis (7.0% vs 4.7%), and nausea (4.7% vs 14.0%).

**Conclusions:** RAINFOREST was terminated before reaching planned sample size and did not meet its primary endpoint (CFB in %SE at EODBT). However, nominally significant improvement in %SE (ZRN vs PBO) was observed when analyzed using only second night PSG measures. Nominally significant ZRN vs PBO REM differences were found on 5 measures of REM sleep that are of uncertain clinical significance but are of interest given that multiple prior studies have reported alterations in REM sleep parameters in patients with MDD. The safety profile of ZRN

was consistent with that observed in other ZRN studies to date. Although RAINFOREST was terminated early, *ad hoc* analyses suggest potential benefits in patients with comorbid MDD and insomnia. Results will inform future trials.