POSTER ABSTRACT BOOK

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Poster Session I

W1. EFFECTS OF SUVOREXANT ON 35% CO2-INDUCED PANIC: A PILOT STUDY

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Abstract: Background: Hypocretins (orexins), a more recently identified class of pro-arousal neuropeptides, are synthesized by neurons in the lateral and posterior hypothalamus (deLecea L et al., 1999). Orexin A (ORX A) and orexin B (ORX B), are both cleaved from a common precursor peptide, prepro-orexin (Sakurai T, 2007). They been implicated in panicogenesis in animal models of panic (Johnson PL et al., 2010). However, there have been no prospective studies of orexin metabolism in humans with panic disorder (PD). Therefore, we previously examined the effects of a 35% CO2 inhalation test on behavioral, physiological, and biochemical (plasma ORX A) measures, in 1 un-medicated PD patient and 2 healthy volunteers. In this paradigm, the PD patient had a panic episode associated with marked early elevations in plasma ORX levels, while volunteers had only mild anxiety with more early minor elevations in plasma ORX. These results were suggestive of a role for ORX in the initiation or elaboration of the human panic response. However, the panicolytic potential of orexin antagonists in this paradigm is yet to be explored, and, therefore, is the focus of the current pilot project. Our main aim, in the new protocol, is to provide evidence that acute administration of suvorexant, a mixed ORX1/2 receptor antagonist, will block 35% CO2-induced panic symptoms in PD, via amelioration of central ORX neuronal hyperactivity. An exploratory aim is to acquire DNA samples for future candidate gene/DNA analysis. Genes of interest with respect to ORX metabolism are the preproORX gene and ORX1 and ORX2 receptor genes.
Methods: We are utilizing a prospective, parallel-group, repeated-measures design to compare behavioral, physiological, and biochemical (plasma ORX A) responses in 2 independent groups of un-medicated, non-depressed PD patients (n=6 in each group), at baseline/resting state, and, after panic provocation with a brief (60 sec) inhalation of a 35% CO2 / 65% O2 mixture. Patients are randomized, in a double-blind manner, to receive either a single, oral dose of the mixed ORX1/2 receptor antagonist, suvorexant (10 mg dose), or identical placebo, administered approximately 120 minutes before CO2 challenge (expected Cmax).
Results: To date, 8 patients have been screened, and 2 patients (both females) have completed the protocol. Following CO2 inhalation, patient # 1's peak increase from baseline visual analog scale (VAS) anxiety score = 13 mm, while their peak increase from baseline in the panic symptom scale (PSS) total score=2. In contrast, patient # 2, had a panic response with a peak increase from baseline in their VAS-anxiety score=50 mm, and peak increase from baseline in the PSS total score = 22 (at +1 min post CO2). Vitals signs were stable during the testing. Orexin levels are pending and are to be analyzed via an ELISA assay. The study blind is being maintained.
Conclusions: The 35% CO2 inhalation paradigm appears to be a feasible approach to examine orexin function in PD. An experimental medicine strategy may be an efficient way of screening for a treatment signal with a novel class of anxiolytics, such as orexin antagonists, while

simultaneously determining the pathophysiologic significance of ORX hyperactivity in PD. Clinical trials.gov#: NCT02593682

W2. META-ANALYSIS OF PRENATAL ANTIDEPRESSANT EXPOSURE AS RISK FACTOR FOR AUTISM: IMPACT OF COMPARISON GROUP DEFINITION

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Abstract: Background: A 2014 position statement by the US Dept. of HHS Agency for Healthcare Research and Quality (AHRQ) posited that studies of prenatal antidepressant (AD) safety are "inadequate to allow well-informed decisions . . . because comparison groups were not exclusively depressed women". Illustrating this concern, existing meta-analyses, concluding prenatal AD exposure is associated with autism, have failed to evaluate the impact of comparison group designation. The current meta-analysis addresses this gap in the literature Methods: A search of 7 databases was performed with keywords including antidepressant or selective serotonin reuptake inhibitor (SSRI), pregnancy, and autism. Observational studies reporting odds (OR) or hazard (HR) ratios for autism following AD exposure qualified. Analyses of prenatal SSRI or AD exposure were performed. Subgroup analyses stratified by population, psychiatric, and sibling comparison groups, and a final composite analysis were conducted. Statistical analyses were performed using Comprehensive Meta Analysis software. Results: Fourteen studies (8 cohort, 6 case-control) were included. Thirteen studies reported results using a population-based comparison group. Psychiatric and discordant sibling comparison groups were reported by 5 and 4 studies respectively.

Population-based analyses uniformly produced significant estimates of autism for exposure to any AD (HR= 1.42 [95% CI: 1.22-1.65]; OR=1.43 [95%CI: 1.21-1.68]) or SSRI (HR= 1.53 [95% CI: 1.37-1.72]; OR=1.55 [95%CI: 1.36-1.75]). Conversely, psychiatric comparison groups demonstrated no significant associations for AD (HR= 1.16 [95% CI: 0.79-1.72]; OR=1.12 [95%CI: 0.84-1.48]) or SSRI (HR= 1.25 [95% CI: 0.79-1.79] OR=0.99 [95%CI: 0.65-1.52]) exposure. Analyses of siblings discordant for autism, arguably enhancing control for both heritability and psychiatric illness risk, suggested SSRI exposure may even afford protective effective (OR=0.79 [95%CI: 0.65-0.97). Other estimates using the sibling comparison group for ADs (HR= 0.95 [95% CI: 0.69-1.31]; OR=0.87 [95%CI: 0.58-1.30]) or SSRIs (HR= 0.82 [95% CI: 0.60-1.12]) were insignificant. A final composite analysis demonstrated no significant effect of exposure to ADs (HR= 0.97 [95% CI: 0.83-1.14]; OR=1.16 [95%CI: 0.88-1.51]) or SSRIs (HR= 0.99 [95% CI: 0.82-1.21]]; OR=1.18 [95%CI: 0.93-1.51]). Results limited to first trimester exposure were similar.

Conclusion: Underscoring concerns raised by the AHRQ, study design, particularly alternative means of defining and selecting comparison groups, leads to discordant conclusions regarding the risk for autism conveyed by prenatal AD exposure. Although population-based comparisons suggest that AD exposure increases autism risk, psychiatric and family-based comparisons do not support this conclusion. Future studies evaluating risks of fetal AD exposure should attend to this important research design concern.

W3. ANTERIOR CINGULATE CORTICAL GLUTAMATE AND EXCITATORY AMINO ACID TRANSPORTER 2 (EAAT2) GENETIC VARIATION IN PATIENTS WITH DEPRESSION

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Abstract: Specific Purpose: There is increasing recognition, both by the neuroscience research and drug development that glutamatergic dysregulation and/or modulation are implicated in the underlying neurobiology of mood disorders. Magnetic resonance spectroscopy (MRS) is a functional brain imaging method uniquely positioned to investigate glutamatergic biochemical drug mechanism of action. This post hoc exploratory study was conducted to evaluate the relationship between 1H-MRS glutamate in anterior cingulate cortex (AC) and polymorphic variants of four genes known to regulate synaptic or extracellular glutamate in the glutamate-glutamine cycle. Single nucleotide polymorphisms (SNPs) from 4 genes included: glutamine synthetase (GS) encoded by GLUL, excitatory amino acid transporter (EAAT) 1 encoded by SLC1A3, EAAT2 encoded by SLC1A2, and EAAT5 encoded by SLCA17.
Methodology: The inclusion criteria included patients age 18-65 with a DSM-IV diagnosis of a current major depressive episode associated with major depressive disorder, bipolar I or II disorder. Exclusion criteria included the inability to speak English or provide informed consent, current treatment with antidepressant, active substance use, abnormal thyroid stimulating hormone, unstable medical illness, hypomanic symptoms (YMRS >12), active suicidal ideation, psychosis, and antipsychotic treatment within 4 weeks.
The midline AC voxel was placed approximately 1 cm above the genu of the corpus callosum, demonstrating a continuous view of the anterior and posterior horns of the lateral ventricles. To optimize glutamate measurement, a 2-dimensional J-resolved averaged PRESS sequence was utilized (TE=35-195 ms in 16 steps, TR=2000 ms, excitations=8).
For genomic analysis, we chose proximal 5' untranslated (UTR), 3'UTR, and exonal regions of GLUL, SLC1A3, SLC1A2, and SLCA17 to identify known essential regulatory elements and synonymous and non-synonymous mutations. We identified 47 SNPs, one SNP was excluded due to poor product quality. In total, 26 depressed patients (15 unipolar,11 bipolar) completed MRS data acquisition, spectra reconstruction and quantification, and genomic analysis. Linear regression models were used to test the additive effect of the minor allele on MRS glutamate.
Results: Two SNPs (rs3812778, rs3829280), in perfect linkage disequilibrium (r2=1), in the 3' UTR of EAAT2 gene SLC1A2 were associated with 2DJ AC glutamate; specifically, heterozygotes, in comparison to rare homozygotes and common homozygotes, had a significant elevation in AC glutamate (p=0.004). There was no association between glutamate levels for any other SNP, nor significant difference by diagnostic subtype and depression subtype.
Importance: SNPs rs3829280 and rs2812778 may downregulate the expression of SLC1A2 and subsequent EAAT2 protein expression, hence reducing the capacity of glutamate clearance from the synaptic cleft. Limitations of this study include small sample size, and lack of non-depressed control group with. Future studies combining neuroimaging, genotyping, and deep clinical phenotyping may provide ability to quantify disease burden based on biological markers.

W4. AN EPIGENETIC BIOMARKER FOR DEPRESSION AND TRAIT OF CHILDHOOD TRAUMA WITH SEX-SPECIFIC EFFECTS

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Abstract: Mechanistic insights from animal studies can inform the development of diagnostics and better treatments for major depressive disorder (MDD), which is a leading cause of ill health and disability worldwide. Converging evidence from our and other groups revealed that animals with an endogenous reduction in the levels of the epigenetic modulator of glutamatergic function with insulin-sensitizing properties, acetyl-L-carnitine (LAC), in plasma and mood-regulatory brain regions (hippocampus and prefrontal cortex) showed depressive and metabolic-like dysfunctions that were rapidly rescued by LAC supplementation. Therefore, our objective was to determine whether patients with MDD differed in LAC levels in comparison to healthy controls(HC).

Plasma distribution of LAC and of internal control free-carnitine were determined in 71 patients with MDD and 45 age- and sex-matched HC using UPLC-MS/MS and ESI-MS/MS. The psychiatric examination included: SCID and MINI, and the two psychiatric scales HDRS-17 and MADRS. Childhood Trauma Questionnaire was used to assess childhood trauma. Two-tailed t-tests, chi-square, and multiple regression were used as appropriate.

LAC was lower in patients with MDD compared to HC($p<0.0001$,effect size=0.8). Of note, LAC was lower in patients who exhibited greater severity and earlier age-of-onset of MDD. Moreover, in those patients with TRD, the reduction in LAC was stronger, and emotional neglect and being a female predicted decreased LAC($p=0.04$,$r=0.66$). Our new findings suggest that LAC may serve as marker to delineate a MDD phenotype, providing a target for precision medicine and rational path forward for novel pharmaceuticals. Future studies will test whether such biologically-defined MDD phenotype could benefit by LAC treatment.

W5. PLASMA TUMOR NECROSIS FACTOR-ALPHA CORRELATES WITH L-SELECTIN IN PATIENTS WITH SCHIZOPHRENIA

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Abstract: Background: Immune dysregulation with abnormal levels of cytokines have been implicated in the pathophysiology of schizophrenia. The pro-inflammatory cytokine tumor necrosis factor-alpha (TNF-α), has been suggested to be a trait marker in schizophrenia. Entry of leukocytes into tissues is a key feature of inflammation, a process involving E-, L-, and P-selectins. Our group has previously reported abnormal levels of the leukocyte adhesion

receptor, L-selectin, in patients with multi-episode chronic schizophrenia. We aimed to evaluate the relationship between plasma TNF-α and L-selectin in patients with schizophrenia. Methods: 106 patients with schizophrenia (diagnosed with MINI) were recruited. Fasting plasma TNF-α and L-selectin were measured using ELISA. Spearman's correlation was used to assess the relationship between TNF-α and L-selectin. 77 patients (mean age 32.9 years (SD =12.28), 72% male, 28% female, 52% Black, 31% White, 15% Hispanic, 2% Asian) had complete data.
Results: TNF-α positively correlated with L-selectin (rho=0.32, p=0.005), a finding which persisted after adjusting for age, sex and race (partial rho= 0.34, p=0.003).
Conclusion: Recent studies have demonstrated that L-selectin reduces premature activation of neutrophils to ensure clearance of pathogens and wound healing without excessive tissue injury. It is therefore possible that increase in L-selectin in tandem with TNF-α is a protective mechanism in schizophrenia, a hypothesis that requires further study.

W6. CHARACTERISTICS OF PATIENTS IN RECOVERY VERSUS PATIENTS WITH RECURRENCE IN A RANDOMIZED PLACEBO-CONTROLLED STUDY WITH ARIPIPRAZOLE ONCE-MONTHLY AS MAINTENANCE TREATMENT FOR BIPOLAR I DISORDER

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Abstract: Background: Baseline patient and disease characteristics may impact recovery or recurrence of mood episodes in patients with bipolar I disorder (BP-I) [1].
Aims: This study describes the background and clinical characteristics of patients in recovery versus those with recurrence of a mood episode during up to 52 weeks of maintenance treatment with aripiprazole once-monthly 400 mg (AOM 400) for BP-I.
Methods: The study (NCT01567527) included outpatients aged 18-65 years with a DSM-IV-TR diagnosis of BP-I and a current manic episode at enrollment [2]. Patients were stabilized on oral aripiprazole, then on AOM 400; those meeting stabilization criteria were subsequently randomized 1:1 to a 52-week double-blind, placebo-controlled withdrawal phase. Recovery was defined as mania and depression scale scores of ≤12 for 8 consecutive weeks. Recurrence of a mood episode was defined by criteria that included hospitalization; mania, depression and global clinical impression scale scores; disease or clinical worsening; discontinuation for lack of efficacy, or active suicidality. Baseline characteristics of the patients treated with AOM 400, including age, gender and key disease characteristics, are summarized by recovery/recurrence status.
Results: A total of 133 patients were treated with AOM 400. Of these, 26.3% (N=35) had recurrence whereas 68.4 % (N=91) were in recovery/remission. Most baseline characteristics in the two outcome groups were similar including age, gender, age at diagnosis of bipolar I and disease severity scores. Patients with recurrence had more mean life-time depressive episodes (11.7) at baseline than patients in recovery/remission (6.5).
Conclusions: Life-time depressive episodes were associated with recurrence; other baseline characteristics were similar between patients with recurrence and those in recovery/remission.

W7. REMISSION AND RECOVERY IN PATIENTS WITH BIPOLAR I DISORDER (BP-I) TREATED WITH ARIPIPRAZOLE ONCE-MONTHLY (AOM 400)

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Abstract: Background: After symptomatic treatment of acute episodes of bipolar I disorder (BP-I), the treatment goal is remission and, ultimately, recovery [1]. Reported here are the results for secondary endpoints assessing remission and recovery rates in patients treated with aripiprazole once-monthly 400 mg (AOM 400) from one double-blind, placebo-controlled 52-week maintenance study [2] and one 52-week open-label study.

Methodology: Assess remission and recovery rates from two clinical trials with AOM 400. Remission was defined as subjects with YMRS and MADRS total scores ≤12. Recovery was defined as meeting criteria for sustained remission for 8 consecutive weeks. The first study (NCT01567527) was a double-blind, placebo-controlled, randomized withdrawal study. Subjects underwent screening for eligibility (6 weeks), followed by a conversion phase to oral aripiprazole monotherapy (4-6 weeks) if needed, an oral stabilization phase (2 to 8 weeks), an AOM 400 stabilization phase (12 to 28 weeks), and a double-blind, placebo-controlled phase where patients were randomized to continue treatment with AOM 400 or placebo for 52 weeks. The second study (NCT01710709) was an open-label, multicenter study that enrolled de novo patients with BP-I and rollover patients who participated in the double-blind placebo-controlled study. This trial was composed of a screening phase followed by: a 4 to 6-week conversion phase (if needed), a 4 to 12-week oral aripiprazole stabilization phase, and a 52-week open-label AOM 400 maintenance phase. De novo subjects entered the trial at screening and proceeded to the conversion phase if they were currently being treated with an antipsychotic (except oral aripiprazole), mood stabilizer, or antidepressant (ADT), thus requiring a switch to oral aripiprazole. Subjects not currently being treated with an antipsychotic, mood stabilizer, ADT or oral aripiprazole proceeded to the oral stabilization phase. Rollover subjects eligible for entry into the open-label trial, and who chose to continue treatment upon completion of the previous trial, entered directly into the AOM 400 maintenance phase.

Results: In the double-blind study, a significantly higher proportion (p=0.0169) of patients on AOM 400 achieved protocol-defined remission at last visit (74%, n=97/131) vs 60.2 % for placebo (n=80/133), and a significantly higher proportion (p=0.0122) were in recovery by last visit (64.9%, n=85/131) vs 49.6% for placebo (n=66/133). The observed remission rate for rollover patients in the open-label study remained stable (98.8%, n=84/85) by last visit, and 80.0% (n=68/85) completed the open-label study.

In the open-label study, de novo patients also had a high proportion of patients meeting the criteria for remission (87.2%, n=328/376) and recovery (77%, n=292/379) by last visit, and 58.8% (n=223/379) completed the study. The overall safety profile showed that AOM 400 was well tolerated.

Conclusion: Current data showed high rates of remission and recovery in patients with BP-I taking AOM 400 both in a placebo-controlled randomized withdrawal study and in an open-label study. Results support AOM 400 as a viable once-monthly option for maintenance monotherapy treatment of BP-I. The injectable once-monthly formulation may contribute to the high rates of remission and recovery observed, perhaps due to adherence benefits of once-

monthly formulations, giving clinicians another option in maintenance monotherapy treatment of adult patients with BP-I.

W8. DEMOGRAPHIC AND CLINICAL COMPARISON OF PATIENTS WITH BIPOLAR DISORDER ON LITHIUM VERSUS LAMOTRIGINE MAINTENANCE TREATMENT

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Abstract: Background: Lithium (Li) and lamotrigine (LTG) are complementary maintenance treatments for bipolar disorder (BD). In this study, we compared demographic and clinical characteristics of BD patients who were on Li maintenance, LTG maintenance, and Li-LTG combination therapy.
Methods: We included adult subjects with a diagnosis of Bipolar I or II disorder who were on Li and or LTG treatment at the time of enrollment in the Mayo Clinic Bipolar Disorder Biobank (1). An Alda score (2) was used to retrospectively assess the clinical response to Li monotherapy and LTG monotherapy. We compared demographic (age, sex), psychosocial (education, work status, relationship), medical and psychiatric comorbidity variables and treatment response (measured using Alda scores) among the 3 groups (Li vs LTG vs Li-LTG). We also compared clinical characteristics of Li and LTG responders compared to non-responders, with treatment response defined as Alda score ≥7.
Results: A total of 356, 334, and 91, subjects were on Li therapy, LTG therapy, and Li-LTG therapy, respectively. Patients on LTG therapy were significantly older, more likely female, had higher rates of bipolar II diagnosis and rapid cycling, lower prevalence of history of psychosis, and had higher respiratory and neurologic comorbidity burden. Patients on Li therapy were more likely to have bipolar-I disorder and history of psychosis and had a lower rate of rapid cycling. The mean Alda score was higher for patients treated with Li compared to LTG, (7.1 +/- 1.8 vs 6.1 +/- 1.9, p=0.0003). Patients on Li therapy were more likely to have bipolar-I disorder and history of psychosis and had a lower rate of rapid cycling.
Compared to Li non-responders, Li responders had an overall significantly lower rate of suicide attempts and suicide attempts at a younger age (≤19 years), lower prevalence of ADHD, rapid cycling, psychiatric comorbidities, neurological comorbidities, number of psychotropic medications, and higher work productivity. Compared to LTG non-responders, LTG responders had a significantly lower rate of suicide attempts, lower prevalence of psychiatric and medical comorbidities (genitourinary, musculoskeletal, and endocrine).
Conclusion: There are significant differences in demographic and clinical phenotypic variables in patients with BD who are on maintenance therapy with Li or LTG. These findings provide significant insights into the clinical utilization of Li and LTG therapy and set the stage to investigate differential biomarkers in 2 complementary maintenance mood stabilization treatments in bipolar disorder.

W9. EFFECT ON FUNCTIONING WITH ARIPIPRAZOLE ONCE-MONTHLY (AOM 400) IN THE LONG-TERM TREATMENT OF BIPOLAR I DISORDER

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Abstract: Background: Despite adequate treatment, few patients with bipolar disorder demonstrate an improvement in functioning [1], which often lags symptomatic improvement [2].
Objective: To assess changes in the Functioning Assessment Short Test (FAST) during stabilization and while receiving long-term maintenance treatment with aripiprazole once-monthly 400 mg (AOM 400) in a sample of de novo patients with bipolar I disorder (BP-I) currently taking oral aripiprazole, or newly initiating oral aripiprazole after a lapse in treatment.
Method: The trial (NCT01710709) included a screening phase and 3 study phases: conversion of de novo patients from their current treatment to oral aripiprazole, followed by stabilization on oral aripiprazole (4-12 weeks), after which patients meeting stabilization criteria entered a 52-week, open-label maintenance phase with AOM 400. Patients entered directly into the oral stabilization phase if they had a lapse in treatment or were already being treated with oral aripiprazole. Functioning was assessed using the FAST, a 24-item questionnaire where higher total scores (possible range: 0 to 72) reflect more impaired functioning; total scores ≥18 indicate moderate/severe impairment. Changes in FAST total score were described using observed case mean summary statistics with standard deviation (SD).
Results: At oral stabilization baseline, FAST total score indicated moderate/severe impairment (mean=17.8 [SD=13.5]; n=364). A mean improvement of -3.9 (SD=9.9) was observed at the last stabilization phase visit, and improvements were maintained over the 52-week maintenance phase AOM 400 (mean=2.87 [SD=9.5; n=217]).
Conclusions: In this study, patients with BP-I showed functional improvements within 4 to 12 weeks after initiating oral aripiprazole. Improvements were sustained throughout 52 weeks of AOM 400 maintenance treatment.

W10. DEVELOPMENT UPDATE ON PIMAVANSERIN, A NOVEL 5-HT2A RECEPTOR INVERSE AGONIST

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Abstract: Psychosis, depression, and other neuropsychiatric symptoms (NPS) are frequently associated with neurodegenerative conditions such as dementia and Parkinson's disease (PD). Successful treatment of NPS often require treatment with atypical antipsychotics (AP). Pimavanserin (PIM) is an atypical AP that acts as an inverse agonist/antagonist at the 5 HT2A receptor and is currently being investigated across a spectrum of neuropsychiatric indications. In addition to motor disturbances associated with PD, non-motor symptoms, such as psychosis, can deeply affect quality of life (QoL) for PD patients and their caregivers. A Phase 3 clinical trial evaluated the efficacy and tolerability of PIM in 199 patients with PD psychosis. PIM

demonstrated a significant reduction in hallucinations and delusions, versus placebo. PIM was also safe and well tolerated and did not negatively impact motor control. In 2016 PIM was approved by the FDA for the treatment of hallucinations and delusions associated with PDP.
A Phase 2 clinical trial evaluated the efficacy and tolerability of PIM in 181 patients with Alzheimer's disease psychosis (ADP). The study demonstrated a significant benefit for PIM over placebo at the primary end-point of 6-week and led to the initiation of a Phase 3 program in dementia-related psychosis (DRP). The Phase 3 study of PIM in DRP employs a relapse prevention study design with a primary endpoint of time to relapse of psychosis. The objective is to evaluate the efficacy and safety in a long-term (chronic) treatment paradigm for DRP. Target study population includes patients experiencing moderate to severe psychotic symptoms associated with multiple major dementia types: AD, dementia associated with PD, dementia with Lewy bodies, frontotemporal degeneration spectrum disorders, and vascular dementia.
Additionally, the antipsychotic properties of PIM are being investigated in patients with schizophrenia. Current medications used to treat schizophrenia have substantial number of limitations, including a range of side effects, inadequate treatment response and limited efficacy on negative symptoms. Data from a Phase 2 trial of PIM as co-therapy in patients with schizophrenia showed that PIM plus a 2 mg dose of risperidone demonstrated comparable efficacy to a 6 mg dose of risperidone, improvement in both positive and negative symptoms of schizophrenia, some indication of possibly faster onset of action and an improved overall side effect profile. Based on these preliminary observations, further clinical studies investigating PIM as adjunctive therapy for patients with inadequate treatment response to atypical antipsychotic and in patients with predominant negative symptoms have been initiated.
It is well established that antagonism at the 5-HT2A receptor potentiate antidepressant effects of SSRIs. This presents therapeutic opportunity for PIM as an adjunctive treatment in patients with inadequate response to standard antidepressant therapy. As such, PIM may present a more suitable alternative to atypical APs currently used adjunctively to treat Major depressive disorder (MDD). A Phase 2 study assessing PIM as adjunctive therapy in MDD is currently ongoing.
Pharmacology of PIM, the results of completed clinical trials, as well as the design and status of PIM development programs in DRP, schizophrenia, and MDD will be reviewed.

W11. ADHD AND CHRONIC ANHEDONIA AS PREDICTORS OF TREATMENT RESPONSE AND SUICIDALITY IN INDIVIDUALS WITH GENERALIZATION ANXIETY DISORDER

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Abstract: Background: Attention deficit hyperactivity disorders (ADHD) and generalized anxiety disorder (GAD) are highly comorbid and associated with reduced quality of life and increased risk of self-harm. Research has demonstrated that ADHD is associated with treatment-resistance in depressed patients prescribed selective serotonin reuptake inhibitors (SSRIs). Yet, little is known about the influence of comorbid ADHD on treatment response to antidepressants in patients with GAD. The aim of this study was to assess the prevalence of

undiagnosed/untreated ADHD and identify predictive factors of treatment-resistance and suicidality in patients with comorbid GAD and ADHD.
Method: Data was collected from consecutive referrals to a tertiary-care mood and anxiety clinic. Participants were administered the Mini International Neuropsychiatric Interview Plus 6.0.0 and select self-report scales. Diagnosis was established using clinical and collateral information. Treatment-resistance was defined as failure of two or more antidepressants/anxiolytics for adequate treatment dose and duration. Preliminary Chi-square analyses (N = 97) were performed to assess predictive factors. At completion Chi-square and logistic regression (N = 160) analyses were conducted on significant factors to obtain odd ratios (ORs).
Results: The result indicated that undetected ADHD was present in 34% of mood and anxiety referrals. ADHD was present in 43.7% of treatment-resistant GAD referrals with 91.9% reporting chronic anhedonia. Features predictive of undiagnosed ADHD included sex (65.4% males, $p < .031$), alcohol ($p = .010$) and substance dependence/abuse ($p = .047$), and number of diagnoses ($p < .001$). Number of current ($p < .001$) and past intake medications ($p < .001$), SSRI failure ($p < .001$), and ADHD ($p = .016$) predicted treatment-resistance. Chronic anhedonia ($p = .042$) and alcohol dependence/abuse ($p = .025$) predicted suicidal ideation, whereas substance abuse was associated with suicide attempt ($p = .013$).
Conclusions: These results support previous findings that ADHD and GAD are highly comorbid disorders. This study demonstrated that ADHD is often unrecognized or untreated in adult referred for the treatment of GAD and may explain risky behaviors, multiple referral diagnoses, and failed medications. As well, chronic anhedonia may be a prognostic indicator of unrecognized ADHD and suicidality. This signifies the importance of ADHD screening in GAD patients with anhedonia in order to improve treatment outcomes and reduce self-harm.

W12. A DOUBLE-BLIND, PLACEBO-CONTROLLED, DOSE-RANGING STUDY OF SPN-812 (EXTENDED-RELEASE VILOXAZINE) IN CHILDREN WITH ADHD

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Abstract: Objective: To determine the effective and safe doses of once-daily, SPN-812 (extended-release viloxazine), a structurally distinct, bicyclic norepinephrine reuptake inhibitor, in children (ages 6-12 years) with attention-deficit/hyperactivity disorder (ADHD).
Methods: In a randomized, double-blind, placebo-controlled, multicenter, 5-arm, parallel-group, dose-ranging study, 222 subjects were randomized to receive either placebo or active treatment (SPN-812 100, 200, 300, or 400 mg) at 1:2:2:2:2. Treatment continued for a total of 8 weeks (including 3 weeks' titration). The primary endpoint was change from baseline (CFB) to end of study in the ADHD Rating Scale-IV (ADHD RS-IV) Total Score; Clinical Global Impression-Severity (CGI-S) and -Improvement (CGI-I) were secondary measures. Safety assessments included laboratory and ECG measurements and reporting of adverse events (AEs).
Results: Mean CFB in ADHD RS-IV Total Scores for the intent-to-treat population (N = 206) improved in all SPN-812 dose groups compared to placebo, and differences were statistically

significant in the 200-, 300-, and 400-mg dose groups at P = 0.031, 0.027, and 0.021, respectively (CFB Least Squares Means [LsMeans] = -18.4, -18.6, and -19.0; LsMean for placebo = -10.5). Similar results were observed for the CGI-S; CGI-I was significant only for the 300-mg group (P = 0.009). The most frequent treatment-emergent AEs (≥15.0% of subjects) were somnolence, headache, and decreased appetite, with the incidence increasing with higher SPN-812 doses.
Conclusions: Treatment with 200, 300, and 400 mg SPN-812 resulted in statistically significant improvement in CFB in ADHD RS-IV Total Scores compared to placebo; the primary efficacy results were confirmed by sensitivity analyses and are supported by results from analyses of secondary efficacy measures. All SPN-812 doses tested were well tolerated. SPN-812 will be further evaluated as a non-stimulant pharmacotherapy for the treatment of ADHD.

W13. IMPROVEMENT IN ADHD-RELATED SYMPTOMS AND BEHAVIORS IN CHILDREN WITH ADHD TREATED WITH DASOTRALINE: RESULTS OF A POST-HOC ADHD-RS-IV ITEM ANALYSIS

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Abstract: Objective: Dasotraline, a potent inhibitor of pre-synaptic dopamine and norepinephrine transporters, is in development for the treatment of ADHD in children and adults. The PK profile of dasotraline is characterized by slow absorption and a long elimination half-life that permits once-daily dosing. The efficacy of the 4 mg/d dose of dasotraline in children with ADHD was demonstrated in a randomized, double-blind, placebo-controlled study. The aim of the current post-hoc analysis was to evaluate change in specific ADHD symptoms and behaviors among children who participated in this study.
Methods: Children age 6-12 years with a DSM-5 diagnosis of ADHD were randomized to 6 weeks of double-blind, once-daily treatment with dasotraline (2 or 4 mg) or placebo. The primary efficacy endpoint was change from Baseline in the ADHD Rating Scale Version IV–Home Version (ADHD RS-IV HV) total score at Week 6. In this post-hoc analysis, change from Baseline to Week 6 for each of the 18 individual ADHD RS-IV items was assessed using an MMRM analysis.
Results: At the primary Week 6 endpoint, treatment with dasotraline was associated with statistically significant Week 6 improvement in the ADHD RS-IV HV total score for the 4 mg/d dose vs. placebo (-17.5 vs. -11.4; P<0.001), but not for the 2 mg/d dose (-11.8 vs. -11.4; ns). A total of 13/18 ADHD RS-IV items were significantly improved on dasotraline 4 mg/d vs. placebo: item-1-poor attention/careless mistakes (P=0.004), 2-fidgeting (P=0.002), 4-difficulty staying seated (P=0.017), 5-difficulty listening (P=0.031), 6-hyperactive (P=0.004), 7-difficulty following instructions/finishing work (P=0.001), 9-disorganized (P=0.032), 10-restless/driven to move (P=0.013), 11-avoidance of tasks requiring effort/focus (P=0.005), 12-talks excessively (P=0.017), 15-easily distracted (P=0.004), 16-difficulty waiting turn (P=0.017), and 17-forgetful in daily activities (P=0.015). Improvement on the following 5-items of the ADHD RS-IV did not achieve significance on the 4 mg/d dose of dasotraline: 3-difficulty sustaining attention (P=0.10), 8-difficulty playing quietly (P=0.079), 13-loses things (P=0.050), 14-blurting out answers before question has been completed (P=0.18), and 18-interrupts/intrudes on others (P=0.054). Treatment with the 2 mg/d dose of dasotraline was not

associated with significant improvement vs. placebo on any of the individual ADHD RS-IV items.
Conclusions: In this placebo-controlled study of children with ADHD, 6 weeks of treatment with dasotraline 4 mg/d (but not 2 mg/d) was effective in treating a wide range of ADHD-related symptoms and behaviors as assessed by the ADHD RS-IV scale.
Clinicaltrials.gov identifier: NCT02428088
Sponsored by Sunovion Pharmaceuticals Inc.

W14. LURASIDONE FOR THE TREATMENT OF MAJOR DEPRESSIVE DISORDER WITH MIXED FEATURES: RESULTS OF A 12-WEEK OPEN-LABEL EXTENSION STUDY

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Abstract: Objective: For patients with major depressive disorder (MDD), DSM-5 introduced a new "mixed features" specifier to permit clinicians to note the presence of subthreshold manic symptoms during an episode. Mixed features are estimated to occur in at least 25% of MDD episodes, and are associated with increased severity, risk of recurrence, functional disability, and poorer prognosis. Lurasidone demonstrated efficacy in a short-term study of patients with MDD with mixed features (1). We now report results of the 12-week, open-label, extension phase of the core study that was conducted in patients in the US.
Methods: In a multi-regional study, patients meeting DSM-IV-TR criteria for MDD, who presented with 2 or 3 protocol-defined manic symptoms, were randomized to 6 weeks of double-blind (DB) treatment with lurasidone 20-60 mg/d or placebo. Patients in the US who completed the core study were eligible to enroll in a 12-week, open-label (OL), flexible-dose (20-60 mg/d) extension study in which patients were continued on lurasidone (Lur-Lur group), or switched from placebo to lurasidone (Pbo-Lur group). The primary efficacy measure was the Montgomery-Åsberg Depression Rating Scale (MADRS) total score.
Results: Of the 52 patients in the US who completed the acute phase study, 48 (92%) enrolled in the current OL extension phase: 39/48 (81.3%) were extension phase completers and 9/48 (18.8%) discontinued prematurely, 4.2% due to adverse events, 4.2% due to insufficient clinical response, and 10.4% due to miscellaneous other reasons. For patients entering the extension study, mean MADRS total scores at DB baseline for lurasidone (n=29) and placebo (n=19) were 32.3 and 34.5, respectively; and mean MADRS total scores at week 6 (OL baseline) were 15.0 and 24.1, respectively. Mean change from OL baseline to week 12 (OC/LOCF) in MADRS total scores for the Lur-Lur group was -4.1/-3.3, and for the Pbo-Lur group was -11.2/-9.7. In the OL study, adverse events (≥5%) were akathisia (10.4%), diarrhea (8.3%), upper respiratory infection (8.3%), and headache, sedation, nausea, fatigue (6.3% each). For the Lur-Lur group, median change from DB baseline to week 12 (observed case) were as follows for metabolic parameters: cholesterol (-6.5 mg/dL), triglycerides (-3.5 mg/dL), and HbA1c (+0.15%). For the Pbo-Lur group, median change from DB baseline to week 12 (observed case) were as follows for metabolic parameters: cholesterol (+1.5 mg/dL), triglycerides (+20.0 mg/dL), and HbA1c (+0.30%). There were no clinically significant changes in body weight. During the OL phase, treatment-emergent mania or hypomania

occurred in 2 patients (4.2%); and 2 patients had treatment-emergent suicidal ideation; there were no suicide attempts.
Conclusions: Treatment with open-label, flexible-doses of lurasidone (20-60 mg/d) was generally safe and well-tolerated for up to 12 weeks in patients with MDD with mixed features. Continued improvement in depressive symptoms was observed.
ClinicalTrials.gov identifier: NCT0142325
Sponsored by Sunovion Pharmaceuticals Inc.

W15. INFLAMMATORY MARKERS AND COGNITIVE PERFORMANCE IN PATIENTS WITH SCHIZOPHRENIA TREATED WITH LURASIDONE

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Abstract: Objective: Elevated C-reactive protein concentration has been shown to be a reliable biomarker for inflammatory states. We conducted an exploratory analysis to investigate the potential influence of inflammation, obesity and lipid metabolism on changes in symptom severity and cognitive performance in patients with schizophrenia treated with lurasidone.
Methods: Patients with an acute exacerbation of schizophrenia were treated with one of two fixed doses of lurasidone (80 or 160 mg/day), placebo, or 600 mg/day quetiapine XR in a 6-week double-blind study. Efficacy was assessed with PANSS, CGI-S and MADRS scores. A wide-range CRP (wr-CRP) assay (equivalent to high sensitivity CRP assay) was used to assess levels of inflammation. CRP was evaluated as a logarithm transformed (log) continuous variable and as a categorical variable divided into low (≤ 2 mg/L), medium (> 2 mg/L and ≤ 5 mg/L) and high (> 5 mg/L) subgroups. Cognitive function was assessed with the Cogstate computerized cognitive battery at baseline and week 6 endpoint. Nonparametric bootstrap resampling method was applied to estimate the main and interactive effects of CRP on ranked cognitive scores based on the 95% percentile bootstrap confidence intervals of 1500 replicates.
Results: Elevated level of CRP (log) was associated with cognitive impairment at study baseline ($P < 0.05$), with significantly lower cognitive performance in the subgroup with high CRP (> 5 mg/L) compared to those with low CRP (≤ 2 mg/L) at study baseline ($P < 0.05$). Higher level of CRP (log) was also associated with significantly higher BMI/body weight, and lower levels of high-density lipoprotein (HDL) and high hemoglobin A1c (HbA1c) at study baseline ($P < 0.05$). No significant associations were found for CRP (log) with low-density lipoprotein (LDL) and total cholesterol at study baseline. High CRP level (> 5 mg/L) at study baseline predicted less improvement of cognitive composite score at week 6 endpoint for all treatment groups, compared to those with low to medium CRP levels (≤ 5 mg/L). The joint effect of CRP (log) and HDL on moderating cognitive efficacy of lurasidone was significant ($P<0.05$), with greater lurasidone (vs. placebo) effect size in patients with low CRP and high HDL concentration. Likewise, the joint effects of CRP (log) and HOMA IR on moderating cognitive efficacy of lurasidone was significant ($P<0.05$), with greater lurasidone (vs. placebo) effect size in patients with low CRP and low HOMA IR concentration Lurasidone treatment was associated with significant reduction in symptom severity as assessed by PANSS, CGI-S, and MADRS change scores from baseline to week 6, independent of CRP, HDL and HOMA

IR levels at study baseline. Lurasidone had no significant effect on change in CRP level from baseline to week 6 endpoint.
Conclusions: In this double-blind, placebo- and active-controlled trial of subjects with an acute exacerbation of schizophrenia, our exploratory analysis findings suggest the joint effects of low CRP level combined with either high HDL or low HOMA IR can predict cognitive improvement in patients treated with lurasidone (vs. placebo). Results from cross-sectional analyses suggest that elevated CRP and disturbances in lipid metabolism may affect cognition in patients with schizophrenia. The overall findings suggest that inflammation and its interactive effects with insulin resistance and lipid parameters in patients with schizophrenia might impact cognition and response to treatment with antipsychotics.

W16. EFFICACY OF LURASIDONE IN CHILD AND ADOLESCENT PATIENTS WITH BIPOLAR I DEPRESSION AND ANXIETY: A POST-HOC ANALYSIS

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Abstract: Objective: Anxiety is a common feature of depression in adults as well as children and adolescents, and is associated with increased depression severity and chronicity, and greater functional impairment. The aim of this post-hoc analysis was to evaluate the efficacy of lurasidone in treating pediatric patients with bipolar depression who presented with high levels of anxiety.
Methods: Data in this analysis were derived from a study (1) of patients 10-17 years of age with a DSM-5 diagnosis of bipolar I depression who were randomized to 6 weeks of double-blind treatment with lurasidone 20-80 mg/d (N=173) or placebo (N=170). The primary endpoint was change from Baseline to Week 6 in the Children's Depression Rating Scale, Revised (CDRS-R) total score; the key secondary endpoint was change in the Clinical Global Impression, Bipolar Severity (CGI-BP-S) depression score. We analyzed efficacy in the subgroup of patients who presented with moderate-to-severe anxiety (higher, with baseline Pediatric Anxiety Rating Scale [PARS] score ≥15) and mild-to-low anxiety (lower, with baseline PARS score <15). Endpoint change in the CDRS-R total and CGI-BP-S depression scores were analyzed using a mixed model for repeated measures analysis for patients with high and low levels of anxiety.
Results: At baseline, 112/343 patients (32.7%) met criteria for high levels of anxiety (mean CDRS-R, 62.1; mean PARS, 19.7) and 67.3% met criteria for low levels of anxiety (CDRS-R, 57.4; PARS, 7.0). Treatment with lurasidone was associated with significantly greater improvement at week 6 vs. placebo on the CDRS-R total score in patients with higher levels of anxiety (-22.9 vs. -15.8; P=0.004; effect size, 0.58) and in patients with lower levels of anxiety (-20.4 vs. -15.3; P=0.004; effect size, 0.40). Treatment with lurasidone was also associated with significantly greater improvement at week 6 on the CGI-BP-S score in patients with higher levels of anxiety (-1.73 vs. -0.98; P=0.0002; effect size, 0.75) and in patients with lower levels of anxiety (-1.38 vs. -1.09; P<0.05; effect size, 0.28). In the higher anxiety group, treatment with lurasidone was associated with numerically greater reduction at week 6 vs. placebo in the PARS score (-6.2 vs. -5.3; n.s.).

Conclusions: In this post-hoc analysis, treatment with lurasidone significantly improved depressive symptoms in child and adolescent patients with bipolar depression who presented with moderate-to-severe levels of concurrent anxiety. Notably, antidepressant effect sizes were larger in patients with prominent anxiety.
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Sponsored by Sunovion Pharmaceuticals Inc.

W17. NEURAL REACTIVITY TO REWARD AS A PREDICTOR OF DEPRESSIVE SYMPTOM CHANGE IN YOUTH FOLLOWING SSRI AND CBT TREATMENT

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Abstract: Cognitive behavioral therapy (CBT) and pharmacological treatments (i.e., selective serotonin reuptake inhibitors [SSRIs]) are well-established treatments for youth anxiety and depression; however, response to treatment is heterogeneous across youth and many remain symptomatic after therapy, raising the need to identify prospective predictors for treatment planning. Altered neural processing of reward has been implicated in youth depression and to a lesser extent anxiety, and improving hedonic capacity is a goal of treatment, particularly CBT. However, little is known about how neural response to reward relates to improvement in depressive and anxiety symptoms among youth following treatment. The current study used the reward positivity (RewP) event-related potential (ERP) component to examine whether neural reactivity to reward would predict depression and/or anxiety symptom change following CBT and SSRI treatment among a sample of children and adolescents with anxiety and depressive disorders.
Methods: Prior to beginning treatment with the SSRI sertraline or CBT, 28 youth (age 7-19 years) completed a guessing reward ERP task. Youth completed self-report measures of anxiety and depressive symptoms at pre- and post-treatment.
Results: At baseline, the RewP was negatively correlated with depression severity, $r = -.44$, $p = .02$, such that youth with higher depressive symptoms exhibited a more attenuated RewP response. Notably, a more attenuated RewP at baseline also predicted a greater reduction in youth's depressive symptoms following treatment, $t(24) = 2.67$, $p = .01$. The RewP was unrelated to anxiety severity at baseline, $r = -.04$, $p = .88$, and did not predict change in youth's anxiety symptoms following treatment ($p = .21$).
Conclusions: CBT and SSRI treatment may be most beneficial in reducing depressive symptoms for children and adolescents who demonstrate decreased reward reactivity prior to treatment. These treatments may target reward brain function, leading to greater improvement in symptoms. These effects may be strongest, and therefore most meaningful, for children and adolescents with reward-processing deficits prior to treatment.

W18. SAFETY AND EFFECTIVENESS OF LONG-TERM TREATMENT WITH LURASIDONE IN CHILDREN AND ADOLESCENTS WITH BIPOLAR DEPRESSION: INTERIM ANALYSIS OF A 2-YEAR OPEN-LABEL EXTENSION STUDY

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Abstract: Objective: Bipolar I disorder frequently has an early onset, with an estimated prevalence of 1.8% in pediatric populations. Early onset is associated with a high degree of chronicity; however, limited data are available on the safety and efficacy of long-term treatment in pediatric patients. The aim of the current study was to evaluate the long-term safety and efficacy of lurasidone in children and adolescents with bipolar depression.
Methods: Patients 10-17 years with a diagnosis of bipolar I depression were randomized to 6 weeks of double-blind (DB) treatment with lurasidone or placebo. The primary efficacy measure was the Children's Depression Rating Scale, Revised (CDRS-R). Patients who completed the study were eligible to enroll in a 2-year, open-label (OL) extension study in which patients were continued on flexibly-dosed lurasidone (20-80 mg/d), or switched from placebo to lurasidone. These data are the 1-year interim analysis results of the 2-year study. Treatment response was defined as ≥50% reduction from DB baseline in the CDRS-R total score. Cognitive function was assessed with the Brief CogState battery, which evaluates four cognitive domains: processing speed, attention/ vigilance, visual learning, and working memory. Based on normative data, an overall cognitive composite Z-score was calculated as the average of the standardized Z-scores for each of the cognitive domains.
Results: In the short-term, DB study, 347 patients were randomized to lurasidone or placebo (mean age, 14.3 years). At Week 6 endpoint, treatment with lurasidone was associated with statistically significant and clinically meaningful improvement compared with placebo in the CDRS-R total score (-21.0 vs. -15.3; P<0.0001; effect size, 0.45). A total of 223 patients entered the extension study. For the extension population, mean CDRS-R total scores at DB and OL baselines were 58.1 and 37.6, respectively. Mean change from OL baseline in the CDRS-R total scores at weeks 12, 28, 40, and 52 were -6.5, -10.0, -10.8, and -10.7, respectively. Responder rates at OL baseline, weeks 12, 28, 40, and 52 were 55.0%, 73.7%, 85.1%, 87.0%, and 92.6%, respectively. At the time of the interim analysis, the most frequent adverse events were headache (19.7%), nausea (14.3%), anxiety (9.9%), somnolence (8.5%), and vomiting (8.1%). Small median changes from DB baseline to weeks 28/52 were noted for total cholesterol (-4.5/-5.0 mg/dL), LDL cholesterol (-3.0/0.0 mg/dL), triglycerides (-2.0/-2.0 mg/dL), and hemoglobin A1c (0.0/+0.1 mg/dL); and mean changes in weight at weeks 28/52 were +3.0/+5.0 kg (vs. an expected weight gain of +2.3/+3.9 kg, based on normative WHO data). During 52 weeks of treatment, 10 patients (4.5%) met criteria for treatment-emergent mania. There were no deaths in the study. A total of 4.5% of patients reported suicidal ideation as an adverse event, and 2.2% of patients made a suicide attempt. The cognitive composite Z-score showed impairment at DB baseline (-0.94). Mean change in Z-score, from DB baseline to OL weeks 0 (OL-baseline), 12, 28, and 52 were observed for the cognitive composite score: +0.00, +0.16, +0.18, +0.23, respectively.
Conclusions: In children and adolescents with bipolar depression, up to 52 weeks of treatment with lurasidone was generally well-tolerated. No deleterious effects on cognition were noted in this pediatric population. Long-term treatment with lurasidone was associated with continued improvement in depressive symptoms.

W19. TASK ENGAGEMENT DURING UNSUPERVISED COMPUTERISED COGNITIVE TESTING: IMPACT OF SELF-REPORTED MENTAL HEALTH ISSUES

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Abstract: Background: Neurological and mental health problems are major contributors to the global burden of disability. We know that cognitive problems such as inattention are commonly reported in major depressive disorder[1]. While this may offer a potential treatment target in psychiatric disorders, the presence of inattention may affect engagement with cognitive testing particularly in unsupervised settings. Web-based cognitive testing has the potential to allow large-scale and high-frequency data collection in a cost-and time effective manner[2], facilitating recruitment of patients affected by objective cognitive deficits. This work aimed to address the impact of self-reported mental health issues on metrics of task engagement during an unsupervised computerised working memory test delivered online.
Methods: 457 participants completed an on-line assessment of spatial working memory (CANTAB SWM), administered online. Participants were asked to report whether they had a history of depression, anxiety or other neurological or psychiatric condition, and 200 participants completed the PHQ-8 rating scale of depression symptoms. Complete data were available from 445 participants, of whom 148 completed the PHQ-8. CANTAB SWM task yields measures of working memory errors and strategy. We also extracted trial-by-trial data related to timing, and browser information. Participants tabbing to a different browser window during testing was considered an "off-task" or inattentive behavior. We examined the predictors of several indicators of task engagement: off-task browser behavior, reaction time and variability in reaction time (SD and Coefficient of Variation (CV)).
Results: Participants were aged on between 18 and 64 (mean 33.93, SD=4.04), and the mean PHQ-8 score was 4.58 (SD = 5.19). PHQ-8 score was significantly higher in those with SR history of anxiety (6.95 vs 2.57, $p=0.0211$), and depression (9.8 vs 2.57, $p<0.001$), and there was a high comorbidity between these two with 42 people reporting a history of both depression and anxiety, and 45 reporting only one. Off-task browser behavior was associated with less accurate, faster responding. There was a significant main effect of off-task behavior on SWM accuracy ($F=7.197$; $p=0.0077$) and reaction time ($F= 6.5$; $p = 0.011$). The effect on strategy failed to reach significance ($F=3.25$; $p= 0.0723$.) When examining the impact of patient characteristics on task engagement, education and gender were not significant predictors in any model are therefore not included here. Age was the only significant predictor of off-task behavior and reaction time variables. Younger participants were more likely to display off-task behavior than older participants. Self-reported history of depression or anxiety were not associated with any off-task behavior or reaction time variables. This finding was confirmed in the sub-sample who completed the PHQ8. There was no significant association between PHQ-8 scores and behavioral indications of task engagement.
Conclusions: Here we report objective markers of task engagement in online testing, and show that participants with a self-reported history of mental health issues perform just as consistently as those with no such history in online testing, suggesting that this method of cognitive assessment can be used for screening into clinical trials or remote large-scale testing in such samples.

W20. EFFICACY AND SAFETY OF LURASIDONE IN ADOLESCENTS WITH SCHIZOPHRENIA: INTERIM ANALYSIS OF A 2-YEAR, OPEN-LABEL EXTENSION STUDY

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Abstract: Objective: Long-term efficacy and safety data from prospective studies in adolescents with schizophrenia are limited. Lurasidone is an atypical antipsychotic that has demonstrated efficacy in the treatment of schizophrenia in both adults and adolescents. The aim of the current open-label trial was to obtain long-term data on the safety and effectiveness of lurasidone in adolescents with schizophrenia.

Methods: Patients ages 13-17 with schizophrenia were randomized to 6 weeks of double-blind (DB) treatment with lurasidone 40 mg/d, 80 mg/d or placebo. Patients who completed this study were eligible to enroll in a 2-year, open-label (OL), flexible-dose (20-80 mg/d) extension study in which patients were continued on lurasidone, or switched from placebo to lurasidone (all patients in the extension study were started on a dose of 40 mg/d). These data are the results of an interim analysis at 1-year timepoint of the 2-year study. Effectiveness measures included the Positive and Negative Syndrome Scale (PANSS) total score (responder criteria, ≥20% reduction from DB baseline).

Results: A total of 271 patients completed 6 weeks of DB treatment and entered the 2-year extension study. At the time of the interim analysis, 132 (48.7%) patients had completed 52 weeks of treatment (24 patients were 2-year study completers; 96 patients were still ongoing; and 12 patients had discontinued after 52 weeks); 57 (21.0%) patients were still ongoing in the first 1-year of treatment; and 82 (30.3%) patients terminated prior to week 52 (28 patients due to withdrawal of consent; 23 due to adverse events; 9 due to lack of efficacy; and 22 for other reasons). Mean PANSS total score at double-blind baseline was 93.5. Overall mean change from DB to OL baseline (after 6 weeks of treatment) was -17.5 (for patients assigned to lurasidone vs. placebo in the initial 6-week study, mean change was: -19.8 vs. -12.9). Overall mean change from DB baseline in the PANSS total score at weeks 28 (n=215), 52 (n=133), 76 (n=86), and 104 (n=24) was -29.2, -34.0, -35.0, and -34.1, respectively. Responder rates at OL baseline, week 52 and week 104 were 63.1%, 91.7% and 100%, respectively. During OL treatment, the most common adverse events were headache (21.8%), nausea (11.8%), anxiety (11.8%), somnolence (11.4%); 6.6% of patients reported an adverse event as severe. Median change in laboratory parameters from DB baseline to weeks 52 and 104, respectively, were: total cholesterol, -2.0 and -5.0 mg/dL; triglycerides, +3.5 and +3.0 mg/dL; hemoglobin A1c, 0.0 and 0.1%; prolactin in female, +0.5 and -0.5 ng/mL and males, +0.15 and +3.5 ng/mL; and mean change from DB baseline in weight at weeks 52 and 104 were 3.8 and 7.2 kg, vs. an expected weight gain of 3.3 and 5.1 kg, based on the gender-and-age specific CDC growth chart.

Conclusions: In adolescents with schizophrenia, long-term treatment with lurasidone was associated with continued improvement in symptoms of schizophrenia. After up to 2 years of lurasidone treatment, minimal effects were observed on body weight, lipids, glycemic indices, and prolactin.

ClinicalTrials.gov identifier: NCT01914393

W21. RANDOMIZED PLACEBO CONTROLLED TRIAL OF HIGH DOSE INTRAVENOUS THIAMINE FOR THE PREVENTION OF DELIRIUM IN ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION

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Abstract: Background: Delirium is the most common psychiatric syndrome in the general hospital setting, experienced by approximately 30% of hospitalized inpatients. It is associated with wide-ranging sequelae, including double the rate of mortality, impaired activities of daily living, and poor long-term psychological and cognitive outcomes. An important and under-recognized contributor to delirium, which has been described in a variety of medically ill populations, is thiamine deficiency. A particularly high-risk population is patients undergoing hematopoietic stem cell transplantation (HSCT), in whom thiamine deficiency has been described in up 100% and delirium in at least 40%. High dose intravenous (HDIV) thiamine is an evidence-based and promising treatment for delirium, but no one has studied prospectively the use of IV thiamine as a prevention strategy in any population. The purpose of this study, funded by the Rising Tide Foundation for Clinical Cancer Research, is to determine if HDIV thiamine decreases the incidence of delirium and examine its effects on neuropsychiatric sequelae of delirium during inpatient hospitalization for HSCT.

Methods: In this randomized double-blind controlled trial, 60 patients admitted for allogeneic HSCT will be randomized to treatment with HDIV thiamine (n=30) versus placebo (n=30). Our sample size calculation was based on a two group chi-squared test with a 0.050 one-sided significance level, which will have 80% power to detect the difference between a usual care proportion of 0.445 and an intervention proportion of 0.155 (odds ratio of 0.229). As this is the first study to evaluate the efficacy of thiamine as a prevention strategy for delirium, no data are available to generate an estimate of delirium incidence in the intervention group. The odds ratio hypothesized for this study is in line with other successful delirium prevention trials. Participants will undergo serial evaluations for delirium, using the Delirium Rating Scale, during their inpatient hospitalization for HSCT. Thiamine levels will be obtained weekly during the inpatient hospitalization period. Finally, we will administer validated measures to assess functional status (ECOG), health-related quality of life (HRQOL, FACT-BMT), depression (PROMIS-D), post-traumatic stress symptoms (PTSS-14), and cognitive function (MOCA) prior to transplant and at one, three, and six months after transplant.

Results: We are three months into a 24 month long recruitment period, and have enrolled nine patients. At the current rate of enrollment, we expect 18 patients to be enrolled by the time of the meeting. Baseline data on demographics, disease characteristics, functional status, HRQOL, and neuropsychiatric symptoms, including depression, post-traumatic stress, and cognitive function, will be presented.

Conclusions: The results of this innovative pilot study will provide critical preliminary data regarding the efficacy of HDIV thiamine as a prevention strategy for delirium in HSCT. Findings will also provide information regarding the temporal relationship between thiamine deficiency and the development of delirium, as well as the potential impact of HDIV thiamine on long-term functional status, HRQOL, and a wider array of neuropsychiatric symptomatology.

W22. FEASIBILITY OF AN ELECTRONIC VERSION OF THE OVERT AGGRESSION SCALE, MODIFIED (OAS-M) IN THE MEASUREMENT OF INTERMITTENT EXPLOSIVE DISORDER SYMPTOMS: CORRESPONDENCE OF PAPER AND ELECTRONIC VERSIONS

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Abstract: Introduction: The Coccaro Overt Aggression Scale-Modified (1) is a widely used primary efficacy measure in industry and government funded trials of problematic aggression and DSM-5 Intermittent Explosive Disorder (IED). This clinician-rated scale classifies patients' aggressive episodes into 4 aggression types, with individual within-episode behaviors weighted in severity, yielding an overall weighted total aggression score. To be used correctly, the scale requires considerable training and practice, as well as a semi-structured interview approach as defined, along with specific conventions, in an 89-page manual. In clinical trials, the scale is administered at baseline and then repeated at regular intervals (e.g., weekly) to assess drug-related change. In an effort to facilitate proper administration, and improve adherence to trained conventions, as well as decrease computation errors associated with manual calculation and summing of weighted scores, we created an electronic OAS-M that provided per-item manualized instructions, scoring conventions, and automated episode tallying, weighted scoring, and total aggression score calculations. In this study, we examined the score correspondence of the electronic and paper versions using a series of standardized patients. We hypothesized that the paper and electronic scoring systems would yield similar scores among trained raters across a series of IED patients.

Method: 4 raters who had undergone extensive full day training by the scale author (EC) independently completed ratings of 8 videotaped IED patients using both the paper and the electronic OAS-M scales (paper vs. electronic counterbalanced for order) with at least 48 hours transpiring between paper and electronic ratings of the same patient video. First, intra-rater ICCs (2,1) (2) were calculated on the total aggression scores to assess the equivalence of the electronic and paper scores for each rater; next, all pair combinations of raters and patients (targets) were calculated, and the equivalence of the electronic and paper total aggression scores across these targets was examined via ICC (2,1). All analyses were performed using SAS (V9.4).

Results: The total aggression scores for the individual patients varied from 37 to 127 points. The lowest intra-rater ICC (2,1) between the paper and electronic scores for each individual rater was 0.97 (range from .97 to 1.00). For the combined analysis, the ICC (2,1) was 0.98.

Conclusions: The results support the equivalence of the paper and electronic (eCOA) means of OAS-M administration. In a clinical trial, as true for other eCOA applications, it is reasonable to expect the automated scoring computations and standardized instructions of our electronic OAS-M to reduce variability and scoring error.

W23. SUCCESSFUL LIFESPAN-TARGETED PATIENT RECRUITMENT STRATEGIES FOR OUTPATIENT PSYCHIATRIC AND NEUROLOGICAL CLINICAL TRIALS

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Abstract: Background/Purpose: The incidence and prevalence of clinical trials failing to meet their pre-specified enrollment-related target dates is very well documented. This persistent problem transcends clinical research involving all six stages of Lifespan development, from Infancy to Older Age. At Pharmacology Research Institute (PRI), the overwhelming majority of the more than 875 clinical studies we've conducted since 1975 have focused on the later three stages: Early Adulthood: 20 to 40 years (including ages 18 and 19); Middle Age: 40 to 64 years; and Older Age: 65+ years. The purpose of this research was to analyze several recruitment avenues and methods across a wide array of CNS indications, to investigate whether the clinical indications should determine the preferred recruitment strategies, or vice versa.

Methodology: We compiled information on more than 600 recently randomized study participants at PRI's three Southern California locations. The specific indications ranged from Adult ADHD to Prodromal Alzheimer's disease. The specific recruitment strategies and techniques [to be presented in detail] can be broadly categorized as: Database, Internet, Outreach and Traditional Advertising. We analyzed all of the recruitment outcomes in a contextual manner, integrating participants' ages, the clinical indications and the chosen recruitment strategy, to see how these variables may influence and impact one another.

Results: While the Internet has strongly supplemented our recruitment arsenal, it has definitely not yet supplanted the traditional methodologies such as radio, television and even newspapers. Furthermore, our overall analysis of recruitment methods indicates a strong correlation with age and virtually no correlation with the specific clinical indication being investigated. While many, if not most, of the current central ad campaigns rely almost exclusively on the Internet in general, and social media in particular, our data indicate this trend may be operationally premature and myopic. When targeting study participants from the upper end of "Middle Age," and especially potential candidates for "Older Age" studies, the aforementioned traditional techniques remain useful and often helpful.

Importance/Conclusions: The frequency of study completion delays being attributed to subject recruitment costs and complexities has plagued the clinical research arena for decades. Yet, somewhat shockingly, it remains one of the most under-investigated and under-analyzed aspects of clinical research. In tandem with the ever-increasing specificity vis-à-vis exhaustive study entry criteria, we believe site-based and especially nationally-orchestrated recruitment campaigns should embrace a more comprehensive "multi-media" (i.e., multi-faceted) integrated strategy. This recommended broadened in depth and breadth approach can often be conceptualized and implemented independent of the specific indication. Demographics supersede specific clinical indications when designing and implementing patient recruitment efforts. At a minimum, when recruiting for trials enrolling participants over the age of 50, and particularly those over the age of 64, traditional tools such as newspaper advertisements, as well as (some) radio and television, should continue to be integrated into the overall recruitment armamentarium.

W24. A DOUBLE-BLINDED, PLACEBO-CONTROLLED RCT OF REPEATED DAILY SESSIONS OF TRANSCRANIAL DIRECT CURRENT STIMULATION

(TDCS) FOR THE AFFECTIVE SYMPTOMS OF CHRONIC LOW BACK PAIN (CLBP)

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Abstract: Background: "Pain" has sensory (nociceptive) and affective (emotional) components. Chronic low back pain's (CLBP's) affective symptoms are significant drivers of disability and psychiatric comorbidity. However, treatments specifically directed at these symptoms (e.g. pain-focused cognitive behavioral therapy) are limited; consequently, there is over-reliance on opioid analgesics with deleterious side effects. tDCS may noninvasively modulate pain-related affective distress. We present full analysis of a first multi-site, double-blinded, placebo-controlled RCT of transcranial direct current stimulation (tDCS) targeting left dorsal anterior cingulate cortex--a region implicated in pain's affective component--in CLBP patients. We hypothesized that this approach would result in selective reduction of pain-related distress symptoms but leave pain intensity unchanged over the course of the tDCS sessions and at a six-week follow-up.

Methods: We recruited participants with CLBP of at least 6 months' duration, pain intensity of at least 4 out of 10 on the Defense and Veterans Pain Rating Scale (DVPRS), and at least one trial of physician-recommended medication. Twenty-one participants completed the study. Carbon-rubber electrodes within 5x7 cm saline-saturated sponges were placed over FC1 (10-20 EEG coordinates) and over the contralateral mastoid (return electrode). We adapted this empirically-based montage from our prior work, verifying it with post-hoc electric field modeling. Participants received 10 daily sessions of sham or active tDCS (20 minutes/session, 2mA, cathodal polarity relative to return electrode) and rated pain-related intensity (DVPRS), acceptance (CPAQ-8), interference (WHYMPI General Activity Subscale), disability (RMDQ), and anxiety (PASS-20), as well as general depression (PHQ-9), general anxiety (GAD-7), treatment expectations (CEQ), and treatment satisfaction (CSQ-8). Sham tDCS briefly ramps the electric current up and then down in order to reproduce transient sensations (e.g. skin tingling) associated with active tDCS to enhance blinding.

Results: A regression analysis following an intention-to-treat approach noted significantly improved WHY-MPI-C ($|z|=3.11$, $p=0.002$), RMDQ ($|z|=3.23$, $p=0.001$), and PHQ-9 ($|z|=2.96$, $p=0.003$) scores at 6-week follow up with active vs. sham tDCS. CEQ scores were significantly increased at Day 10 ($|z|=2.08$, $p=0.038$) with active vs. sham tDCS. Post-hoc tests also noted significant main effects of active vs. sham tDCS on WHY-MPI-C ($X^2=4.34$, $p=0.037$) and RMDQ ($X^2=4.84$, $p=0.028$) when Day 1 baseline scores were excluded. Participants prescribed opioids significantly differed from non-opioid participants only by having lower Day 1 CPAQ-8 ($|z|=3.59$, $p<0.001$).

Conclusions: To the authors knowledge, this is the first double-blinded, placebo-controlled RCT of multiple tDCS sessions targeting left dACC in an attempt to modulate the affective component of CLBP. Participants who received active tDCS showed improvements in pain

disability and depression. Future replication studies would benefit from larger sample sizes to increase power.

W25. A META-ANALYSIS OF THE NEUROCOGNITIVE FUNCTIONING IN CANNABIS-USER AND NON-USER PATIENTS WITH FIRST-EPISODE PSYCHOSIS

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Abstract: Background: Effects of cannabis use on the neurocognitive functioning of patients with first episode psychosis (FEP) are still unclear. Several studies suggest an improvement in the cognitive functioning in FEP cannabis users whilst others show a decrease in the executive function, verbal memory and working memory of this group (González-Pinto et al., 2016) or even absence of neurocognitive differences between FEP cannabis users and non-users (Burgra et al., 2013). This meta-analysis aims to explore the magnitude of effect of cannabis use on neurocognition in patients with FEP.
Methods: Scientific manuscripts were identified through an extensive literature search using online databases, which included PubMed (Medline) and PsycINFO. The search was limited to English language articles. The used keywords were: "first episode psychosis" OR, "neurocognition and cannabis", in combination with a number of neuropsychology-related terms including "neurocog*" and "neuropsycholog*". Given that other substances such as alcohol, cocaine, and other stimulants are associated with altered cognitive performance, studies in which participants met criteria for poly-substance use disorders, even if there was preferential use towards cannabis, were excluded. Eight studies from 2008 to 2018 met inclusion criteria from a total sample of 16 initial studies. Five hundred and eighteen of these participants were cannabis users with FEP, and 639 were patients with no cannabis use. A total of 58 effect sizes of neuropsychological test variables were categorized into 4 cognitive domains (premorbid IQ, executive functioning, working memory and verbal memory and learning). Age of first cannabis use, duration of cannabis use, percentage of males and age were abstracted and assembled as moderator variables. Standardized mean differences were computed for each cognitive domain between cannabis-using patients and patients with no history of cannabis use. Negative effect sizes would display better cognitive functioning of non-cannabis users. We employed a meta-analytic three level model to combine effect sizes across studies.
Results: Effect sizes were not significantly different from zero in any of the neurocognitive domains when FEP cannabis users and non-users patients were compared [working memory (d= -0.03, SE=0.15, CI = -0.33–0.26, p=0.83), executive function (d= 0,14, SE=0.16, CI = -0.17–0.45, p=0.37), verbal memory and learning (d= 0.04 , SE=0.15, CI = -0.25–0.33, p=0.27) and premorbid IQ (d= 0.06 , SE=0.09, CI = -0.24–0.12, p=0.50)]. Only one moderator variable resulted significant in the executive function denoting superior performance in FEP cannabis-using patients as they were older.
Discussion: Cannabis use is not related to an ameliorated or improved neurocognitive functioning in patients with first episode psychosis. This is consistent with previous studies which showed absence of differences in the neurocognitive functioning between FEP cannabis

users and nonusers (Burgra et al., 2013). However, it has been demonstrated that continued cannabis intake worsens cognitive performance although some of the FEP patients had better premorbid capacities (González-Pinto, 2016). Moreover, the doses and the different types of cannabis preparations may interfere the present results. Meta-analysis on longitudinal studies which include these potential moderator variables may be performed in the future.

W26. THE GABA-A RECEPTOR POSITIVE ALLOSTERIC MODULATORS BREXANOLONE IV AND SAGE-217 IN THE TREATMENT OF MOOD DISORDERS: RESULTS FROM RECENT PLACEBO-CONTROLLED STUDIES

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Abstract: Gamma-aminobutyric acid (GABA) is the primary inhibitory neurotransmitter in the brain and acts through synaptic and extrasynaptic GABA-A receptors to mediate phasic and tonic inhibition. Dysregulation of GABAergic signaling, including altered expression levels of GABA and GABA-A receptors or aberrations in functionally-linked stress pathways (i.e. the hypothalamic-pituitary-adrenal axis), is thought to be associated with mood disorders, such as postpartum depression (PPD) and major depressive disorder (MDD). Positive allosteric modulators (PAMs) of GABA-A receptors may offer a novel mechanism of action for exploration as potential PPD and MDD therapeutics.

Brexanolone iv (USAN; formerly SAGE-547 injection) is a soluble, proprietary formulation of the GABA-A receptor PAM allopregnanolone that is being developed as a potential therapy for PPD. To evaluate the efficacy and safety of brexanolone iv, three pivotal, double-blind, randomized, placebo (PBO)-controlled studies (Study A: NCT02614547; B: NCT02942004; C: NCT02942017) were conducted in women stratified by PPD severity (17-item Hamilton Rating Scale for Depression [HAM-D] total scores of ≥26 in Studies A and B and 20-25 for in Study C). Treatment consisted of a 60-hour continuous inpatient infusion, and across the three studies, 107 women received PBO and 102 received brexanolone iv at a dose of 90 µg/kg/h (BRX90). Using pooled data, at Hour 60 (primary endpoint), there was a significantly larger mean reduction from baseline in HAM-D total score with BRX90 (-17.0) than with PBO (-12.8; $p<0.0001$). Significant treatment differences were also observed at Hour 24 ($p=0.0012$), Hour 48 ($p<0.0001$), Hour 72 ($p<0.0001$), Day 7 ($p=0.0007$), and Day 30 ($p=0.0213$). Brexanolone iv was generally well tolerated.

SAGE-217 is a novel GABA-A receptor PAM that was rationally designed for oral bioavailability and once daily dosing. A Phase 2, double-blind, randomized, PBO-controlled study evaluated the efficacy and safety of SAGE-217 in men and women with moderate to severe MDD (HAM-D total score ≥22). Patients received an evening dose of study drug for 14 days. At Day 15 (primary endpoint), the SAGE-217 group showed a significantly greater LS mean reduction from baseline in HAM-D total score versus the placebo group (-17.4 versus -10.3; $p<0.0001$). These significant differences from placebo were observed as early as Day 2 ($p=0.0223$) and were maintained through Day 28 ($p=0.0243$). SAGE-217 was generally well tolerated.

Brexanolone iv and SAGE-217 are examples of developmental programs for novel GABA-A receptor PAMs that showed rapid and sustained reductions in depressive symptoms. These results will support a regulatory filing this year for brexanolone iv for the treatment of PPD and continued development of SAGE-217 as a potential therapy for MDD.

W27. EFFICACY AND SAFETY OF ESKETAMINE NASAL SPRAY PLUS AN ORAL ANTIDEPRESSANT IN ELDERLY PATIENTS WITH TREATMENT-RESISTANT DEPRESSION

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Abstract: Background: Estimates of 18-40% of elderly patients with depression suffer from treatment-resistant depression (TRD) [1], defined as non-response to at least two antidepressants. Elderly patients experience greater disability and functional decline, decreased quality of life, and greater mortality from suicide than younger patients [2]. Esketamine nasal spray is being investigated for treatment of TRD. We evaluated the efficacy, safety, and tolerability of flexibly dosed esketamine (ESK) nasal spray (28 mg, 56 mg or 84 mg) plus a newly initiated oral antidepressant (AD), compared with AD plus intranasal placebo (PBO), for the treatment of TRD in elderly patients.
Methods: Patients ≥ 65 years of age (N=138) in this double-blind, multicenter, phase 3 study (NCT02422186) were randomized (1:1) to either ESK+AD (N=72) or AD+PBO (N=66). The primary efficacy endpoint – change from baseline to day 28 in Montgomery–Åsberg Depression Rating Scale (MADRS) total score – was assessed by mixed-effects model at a one-sided 0.025 significance level. Pre-specified subgroup analyses were performed for ages 65-74 years (n=116) and ≥75 years (n=21). Remote raters, blinded to the treatment arm, conducted the MADRS assessments by telephone.
Results: The mean (SD) patient age was 70.0 (4.52) years and mean (SD) baseline MADRS total score was 35.2 (6.16). The mean (SD) change in MADRS total scores from baseline to day 28 was -10.0 (12.74) for ESK+AD and -6.3 (8.86) for AD+PBO. The median-unbiased estimate of the difference between ESK+AD and AD+PBO was -3.6 (95% CI: -7.20, 0.07; one-sided p=0.029). A treatment difference favoring ESK+AD was seen for the 65-74 years subgroup. The difference in LS mean (SE) change at day 28 was -4.9 (2.04) for 65-74 years (one-sided p=0.009) and -0.4 (5.02) for ≥75 years (one-sided p=0.465). The most common treatment-emergent adverse events (TEAEs) in the ESK+AD group were dizziness (20.8%), nausea (18.1%), headache (12.5%), fatigue (12.5%), increased blood pressure (12.5%), vertigo (11.1%) and dissociation (11.1%). The most common TEAEs in the AD+PBO group were anxiety (7.7%), dizziness (7.7%) and fatigue (7.7%).
Conclusions: While treatment with ESK+AD did not demonstrate a statistically significant difference vs AD+PBO on the primary outcome, a statistically significant and clinically meaningful treatment effect was observed for patients aged 65-74 years. Safety results were consistent with previous studies in younger adult populations; no new safety concerns were identified.

W28. EFFECTS OF THE KCNQ CHANNEL OPENER EZOGABINE ON FUNCTIONAL CONNECTIVITY OF THE VENTRAL STRIATUM AND CLINICAL SYMPTOMS IN PATIENTS WITH MAJOR DEPRESSIVE DISORDER

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Abstract: Major depressive disorder (MDD) is a leading cause of disability worldwide, yet current treatment strategies are limited in their mechanistic diversity, and are only partially effective. Recent evidence has highlighted a promising novel pharmaceutical target—the KCNQ-type potassium channel—for the treatment of depressive disorders, which may exert a therapeutic effect via functional changes within the brain reward system, including the ventral striatum. The current study assessed the effects of the KCNQ channel opener ezogabine (also known as retigabine) on reward circuitry and clinical symptoms in patients with MDD. Eighteen medication-free individuals with MDD currently in a major depressive episode were enrolled in an open-label study and received ezogabine up to 900 mg/day orally over the course of ten weeks. Resting state functional magnetic resonance imaging data were collected at baseline and post-treatment to examine brain reward circuitry. Reward learning was measured using a computerized probabilistic reward task. Ezogabine significantly reduced depressive symptoms (Montgomery-Asberg Depression Rating Scale score change: -13.7±9.7, $p<0.001$, $d=2.08$). It also significantly reduced anhedonic symptoms (Snaith-Hamilton Pleasure Scale score change: -6.1±5.3, $p<0.001$, $d=1.00$), even when controlling for overall depression severity. Improvement in depression was associated with decreased functional connectivity between the ventral caudate and clusters within the mid-cingulate cortex and posterior cingulate cortex (voxel-wise $p<0.005$, cluster-wise $\alpha<0.05$). In addition, a subgroup of patients tested with a probabilistic reward task (n=9) showed increased reward learning following treatment. These findings highlight the KCNQ-type potassium channel as a promising target for future drug discovery efforts in mood disorders.

W29. ONABOTULINUMTOXINA FOR THE TREATMENT OF MAJOR DEPRESSIVE DISORDER IN WOMEN: A PHASE 2, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL

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Abstract: Background: Prior single-center clinical studies show that a single therapeutic intervention with onabotulinumtoxinA (onabotA; BOTOX), injected into facial muscles, may represent a novel, safe, and well-tolerated treatment for major depressive disorder (MDD) with symptomatic relief lasting 6-16 weeks. This study evaluated the safety and efficacy of onabotA vs placebo (PBO) to treat MDD in adult females (NCT02116361).

Methods: This was a large phase 2 multicenter randomized double-blind PBO-controlled parallel-group 24-week study. Female patients (18-65 years) had moderate to severe MDD (DSM-IV-TR criteria), current depressive episode ≥4 weeks, Hamilton Rating Scale for Depression 17-item Version (HAM-D17) score ≥ 18, and Clinical Global Impression-Severity (CGI-S) score ≥4. Patients were randomized 1:1:2 to onabotA 30 U, onabotA 50 U, or PBO. Two treatment regimens were evaluated: (1) 6 intramuscular (IM) injections of onabotA 30 U (n=65) vs matching PBO (n=58) and (2) 8 total injections (6 IM, 2 subcutaneous) of onabotA 50 U (n=65) vs matching PBO (n=67). All injections were administered into the glabellar region in a single treatment session (Day 1). The primary endpoint was change from baseline to Week 6 in MADRS total score. Secondary efficacy measures were change in CGI-S score and HAM-D17 total score.

Results: A total of 258 patients were randomized; 255 received treatment. Premature discontinuations before Week-6 and Week-12 visits were similar between groups (Weeks 6/12 [%]: PBO=10.2/19.5, onabotA=7.7/16.2). OnabotA 30 U demonstrated numerically greater change from baseline in MADRS total score compared with PBO (least squares [LS] mean change: PBO=–7.9, 30 U=–11.6), and although differences did not reach statistical significance (P=0.053) at level P<0.05 (2-sided) at Week 6, but the change was significant at Weeks 3 (P=0.005) and 9 (P=0.049) at level P<0.05 (2-sided). OnabotA 30 U MADRS LS mean difference versus PBO for Weeks 3-9 (-3.6 to -4.2) was greater than the 2-point change considered clinically relevant, and effect sizes from Week 3-9 (0.348-0.521) were similar to mean treatment effect sizes for published oral pharmacological antidepressants. OnabotA 30 U CGI-S changes at Week 6 would have been considered statistically significant at level P<0.05 (2-sided) [P=0.036] had the primary endpoint been met. Onabot 30 U reduced HAMD-17 scores (LS mean difference: 2.5), but the change did not reach statistical significance. OnabotA 50 U did not show numerical advantage over PBO on primary or secondary efficacy parameters through Week 9. Approximately 52% (132/255) of patients experienced ≥1 treatment-emergent AE (TEAE; onabotA, 54.6%; PBO, 48.8%). Most TEAEs were local to the site of injection and mild or moderate in intensity. The only TEAE that occurred in ≥10% of patients in any treatment group was headache, which occurred with similar frequency between combined groups. The safety and tolerability profiles of 30 U and 50 U onabotA were consistent with previous studies.

Conclusions: While statistical significance was not achieved in the primary endpoint, the overall efficacy results suggest benefit for onabotA 30 U in the treatment of MDD in adult female patients. OnabotA 30 U, administered in a standardized injection paradigm, may represent a novel treatment of depressive symptoms with a potentially superior safety and tolerability profile compared with approved antidepressant drugs currently used for treatment of patients with MDD.

W30. RANDOMIZED, DOUBLE-BLIND STUDY OF FLEXIBLY-DOSED ESKETAMINE NASAL SPRAY PLUS ORAL ANTIDEPRESSANT VS. ACTIVE CONTROL IN TREATMENT-RESISTANT DEPRESSION

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Abstract: Background: About 30% of the patients with major depressive disorder (MDD) fail to achieve remission despite treatment with multiple antidepressant medications, and are considered to have treatment-resistant depression (TRD).
Methods: This was a Phase 3, double-blind, active-controlled, multicenter study (NCT02418585) using blinded raters, conducted at 39 sites in Spain, Germany, Czech Republic, Poland, and the United States from August 2015 to June 2017. The study enrolled adults with moderate-to-severe, non-psychotic, recurrent or persistent depression, and history of non-response to ≥2 antidepressants in the current episode of depression, with 1 of them assessed prospectively. Non-responders were randomized (1:1) to flexibly-dosed esketamine nasal spray (56 or 84 mg twice weekly) and a new oral antidepressant or placebo nasal spray and a new oral antidepressant (active control). The primary efficacy endpoint – change from baseline to endpoint (day 28) in Montgomery-Asberg Depression Rating Scale (MADRS) total score – was assessed among patients who received ≥1 dose of (intranasal and oral) study medication by mixed-effects model using repeated measures. Remission rate, a secondary endpoint, was assessed using Generalized Cochran-Mantel-Haenszel (CMH) test, adjusting for country and class of oral antidepressant (SNRI or SSRI) as a post hoc analysis.
Results: 435 patients were screened, 227 randomized, and 197 completed the double-blind period. Change (LS mean [SE] difference vs. placebo) in MADRS total score with esketamine nasal spray and oral antidepressant was superior to oral antidepressant and placebo nasal spray at day 28 (-4.0 [1.69], 95% CI: -7.31, -0.64; one-sided p=0.010), as well as at earlier timepoints (one-sided p≤0.009 at 24 hours postdose and days 8 and 22). Remission rate (MADRS total score ≤12) at day 28 was 52.5% (53/101) and 31.0% (31/100) for the respective groups (one-sided p=0.001). The most common adverse events reported for the esketamine plus oral antidepressant group were dysgeusia, nausea, vertigo, and dizziness; the incidence of each (20.9-26.1%) was >2-fold higher than for the oral antidepressant plus placebo group.
Conclusions: Robust efficacy of esketamine nasal spray and superiority to an active control were demonstrated on the primary efficacy endpoint result. More than half of the esketamine-treated TRD patients achieved remission by the 4-week endpoint. Favorable safety and tolerability of esketamine reported in this study suggest a positive risk-benefit profile of esketamine nasal spray.

W31. ALKS 5461 (A BUPRENORPHINE-SAMIDORPHAN COMBINATION) FOR ADJUNCTIVE TREATMENT OF MAJOR DEPRESSIVE DISORDER: RESULTS FROM ANALYSES OF U.S. PATIENTS FROM THREE PLACEBO-CONTROLLED TRIALS

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Abstract: Background: A substantial proportion of patients with major depressive disorder (MDD) experience inadequate treatment response and persistence of clinically significant symptoms despite treatment with available antidepressants that target monoaminergic pathways. There is evidence for dysregulation of the endogenous opioid system in patients with MDD.1 ALKS 5461 is an investigational opioid system modulator for the adjunctive treatment of MDD that combines buprenorphine (BUP), a μ-opioid receptor partial-agonist and κ-opioid receptor antagonist, and samidorphan (SAM), a potent μ-opioid receptor antagonist added to address the abuse and dependence potential of BUP. ALKS 5461 has been evaluated in multiple placebo (PBO)-controlled studies; two studies met their pre-specified endpoint (ALK5461-202, NCT01500200 and FORWARD-5, NCT02218008) and one (FORWARD-4, NCT02158533) missed the pre-specified endpoint, but demonstrated efficacy at multiple time points. In order to account for any geographic differences in reporting symptoms2, this post-hoc analysis evaluated the efficacy of ALKS 5461 among clinical trial participants in the United States (US) across 3 multicenter, PBO-controlled, double-blind studies that utilized the same study design.

Methods: The US population from 1 phase 2 (ALK5461-202) and 2 phase 3 studies (FORWARD-4 and FORWARD-5) were analyzed. All 3 studies utilized the Sequential Parallel Comparison Design (SPCD). ALKS 5461 dose 2 mg/2 mg (BUP/SAM) was common to all 3 studies. Efficacy was evaluated using the Montgomery-Åsberg Depression Rating Scale (MADRS). Changes were assessed from baseline to average of Week 3 through end of treatment (MADRS-10AVG) and at the end of treatment (MADRS-10EOT). Treatment-emergent adverse events (AEs) and Columbia-Suicide Severity Rating Scale (C-SSRS) scores were assessed throughout the study. Clinical Opiate Withdrawal Scale (COWS) scores were monitored following discontinuation of the study drug.

Results: Demographics and baseline characteristics were similar across ALK5461-202 (n = 98 PBO and 24 ALKS 5461), FORWARD-4 (n = 218 PBO and 52 ALKS 5461), and FORWARD-5 (n = 229 PBO and 52 ALKS 5461). Statistically significant improvements in MADRS scores were observed with ALKS 5461 versus PBO in all 3 studies at multiple time points. The least squares mean difference for MADRS-10EOT (standard error) score versus PBO were -5.2 ([1.66]; P = 0.002), -3.5 ([1.40]; P = 0.012), and -2.4 ([1.07]; P = 0.028) in the ALK5461-202, FORWARD-4, and FORWARD-5 studies, respectively. In addition, there were statistically significant reductions in the MADRS-10AVG score versus PBO across the 3 studies: -3.6 ([1.52]; P = 0.019), -2.7 ([1.19]; P = 0.025), and -2.7 ([0.95]; P = 0.005), respectively.

Most AEs were of mild or moderate severity. AEs occurring in ≥5% of patients with ALKS 5461, and more frequently than placebo, in any study included nausea, constipation, dizziness, vomiting, sedation, and fatigue. The incidence of euphoria related AEs was low with ALKS 5461 and placebo. There was no pattern of AEs indicative of opioid dependence or withdrawal. Further, there was no evidence of withdrawal as assessed by COWS and no pattern of treatment-emergent suicidal ideation or behavior assessed by the C-SSRS or AEs.

Conclusions: Treatment with ALKS 5461 2 mg/2 mg as an adjunct to current antidepressant therapy demonstrated statistically significant and consistent efficacy versus PBO in US patients across 3 independent studies in this post-hoc analysis. ALKS 5461 was generally well tolerated and showed no evidence of abuse potential or withdrawal.

W32. GENDER DIFFERENCES IN RESPONSE TO AND TOLERABILITY OF KETAMINE AS A TREATMENT FOR ACUTE DEPRESSION

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Abstract: Ketamine has been increasingly studied as a therapy for major depressive disorder (MDD) and treatment resistant depression (TRD). Ketamine, an antagonist of N-methyl-d-aspartate receptors (NMDAr), has been demonstrated to provide robust and rapid antidepressant effects. The RAPID Studies were conducted collaboratively between the MGH Clinical Trials Network and Institute (CTNI), multiple academic sites, and the NIMH. The aims of these studies were to assess promising treatments for the rapid improvement in MDD on a scale of 1-3 days, rather than the several weeks required for most available standard treatments. A randomized, double-blind, placebo-controlled study involving N=99 outpatients (N=50 male; N=49 female) was conducted to investigate the acute efficacy of intravenous ketamine versus active placebo added to ongoing, stable, and adequate antidepressant therapy in the treatment of TRD. Patients were assigned to one of five possible arms, with four groups treated with one-time administration of ketamine receiving varying doses of up to 1.0 mg/kg of intravenous ketamine (i.e., 0.1, 0.2, 0.5, and 1.0 mg/kg), and one group receiving active placebo (intravenous midazolam). The primary outcome of the trial was a positive treatment response in the ketamine groups compared to placebo on the primary outcome measure (HAM-D6). In this poster, we present the results of a priori planned exploratory analyses to compare treatment responses between women and men, as well pre- vs. postmenopausal reproductive lifespan status among women. Results from previous animal and human studies suggest there may be sex differences in treatment response and adverse effects to ketamine. In order to carefully assess the impact of sex and reproductive lifecycle status upon response to and toleration of ketamine, we used questionnaires to specifically capture data pertinent to these topics, which included reproductive lifespan status among women (pre-, peri-, or postmenopausal), as part of the MGH Female Reproductive Lifecycle and Hormones Questionnaire. Analyses revealed that there were no significant differences between women and men in terms of ketamine treatment response ($F(1,84)=0.10$, $p=0.75$). In terms of tolerability, there were also no differences between women and men in the frequency of adverse effects (AEs) reported by those assigned to the ketamine groups ($p>0.21$ for all AEs reported more than once study-wide), though women reported more headaches (12% vs. 6%, $p=0.30$), and nausea (10% vs. 6%, $p=0.47$). In comparing women in different reproductive life cycle groups (pre- vs. postmenopausal), no differences in efficacy were observed ($F(1,33)=0.35$, $p=0.56$). These findings support the use of ketamine as an equally effective and safe treatment for TRD for both women and men. However, further research is needed to confirm or expand upon these results, given that larger trials with these a priori aims have not yet explored these differences.

W33. THE NATIONAL PREGNANCY REGISTRY FOR ATYPICAL ANTIPSYCHOTICS: EFFECTS OF FETAL EXPOSURE TO LURASIDONE ON RISK FOR MAJOR MALFORMATIONS

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Abstract: Background: Atypical antipsychotics are commonly prescribed to women of reproductive age for the treatment of a number of psychiatric disorders. To investigate the reproductive safety of this class of medications, the National Pregnancy Registry for Atypical Antipsychotics (NPRAA) was established in 2008 at Massachusetts General Hospital. While preliminary data from the NPRAA have not demonstrated a significantly increased risk of major malformations following in utero exposure to atypical antipsychotics as a class, the reproductive safety of individual medications has yet to be systematically investigated. Understanding lurasidone's safety profile is critical for women who are pregnant or planning to conceive, given it is used increasingly as monotherapy and as an adjunctive treatment for bipolar disorder and schizophrenia, as well as for unipolar depressive mixed episodes. The goal of current analyses is to determine the risk of major malformations among infants exposed to lurasidone during pregnancy compared to a group of infants whose mothers had histories of psychiatric morbidity but who did not use an atypical antipsychotic medication during pregnancy.
Website: www.womensmentalhealth.org/pregnancyregistry Toll-free number: 1-866-961-2388
Methods: Pregnant women ages 18-45 are prospectively followed during pregnancy and the postpartum period using 3 phone interviews, conducted at enrollment, 7 months gestation, and 3 months postpartum. Inclusion in the exposure group requires first-trimester use of lurasidone during pregnancy. The comparison group is comprised of women who have not taken atypical antipsychotics during pregnancy. Maternal and pediatric medical records are reviewed for the occurrence of major malformations, and identified cases are adjudicated by a blinded dysmorphologist. A scientific advisory board, consisting of experts in the fields of teratology, pharmacoepidemiology, and psychiatry, governs the release of findings.
Results: As of January 11, 2018, total enrollment in the Registry was 1,171 women: 635 women were exposed to atypical antipsychotic medications, and 536 women were in the comparison group. A total of 611 women have completed the study and were eligible for inclusion in the analysis. Medical records were obtained for 83.5% of study subjects. Among patients exposed in the first trimester to lurasidone with evaluable data, 1 of 67 subjects had a major malformation, consistent with baseline rates in the general population.
Discussion: The NPRAA is a mechanism for the collection of prospective reproductive safety information that can be utilized to inform the care of women who require atypical antipsychotics to sustain psychiatric well-being. This study represents the largest prospective analysis of neonatal malformations in infants exposed to lurasidone, providing reassuring data to clinicians who prescribe to reproductive age women and to women taking lurasidone during pregnancy. However, further information is needed to better estimate risk. The importance of pregnancy registries is underscored by recent FDA guidance,

(http://www.fda.gov/Drugs/DevelopmentApprovalProcess/ Development Resources/ Labeling/ucm093307.htm), and information about enrollment in the NPRAA can be found in the FDA label for lurasidone as well as other psychiatric medications.

W34. LONG-TERM EFFICACY, SAFETY, AND TOLERABILITY OF ADJUNCTIVE ALKS 5461 IN PATIENTS WITH MAJOR DEPRESSIVE DISORDER ENROLLED IN AN ONGOING PHASE 3 STUDY

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Abstract: Introduction: There is evidence for dysregulation of the endogenous opioid system in patients with major depressive disorder (MDD). ALKS 5461, an investigational opioid system modulator for depression, is a combination of buprenorphine (BUP; a μ-opioid receptor partial agonist and κ-opioid receptor antagonist) and samidorphan (SAM; a sublingually-bioavailable μ-opioid antagonist). ALKS 5461 has shown efficacy versus placebo as an adjunctive treatment for MDD and a consistent safety profile in previously reported, short-term clinical studies.1,2 We report from an ongoing, 12-month, open-label, extension study, ALK5461-208 (clinicaltrials.gov ID: NCT02141399), long-term efficacy, safety, and tolerability of ALKS 5461.
Methods: The ALK5461-208 study enrolled patients who participated in 1 of 4 short-term studies (FORWARD-4 [ALK5461-205; NCT02158533], FORWARD-3 [ALK5461-206; NCT02158546], FORWARD-5 [ALK5461-207; NCT02218008], FORWARD-1 [ALK5461-210; NCT02085135]), as well as de novo patients. Data presented are from patients who received ≥ 1 dose of ALKS 5461 in ALK5461-208 and completed or terminated the study early as of April 30, 2017. These patients represent approximately 98% of all enrolled patients. All patients had a confirmed diagnosis of MDD and a history of inadequate response to standard antidepressant therapy (ADT). All patients were treated with an adequate dose of an established ADT for ≥ 8 weeks before initiation of the study drug, and although dosage of the ADT could be titrated, no change in the ADT was allowed. Patients received sublingual ALKS 5461 2 mg/2 mg (BUP/SAM) as adjunctive treatment for up to 52 weeks in ALK5461-208. Change from baseline in the Montgomery-Åsberg Depression Rating Scale (MADRS-10) was the primary efficacy measure with baseline defined as time of ALKS 5461 initiation (in ALK5461-208 or the prior study, as applicable). Remission, defined as a MADRS-10 score of ≤ 10, was also evaluated using the last observation carried forward. Time to remission was analyzed using Kaplan-Meier methods. Safety was assessed via adverse events (AEs), vital signs, laboratory analytes, and electrocardiography. Suicidal ideation or behavior was evaluated by the Columbia Suicide Severity Rating Scale (C-SSRS). Withdrawal symptoms were assessed by the Clinical Opiate Withdrawal Scale (COWS).
Results: From a total of 1454 patients, 49% completed the 1-year study, 11% discontinued due to an AE, and 40% discontinued because of other reasons. Mean MADRS-10 scores decreased from baseline and this decrease was maintained at end of study. Remission rate at 12 months and Kaplan-Meier median time to remission were 52.5% and 59.0 days, respectively. AEs

occurring at any time during ALKS 5461 exposure with a frequency of at least 5% were nausea, headache, constipation, dizziness, somnolence, vomiting, dry mouth, fatigue, upper respiratory infection, insomnia, nasopharyngitis, sedation, and hyperhidrosis. AEs typically occurred at ALKS 5461 initiation and resolved with continued treatment. There was no evidence of increased risk of suicidal ideation or behavior observed with ALKS 5461. Reports of withdrawal post discontinuation were uncommon (0.4%) and of mild or moderate severity. ALKS 5461 was not associated with any changes in laboratory or metabolic parameters, or change in body weight.
Conclusions: Overall, ALKS 5461 showed durability of an antidepressant effect for up to 52 weeks of treatment in patients with MDD. ALKS 5461 was well tolerated with an AE profile consistent with the short-term studies.

W35. ASSESSMENT IN WORK PRODUCTIVITY AND THE RELATIONSHIP WITH COGNITIVE SYMPTOMS (ATWORC): FINAL ANALYSIS FROM A CANADIAN OPEN-LABEL STUDY OF VORTIOXETINE IN FIRST TREATMENT AND SWITCH PATIENTS WITH MAJOR DEPRESSIVE DISORDER

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Abstract: Objectives: AtWoRC (Assessment in Work productivity and the Relationship with Cognitive symptoms in patients with Major Depressive Disorder [MDD] taking vortioxetine; NCT02332954) is an interventional, open-label Canadian study designed to assess the association between cognitive symptoms and work productivity in gainfully employed patients with MDD treated with vortioxetine.
Methods: Patients diagnosed with MDD were prescribed vortioxetine and assessed over a total of 52 weeks at routine care visits that emulated a real-life setting. Patients were classified as those receiving vortioxetine as the first treatment for a current major depressive episode (first treatment) or having inadequate response to a previous antidepressant (switch). The primary analysis was partial correlation between changes in self-reported cognitive symptoms scores (20-item Perceived Deficits Questionnaire; PDQ-D-20) and self-reported work productivity loss scores (Work Limitations Questionnaire; WLQ) over 12 weeks of vortioxetine treatment. Additional assessments were performed over 52 weeks at specific timepoints; these included changes in symptom and disease severity, cognitive performance, functioning, and pharmacoeconomics, as well as safety and tolerability. All analyses were conducted in both first treatment and switch patients. We report here the 52-week results of the AtWoRC study.
Results: A total of 198 eligible patients (96 first treatment, 102 switch) at 26 sites were enrolled, received at least one treatment dose, and attended at least one post-baseline study visit. As previously reported, a significant correlation between patient-reported PDQ-D-20 and WLQ productivity loss scores was observed at 12 weeks in both first treatment ($r = 0.676$; $p<0.001$; $n = 79$; observed cases [OC]) and switch patients ($r = 0.515$; $p<0.001$; $n = 75$; OC). This association remained in both groups at Week 52 ($r = 0.710$, $p<0.001$, $n = 56$, OC; $r = 0.788$, $p<0.001$, $n = 51$, OC). In addition, significant improvement in various mood, cognitive, and functional assessments (e.g., Quick Inventory of Depressive Symptomology–Self-Rated, Digit Symbol Substitution Test, Sheehan Disability Scale) was observed at 12 weeks and continued for 52 weeks. Both groups also showed improvement in anxiety symptoms as measured by the

Generalized Anxiety Disorder 7-item scale at Weeks 12 and 52. After 52 weeks of treatment, rates of response, defined as a change in QIDS-SR of ≥50% from baseline, were 71% and 83% for first treatment and switch patients, respectively; rates of remission, defined as a QIDS-SR total score of ≤5, were 45% and 67%, respectively. Safety and tolerability in short- and long-term treatment were consistent with the label information for vortioxetine.
Conclusions: Improvements in self-reported cognitive symptoms were significantly associated with improvements in self-reported workplace productivity in Canadian patients with MDD after 12 weeks of treatment with vortioxetine, with continued improvement for 52 weeks. Importantly, both first treatment and switch patients also demonstrated clinically relevant improvements in mood, cognitive function, and overall functional outcomes, as well as rates of treatment response and remission after 52 weeks of treatment. These results demonstrate the long-term benefit of vortioxetine and are among the first to show a relationship between cognitive symptoms in MDD and workplace productivity in a real-world setting.

W36. A PHASE 2, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF NSI-189 PHOSPHATE, A NEUROGENIC COMPOUND, AMONG OUTPATIENTS WITH MAJOR DEPRESSIVE DISORDER

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Abstract: Background: NSI-189 is a novel compound developed for major depressive disorder (MDD), based on evidence of enhancing hippocampal neurogenesis. This trial evaluated oral NSI-189 as monotherapy for MDD. To improve signal detection, the sequential-parallel comparison design (SPCD) was chosen.
Methods: 220 subjects were randomized to: NSI-189 40mg (n=44), 80mg (n=44), or placebo (n=132) for 6 weeks (stage 1). Placebo- non-responders were re-randomized to NSI-189 40 mg (n=22), 80 mg (n=22), or placebo (n=22) for 6 more weeks (stage 2). Patients on NSI-189 completing stage 1 continued the same dose for another 6 weeks. The primary outcome measure was the Montgomery-Asperg Depression Rating Scale (MADRS). Secondary measures included the Hamilton Depression Rating Scale (HAMD-17), Symptoms of Depression (SDQ) and Cognitive and Physical Functioning (CPFQ) Questionnaires, patient-rated Quick Inventory of Depressive Symptomatology (QIDS-SR), and CogScreen/Cogstate computerized cognitive tests. Results from stage 1 were pooled (50:50 weighted average) with stage 2 results from re-randomized patients.
Results: MADRS or HAMD-17 score reduction versus placebo did not reach statistical significance for NSI-189. However, the 40 mg dose demonstrated greater overall (pooled stage 1 and 2) reduction on the SDQ (p=0.04), and CPFQ (p=0.03), and on the QIDS-SR in stage 2 (p=0.04) versus placebo. The 40mg dose also showed statistical advantages on the CogScreen test.
Discussion: NSI-189 did not demonstrate an advantage over placebo on the primary outcome measure. However, all three self-rated symptom measures showed significant advantages for NSI-189. Pro-cognitive effects were also shown on objective measures. Further evaluation of the antidepressant and pro-cognitive effects of this compound is warranted.

W37. A SYSTEMATIC REVIEW OF PSILOCYBIN IN THE TREATMENT OF DEPRESSION AND ANXIETY

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Abstract: We present a targeted literature review examining the use of the psychoactive drug psilocybin for treatment-resistant mood disorders. There is a growing interest in the use of this agent and others in this class as potential therapeutic interventions, and a surprising number of studies underway. In this poster presentation we will review the various intricacies of navigating and receiving federal, state, and institutional approval for working with DEA Schedule I substances.

Psilocybin is currently under investigation in a number of studies globally for its potential use in mood disorders. Due to notable restrictions on its use, studies involving the drug require additional approvals by the DEA and the FDA, and other agencies as well depending on the local IRB. Consequently, approval to begin research is both resource and time intensive. Trials in healthy, depressed, and terminally ill patients have yielded significant decreases in anxious and depressive symptoms, as well as reported improvement in quality of life. These early findings suggest the potential for psilocybin as a therapeutic tool in treating depression and anxiety.

Psilocybin has a low toxicity and a comparatively low potential for harm. Studies in healthy controls suggest that the effects of psilocybin may be surprisingly durable with recent studies finding a majority of participants reporting improved scores in attitude, mood, behavior, and coping with death for up to 6 months post-treatment, with no apparent long-term side effects Griffiths et al. (2011, 2017) and Hasler et al. (2004). Suspected potential mediators of response in recent studies have included the experience of a 'peak' emotional state, enhanced dynamic emotional expression, experience of an altered state of consciousness, feelings of connectedness to nature, and decreased blood flow to the amygdala in the temporal cortex. To date neuroimaging studies are limited, though a number are in progress.

While early results are promising, there are still relatively few controlled trials of psilocybin in the treatment of depression or anxiety. The following controlled trials have been recently completed in depression: Griffiths et al. (2016), Ross et al. (2016), and Stroud et al. (2017). Results suggest that at moderate doses, psilocybin yields evidence for a significant antidepressant effect in depression symptoms in some studies and a reported improved quality of life sustained for up to 6 months. Recent placebo controlled studies focusing on anxiety include: Griffiths et al. (2016), Ross et al. (2016), and Grob et al. (2011). Results of these studies show evidence for a significant anxiolytic effect of psilocybin and reported improved quality of life for up to 6 months in cancer patients. Consideration of these recent controlled trials including strengths and limitations, as well as details of the results, will be presented.

In this poster, we will present the recent clinical studies exploring the use of psilocybin as a treatment for depression and anxiety. Conclusions of these studies, including potential mediators and moderators will be reviewed. Current studies and suggested future directions for future studies of psilocybin will be discussed. As well, the approvals required to conduct this type of clinical research and navigation of multiple federal agencies will be discussed.

W38. ELECTROENCEPHALOGRAPHIC PARAMETERS DURING ELECTROCONVULSIVE THERAPY: RELATIONSHIP TO CLINICAL RESPONSE

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Abstract: Background: Electroconvulsive therapy (ECT) is more effective and has a faster onset of action than most other treatments of major depressive disorder (MDD) with remission rates of up to 83% in nonpsychotic depression and 95% in psychotic depression (Petrides et al., 2001). In comparison, only 50% of patients with MDD reached full remission in the largest clinical trial investigating efficacy of antidepressant medications (Rush, 2007). Despite the major therapeutic advantage of ECT, its mechanism of action is not fully understood, and we lack reliable markers for predicting clinically therapeutic treatments. Objective: To analyze the effect of various ictal and postictal electroencephalographic (EEG) parameters on clinical efficacy of ECT in order to identify areas of focus for optimization of clinical outcomes. Methods: Searched PubMed using the MeSH terms "electroconvulsive therapy" AND "EEG." Studies including open-label trials, randomized control trials, and case reports were identified. Studies that were not relevant to clinical efficacy were excluded.
Results: Twenty-seven studies met my inclusion criteria. The studies identified investigated the effects of ictal amplitude, postictal suppression, onset and degree slow wave activity, ictal regularity and stereotypy, polyspike phase duration, interhemispheric coherence, and interictal EEG changes on therapeutic effect of ECT.
Conclusions: Patients who exhibited high amplitude, symmetrical seizure activity that was associated with early onset slow wave activity and postictal suppression experience maximum therapeutic benefit. Moreover, several persistent postictal changes correlate with degree of symptom improvement. On the other hand, ictal EEG regularity does not appear to have a significant correlation with patient response. Clinical efficacy can be enhanced using individualized, patient-specific approaches borne out of our understanding of the effects of EEG parameters on clinical outcome. Furthermore, a deeper understanding of EEG parameters and their clinical relevance opens a window on examining the neurobiologic basis of the efficacy of ECT and allows us to refine ECT techniques to produce the greatest clinical efficacy.

W39. COMPONENTS AND TRENDS IN TREATMENT EFFECTS IN RANDOMIZED PLACEBO-CONTROLLED TRIALS IN MAJOR DEPRESSIVE DISORDER 1979-2016

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Abstract: The Division of Psychiatry Products at FDA has constructed a database of all randomized placebo-controlled trials of antidepressants in the treatment of Major Depressive Disorder submitted between 1979 and 2016. These 228 studies enrolled 73,178 subjects; 66.3% were assigned to antidepressants and 33.7% to placebo. Over time, mean baseline severity was the equivalent of 23.0 points on the HAMD17 scale and has fluctuated modestly, in the range of 1.5 points. Placebo response showed little change over time averaging 8.1 points. There was

a strong tendency towards spontaneous improvement in more severely ill patients and worsening in less-severe patients, both averaging 32% of the difference between individual subject baseline severity and the population average. Net drug effect over placebo has averaged 1.8 points but has gradually improved over time at the rate of ~0.35 points per decade. Treatment response was also influenced by baseline severity, with the equivalent improvement of 2.0 points in subjects with a baseline severity of 30 points and 1.5 points in subjects with baseline severity of 17 points. Both drug and placebo responses showed evidence of bimodal distribution with 50% of drug subjects and 40% of placebo subjects showing improvements of nine points or more. Baseline depression severity varied modestly with age, and was generally less severe in younger (<25) and older (>65) subjects compared to subjects aged 25-65. Placebo response diminished with increasing age and observed response with active treatment was less in older subjects. The greatest improvement relative to placebo was in subjects aged 35 to 60. In male subjects, mean baseline severity was slightly less (0.3 points) and net drug effect over placebo was also slightly less (by a similar amount).

W40. WITHANIA SOMNIFERA AND SCHIZOPHRENIA: A RANDOMIZED, PLACEBO-CONTROLLED, DOUBLE-BLIND CLINICAL TRIAL OF AN ADJUNCTIVE TREATMENT FOR MOOD AND NEGATIVE SYMPTOMS

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Abstract: Withania somnifera (WSE), or Ashwaghanda, has traditionally been used as an adoptogen in Ayurvedic medicine, and a growing body of evidence suggests that it may have efficacy in the treatment of many disease states recognized in allopathic medicine, including psychiatric disorders. Our group's research focuses on WSE's utility in the treatment of exacerbated schizophrenia spectrum disorders. Exacerbations are not limited to positive symptoms but can extend to negative symptoms as well as anxiety, depression and other general psychopathology. All such symptoms are considered challenging to treat in this population and are not always responsive to antipsychotic medication alone. Moreover, negative, depression and anxiety symptoms significantly impact resolution of symptoms and return to community functioning. In our study, we enrolled 66 patients with schizophrenia spectrum disorders who were experiencing an exacerbation of symptoms in a 12-week randomized, placebo-controlled, double-blind parallel-group clinical trial. Active treatment was with 1000mg/day of a standardized extract of WSE, and the primary outcome was to determine if this treatment improved PANSS total, positive, negative, and general symptoms. Secondary outcomes evaluated stress using the Perceived Stress Scale (PSS) and the inflammatory indices S100B and C - reactive protein (CRP). Beginning at 4 weeks, and continuing to the end of treatment, WSE produced significantly greater reductions in PANSS negative, general and total symptoms (Cohen's d: 0.83, 0.76, 0.83), but not positive symptoms, when compared to placebo. PSS scores improved significantly with WSE treatment compared to placebo (Cohen's d: 0.58). CRP and S100B declined more in the WSE group but were not significantly different from placebo. These findings suggest that WSE may have promise in the treatment of negative and general symptoms and associated stress in exacerbated schizophrenia. Additional analyses were then undertaken to determine outcomes for depressive and anxiety symptoms. The PANSS single item depression score was thus isolated, as was the PANSS anxious/depression cluster, which encompasses PANSS measures of somatic concern, anxiety, guilt feelings, and depression. The mean change scores for depression single-item and anxiety-depression cluster scores for patients who received WSE

were significantly better than the mean change scores for patients who received placebo. Medium effect sizes of 0.68 and 0.65 favoring WSE over placebo were observed for depression single-item and anxiety-depression cluster scores respectively. As such, our findings suggest that depression and anxiety symptoms in exacerbated schizophrenia may also be significantly improved with adjunctive treatment with WSE. Adverse events were mild to moderate and transient. While the mechanism of its clinical efficacy requires more exploration, and pending independent replication, the summary of our research, including our findings relating to depression and anxiety, suggest that WSE may have promise as adjunctive treatment in targeting a broad spectrum of symptoms seen in exacerbated schizophrenia.

W41. CLINICAL EVALUATION OF ABUSE POTENTIAL OF ALKS 5461

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Abstract: Introduction: ALKS 5461 is an opioid system modulator being investigated as an adjunctive treatment for major depressive disorder (MDD). ALKS 5461 is a fixed-dose combination of buprenorphine (BUP), a partial μ-opioid receptor agonist and κ-opioid receptor antagonist, and samidorphan (SAM), a μ-opioid receptor antagonist added to address the abuse and dependence potential of BUP.1,2 We assessed the effects of SAM on the abuse potential of BUP in the ALKS 5461 combination in two ways: (1) a dedicated human abuse potential (HAP) study in volunteers; and (2) an evaluation of the clinical experience across multiple studies of patients with MDD.

Methods: Study 212 (ClinicalTrials.gov ID: NCT02413281) was a HAP study in nondependent, recreational, adult opioid users. Following a qualification period, participants were randomized to 6 treatments in a blinded, crossover design: placebo (PBO), ALKS 5461 at the target therapeutic dose (BUP/SAM 2 mg/2 mg), at 4X (8 mg/8 mg) and 8X (16 mg/16 mg) supratherapeutic doses, and BUP alone (8 mg and 16 mg). The primary endpoint was maximum effect (Emax) for Drug Liking ('at this moment') visual analog scale (VAS).

The clinical program for ALKS 5461 included 4 PBO-controlled studies of patients with MDD (n = 961). Pooled safety data were interrogated for adverse events (AEs) that may be associated with abuse, dependence, or withdrawal, as well as for objective signs of withdrawal with the Clinical Opioid Withdrawal Scale (COWS).

Results: In Study 212 (n = 38), Emax Drug Liking VAS scores for the ALKS 5461 2 mg/2 mg dose were similar to those for PBO (median within-subject difference [90% CI]: 2.5 [0.0-9.0]). Emax Drug Liking VAS scores for all ALKS 5461 dose groups, including supratherapeutic doses, were significantly lower than those observed for either BUP dose. The supratherapeutic doses of ALKS 5461 (8 mg/8 mg and 16 mg/16 mg) had higher Emax Drug Liking VAS scores than placebo, but the differences were small.

In the MDD controlled studies, the incidence of euphoria-related AEs was low for ALKS 5461 2 mg/2 mg and PBO (1.6% vs 0.2%, respectively) and there was no evidence of dependence or withdrawal by reported AEs or COWS assessment. Euphoria events typically occurred with treatment initiation and resolved with continued treatment. No patients randomized to ALKS 5461 reported abuse behavior AEs.

Conclusions: These findings indicate that SAM mitigates the abuse potential of BUP in the ALKS 5461 combination.

W42. CANNABIDIOL: A NOVEL NEUROMODULATORY PHARMACOLOGICAL INTERVENTION TO TREAT NEUROPSYCHIATRIC DISORDERS

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Abstract: Since most patients with some neuropsychiatric disorders do not respond properly to treatment, scientific effort has been driven to the development of new compounds acting on pharmacological targets beyond the monoaminergic system. Cannabidiol (CBD), a major nonpsychotropic constituent of Cannabis, has multiple pharmacological actions, including anxiolytic, antipsychotic, antiepileptic and anti-inflammatory properties. Therefore, the aim is to present recent basic and clinical research findings from our studies evaluating the effects of cannabidiol (CBD), an inhibitor of the reuptake and metabolism of anandamide and several other effects on nervous system on the prevention and treatment of neurological and psychiatric conditions. The evidence observed by our group to date shows that CBD acts in pathways associated with neuropsychiatric symptoms and that it may be important agents in the management of prodromal states, particularly in psychosis and neurodegenerative disorders, such as schizophrenia and Parkinson´s. We also observed that CBD has a safe profile as assessed by translational approaches. These observations underscore the relevance of further research on the effects of this compound and others that mediate the activity of the cannabinoid system, as well as comparative studies of their neuropsychopharmacological effects and those of other drugs currently used to treat neuropsychiatric conditions.

W43. DO MULTIPLE PSYCHIATRIC DIAGNOSIS IN SMOKERS AFFECT THEIR DEPENDENCE AND WITHDRAWAL FROM NICOTINE?

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Abstract: Background: Nicotine use and dependence are major public health concerns. Similarly data suggests that anxiety and depression are prevalent amongst nicotine users. There is general observation that patients with complex psychiatric histories are often using nicotine. These patients find it very difficult to quit their nicotine use. Some studies suggest that the more active the psychiatric symptoms the more difficult it is for the patient to quit smoking. We wanted to see if this assumption was accurate by utilizing objective measures to find any relationship between nicotine dependence and withdrawal and the total number of diagnosis a patient had in our cohort of participants. We used Mini International Neuropsychiatric Interview (MINI) to assign patients appropriate clinical psychiatric diagnosis. We used Penn State Cigarette Dependence Index (PSCDI) to measure nicotine dependence and the Minnesota Nicotine Withdrawal Scale (MNWS) to measure the nicotine withdrawal.
Method: We recruited 188 current smokers who had no plans to quit smoking in the next 6 months to participate in a randomized clinical trial to observe the efficacy of reduced nicotine cigarettes in patients with anxiety and depressive disorders. Mini International Neuropsychiatric Interview (MINI) was used to screen and diagnose psychiatric disorders prior

to the participants enrolling in our study. Only nicotine users/smokers with a current or past diagnosis of anxiety or depressive disorder were enrolled in our study. Each participant was assigned 0, 1, 2, 3 (or more) diagnosis based on their current symptoms on MINI. We used PSUCDI and MNWS to measure nicotine dependence and withdrawal symptoms at baseline, while participants were still smoking their usual number and brand of cigarettes. Spearman's rank correlation coefficient was used to test the correlation between the scores PSUCDI, MNWS and the total number of anxiety and depressive disorders diagnoses per participant.
Results: There was a pattern in which increasing the number of current MINI anxiety and depressive disorder diagnoses (0 current MINI diagnosis n=70, 1 diagnosis n=60, 2 diagnosis n=22, 3 or more diagnosis n=36) was positively correlated with MNWS and PSUCDI scores. The correlation for MNWS was moderately positive (0.52, Mean scores: 0 diagnoses=8.0; 1=12.2, 2=16.3, and 3+=18.6). The correlation for PSCDI was positive but weak (0.26, Mean scores: 0=12.4, 1=13.1, 2=13.2, 3+=14.8).
Discussion: There is data to suggest that there is high use of nicotine in patients with psychiatric disorders. There is also data that suggests that the more complex the psychiatric disorder the more difficult it is to quit smoking. It is unclear why this is the case. Patient with chronic psychiatric illness who smoke can be prone to numerous medical complications down the road. Decreasing and discontinuing smoking would decrease the burden of medical complications in these patients. We wanted to see the relationship between different total number of psychiatric diagnoses and its effect on nicotine dependence and withdrawal. Our data suggests that with the increase in the total number of psychiatric diagnoses there is a positive correlation between nicotine dependence and withdrawal. Providers caring for these patients need to be aware of this relationship. Emphasis should be placed on treating both the psychiatric symptoms and the nicotine dependence in these patients. We encourage additional studies to explore our findings.

W44. THE EVALUATION OF ADHERENCE TO TREATMENT AND REAL-WORLD OUTCOMES IN TWO COHORTS OF PATIENTS WITH SERIOUS MENTAL ILLNESS (SMI)

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Abstract: Objective: Evaluate adherence to treatment and real-world outcomes in two cohorts of patients with serious mental illness (SMI).
Methods: A retrospective cross-sectional analysis was used to compare patient characteristics and outcomes using a large sample of commercial, Medicare Advantage, and managed Medicaid claims data. Patients were included if they: 1) were enrolled with medical and pharmacy benefits for at least 180 days before and 360 days after the index event; 2) had at least one inpatient or two outpatient claims with a diagnosis for SMI and at least one prescription claim for an antipsychotic anytime between January 1, 2011 and June 30, 2016; and 3) were ≥ 18 and <65 years old at index date. The recently discharged (RD) cohort included patients with ≥1 SMI related hospitalization (first used as index event). The early episode (EE) cohort included patients with ≥ six-months of pre-index enrollment with no evidence of an antipsychotic or SMI diagnosis (first claim with either used as index event). The RD cohort

included 11,050 patients: 62% female; Age: 9% 18-25, 35% 26-45, 56% 46-65. The EE cohort included 40,655 patients: 63% female; Age: 12% 18-25, 39% 26-45, 49% 46-65.
Results: Adherence to oral antipsychotic medications (defined as PDC ≥.80) was 52.5% on average in the RD cohort, but only 16.1% on average in the EE cohort. Utilization rates per 1,000 patients were significantly higher in the RD cohort: PCP visits (6,170 vs 5,770); observation stays (400 vs. 160); emergency department visits (2,050 vs 1,170). Inpatient readmission rates were 220/1,000 in the EE cohort compared to 600/1,000 in the RD group.
Conclusions: Adherence to treatment is low and variable among SMI patients, resulting in high rates of healthcare utilization. These stratified outcomes can be used by providers to target specific SMI patients to reduce utilization and costs of care.
Sponsorship: Otsuka Pharmaceutical Development & Commercialization, Inc.

W45. DASOTRALINE FOR TREATMENT OF ADULTS WITH BINGE-EATING DISORDER: EFFECT ON BEHAVIORAL OUTCOMES

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Abstract: Objective: Binge-eating disorder (BED), the most common eating disorder in the US (lifetime prevalence, 2.8%), is associated with impairment in quality of life and functioning. BED is typically associated with obsessive and dysphoric thoughts and compulsive behaviors relating to a range of eating and body image concerns. Dasotraline, a potent inhibitor of dopamine and norepinephrine transporters, has a PK profile characterized by slow absorption, and a long elimination half-life (t½, 47-77 hours) permitting once-daily dosing. In a recent study, dasotraline demonstrated robust efficacy in treating adults with moderate-to-severe BED. We now report secondary behavioral and psychological outcomes from this study.
Methods: Patients with moderate to severe BED, based on DSM-5 criteria, were randomized, double-blind, to 12 weeks of treatment with flexible doses of dasotraline (4, 6, and 8 mg/d), or placebo. The primary efficacy endpoint was number of binge eating (BE) days/week, assessed using a mixed model for repeated measures analysis. Secondary behavioral and functional outcome measures included the Yale-Brown Obsessive-Compulsive Scale Modified for Binge Eating (Y-BOCS-BE); and the Eating Disorder Examination Questionnaire Brief Version (EDE-Q7), which consists of a global score, and 3 subscale scores (dietary restraint, shape concern, and weight concern).
Results: The safety population consisted of 317 patients who were randomized and received at least 1 dose of study drug (female, 84%; mean age, 38.2 years). On the primary endpoint, LS mean (SE) reduction from baseline in the number of BE days per week was significantly greater for dasotraline vs. placebo at week 12 (-3.74 [0.12] vs. -2.75 [0.12]; P<0.0001; effect size [ES] = 0.74). LS mean [SE] change from baseline to week 12 was significantly greater for the dasotraline vs. placebo on the Y-BOCS-BE total score (-17.05 [0.68] vs. -9.88 [0.65]; P<0.0001; ES, 0.96), the obsession subscale score (-8.32 [0.36] vs. -4.58 [0.34]; P<0.0001; ES, 0.95), and the compulsion subscale score (-8.69 [0.36] vs. -5.35 [0.34]; P<0.0001; ES, 0.87). LS mean [SE] change from baseline to week 12 was also significantly greater for the dasotraline vs. placebo on the EDE-Q7 global score (-0.85 [0.18] vs. -0.23 [0.11]; P<0.001;

ES, 0.49), dietary restraint subscale score (-0.55 [0.15] vs. +0.15 [0.14]; P<0.001; ES, 0.44), shape concern subscale score (-0.93 [0.14] vs. -0.43 [0.13]; P=0.011; ES, 0.33), and weight concern subscale score (-1.03 [0.14] vs. -0.44 [0.14]; P<0.01; ES, 0.38).
Conclusions: In this double-blind study of patients with binge eating disorder, treatment with dasotraline (4-8 mg/d) was associated with significant improvement in behavioral and psychological outcomes, including measures of obsessions and compulsions associated with BED. In addition, significant improvement was observed in measures of weight and shape concern, and intensity of attempts to restrict food intake.
Clinicaltrials.gov number: NCT02564588
Sponsored by Sunovion Pharmaceuticals Inc.

W46. TEACHING AND PRACTICE OF CLINICAL PSYCHOPHARMACOLOGY

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Abstract: Background: In the 1970s, in response to a strong need to develop content for the developing field of psychopharmacology in the United States and Europe, the ACNP Educational Committee developed a "model curricula for teachers of psychopharmacology". This curriculum, now in its 9th edition, has been widely adapted with diverse utilization of differing parts by residency programs in the United States. This poster details recent pedagogical efforts globally - especially in low to middle income countries.
Methods: In 2016, the World Psychiatric Association (WPA), purchased 100 copies of the 8th edition of the ASCP Model Psychopharmacology Curriculum - specifically targeted to low and middle-income countries. They sent this to 43 countries and did an informal survey of its usefulness in April 2017.
Results: This survey revealed that many countries did not have systemic, psychiatric academic teaching programs. In addition, they did not have teachers with psychopharmacologic expertise to teach the theory and practice of clinical psychopharmacology. In some countries, psychopharmacology was taught by family physicians. In programs that responded, they noted 1) "useful for academic purposes," 2) "well-structured curriculum on neuropsychopharmacology," and 3) "useful for medical students and for master students who study social psychiatry". There were no comments focused on either the teaching-learning process or its effects on clinical practice at this point.
Conclusions: Like the initial distribution of the first ACNP model curriculum, teachers of all specialties have difficulty adopting a curriculum of any sort. Follow up to all countries must ensure that programs have 1) actually received it, 2) have passed it along to teachers of psychiatry and psychopharmacology, and 3) subsequently adopted the curriculum to their programs regardless of their culture or their psychiatry/family practice programs. Personal contact and consultation may well be the crucial missing step necessary to integrate the curriculum to a local setting. Further systemic evaluation and follow up will be necessary to improve the teaching and clinical practice in these countries.

W47. BRIEF HISTORY OF CLINICAL PSYCHOPHARMACOLOGY IN CHINA

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Abstract: The development of clinical psychopharmacology in China can be roughly divided into three stages: The first stage: from 1950 to 1980. Since the synthesis of chlorpromazine and its use in the treatment of mental illnesses [1], China thoroughly replicated the majority of psychotropic drugs marketed abroad. Clozapine, as an example, was extensively used for the treatment of Schizophrenia. China leads the world in Clozapine use, recognizing early on its clinical value for refractory patients.

The second stage: from 1980 to 2008. With the successful research and development of SSRI antidepressants and atypical antipsychotics, a large number of new psychotropic medicines have been introduced into China by a number of global pharmaceutical companies and led to a new round of domestic imitation. However, there are only a few psychotropic medicines researched and developed independently in China. The Shanghai Institute of Medicine, Chinese Academy of Sciences has developed huperzine A for the treatment of Alzheimer's disease (AD) and some traditional Chinese medicines (TCM) for the treatment of depression and insomnia. During this stage, drug clinical trials were required to be implemented at regulatory authorized hospitals. In 1998, the Ministry of Health (MOH) named it as "Base for Drug Clinical trial". Six hospitals including the Shanghai Mental Health Center were first qualified thereafter as a national base for drug clinical trials in psychiatry. The number of bases expanded to 10 later on. After the establishment of SFDA, it changed its name to the "Medical Institute conducting Clinical Trial for human used drug" and gradually expanded to more than 20 institutions that were qualified as having psychiatric expertise. In 2003, the promulgation and implementation of China's Good Clinical Practice (GCP) originally from ICH E6 (R1) was widely accepted as the core standard for drug-registration clinical trials. Under the active implementation of the sponsors, a number of research teams focusing on clinical trials of psychotropic drugs have been gradually formed.

The third stage: from 2008 to now. Benefiting from the funding of the National Science and Technology Major Project on "Significant New Drug Creation", domestic pharmaceutical companies are devoted to the research and development of new psychotropic drugs. Up till now, more than 10 drugs have being investigated in different phases of clinical trials, some of which will soon be completed on phase III . For example, the striking AD treatment "GV-971" (a new product with novel target) project has completed its clinical enrollment and is about to conclude in August 2018. As we know, there almost has not been a new drug for AD during the last decade over the world. The value might outweigh artemisinin for malaria if the outcome is positive. The repeated expansion of the drug clinical trial institutions results in 54 institutions so far specializing in psychiatry. With the formal participation of the CFDA in the International Council for Harmonisation (ICH) in June 2017, the Good Clinical Practice (GCP), which is highly consistent with the ICH E6 (R2) document, is about to be issued (the revision edition has completed multiple rounds of consultations). Learning from the Western regulatory model, the latest policy in China (Oct. 8 2017, the General Office of the CPC Central Committee and the General Office of the State Council) has clearly established that the institution should be qualified to implement registration management, IRB systems required to improve and the efficiency of IRB review should be increased. The numbers of hospitals that undertake drug clinical trials will gradually increase while it is challenging to emphasize supervision in process and afterwards.

W48. EFFICACY AND SAFETY OF MIN-101: A NEW COMPOUND FOR THE TREATMENT OF NEGATIVE SYMPTOMS IN SCHIZOPHRENIA A 12-WEEK RANDOMIZED, DOUBLE BLIND, PLACEBO-CONTROLLED TRIAL

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Abstract: Objective: To compare the efficacy, safety, and tolerability of MIN-101, a compound with high affinities for sigma 2 and 5-HT2A receptors, to placebo in treating negative symptoms, of patients with stable symptoms of schizophrenia.
Methods: This multi-national Phase 2b trial enrolled 244 patients diagnosed with schizophrenia who were symptomatically stable for ≥ 3 months prior to entering the trial and had scores ≥ 20 on the three factors negative subscale of the PANSS. Patients were randomized to daily monotherapy with MIN 101 32 mg, MIN-101 64 mg, or placebo in a 1:1:1 ratio. The primary endpoint was the PANSS negative symptom score based on the five factors (pentagonal) model. Secondary outcomes were the rest of the PANSS score, the CGI, the Brief Negative Symptoms Scale (BNSS), the Brief Assessment of Cognition in Schizophrenia (BACS), the Calgary Depression Scale for Schizophrenia (CDSS), and the Personal and Social Performance (PSP) scale. Safety parameters included treatment-emergent adverse events (TEAE), clinical laboratory, vital signs, electrocardiograms, Sheehan-suicidality tracking scale (S-STS), and the Abnormal Involuntary Movement Scale (AIMS). The Mixed-Effect Model Repeated Measure (MMRM) was used for analyzing the efficacy data.
Results: Statistically significant and dose dependent reduction in the primary endpoint score was demonstrated for MIN-101 32 mg and 64 mg compared to placebo ($p \leq 0.022$; ES 0.45 .and ≤ 0.003; ES 0.58 respectively). The ES were particularly high ES=1.3 in the younger patients. The validity of effects on the primary endpoint was supported by similar effects on most of the secondary measurements including: PANSS three factors negative symptoms subscale, PANSS total score, CGI, CDSS, and PSP. There were no statistically significant differences in PANSS positive subscale scores between MIN 101 and placebo.
No weight gain or clinically significant changes in vital sings, prolactin levels, routine laboratory values, metabolic indices and extrapyramidal symptom scores (EPS) were observed. One patient on 64 mg MIN-101 was discontinued from the trial based on a-priori established QT interval prolongation criteria and a second one following an episode of syncope. Completion rates for randomized patients in this 12-week study were as follows: MIN-101 62 mg = 64%, MIN-101 32 mg = 58% and placebo = 53%. The three treatment groups were balanced on all demographic and illness-related baseline characteristics.
Conclusions: MIN-101 at dosages of 32 and 64 mg/day demonstrated statistically significant efficacy of medium ES in reducing negative symptoms and good tolerability in stable schizophrenia patients. Since positive symptoms and EPS did not change, the improvement in negative symptoms was not secondary to improvement in positive symptoms or EPS, suggesting that MIN-101 might be the first specific treatment to have a direct effect on negative symptoms.

W49. DIGITAL PHENOTYPING IN SCHIZOPHRENIA: DO CLINICAL ASSESSMENTS MATTER ANYMORE?

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Abstract: Introduction: There has been increasing study of the use of wearables and mHealth for improving patient outcomes across a range of indications. The potential to improve clinical outcomes, predict adverse events or even relapse would be a powerful addition to any clinician's toolbox. Digital phenotyping, a term coined by Torous et al, 2015 and expanded by Insel et al, 2017, refers to the process of gathering passive (biometric and/or smart phone data) and active (self-report questionnaire data) to develop illness signatures that can inform treatment decisions. In schizophrenia and other psychosis there have been studies on adherence and acceptability (e.g., Killikenny et al, 2017), interest (Firth et al, 2017), autonomic activity compared to healthy normal volunteers (Cella et al, 2017), but little on linking these digital data signatures to the anchoring clinical assessments. In this study we analyzed data from a pilot study that used wearables and mHealth applications ("apps") alongside clinical assessment to assess relapse risk in schizophrenia.
Methods: Data was analyzed from a single-site pilot study using wearable devices and mHealth apps with recently discharged, stable, patients with a diagnosis of schizophrenia or schizoaffective disorder. The clinical assessments were performed at biweekly intervals during the trial and included the PANSS, BPRS and CGI-S.
Results: The mean PANSS total score for all visits was $\mu = 35$ ($\sigma = 4.6$) with the BPRS mean total score of $\mu = 25$ ($\sigma = 4.3$) for all visits indicating subclinical severity across the n=40 population. The mean CGI-S score was $\mu = 3.7$ approximating a CGI-S of "moderate severity".
Conclusions: The values obtained do not correspond with normative data for a schizophrenia population; we would expect much higher scores in an outpatient context. Hermes et al, 2013 noted that in the CATIE dataset, for example, a sub-population (n=707) of stable subjects that had a mean PANSS score of 76.0 ($\sigma = 17.4$). Because the clinical assessment indicated sub-clinical or doubtful symptom severity, a digital phenotype of any consequence failed to emerge. An adequate monitoring program would have identified that this patient sample and/or rater cohort was not optimal. In order for digital phenotyping to gain traction there must first be rigorous clinical assessments as anchors for the diagnosis and severity of the illness; without this it may be a false dawn for this compelling technology.

W50. LONG-TERM OUTCOMES WITH ARIPIPRAZOLE LAUROXIL FOR THE TREATMENT OF SCHIZOPHRENIA: A 2-YEAR, PHASE 3, MULTICENTER EXTENSION STUDY

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Abstract: Background: One of the challenges in long-term studies of schizophrenia is that clinical outcomes are often confounded by covert nonadherence to the prescribed oral antipsychotic. This is a post hoc analysis of the symptoms and illness trajectory of patients followed for over 2 years on the long-acting injectable antipsychotic aripiprazole lauroxil (AL). Because adherence to long-acting antipsychotic medication can be monitored, these data

provide an opportunity to assess outcome trajectories unaffected by medication discontinuations that may potentially occur with oral antipsychotics.
Methods: The efficacy, safety, and tolerability of once-monthly AL (441 or 882 mg) for the treatment of schizophrenia were previously demonstrated in a phase 3, 12-week, placebo-controlled randomized trial.1,2 This was followed by a 52-week, long-term safety study of two fixed doses of AL (either 441 mg or 882 mg every 4 weeks; patients continuing from the 12-week study remained on their fixed AL dose) (ClinicalTrials.gov identifier, NCT01626456), after which patients could enroll in a second long-term extension study. Patients entering the second long-term study continued on the same fixed AL dose, with a variable follow-up period up to an additional 128 weeks (ClinicalTrials.gov identifier, NCT01895452). In this post hoc analysis, the two extension studies were combined to provide continuous outcome data over 2 years of follow-up. The 12-week assessment visit (rather than the first visit) in the first extension study was chosen as the baseline time point to take into account patients entering the first extension study with variable AL exposure histories (with or without prior AL exposure). We now report on the trajectory of symptoms and illness severity for over 2 years (up to 112 weeks) after the 12-week visit using the Positive and Negative Syndrome Scale total (PANSST) score and Clinical Global Impression-Severity (CGI-S) assessments. Course of illness was measured as the difference in PANSST and CGI-S scores within dose groups from baseline to end of follow-up, analyzed using the MMRM approach.
Results: Overall, 432 of the 478 patients entering the initial 52-week study were included in the post hoc analysis. Baseline PANSST scores (mean ± standard deviation [SD]) were 59.91 ± 16.25 and 56.27 ± 12.89, and baseline CGI-S scores (mean ± SD) were 2.99 ± 0.97 and 2.79 ± 0.79, for the AL 441 mg and 882 mg groups, respectively. Among these 432 patients, approximately 49% (N = 211/432) remained for the entire 112 weeks of follow-up. Over this period, the trajectory of PANSST scores improved significantly compared with baseline for both the 441 mg and 882 mg dose groups, with changes from baseline (least squares mean ± standard error) of −5.46 ± 0.92 ($P < .0001$) and −5.00 ± 0.53 ($P < .0001$), respectively. Similar patterns of improvement were observed in CGI-S scores for both dose groups with changes from baseline of −0.32 ± 0.07 ($P < .0001$) and −0.28 ± 0.04 ($P < .0001$) for the AL 441 mg and 882 mg groups, respectively. Overall, AL was generally well tolerated, with a safety profile over a 2-year follow-up that was consistent with the initial 52-week safety results.
Conclusion: This post hoc analysis demonstrates the safety and continued therapeutic efficacy of long-term treatment with AL in patients with schizophrenia. There were no apparent dose differences in the trajectory of symptom changes over the course of a 2-year follow-up.

W51. A PROOF-OF-MECHANISM STUDY OF THE PDE10 INHIBITOR RG7203 IN PATIENTS WITH SCHIZOPHRENIA AND NEGATIVE SYMPTOMS PROBING REWARD FUNCTIONS WITH IMAGING AND BEHAVIORAL APPROACHES

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Abstract: Background: The enzyme phosphodiesterase 10A (PDE10A) is highly expressed in the striatum where it modulates both dopamine D2 and D1 dependent signaling. Its inhibition leads to a suppression of D2 mediated signaling –similar to effects of D2 antagonists - and an enhancement of D1 dependent signaling. D1-dependent signaling has been implicated in reward-based learning. Its deficient activation may be a key factor underlying deficient reward functions including reward anticipation and reward-based learning that have been implicated as major drivers of negative symptoms of schizophrenia. Therefore inhibition of PDE10 could be a way to ameliorate such deficits and consequently negative symptoms. In healthy volunteers the PDE10 inhibitor RG7203 indeed enhanced performance in tasks that probed reward functioning suggestive of its potential utility to treat negative symptoms in schizophrenia. We therefore tested the hypothesis that it should enhance imaging and behavioral markers of reward functions in patients with moderate negative symptoms in order to establish mechanistic proof of its utility as treatment of negative symptoms.
Methods: In a three-way cross-over study we investigated the effects of two doses of RG7203 (5 mg and 15 mg) and placebo given as adjunctive treatment to stable background antipsychotic treatment on reward functioning and reward-based effortful behavior using the monetary incentive delay (MID) task during fMRI and the effort choice task in patients with chronic schizophrenia and moderate levels of negative symptoms (PANSS negative symptom factor score ≥ 18 points). Each treatment period lasted three weeks followed by a 2 week washout period. fMRI and behavioral tasks were administered at the end of each treatment period. Key outcome measures were the differential BOLD during reward anticipation and overall BOLD activity during the MID task and the percentage of high-effort high-reward choices when the probability of reward was 100% during the effort choice task.
Results: Thirty-three patients with schizophrenia (30 male; 21 B, 9 W, 3 A; mean age 36.6±7 y; PANSS NSFS = 22.8 (±1.4) at screening) were recruited at three study centers in the US. Twenty-four subjects finished the entire study. RG7203 at 5 mg significantly increased differential BOLD activity during reward anticipation in the MID task. However, this enhancement occurred in the context of a significant decrease of BOLD activity across all conditions during the MID task under treatment with RG7203 . RG7203 significantly worsened reward-based effortful behavior in the effort choice task (the high-effort high-reward choice: 67% for both doses of RG7203 versus 73% for placebo). Multiple regression revealed that the decrease in effortful behavior was significantly related to the decrease in overall BOLD activity during the MID task and not related to the difference of BOLD activity during reward anticipation versus the control condition.
Conclusions: In contrast to our expectation and previous results in healthy volunteers, RG7203 worsened indices of reward functions which we hypothesize may be due to a further enhancement of D2 antagonistic activity. The results do not support the utility of a PDE10 inhibitor as adjunctive treatment for negative symptoms in patients with schizophrenia. Given the previous observation that RG7203 enhanced reward functions in healthy volunteers who were not treated with D2 antagonist, the results of our study point to potentially deleterious effects of D2 blockade on reward functions and by extension on negative symptoms of schizophrenia. They raise the question if the presence of D2 antagonistic treatment curtails the potential effects of any adjunctive treatment for negative symptoms.

W52. TREATMENT PATTERNS AND HEALTHCARE RESOURCE UTILIZATION AMONG YOUNG ADULTS WITH SCHIZOPHRENIA TREATED WITH PALIPERIDONE PALMITATE OR ORAL ATYPICAL ANTIPSYCHOTICS

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Abstract: Background: A large proportion of the burden associated with schizophrenia is attributed to early onset of the disease and its chronic nature.1 Recent findings suggest that treatment with long-acting injectable therapies such as once-monthly paliperidone palmitate (PP) is associated with lower healthcare resource utilization (HRU) and better adherence as compared to oral atypical antipsychotics (OAAs) among adult patients with schizophrenia.2 This study aimed to further evaluate the real-world effectiveness of these therapies among young adults (18-35 years) with schizophrenia.
Objective: To compare treatment patterns and HRU in patients with schizophrenia treated with PP versus OAAs with a focus on young adults (18-35 years).
Methods: Adult patients with a diagnosis of schizophrenia and ≥2 claims for PP or OAA from 1/1/2010 to 12/31/2014 were selected from the Truven Health MarketScan® Medicaid database. Index date was assigned as the date of the first observed claim of PP or OAA. Patients were required to be continuously enrolled for ≥12 months pre-and post-index date, with no PP or OAA use during the 12-month baseline pre-index period. Treatment patterns and HRU outcomes for patients aged 18-35 were compared between PP and OAA treatment groups following inverse probability of treatment (IPT) weighting to adjust for potential differences. Outcomes were compared between groups using Pearson's chi-square for categorical variables and Student's t-test for continuous variables after IPT weighting. Twelve-month HRU outcomes were estimated using weighted Poisson regression models.
Results: A total of 15,598 patients met the study criteria, among which 6,250 were aged 18-35 (439 PP patients and 5,811 OAA patients). After IPT weighting, the young adult PP and OAA cohorts were comprised of 3,095 and 3,155 patients, respectively, and were well-balanced (standardized difference ≤10%) on most baseline characteristics. During the 12-month post-index period, PP patients had a higher duration of continuous treatment exposure (168.2 vs. 132.5 days, p=0.004), better adherence on the index medication (proportion of days covered [PDC]≥ 80%: 19.0% vs.17.1%, p < 0.049) as well as less use of other psychiatric medications as compared to OAA young adult patients. Furthermore, young adult patients treated with PP were 37% less likely to have an all-cause inpatient admission (odds ratio [OR]: 0.63, 95% confidence interval [CI]: 0.53-0.74) and 33% less likely to have an ER visit (OR: 0.67, 95% CI: 0.55-0.81) compared to OAA young adult patients, but 27% more likely to have an all-cause outpatient office visit (OR: 1.27, 95% CI: 1.02 – 1.56). Patients treated with PP also had lower mean rates of all types of resource utilization, including inpatient admissions, ER visits, outpatient office visits, and other outpatient services. These findings were consistent when all adult patients (≥18 years) were observed in the analysis.
Conclusions: This analysis suggests that Medicaid schizophrenia patients aged 18-35 treated with PP are associated with higher medication adherence and fewer hospitalizations as compared to patients treated with OAAs. PP is a viable treatment option for young adult schizophrenia patients and may lead to reduced overall healthcare utilization and improved clinical outcomes.

W53. UTILITY OF MRI IN INVESTIGATING ANTIPSYCHOTIC-INDUCED METABOLIC ABNORMALITIES: A PILOT STUDY

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Abstract: Background and Significance: Mortality rates in patients with schizophrenia are two- to three-fold higher than the general population with cardiovascular disease (CVD) identified as the main culprit. For these patients, many factors contribute to the development of CVD including the use of atypical antipsychotics (AAPs) which are known to cause weight gain, dyslipidaemia and insulin resistance. One potential underlying mechanism focuses on visceral adiposity as an independent risk factor for CVD and is particularly relevant when we consider the metabolic dysregulation induced by AAPs. Adolescents in their first episode of psychosis are particularly vulnerable to the metabolic side effects of AAPs and they warrant investigation given that data suggest risk for CVD occurs early in the illness contributing to the 20-year reduction in life expectancy for schizophrenia patients. Our aim is to obtain abdominal magnetic resonance images (MRI) to 1) quantify the accumulation of hepatic fat and 2) correlate this fat deposition with anthropometric and laboratory metabolic indices in adolescents using antipsychotics for the first time.
Methods: Ten patients (4 female, 6 male) with an average age = 21.4 (range = 16-29) participated in the study. Patients were recruited from the Emergency Department and/or inpatient ward for Early Psychosis. All antipsychotics were prescribed and titrated by their primary physician as required. Diagnoses included Schizophrenia (2), Other Specified Schizophrenia and Other Psychotic Disorders (6), Major Depressive Disorder (1) and Autism Spectrum Disorder (1). Medications included risperidone (4), paliperidone (2), lurasidone (2) and aripiprazole (2). All medications were prescribed orally. At baseline and at 12 weeks, we completed a medical history and physical examination (including height, weight and waist circumference), lipid panel (including triglycerides, total cholesterol, low-density lipoprotein and high-density lipoprotein), fasting glucose and an oral glucose tolerance test (OGTT). Abdominal MRI included 60-80 axial 5 mm contiguous slices, covering from the top of liver to L5 vertebrae. Measured adipose tissue volumes (subcutaneous and visceral components) and liver fat fraction averages were compared across time.
Results: We identified significant increases in weight (p=0.017), BMI (p=0.014), waist circumference (p=0.009) and LDL (p=0.008) when 3 month follow-up data were compared to baseline measurements. Though there was not a significant difference in change in liver fat or overall visceral adipose tissue, a number of relationships were identified as significant. Notably, change in weight correlated significantly with the change in waist circumference (r=0.7, p=0.03), post-OGTT (120mins) glucose measurement (r=0.8 , p=0.007), visceral adipose tissue (r=0.7, p=0.003) and liver fat (r=0.6 ,p=0.048). A strong correlation was observed between the change in post-OGTT (120mins) glucose measurement and the change in liver fat (r=0.9, p=0.004).
Conclusions: The results of our pilot study suggest that metabolic dysfunction due to AAP use is multi-level and multi-systemic. Significant correlations between imaging, anthropometric and blood-based measures of metabolic health raise the possibility of using imaging techniques to predict or detect these abnormalities early. Future research should investigate the utility of low-cost imaging techniques (e.g. ultrasound) to predict the onset of antipsychotic-induced

metabolic abnormalities. These findings have important implications for prompting early behavioral and pharmacological interventions to mitigate these treatment effects.

W54. LUMATEPERONE IMPROVES NEGATIVE SYMPTOMS RELATED TO EMOTIONAL EXPERIENCE IN PATIENTS WITH SCHIZOPHRENIA

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Abstract: Recent research on negative symptoms in schizophrenia has suggested that there are two critical dimensions, reduced emotional expression and reduced emotional experience (often referred to as avolition/anhedonia). The results of recent studies suggest that, among negative symptoms, reduced emotional experience measured by the Positive and Negative Syndrome Scale (PANSS), comprised of three items (active and passive social withdrawal and emotional withdrawal), accounts for all of the predictive variance in poor social outcomes in schizophrenia. This influence of reduced emotional experience on social function is found to be greater than reduced expression as well as cognition, psychosis, and social competence. Here we present the results of two treatment studies with a novel investigational treatment for schizophrenia, lumateperone (ITI-007), which examine the effects of this drug on different domains of negative symptoms, as well as psychosis, mood symptoms, and social function.
Methods: The effects of lumateperone were compared to placebo on PANSS total score and individual PANSS items from two positive, randomized placebo-controlled trials [ITI-007-005 (ITI-007 60 mg, N=84; Placebo, N=82) and ITI-007-301 (ITI-007 60 mg, N=150; Placebo, N=149)] in subjects with acute exacerbated schizophrenia. Post-hoc hierarchal cluster analyses of individual PANSS items were performed on each study and the studies combined. PANSS-derived emotional experience (N2, N4 and G16) and emotional expression (N1, N3, N6, G7) factors were examined in each study separately and the studies combined in subjects with and without prominent negative symptoms at baseline. In ITI-007-301, the effects of lumateperone were compared to placebo also on the Personal and Social Performance scale (PSP).
Results: Lumateperone, in addition to improving the PANSS total score, specifically reduced a cluster of PANSS items representing positive symptoms, anxiety and social avoidance. PANSS symptoms related to emotional experience were improved whereas those related to emotional expression were not improved relative to placebo-treated subjects. Improvements in emotional experience by lumateperone were independent of changes in anxiety and psychosis. Lumateperone also improved social function as measured by the PSP. Further analyses of these data are continuing.
Discussion: The results of studies suggest that lumateperone specifically improves PANSS symptoms of reduced emotional experience compared to reduced emotional expression. Clearly, the results suggest the potential of improvement of social deficits in schizophrenia and represent the first replicated findings on improvement of negative symptoms domains with a pharmacological agent. Improvements in emotional experience predicts improved social outcomes. These results are consistent with improved social function with lumateperone.

W55. SUBMISSION WITHDRAWN

W56. EFFECTS OF TARDIVE DYSKINESIA ON EYE MOVEMENT MEASURES IN TREATMENT-RESISTANT SCHIZOPHRENIA

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Abstract: Tardive Dyskinesia (TD) is a condition characterized by abnormal, involuntary movements due to chronic treatment with neuroleptic medication. Prior reports indicate TD is associated with impaired oculomotor functioning, implicating a modulating influence of neuroleptic exposure on sensorimotor and cognitive control functions within frontal-striatal systems as assessed by eye movement (EM) paradigms. In the current study we sought to replicate and extend these findings among treatment-resistant patients evaluated on an oculomotor battery assessing automatic and executive control of eye movement and their relationship to measures of neuropsychological functioning. Sixty patients diagnosed with treatment-resistant schizophrenia (TRS) with (n=9) or without (n=51) TD completed EM testing, including: 1) a prosaccade task in which they were to shift gaze to visual targets, 2) an antisaccade task in which they were to inhibit a response towards a target and shift gaze in the opposite direction, and 3) an oculomotor delayed response task in which they were to shift gaze to the remembered location of a prior target. Neuropsychological functioning was assessed using the Wisconsin Card Sorting Test, Category Fluency Test, and Rey Auditory-Verbal Learning Test. Patients with and without TD did not differ on demographic variables, measures of symptom severity, type of medication use or current neuroleptic dosage. Linear mixed-effects models evaluating differences between TD and non-TD groups revealed the TD group had decreased peak prosaccade velocity ($p<.05$), and increased latency on the prosaccade ($p<.001$) and antisaccade ($p<.001$) tasks, indicating longer automatic and volitional shifts of visual attention. Antisaccade error rate did not differ between groups. Patients with TD had reduced accuracy on the oculomotor delayed response task ($p<.001$), reflecting reduced spatial working memory. On neuropsychological measures, TD subjects had significant reduction in short-term auditory-verbal memory ($p < .05$), decreased set-shifting abilities as displayed by fewer categories achieved on the WCST ($p < .05$), as well as decreased verbal fluency ($p < .05$). Antisaccade error rate and latency, and oculomotor delayed response accuracy were associated with neuropsychological measures across all subjects, indicating executive control deficits assessed by eye movements relate to neuropsychological test performance. Our findings indicate that tardive dyskinesia among individuals with treatment-resistant schizophrenia results in decreased speed of reflective and volitional attentional shifting, decreased spatial working memory accuracy, and poorer performance on tests of neuropsychological function. These findings suggest that oculomotor measures assessing cognitive control and neuropsychological measures differentiate treatment resistant patients with and without TD, and implicate greater frontal-striatal impairment among individuals with TD.

W57. THE IMPACT OF SECOND-GENERATION ANTIPSYCHOTIC MEDICATION SIDE-EFFECTS ON FUNCTIONING FROM A SCHIZOPHRENIA PATIENT PERSPECTIVE: A CROSS-SECTIONAL, OBSERVATIONAL, PATIENT CENTERED, WEB SURVEY STUDY

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Abstract: Background: Second-generation anti-psychotics (SGAs) used to treat patients with schizophrenia generally have lower risk of motor side effects than first generation anti-psychotics but are associated with other well-known side-effects (SE). The goal of the study was to understand how specific side effects of SGAs impact daily functioning, emotional well-being, and overall quality of life (QoL) of patients from the patient's perspective.
Methods: This study was a cross-sectional, patient-reported web survey, conducted in the United States (n=180) in the fall of 2017. The survey included patient socio-demographics, the Quality of Life Enjoyment and Satisfaction Questionnaire Short Form (Q-LES-Q-SF), the Glasgow Antipsychotic Side-Effect Scale (GASS), and questions about the impact of SEs on functioning and emotions. Patients noted on a visual analog scale (VAS) the degree of impact each reported SE had, 0 indicating 'no impact at all', and 100 indicating the 'largest degree of impact'. Patients with schizophrenia (≥18 years), stable for at least one month, taking an SGA for 1-12 months, and self-reporting at least one SE were included.
Results: The 180 participants had a mean age of 35 (range 18-61) years, with 58.3% being female. 69.4% were White, and 16.7% were Black or African American. The majority (63.9%) of the participants were diagnosed within the last 5 years: 58.3% reported living with a spouse, partner, or child, while 17.8% lived with a parent/s, and 11.1% lived alone. The lowest Q-LES-Q-SF (1=Very Poor to 5=Very Good) scores were satisfaction with one's 'economic status' (M=2.61, SD=1.12), followed by 'sexual drive' (2.72, 1.22), 'work' (2.75, 1.15), 'mood' (2.88, 1.02), and 'social relationships' (2.94, 1.23). The most prevalent SEs were 'difficulty sleeping' (81.1%), 'feeling sleepy during the day' (77.2%), 'dry mouth' (70.6%), and 'restlessness' (60.6%). Almost half (48.0%) of the participants stated they have experienced gaining weight. Feeling "drugged or like a zombie", "sleepy during the day", having "difficulties sleeping", feeling "restless", and gaining weight were self-reported as having an impact on their functioning (Yes, No) by 80.6%, 63.7%, 63.3%, 62.4%, and 63.1% of participants respectively. These SEs had at least a moderate to severe impact (defined by a VAS score ≥ 50) on all aspect of functioning (physical, psychological, social, and vocational). For" difficulty sleeping", the highest impact on functioning was on one's" energy level" (VAS=72.3). Having "shaky hands" or "feeling restless" had the most severe effect on one's" ability to get or do a job" (mean VAS score of 76.1 and 69.8 respectively) as had "feeling sleepy" (mean VAS score=68.8)." Feeling drugged/like a zombie" had the greatest effect on one's" ability to concentrate" (mean VAS score 70.2) while gaining weight had the most impact on "one's fear of being rejected" (mean VAS score 79.7). "Problems enjoying sex" affected "intimate relationships" (mean VAS score=74.8).
Discussion: Findings suggest that patients taking SGAs have many SEs including activating SEs (restlessness, difficulty sleeping) and sedating SEs (feeling drugged, sleepiness) and weight gain. These SEs have considerable negative impact on patient's daily functioning and quality of life satisfaction, including on work, sexual drive and psychosocial effects.

W58. AMOTIVATION IS ASSOCIATED WITH SMALLER VENTRAL STRIATUM VOLUMES IN OLDER PATIENTS WITH SCHIZOPHRENIA INDEPENDENTLY OF ANTIPSYCHOTIC OCCUPANCY OF DOPAMINE D2 RECEPTORS

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Abstract: Motivational deficits are prevalent in patients with schizophrenia, persist despite antipsychotic treatment, and predict long-term outcomes. Evidence suggests that patients with greater amotivation have smaller ventral striatum (VS) volumes. We wished to replicate this finding in a sample of older, chronically medicated patients with schizophrenia. Using structural imaging and positron emission tomography, we examined whether amotivation uniquely predicted VS volumes beyond the effects of striatal dopamine D2/3 receptor (D2/3 R) blockade by antipsychotics. Data from 41 older schizophrenia patients (mean age: 60.2 ± 6.7; 11 female) were reanalysed from previously published imaging data. We constructed multivariate linear stepwise regression models with VS volumes as the dependent variable and various sociodemographic and clinical variables as the initial predictors: age, gender, total brain volume, and antipsychotic striatal D2/3 R occupancy. Amotivation was included as a subsequent step to determine any unique relationships with VS volumes beyond the contribution of the covariates. In a reduced sample (n = 36), general cognition was also included as a covariate. Amotivation uniquely explained 8% and 6% of the variance in right and left VS volumes, respectively (right: β = -.38, t = -2.48, P = .01; left: β = -.31, t = -2.17, P = .03). Considering cognition, amotivation levels uniquely explained 9% of the variance in right VS volumes (β = -.43, t = -0.26, P = .03). We replicate and extend the finding of reduced VS volumes with greater amotivation. We demonstrate this relationship uniquely beyond the potential contributions of striatal D2/3 R blockade by antipsychotics. Elucidating the structural correlates of amotivation in schizophrenia may help develop treatments for this presently irremediable deficit.

W59. LONG-ACTING ATYPICAL ANTIPSYCHOTICS AND PSYCHOSOCIAL FUNCTION IN SCHIZOPHRENIA: A SYSTEMATIC REVIEW AND META-ANALYSES

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Abstract: Objective: Impairment in psychosocial function is common in schizophrenia. Long-acting injectable atypical antipsychotics (LAI-A) are thought to enhance psychosocial function by boosting adherence. However, no systematic review has examined the effects of LAI-A on psychosocial function in clinical trials.
Method: Major databases including PUBMED, EMBASE, and the Cochrane trial registry were searched for randomised controlled trials that compared LAI-A to placebo, oral antipsychotics or LAI-A for all years till 2017. Data on change in psychosocial functioning were meta-analysed using a random effects model. We performed a systematic review of the predictors of psychosocial function.

Results: Eighteen studies with 7270 adults and 65.5% males were included. LAI-A improved psychosocial function compared to placebo (standardized mean difference [SMD] =0.38, 95% Confidence Interval [CI] =0.29, 0.46; p<0.001), however the advantage over oral medications was not statistically significant (SMD= 0.12; 95% CI= -0.02, 0.27; p=0.09). Compared to placebo-controlled trials (I^2 =0%), heterogeneity was high in oral-controlled trials (I^2 = 73%). Poor psychosocial function was predicted by longer treatment duration, severe symptoms, poor cognition, and poor insight. Functioning was not the primary outcome in most studies. Other sources of bias include poor blinding, and reporting of randomization and outcome.
Discussion: LAI-As are beneficial to psychosocial function recovery, but their benefit over oral medications is not apparent in the context of supportive monitoring of adherence in clinical trials. Severe psychopathology can help predict those who may benefit from intensive psychosocial therapies. Future trials should address methodological biases and include psychosocial function as main outcome a priori.

W60. GALANTAMINE AND MEMANTINE COMBINATION TARGETS TRIPLE HYPOTHESES IN SCHIZOPHRENIA: WILL THIS END D2 ME TOO?

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Abstract: Background: Cognitive Impairments Associated with Schizophrenia (CIAS) is a major public health problem. There are no effective treatments available or on the horizon for CIAS. CIAS is the best predictor of functional outcome. Cholinergic and glutamatergic systems, alpha-7 nicotinic acetylcholine receptor (alpha-7nAChR) and N-methyl-D-aspartate (NMDA) receptors have been strongly implicated in the pathophysiology of CIAS. Galantamine is an acetylcholinesterase inhibitor and positive allosteric modulator of the α4β2 and α7nAChR. Memantine is an N-methyl-D-aspartate receptor (NMDA-R) antagonist. Both these medications are approved for the treatment of Alzheimer's disease (AD). Seven studies in animals showed that the galantamine-memantine combination was effective for cognition; five studies showed superior effect compared to either medication alone—synergistic benefits were shown in three studies. The galantamine-memantine combination was significantly better for cognition than donepezil-memantine combination in patients with AD. There is mounting evidence that kynurenine pathway (KP) metabolites are associated with CIAS. Kynurenic acid (KYNA) concentration is elevated in schizophrenia. KYNA is an antagonist to the alpha-7nAChR and NMDA-R.
The objective of this study was to examine whether the galantamine-memantine combination was effective for CIAS.
Methods: In this 6-week open-label clinical trial, three participants with schizophrenia were enrolled; two completed the study. Participants received galantamine ER 24 mg and memantine XR 21 mg for four weeks (two weeks titration). Blood was collected and the isolated plasma was analyzed for KP metabolites. KP metabolites were measured using a positive ion mode liquid chromatography mass spectrometry method.
Results: In a 36-year old male with schizophrenia, scores improved in five of seven MATRICS Consensus Cognitive Battery (MCCB) domains except working memory and verbal learning. In a 45-year old male with schizoaffective disorder, there were improvements in speed of processing and working memory. Picolinic acid (PIC) concentration decreased in both

participants. KYNA concentration decreased in both participants, and kynurenine concentration decreased in one participant.
Discussion: This is the first study suggest potential correlation of MCCB and KP metabolites in schizophrenia. Furthermore, this is the first study in people with schizophrenia where the cholinergic and glutamatergic systems have been simultaneously targeted. The galantamine-memantine combination has synergistic effects of α-7nAChR and NMDA receptor. The decrease in PIC concentration with the treatment is a promising finding because high concentrations of PIC are toxic to the brain. PIC is an NMDA agonist; hence, the decrease in concentration could be explained by the NMDA antagonist action of memantine. KP metabolites may be putative biomarkers to detect the severity of cognitive impairments and monitor the progress with treatment. This combination may broaden the number of cognitive domains that may become significantly better compared to the placebo and potentially increase the composite score. This combination targets the nicotinic-cholinergic, glutamatergic/NMDA and kynurenic acid hypotheses concurrently. Although this pilot study is not powered, the data are promising. Randomized controlled trials are warranted to validate the findings.

W61. PAROXETINE, BUT NOT VORTIOXETINE, IMPAIRS SEXUAL FUNCTIONING COMPARED TO PLACEBO IN HEALTHY ADULTS

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Abstract: Background: Sexual dysfunction is a frequently reported symptom in patients with major depressive disorder (MDD). Antidepressant treatment may alleviate problems with sexual functioning, but for many patients, especially those taking selective serotonin reuptake inhibitors (SSRIs), antidepressant treatment is linked to treatment-emergent sexual dysfunction (TESD).[1] Vortioxetine is a multimodal antidepressant that has shown low rates of sexual dysfunction in several MDD trials.[2]
Methods: This phase 4, multicenter, randomized, double-blind study compared the effect of vortioxetine (VOR) (10 and 20 mg) with paroxetine (PAR) (20 mg), an SSRI known to cause sexual dysfunction, and with placebo (PBO) on sexual functioning after 5 weeks (Wks) of treatment in healthy volunteers. Subjects were assessed at each weekly visit using the self-reported Changes in Sexual Functioning Questionnaire Short-Form (CSFQ-14). The primary endpoint was change from baseline in CSFQ-14 total score difference (diff) for VOR versus (vs) PAR at Wk 5. To adjust for noncompliance, 2 prespecified modified full analyses set (mFAS) populations were defined based on pharmacokinetic (PK) data: subjects with drug concentrations below the limit of quantification at all PK collections (mFAS1) and at any PK collection (mFAS2). Safety and tolerability were also evaluated.
Results: A total of 361 subjects with normal sexual functioning (CSFQ-14 men >47; women >41) were randomized to PBO (n=92), PAR (n=85), VOR 10 mg (n=91), or VOR 20 mg (n=93). Demographics and baseline characteristics were similar among all treatment groups (age: 53.5% ≤28 years; sex: 51.2% male, 48.8% female; race: 57.3% white, 34.3% black; BMI mean 26.26; baseline CSFQ-14 >60: 44.9%). The PAR group had significantly more TESD than PBO (CSFQ-14 least-square (LS) mean diff: -2.77, P=0.007; Wk 5). VOR 10 mg was associated with statistically significantly less and VOR 20 mg with numerically less TESD than PAR at Wk 5 (CSFQ-14 LS mean diff: +2.74, P=0.009 and +1.05, P=0.303, respectively).

Neither VOR dose was associated with statistically significantly greater TESD than PBO. Sensitivity analyses confirmed the primary analyses. The removal of noncompliant subjects (mFAS1/2) resulted in worsened sexual function for the PAR group. In mFAS1/2, PAR was associated with more TESD vs VOR 20 mg at Wk 5 (mFAS1: CSFQ-14 LS mean diff +1.63, P=0.129; mFAS2: CSFQ-14 LS mean diff: +3.06, P=0.005). Change from baseline at Wk 5 in CSFQ-14 subscales favored VOR 10 mg vs PAR in the 3 phases of sexual function (FAS, domain scores: desire [P=0.010], arousal [P=0.020], orgasm/completion/ejaculation [P=0.022]) and 5 dimensions of sexual dysfunction (pleasure P=0.009], desire/frequency [P=0.011], desire/interest [P=0.026], arousal/erection [P=0.020], orgasm [P=0.022]). More subjects in the PAR group had clinically meaningful worsening of sexual function (predetermined definition: a decrease from baseline CSFQ-14 total score ≥3 at Wk 5) (44.6%) than either VOR (23.5%, 10 mg; 30.8%, 20 mg) or PBO (29.2%) group. Vortioxetine was generally safe and well tolerated. Spontaneously reported sexual dysfunction TEAEs were 35.7% for PAR, 25.3% and 19.8% for VOR 10 mg and 20 mg, respectively, and 17.6% for PBO.
Conclusion: VOR 10 mg was associated with statistically significantly less TESD and VOR 20 mg with numerically less TESD than PAR. PAR was associated with statistically significantly greater TESD than PBO, while neither dose of VOR showed greater TESD than PBO. Patients who experience sexual dysfunction with VOR 20 mg may have their dose reduced to alleviate adverse events. VOR was safe and well tolerated with a safety profile comparable to that observed in previous studies in healthy volunteers.

W62. ELEMENTS OF DESIRE QUESTIONNAIRE ASSESSMENT OF BREMELANOTIDE EFFICACY FOR HYPOACTIVE SEXUAL DESIRE DISORDER IN THE RECONNECT STUDY

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Abstract: Objective: Bremelanotide (BMT) is a melanocortin-4 receptor agonist, an analog of the endogenous neuropeptide α-melanocyte stimulating hormone, which is taken as-desired to improve sexual desire and decrease personal distress in premenopausal women diagnosed with hypoactive sexual desire disorder (HSDD). The objective of this study was to investigate the efficacy of BMT using the recently developed Elements of Desire Questionnaire (EDQ) in the context of the RECONNECT studies. The EDQ was developed to provide a more nuanced view of women's sexual desire than was available from the female sexual function index (FSFI) desire domain alone.
Materials and Methods: The RECONNECT studies were two phase 3 multicenter, randomized, double-blind trials that demonstrated clinically meaningful and statistically significant improvements in desire and a decrease in distress with BMT vs placebo in premenopausal women with HSDD. Participants self-administered 1.75 mg BMT or placebo subcutaneously via an auto-injector pen, as desired, prior to sexual activity for the 24-week randomized treatment period. Co-primary endpoints were the change in the desire domain of the FSFI and female sexual distress scale – desire arousal orgasm (FSDS-DAO) Item 13 score. The EDQ is

a 9-item validated instrument, developed consistent with FDA guidelines for patient-reported outcome measures, and was used to explore changes in aspects of desire over the course of the clinical trials. A daily and a monthly recall version were developed. Participants completed the EDQ daily version for 7 consecutive days prior to select monthly clinic visits (screening, baseline, month 3, and month 6). The monthly recall version was completed at each monthly clinic visit. The analysis population consisted of all subjects with FSFI data at baseline and ≥1 follow-up visit. To qualify for inclusion in the daily EDQ analysis, participants were required to complete the EDQ ≥4 days per week.
Results: The primary efficacy population for the two studies comprised 1202 participants; 1144 and 676 subjects completed the monthly and daily recall EDQs at baseline, respectively. Mean (SD) monthly and daily recall total EDQ scores at baseline were 1.94 (0.610) and 1.61 (0.489), respectively, for BMT, and 1.93 (0.586) and 1.61 (0.497), respectively, for placebo. After 6 months, there was a statistically significant greater improvement for BMT vs placebo in both the monthly and daily EDQ recall, with treatment differences of 0.33 (95% CI 0.22, 0.44; P<0.0001) and 0.33 (95% CI 0.19, 0.47; P<0.0001), respectively. Monthly recall EDQ scores correlated closely with FSFI total scores at baseline and month 3 (r=0.63, P<0.0001 and r=0.75, P<0.0001, respectively); similar correlations were seen for daily recall EDQ.
Conclusions: BMT was associated with significant improvements as measured by daily or monthly EDQ scores compared with placebo over the course of the 24-week study, indicating that BMT improved sexual desire in women with HSDD, consistent with other validated questionnaires used in the phase 3 trials. The monthly and daily EDQs yielded similar results.

W63. THE EFFECT OF PRENATAL EXPOSURE TO ATYPICAL ANTIPSYCHOTICS ON CHILD DEVELOPMENT AND BEHAVIOR

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Abstract: Background: Women of reproductive age are frequently affected by mental health disorders, and many may require continued treatment with psychiatric medications during pregnancy including atypical antipsychotics. However, data regarding long-term behavioral outcomes in children with histories of fetal exposure to this class of psychotropics are sparse. Data regarding effects of in utero exposure to psychiatric medications on the risk for later child psychopathology are even sparser.
Methods: The National Pregnancy Registry for Atypical Antipsychotics at Massachusetts General Hospital was first established to determine the risk of major malformations among infants exposed to second generation antipsychotics (SGAs) relative to a comparison group of unexposed infants of mothers with psychiatric morbidity. We are conducting a cross-sectional assessment of children exposed in utero to SGAs compared to children who have not been exposed to this class of agents. The current study includes: 1) mothers who were followed by the Registry with a child who is now 9 months to 9 years old, and 2) for whom obstetric, labor, delivery, and pediatrics records of the child were obtained. Children's development and behavior are assessed by parent-completed questionnaires, including the Ages and Stages

Questionnaires (ASQ3) for children 9 months to 5.5 years, the Parents' Evaluation of Developmental Status (PEDS) questionnaire for children 5.5 years to 8 years, the Ages and Stages Questionnaires: Social Emotional for children under 1.5 years, and the Child Behavior Checklist (CBCL) for children over 1.5 years. The child's medical history is also obtained.
Results: Currently over 400 children are eligible for this follow-up study, with exposures and comparisons eligible in a roughly 2:1 ratio, with over 95% older than 1 year. Data have been collected on over 30% of the sample and we anticipate a response rate greater than 60% by the end of March 2018. The analytic plan includes the evaluation of differences between children exposed and unexposed to SGAs, including the proportion of children whose ASQ or PEDS results indicate elevated risk of delay, and the proportion with internalizing, externalizing, or total problems scores above the clinical cutoff on the CBCL. Additional analyses will include subscale evaluations of the ASQ and the CBCL. Multivariable regression will be performed to evaluate predictors of outcomes, including child age, prematurity, maternal mental illness, duration of drug exposure in utero, polypharmacy, and breastfeeding.
Conclusions: The current study is, to our knowledge, one of the first to examine the long-term outcomes of children over one year of age exposed prenatally to atypical antipsychotics where the cohort of mothers has been followed prospectively across pregnancy. These data will provide women and their clinicians a more complete understanding of the risks and benefits of these medications when used during pregnancy.

W64. THE NATIONAL PREGNANCY REGISTRY FOR PSYCHIATRIC MEDICATIONS: EFFECTS OF FETAL EXPOSURE TO ATYPICAL ANTIPSYCHOTICS ON RISK FOR MAJOR MALFORMATIONS

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Abstract: Background: Despite widespread use of atypical antipsychotics in women of childbearing potential, reproductive safety data across these medicines are sparse. The National Pregnancy Registry for Atypical Antipsychotics (NPRAA) at Massachusetts General Hospital was established in 2008 to address this knowledge gap.
Website: www.womensmentalhealth.org/pregnancyregistry Toll-free number: 1-866-961-2388
Methods: Data are prospectively collected from pregnant women, ages 18-45 years, using 3 phone interviews conducted at the time of enrollment, 7 months gestation, and 3 months postpartum. The exposed group is comprised of women who have taken one or more atypical antipsychotics during pregnancy; the comparison group is comprised of women who have not taken this class of medication during pregnancy. Information regarding the presence of major malformations is abstracted from the medical records along with other data regarding maternal and neonatal health outcomes. Identified cases of major malformations are sent to a dysmorphologist blinded to drug exposure for adjudication. A scientific advisory board, consisting of experts in the fields of teratology, pharmacoepidemiology, and psychiatry, governs the release of findings.

Results: As of January 11, 2018, total enrollment in the Registry was 1171 women: 635 women in the exposed group and 536 women in the comparison group. A total of 611 women have completed the study and were eligible for inclusion in the current analysis. The proportion of study subjects for whom medical records were obtained was 83.5%. Updated relative and absolute risks of major malformations in the exposed vs comparison group are forthcoming in May 2018. At the time of previous analysis in 2017, the absolute risk of major malformations was 1.3% among infants exposed to an atypical antipsychotic during the first trimester and 0.6% among unexposed infants (n=539 exposed, n=217 unexposed; n=489 eligible for inclusion in analysis). The risk ratio for major malformations was 2.27 (95% CI: 0.26-20.15) comparing exposed to unexposed infants, not reaching statistical significance. At the direction of our scientific advisory board and now that the sample size has grown, the absolute and relative risk of major malformations observed in the cohort are ready for an updated analysis.
Discussion: The NPRAA offers a systematic way to collect prospective reproductive safety information which informs the care of women who may use atypical antipsychotics to sustain psychiatric well-being. This preliminary analysis indicates that these agents are not major teratogens but further information is needed to better estimate risk. The scientific advisory board for the NPRAA advised that new aggregate data be released with more specific risk assessments. Forthcoming data will provide an update on current findings from the NPRAA. The importance of pregnancy registries is underscored by recent FDA guidance (http://www.fda.gov/Drugs/DevelopmentApprovalProcess/ Development Resources/ Labeling/ucm093307.htm), and the inclusion of the National Pregnancy Registry for Psychiatric Medications inclusion in the FDA label for atypical antipsychotics among other medications.

W65. RELIABILITY AND VALIDITY OF A SELF-REPORT SCALE FOR DAILY ASSESSMENTS OF THE SEVERITY OF DEPRESSIVE SYMPTOMS

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Abstract: Introduction: To evaluate the efficacy of rapidly effective treatments for depression it is necessary to use measures that are designed to assess symptom severity over short intervals. Both the content and the rating instructions of existing scales need to be modified when the time frame of assessment is daily. In the present report from the Rhode Island Methods to Improve Diagnostic Assessment and Services (MIDAS) project we modified our previously published depression scale and examined the reliability and validity of the daily version of the Clinically Useful Depression Outcome Scale (CUDOS-D).
Methods: One thousand one hundred and fifteen patients presenting for treatment of DSM-IV/DSM-5 major depressive disorder (MDD) to a partial hospital program (PHP) completed the CUDOS-D as part of their initial paperwork and on a daily basis thereafter. To examine discriminant and convergent validity the patients completed the Remission from Depression Questionnaire. Test-retest reliability was examined in a subset who completed the CUDOS-D twice. A subset of 69 patients were interviewed by a trained diagnostic rater who administered the 17-item Hamilton Depression Rating Scale (HAMD) at baseline and on the day of discharge from the PHP.

Results: The CUDOS-D had high internal consistency and test-retest reliability, was more highly correlated with another measure of depressive symptoms than nondepressive symptoms. CUDOS-D scores progressively declined during the course of treatment and the scores on each successive day were significantly lower than the preceding day. The change in CUDOS-D scores was significantly correlated with a change in HAMD scores (r=.65, p<.001). A large effect size was found for both measures (CUDOS-D: d=1.63; HAMD: d=1.56).
Conclusions: In a large sample of partial hospital patients, the CUDOS-D was a reliable and valid measure of the DSM-5 symptoms of MDD assessed on a daily basis.

W66. DASOTRALINE FOR THE TREATMENT OF ATTENTION DEFICIT HYPERACTIVITY DISORDER IN ADULTS: POOLED ANALYSIS OF TWO DOUBLE-BLIND STUDIES

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Abstract: Objective: Dasotraline is a potent inhibitor of pre-synaptic dopamine and norepinephrine transporters with a profile characterized by slow absorption, a long elimination half-life, and low abuse potential. The aim of this pooled post-hoc analysis was to evaluate the efficacy and safety of dasotraline in once-daily doses ranging from 4-8 mg in adults with ADHD.
Methods: Data were pooled from two randomized, double-blind, placebo-controlled studies of fixed-doses of dasotraline for the treatment of adults with ADHD. Study 1 was a 4-week study utilizing dasotraline in fixed doses of 4 mg/d and 8 mg/d vs. placebo. Significant efficacy was demonstrated on the primary a priori endpoint on the 8 mg/d dose, and trend significance on the 4 mg/d dose. Study 2 was an 8-week study utilizing dasotraline in fixed doses of 4 mg/d and 6 mg/d vs. placebo. The 4 mg/d dose was not significant on the primary endpoint; the 6 mg/d dose showed trend significance. The current pooled analysis included efficacy data from the first 4 weeks of Study 2 (the last common assessment time-point in both studies), and safety data from the full 8 weeks. Efficacy assessments included the ADHD Rating Scale (ADHD RS-IV), and the Clinical Global Impression, Severity scale (CGI-S; modified for ADHD symptoms), and were analyzed using a mixed model for repeated measures (MMRM) analysis.
Results: The pooled safety sample consisted of 973 patients (mean age 34 years, 53% male; mean ADHD RS-IV score, 38.5). For the pooled sample, treatment with dasotraline was associated with statistically significant Week 4 improvement in the ADHD RS-IV total score for the 4 mg/d dose (-13.5; p=0.007), 6 mg/d dose (-13.2; p=0.044), and 8 mg/d dose (-15.1; p=0.007) compared to placebo (-11.1). Treatment with dasotraline was associated with statistically significant Week 4 improvement in the CGI-Severity score for the 4 mg/d dose (-1.1; p=0.015), 6 mg/d dose (-1.1; p=0.031), and 8 mg/d dose (-1.3; p=0.003) compared to placebo (-0.9). Discontinuation rates for the pooled sample were as follows (based on the full duration of each study): dasotraline 4 mg/d (30.1%), 6 mg/d (38.6%), 8 mg/d (48.6%), and placebo (19.5%). The 3 most frequent adverse events associated with dasotraline were insomnia, decreased appetite, and dry mouth. The majority of adverse events were mild-to-

moderate in severity. There were no clinically meaningful changes blood pressure or heart rate on dasotraline.
Conclusions: This pooled post-hoc analysis found once-daily dosing with dasotraline (4-8 mg to be a safe and efficacious treatment for ADHD in adults.
Clinicaltrials.gov identifiers: NCT01692782 and NCT02276209
Sponsored by Sunovion Pharmaceuticals, Inc.

W67. USING COMPUTER VISION AND MACHINE LEARNING TO IDENTIFY PATTERNS OF FRAUDULENT PARTICIPANT ACTIVITY IN CNS TRIALS

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Abstract: Objective: Artificial Intelligence (AI) and Machine Learning (ML) are increasingly being applied to medicine to improve clinical decision-making, implement efficiencies, and drive behavioral modifications. In clinical research, participant dosing is indirectly monitored through inaccurate and unreliable measures such as pill counts and self-reports, leaving nonadherence to go undetected. Intentional nonadherence – 'professional subjects' who enroll in trials and feign adherence but who have no intention of taking the study drug – has been receiving increased attention. While discrepancies have been demonstrated between pharmacokinetic data and pill counts, and non-usage of technologies could be indicative of intentional nonadherence, real-time evidence of fraudulent behavior has not yet been captured. An AI platform, which uses computer vision and ML to visually monitor drug intake, was used in CNS trials to monitor drug administration and ensure protocol adherence. Fraudulent data were captured.
Design: Subjects enrolled in 7 ongoing CNS studies use the AiCure platform to ensure protocol adherence. Trials vary in indication, design, treatment duration, dosing regimen, and phase. Subjects are given smartphones with the AI application downloaded and asked to use the AI application for each administration. In addition to logging adherence-related parameters into five mutually exclusive categories (visual confirmation of ingestion; self-reported dose; dose reported to the site; in-clinic dosing; and missed dose), the platform uses computer vision and ML to detect misuse of the platform. Misuse, or fraudulent behavior, includes the following activities: removing the study drug from the mouth; 'cheeking' the study drug; presenting something other than the study drug; and spitting out the study drug. The participant is not notified of the deliberate misuse. Instead, algorithms and review on the back end detect the actions and build a behavioral pattern of the participant.
Results: The AI platform identified 102 participants across 7 studies who misused the platform. The proportion of fraudulent participants per trial ranges from 8.3% (ADHD) to 38.3% (addiction). The mean age is 37.3 years and 66.1% of the subjects are male. The fraudulent behaviors identified are: obstructing view of the mouth (64.9%); spitting out the study drug (11.7%); cheeking (9.1%); consistently leaning out of the field of view (3.9%); presenting something other than the study drug (3.9%); miming administration actions (3.9%); and incorrect participant (2.6%).
Conclusion: 'Professional subjects', who feign drug administration by self-reporting optimal adherence or correctly emptying out their blister packs prior to clinic visits may represent up to 38% of enrolled participants. Failing to identify these participants may impact the sample size requirement and decrease the observed effect size. An AI Platform used to visually monitor

and assess participant behavior identified fraudulent participants based on 8 types of visual activity. To our knowledge, this is the first time that a technology platform has been used to provide real-time evidence of intentional nonadherence on a dose by dose basis, in ambulatory participants enrolled in clinical trials.

W68. A RANDOMIZED WITHDRAWAL, DOUBLE-BLIND, MULTICENTER STUDY OF ESKETAMINE NASAL SPRAY PLUS AN ORAL ANTIDEPRESSANT FOR RELAPSE PREVENTION IN TREATMENT-RESISTANT DEPRESSION

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Abstract: Abstract will be provided on Tuesday, May 29, 2018 at 4:00 PM EDT.

W69. INACCURATE PRESCRIBING WARNINGS IN ELECTRONIC MEDICAL RECORD SYSTEMS: RESULTS FROM AN AMERICAN SOCIETY FOR CLINICAL PSYCHOPHARMACOLOGY MEMBERSHIP SURVEY

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Abstract: Background: Electronic prescribing is becoming widespread. All states allow it, and some require it; many institutions also require electronic prescribing. Many electronic prescribing systems give prescribers warnings when the system detects a potential prescribing error -- for example, regarding dosing, drug interactions, or contraindications. Although such warnings have potential benefits, they may also have limitations. To examine this issue, we surveyed members of the American Society for Clinical Psychopharmacology (ASCP); the topic of prescribing alerts has received very little research attention.
Methods: The authors developed a 30-item survey, hosted by Survey Monkey, a free on-line survey tool, that asked about prescribers' experience with prescribing warnings in electronic medical record prescribing systems. The survey also elicited comments from respondents. An email was sent to 1,223 current active ASCP members requesting them to complete the survey. Summary statistics were calculated.
Results: One hundred and eighteen members completed the survey (9.6% response rate). Respondents were from 33 states; 72.4% were male. Among the respondents, 78.0% used an electronic prescribing system; 43.2% reported that use of an electronic prescribing system was mandatory in their state or institution. A total of 31 different electronic prescribing systems

were used. Regarding prescribing warnings, 83.1% of respondents reported that their electronic prescribing system can provide a warning if a prescription is potentially problematic. Among these individuals, 33.3% believed that their electronic prescribing system has provided incorrect warning information; 33.4% believed that warnings were inaccurate 50% of the time or more. Types of reported errors were: dosing range (54.2% of respondents), drug interactions (50%), contraindications (41.7%), dosing frequency (37.5%), dosing time (12.5%), indications (12.5%), and other (8.5%). Examples of warning errors included: the maximum daily dose of fluoxetine is 40 mg/day, fluoxetine should not be combined with clonazepam, three doses a day of Effexor XR 37.5 mg exceeds the recommended maximum of one a day, prescribing bupropion and fluoxetine concurrently is contraindicated, aripiprazole is contraindicated for patients ages 6 through 18, and SSRIs are contraindicated for patients under age 18. Nearly all respondents (95.8%) reported that their prescribing system allows them to provide a rationale for their prescription or override the system, thereby enabling them to prescribe despite the warning; however, 76.2% reported being unable to alert the system that the prescribing warning was incorrect or inaccurate. Regarding the burden of responding to prescribing data alerts that were believed to be inaccurate (e.g., in terms of time required, frustration, or extra steps needed to complete prescriptions), only 4.2% reported that the warnings were not at all burdensome; 45.8% reported slight burden, 45.8% reported moderate burden, and 4.2% reported severe burden.

Discussion: These survey results suggest that some electronic prescribing system warnings are inaccurate. Study limitations include the relatively low response rate, and the small number of responses for some questions. Given the increasing use of e-prescribing and potential clinical implications of inaccurate prescribing warnings, additional studies of this important topic are needed.

W70. INDEPENDENT AND SITE-BASED RATINGS OF SYMPTOM SEVERITY IN PHARMACOGENETICS CLINICAL TRIALS

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Abstract: Background: Personalized medicine and pharmacogenomics hold strong promise for psychiatry. Studies in this area require novel approaches to ensure endpoint reliability and validity, reduce the impact of treatment unblinding, and minimize other confounds that reduce signal detection. The current program utilized a combination of novel assessment methods, including remote, independent ratings to evaluate adherence to inclusion criteria and efficacy in a trial of major depressive disorder (MDD).

Methods: The 16-item Quick Inventory of Depression Symptomology (QIDS-C16) and Hamilton Depression Rating Scale-17 (HAMD-17), were used in a 60-site randomized trial of pharmacogenomics in depression (n=1,514). The QIDS-C16 was used at screening and both scales were given at baseline and follow up visits. Baseline QIDS-C16 scores ≥11 were used as inclusion cutoffs. Site-based raters administered the QIDS-C16, while the HAMD-17 was remotely administered by telephone by a cohort of independent, calibrated clinicians. To evaluate QIDS-C16 score accuracy at screening, the percentage of scores near the inclusion threshold (defined as scores 11-13) was calculated per site. Next, site-administered QIDS-C16 scores were translated into HAMD-17 scores using published guidelines for the purposes of

comparison. HAMD-translated QIDS-C16 scores were then subtracted from the independently-rated scores.
Results: The overall means (SD) of total scores at baseline were 16.01 (2.9) for QIDS-C16 and 20.57 (4.9) for HAMD-17. The correlations between original and HAMD-17 translated scores were low at baseline ($r = .45$, $p < .0001$) compared to subsequent visit at week 4 ($r = .70$, $p < .0001$), indicating less agreement at baseline. At the site level, percentages of assessments at or near the inclusion threshold ranged from 0-61%, with more than half of the sites having at least 20% of their assessments in the 11-13 range for the QIDS-C16. The mean difference scores also identified sites with positive scores, suggesting inflation of scores at baseline; however, there was little overlap between percentages at the inclusion threshold and positive mean difference score.
Conclusions: In this study, sites with high percentages of subjects at or near the inclusion threshold did not show significant evidence of inclusion bias. Differences between site-based and independent, remote raters suggests that some patients may have been differentially rated by the two methodologies, but not in a systematic way when evaluated at the site level. Efforts to identify and remedy data quality issues and bias remain critical, both to help minimize noise and increase signal detection and to help ensure objectivity of results for the next generation of personalized medicine studies.

W71. MAZINDOL CONTROLLED RELEASE (CR) FOR THE TREATMENT OF ADULTS WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD): A PHASE II STUDY

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Abstract: Mazindol was approved by the United States (US) Food and Drug Administration in 1973 for the short-term treatment of obesity in adults; however, it was voluntarily withdrawn by the early 2000s because of low sales. When marketed in the US Mazindol (5-(p-chlorophenyl)-2,5-dihydro-3H-imidazo-[2,1a] isoindol-5-ol) immediate release (IR) was classified as Schedule IV. It has been available in the European Union for compassionate use in the treatment of narcolepsy and idiopathic hypersomnias. A novel controlled-release (CR) formulation of mazindol was developed to allow once daily dosing. Objective: To evaluate efficacy, safety, tolerability and Pharmacokinetics (PK) of mazindol CR in adults with Attention Deficit Hyperactivity Disorder (ADHD). Design: A randomized, double-blind, placebo-controlled trial was conducted for 6 weeks. Methods: 85 Subjects with an ADHD Rating Scale score >28 [based on the exact wording of symptoms from the Diagnostic and Statistical Manual of Mental Disorders 5th Edition (ADHD-RS-DSM5)] were randomized to receive placebo (n=42) or mazindol (n=43) for 6 weeks. Those assigned to mazindol CR began with 1 mg and, based on clinical decision, could increase to 2 mg at their next weekly visit then 3mg (top dose). The primary endpoint was the reduction from baseline in the ADHD-RS-DSM5 score on Day 42. Secondary endpoints were response rates defined by change in ADHD-RS-DSM5 (>30% or >50% reduction) and dichotomized Clinical Global Impression–Improvement (CGI-I) score (1 or 2). An exploratory endpoint of functional

impairment as measured by the target impairment scale examined individualized deficits in specific settings. Safety, tolerability and pharmacokinetics were assessed. Results: 75 adults completed the 6 week trial. Weekly ADHD-RS-DSM5 measurements after mazindol differed from placebo beginning at Day 7, with a least squares mean difference (Active-Placebo) of 13.2 at Day 42 and an effect size of 1.09. There were substantially more ADHD-RS-DSM5 (55-70%) and CGI-I responders (63%) for mazindol CR than placebo (16-21%). For the 30% or more reduction in ADHD-RS-DSM5 (minimal response), the same pattern of differences (active-placebo) was seen Day 7 to Day 42. For the CGI-I (1 or 2) and for the 50% or more reduction in ADHD-RS-DSM5 (measures of excellent response) the differences began at Day 14 and continued to Day 42. Functional impairment was significantly different in the proportion achieving at least a 50% reduction in target impairment score (42.9% mazindol CR vs. 11.9% placebo) by Day 42. Dry mouth, headache, nausea, fatigue, heart rate (HR) increased, decreased appetite, somnolence, middle insomnia, and constipation were more prevalent for mazindol CR versus placebo. Overall, mazindol CR had minimal effects on blood pressure and small effects on HR. Conclusion: Mazindol CR was well-tolerated and effective in the treatment of adults with ADHD, and the results support the progression to Phase 3. (Clinicaltrials.gov Registration No. NCT02808104)

Thursday, May 31, 2018

Poster Session II

T1. LOFEXIDINE FOR TREATMENT OF OPIOID WITHDRAWAL SYMPTOMS: A DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER TRIAL IN OPIOID-DEPENDENT SUBJECTS

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Abstract: Introduction: The first and potentially most critical step in treating opioid use disorder is managing the severe opioid withdrawal symptoms (OWS) that inevitably emerge during discontinuation of the misused opioid. Patients commonly report OWS as the primary reason for continuing opioid use. Failure to effectively mitigate OWS may cause patients to abandon their attempt at recovery. Lofexidine is an alpha2-adrenergic receptor agonist that opposes the adrenergic hyperactivity resulting from opioid withdrawal. It is under development for treatment of OWS and facilitation of completion of opioid discontinuation. If FDA-approved, lofexidine would be the first non-opioid medication indicated for OWS treatment.
Methods: Men and women ≥18 years of age seeking treatment for dependence on short-acting opioids and meeting dependence criteria based on Mini International Neuropsychiatric Interview were randomized to placebo, lofexidine 0.6 mg qid (2.4 mg/day) or lofexidine 0.8 mg qid (3.2 mg/day) treatment for 7 days after abrupt opioid discontinuation. Short Opiate Withdrawal Scale of Gossop (SOWS-G), a validated, subject-rated, 10-item inventory of common OWS was the primary outcome measure and study completion rate was the secondary outcome. Clinical Opiate Withdrawal Scale (COWS), a validated, clinician-rated, 11-item inventory of opioid withdrawal signs and symptoms, was a tertiary outcome. For SOWS-G and

COWS, higher scores indicate worse OWS. Vital signs, ECGs, and adverse events (AEs) were monitored for safety.
Results: A total of 602 subjects (71% male; mean age 35 ±11 years) were randomized and received study drug. Most were dependent on heroin (83%). The differences from placebo in overall SOWS-G LS means were significant in both lofexidine groups (–0.21 for lofexidine 2.4 mg, P = .02; and –0.26 for lofexidine 3.2 mg, P = .003), indicating OWS improvement. A significantly greater proportion of lofexidine-treated subjects completed the 7-day trial: 41.5% in the 2.4-mg group (odds ratio [OR], 1.85; P = .007) and 39.6% in the 3.2-mg group (OR, 1.71; P = .02) vs 27.8% for placebo. Mean COWS scores were significantly lower in the lofexidine groups vs placebo on days 1-5 ($P \leq 0.01$). Most AEs were mild or moderate in severity. Hypotension, orthostatic hypotension, and bradycardia were the most frequent lofexidine-associated AEs but resulted in few study discontinuations (2% per AE).
Conclusions: Lofexidine significantly improved OWS and significantly increased completion of a 7-day opioid discontinuation treatment compared with placebo. AEs related to lofexidine's sympatholytic activity were most frequent but rarely severe enough to interfere with completion of the trial. Successful recovery from opioid dependence requires successful treatment of OWS, especially during the first several days of opioid withdrawal when symptom severity peaks. Lofexidine's anti-adrenergic mechanism of action provides a non-opioid treatment option that could be widely accessible to opioid-dependent patients through a variety of healthcare providers in both metropolitan and rural settings.

T2. DURATION OF OPIOID USE DISORDER IS ASSOCIATED WITH PROLONGED SLEEP LATENCY IN SUBJECTS WITH OPIOID USE DISORDER ON BUPRENORPHINE

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Abstract: Introduction: Sleep disturbance is common in up to 70% of subjects with opioid use disorders (1). Persistent insomnia is a risk factor for relapse in substance use disorders (2), including opioid use disorder. Buprenorphine is commonly used in the treatment of opioid use disorders and can lead to sleep disturbance. Sleep disturbance in opioid use disorder can be related to various factors including duration of opioid use, life time duration of abstinence and treatment with buprenorphine. In this study, we explore the associated between prolonged sleep latency and duration of opioid use, duration of buprenorphine treatment, history of insomnia prior to and with initiation of opioids, in in a sample of opioid disorder patients enrolled in a buprenorphine (OUD) maintenance program.
Methods: OUDs (n=226) were recruited from a buprenorphine maintenance program in central Pennsylvania. Subjects completed a sociodemographic survey and the Pittsburgh Sleep Quality Index (PSQI) to measure sleep quality. Sociodemographic questionnaire included information about their age, sex, marital status, life time duration of abstinence, duration of opioid use prior to treatment with buprenorphine, duration of treatment with buprenorphine, number of rehabilitation admissions, reported severity of depression and anxiety, sleep latency, total sleep time, total PSQI score, onset of sleep disturbance before or with starting opioid use. Multiple linear regression analysis with sleep latency as the dependent variable and the above

sociodemographic and clinical factors as independent factors was used to predict factors associated with prolonged sleep latency.
Results: The mean age was 35 (±9.5) years, life time duration of abstinence was 27 (±39) months with 2.3 (±3) rehabilitation admissions. The mean duration on buprenorphine treatment was 16 (±24) months. The subjects were predominantly Caucasian (83%) and 48% of them were females. The mean sleep latency was 43 (±44) minutes, total PSQI score was 9.7 (±4.7). On regression analysis- duration of opioid dependence (β=0.1, $p<0.01$), less number of rehabilitation admissions (β=-2.2, $p=0.047$), onset of sleep disturbance before (β=19.8, $p=0.006$), or with starting opioid use (β=13.8, $p=0.049$) were associated with poor sleep latency.
Conclusions: Duration of opioid use prior to buprenorphine treatment (and not duration of treatment with buprenorphine or life time duration of abstinence) is associated with prolonged sleep latency. Further, prolonged sleep latency is persistent with buprenorphine treatment irrespective of the onset of sleep disturbance before or after the onset of opioid use. Hence sleep disturbance can be considered as an independent comorbidity and aggressively treated in subjects with opioid use disorders and thereby prevent relapse.

T3. PSYCHIATRIC AND NON-PSYCHIATRIC IMPLICATIONS OF SUBSTANCE USE DISORDERS IN OLDER ADULTS

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Abstract: Background: Epidemiological studies have projected significant changes in rates of substance use disorders (SUDs) among older adults in the U.S., with estimates of up to 5.7 million older individuals affected by 2020.(1) Substance use disorders are associated with increased morbidity and mortality across all age groups,(2,3) and older individuals seem to be more vulnerable to the negative outcomes associated with SUDs.(4) While recreational and illicit substance use are relatively uncommon among older persons compared to younger counterparts, alcohol and tobacco remain the most commonly used substances in this age group, and misuse of prescribed drugs, such as opioids, is a growing public health concern in geriatric populations.
Objectives: To examine the frequency of SUDs in older adults (age > 50 years) by type and the presence of SUDs as a predictor of clinical outcomes, measured by length of hospital stay, number of psychiatric (non-SUD) and non-psychiatric medical comorbidities.
Methods: Electrical Medical Records of 7,258 individuals age 50 and older admitted to a community psychiatric hospital from 2010 to 2016 were reviewed. Data analyses examined prevalence rates for SUDs by individual substances. Regression models examined the effect of SUD status on parameters of morbidity, including length of stay (LOS), total psychiatric (non-SUD) disorders, and total comorbid medical (non-psychiatric) diagnoses.
Results: SUD rates of 26% were found in this sample. Cocaine was the most common SUD (~10%), followed by opioids (~3.77%). SUD status and total SUDs were predicted by longer LOS and more non-psychiatric comorbid conditions. Cocaine SUD was the strongest predictor of LOS, while opiate SUD was the strongest predictor of comorbid medical (non-psychiatric) diagnoses.

Discussion: The rates of SUD found in our sample exceed community estimates of SUD in older adults, raising concerns of SUD being underestimated and likely undertreated late in life. Particularly worrisome, misuse and abuse of prescription medications are often difficult to recognize and associated with psychiatric and non-psychiatric comorbidities, as observed in our study. Multiple medical problems, atypical clinical presentations, and clinicians' misconceptions that older individuals are less likely to develop maladaptive patterns of substance use seem to be some of the challenges in clinical practice. Moreover, to date, most pharmacological agents for the treatment of SUDs have not been well-studied in older adults and/or treatment options are still limited, sub-optimal in clinical response and efficacy, and frequently associated with several drug-to-drug interactions and more severe side effects in geriatric populations. Hopefully, increasing awareness of the SUD problem in older individuals will lead to early detection and prompt interventions specifically tailored to this population, translating into more favorable clinical outcomes, prognosis and quality of life in older individuals.

T4. PREMATURE DISCHARGE FROM MEDICATION-ASSISTED TREATMENT (MAT) FOR OPIOID DEPENDENCE: A MULTI-SITE NATURALISTIC COMPARISON OF BUPRENORPHINE VS METHADONE

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Abstract: Background & Aim: The United States is currently in the midst of what many researchers and health care professionals have referred to as an "opioid epidemic," with increases in opioid use, opioid use disorder, and opioid-related overdose mortality reported annually (Rudd et al., 2016; SAMHSA, 2015; Volkow et al., 2014). Given the chronic and relapsing course of opioid dependence, treatment requires long-term management. Medication-assisted treatment (MAT) with methadone or buprenorphine has shown demonstrated effectiveness for opioid dependence; while premature MAT discharge is associated with a variety of adverse outcomes such as higher rates of relapse, mortality, subsequent treatment admissions, and criminality relative to patients who successfully complete treatment. Specific reasons for premature discharge generally fall into two main categories (i.e., patient- and program-initiated). Administrative discharge is a common program-initiated reason, while discharge Against Medical Advice (AMA) is considered a patient-initiated reason. Previous studies have typically failed to distinguish between different types of discharge reasons among patients who leave treatment early, and instead, often classify all patients who leave treatment early, irrespective of reason (administrative, AMA, etc.), as "treatment dropouts." This naturalistic study sought to determine whether prescribed medication (i.e., methadone vs. buprenorphine) was associated with differential discharge reasons among a large national sample of MAT patients who were prematurely discharged.
Method: Data were derived from patient records for 5,486 opioid-dependent patients (55. 8% male) prematurely discharged from 34 treatment facilities located throughout the U.S. between 2012 and 2013. All patients presented for MAT and were subsequently treated with methadone or buprenorphine. Patients were studied through retrospective electronic chart review until premature treatment discharge. Separate hierarchical binary logistic regression models were fitted to the data to test the hypothesis regarding whether premature discharge reason could be predicted by medication group after adjustment for significant baseline differences. Covariates

included baseline group differences related to age, payment method, and UDS+ for amphetamines, benzodiazepines, and cocaine.
Results: Buprenorphine patients were 2.18 times (95% CI: 1.89-2.53) more likely to leave treatment prematurely and to be discharged AMA relative to methadone patients after controlling for baseline differences. Methadone patients were 1.76 times (95% CI: 1.47-2.10) more likely to be administratively discharged compared to buprenorphine patients after adjustment for relevant covariates.
Conclusions: The opioid epidemic is one of America's foremost health crises. The observed findings suggest that ongoing review of program rules and policies may benefit patients prescribed methadone, who are nearly twice as likely to be discharged for an administrative, program-initiated reason. Conversely, strategies including contingency management, motivational incentives, and psychoeducation regarding the advantages of treatment retention may be indicated for buprenorphine patients who are over two times more likely to leave treatment early due to a patient-initiated reason (i.e., AMA). Further research is warranted to determine whether individually-tailored strategies may improve retention for certain patients based on prescribed medication.

T5. DETERMINING HUMAN BRAIN MODULAR ARCHITECTURE USING SUBJECT-LEVEL FUNCTIONAL NETWORKS

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Abstract: Background: Network disturbances have long implicated in the pathophysiology of psychiatric disorders. However, to date, the identification of brain modular structure has been largely derived from group-level averaged networks, where individual variability in topological architecture and low-strength connections may be lost. Such subtle changes may be of particular relevance to psychopathology-related disturbances, where for example in major depressive disorder, weak functional connections are differentially affected.
Methods: We used resting-state fMRI data from the Human Connectome Project (n = 990), and a recently developed cortical multimodal parcellation [360 regions of interest (ROI)] supplemented by a subcortical-cerebellar parcellation [36+34 ROI]. Networks were generated from the fMRI time-series using cross-correlation (weighted and signed). Starting with a multi-resolution Louvain community detection algorithm applied on a subject-by-subject basis, we used modularity and Rand index maximization to identify one representative partition per individual for each resolution scale. An association-reclustering approach was then used to achieve a stable, near-degenerate partition per resolution scale. Finally, a recently developed hierarchical algorithm was used in a meta- reclustering process across the pooled resolution scales to identify an optimal hierarchical modular architecture for the functional brain networks. The benchmark for statistical testing was based on a permutation null model (α = 0.05).
Results: The preliminary analyses revealed a hierarchical organization with 15 independent networks at the finest statistically-significant scale (range = 2-15 networks). Previously described (e.g., visual) and novel cortical-subcortical networks were identified. While certain networks were highly consistent across individuals (e.g., default mode), evidence for a relatively high level of variability was found in others.

Conclusions: The proposed network atlases can be adopted in future studies depending on the desired spatial scale. Evidence of variability across individuals in certain networks may have implications with regard to biomarker development. Pragmatic data-driven recommendations are made to future investigators based on dataset characteristics/use scenario.

T6. INFLAMMATORY CORRELATES OF SPECIFIC SYMPTOMS OF DEPRESSION

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Abstract: Extensive research suggests that depression is linked with elevated inflammation. Most studies relating these factors have focused on depression as a whole syndrome, and less attention has been given to symptom dimensions of depression in relation to inflammation.
Our goal in the present study was to examine the associations between the mood/cognitive and neurovegetative dimensions of depression and basal levels of pro- (IL-1β, IL-6, IL-8, TNF-α) and anti-inflammatory cytokines (IL-4, IL-10) among depressed patients and healthy controls. The relationships between individual depressive symptoms and inflammation were also examined.
Subjects were assessed by a diagnostic psychiatric interview (Mini-International Neuropsychiatry Interview) and classified into healthy or depressed groups. Depressive symptoms were assessed by the patient health questionnaire (PHQ-9). The mood/cognitive dimension was calculated by summing up the items: little interest, feeling depressed/hopeless, feeling bad about yourself, trouble concentrating, thoughts of death. The neurovegetative dimension was calculated by summing up the items: sleep problems, feeling tired/low energy, poor appetite/overeating, psychomotor agitation/retardation. Analyses controlled for BMI and antidepressant use.
Fifty subjects (mean age=21.5, 60% women) were included in the study. In the depression group (n=29, six of these medicated) a positive association was observed between total depression score and TNF-α ($p<0.01$). In addition, higher scores on the mood/cognitive dimension were associated with higher TNF-α ($p<0.01$) and IL-1β ($p=0.05$), and higher scores on the neurovegetative dimension were associated with higher TNF-α ($p<0.05$). Regarding the individual items, the following positive associations were found: "feeling depressed" and "feeling bad about yourself" with IL-1β, IL-8 and TNF-α ($p<0.05$); "concentration" and "thoughts of death" with TNF-α ($p<0.05$); "retardation/agitation" with IL-1β ($p<0.05$).
In the healthy control group (n=21), no associations were observed between inflammation and either total depression score or neurovegetative dimension. However, higher scores on the mood/cognitive dimension were associated with higher IL-8 and IL-10 ($p<0.05$). Regarding the individual items, the following positive associations were found: "feeling depressed" and "feeling bad about yourself" with IL-6, IL-8, TNF-α, and IL-10 (respectively, $p<0.05$ & $p<0.01$); "feeling tired" with IL-8, TNF-α, and IL-10 ($p<0.05$).
We also examined these associations in the entire sample with a focus on gender differences. Interestingly, the associations between symptom dimensions, as well as the individual items, and inflammation were mainly driven by women, not men (data will be presented in the meeting).

These results suggest that in young adults, the mood/cognitive dimension of depression more closely correlates with inflammatory changes, and may be a more sensitive predictor of inflammation, than neurovegetative symptoms. This might be indicative of different underlying biology that is associated with each dimension. Further, these findings suggest that examining the association between inflammation and different dimensions of depression may provide valuable data beyond what can be learned from only focusing on total depression score.

T7. EFFECT OF LISDEXAMFETAMINE ON PREFRONTAL BRAIN DYSFUNCTION IN BINGE EATING DISORDER

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Abstract: Background: Placebo-controlled trials demonstrate that the stimulant prodrug lisdexamfetamine (LDX) is efficacious in binge eating disorder (BED). The therapeutic effect of stimulants are thought to involve catecholamine neurotransmission within prefrontal cortex (PFC) and BED has been associated with PFC dysfunction. In one neuroimaging study, food provocation increased left PFC activation in participants with BED relative to obese controls. In another, participants with BED showed greater medial-orbito PFC activation to food pictures relative to normal-weight, overweight, and bulimia nervosa controls. Generally, PFC is implicated in appetite dysregulation, obesity, food cravings and impulsivity, all of which are closely related to BED. Based on the integration of PFC-subcortical circuits and the brain dysfunction found in BED, some researchers have suggested that heightened PFC reactivity to food results in loss of appetite control.

Two imaging studies examined whether treatment alters brain function in BED. In one placebo-controlled study of sibutramine, frontal and striatal activity to monetary reward anticipation increased in individuals that stopped binge eating following treatment. In another, treatment with the mu-opioid receptor antagonist GSK1521498, compared to placebo, was associated with reduced striatal response to high calorie food pictures, and reductions in pleasurable ratings of sweet foods and calorie intake. Although these data suggest abnormal PFC and striatal activity in BED, and normalization with treatment, the exact mechanisms of action remain unclear considering the opposing directions of signal change with treatment. With these considerations in mind, we examined the effects of LDX treatment on PFC and striatal brain activation in BED. We hypothesized that participants with BED would have an abnormal emotional brain network response to food cues, and that PFC and striatal brain regions mediating affect and decision-making would normalize in response to food cues after LDX treatment.

Methods: Twenty women with BED and 20 matched controls consented to a 12-week, open-label trial of LDX with fMRI assessments before and after treatment. Scans were conducted in the morning following an overnight fast. LDX was started at 30 mg/d, increased to 50 mg/d at week 1 and to 70 mg/d at week 2. A single downward dose titration to 50 mg/d was allowed during week 3 for tolerability. The LDX dose at week 4 (50 or 70 mg/d) was maintained for the next 8 weeks.

Results: At baseline, pretreatment, women with BED showed greater activation in regions of PFC and striatum to food pictures relative to controls. Moreover, among BED women, levels of emotional network activation to food pictures at baseline predicted clinical outcome at 12 weeks. After 12 weeks, LDX treated women showed marginal, albeit not statistically significant, reductions in PFC activation. Reductions in ventromedial PFC activation specifically were correlated with Binge Eating Scale reductions.
Conclusions: This pilot study suggests potential brain markers of LDX response in BED. Results indicate 1) that BED is characterized by an abnormally large PFC-subcortical brain response to high-calorie foods, 2) that LDX treatment may help normalize PFC over-activation, and 3) that PFC-subcortical activation at baseline is a potential biomarker of LDX response. These findings may provide a neurofunctional signal to inform larger treatment studies of BED.

T8. ASSESSMENT OF FUNCTIONAL RECOVERY AFTER LONG-TERM ARIPIPRAZOLE ONCE-MONTHLY MAINTENANCE TREATMENT OF BIPOLAR I DISORDER

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Abstract: Background: Functional assessment is complex and often overlooked in patients with bipolar I disorder (BP-I). The Functioning Assessment Short Test (FAST) measures a combination of elements to assess optimal functioning in these patients [1]. Recovery rates and functioning according to the FAST were assessed in patients with BP-I after long-term (52 weeks) treatment with aripiprazole once-monthly 400 mg (AOM 400).
Method: Results from two long-term studies were assessed. Functioning was assessed using the FAST, a 24-item questionnaire where higher total scores (possible range: 0-72) reflect more impaired functioning [1]. A strict criterion of patients having a total score of 11 or less in the FAST test for 8 consecutive weeks was considered as functional recovery. FAST total score was described using observed case mean summary statistics with standard deviation (SD).
Results: In the long-term efficacy study (NCT01567527) [2], 116 patients received AOM 400 treatment and 113 patients received placebo for 52 weeks and had at least one post-baseline FAST assessment.
In the open-label, long-term safety study (NCT01710709), 402 patients received AOM 400 treatment for 52 weeks and had at least one post-baseline FAST assessment. Of these patients, 321 were de novo patients and 81 were rollover patients who had completed the long-term efficacy study. Some of the rollover patients had already received treatment with AOM 400 for up to 52 weeks at baseline in the long-term efficacy study. The total treatment duration for the rollover patients was between 52 and 80 weeks whereas for the de novo patients it was up to 52 weeks.
In the long-term efficacy study, 30.2 % (n=35) were functionally recovered after 52 weeks of AOM 400 treatment and 24.8 % (n=28) in the placebo group. The difference was not statistically significant (p-value: 0.3944).
After completing the long-term efficacy study, the mean FAST total score in the recovered patients in the AOM 400 group was 3.6 (n=35, SD=3.6).

In the open-label, long-term safety study, 36 % (n=116) of the de novo patients and 43 % (n=35) of the rollover patients had functionally recovered after 52 weeks of AOM 400 treatment.
Of the rollover patients who met the FAST criteria for functional recovery after completing the long-term efficacy study (n=35), 57 % (n=20) remained recovered after completing the 52 weeks' long-term treatment phase.
After completing the long-term safety study, the mean FAST total score in the functionally recovered patients was 3.7 (n=116, SD=3.4) in the de novo patients and 3.5 (n=35, SD=3.4) in the rollover patients.
Conclusions: The studies both show the same trend that approximately 30-43% of the patients achieved functional recovery after 52 weeks' long-term treatment with AOM 400. In the long-term efficacy study, the lack of statistical separation from placebo may be due partially to a survivor effect, where patients stabilized on placebo for a minimum of 8-weeks are able to remain functionally recovered. The FAST total score in the functionally recovered patients was quite low (3.5-3.7) compared to the FAST recovery criteria, which means that the patients should have very good functioning. A high proportion (57%) of the patients who were functionally recovered on AOM 400 treatment, with a FAST total score of 11 or less, remained functionally recovered after up to 52 weeks of long-term treatment.

T9. THE IMPACT OF OBESITY ON PREGNANCY OUTCOMES AMONG WOMEN WITH PSYCHIATRIC DISORDERS

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Abstract: Background: Rates of obesity during pregnancy have increased in recent years, which is of great concern due to the increased risk of adverse neonatal and obstetrical outcomes associated. We examined the effect of obesity on adverse obstetrical and neonatal outcomes in women with psychiatric disorders.
Website: www.womensmentalhealth.org/pregnancyregistry Toll-free number: 1-866-961-2388
Methods: Data was prospectively collected from pregnant women, ages 18-45 years, enrolled in the Massachusetts General Hospital National Pregnancy Registry for Psychiatric Medications, beginning during pregnancy until 6 months postpartum. Maternal BMI was used to categorize participants at baseline as normal, overweight, and obese, with risk of adverse outcomes assessed between groups.
Results: Of enrolled participants, 584 were evaluable (N=252 normal weight; N=170 overweight; N=162 obese). The unadjusted odds ratio of major malformations in infants born to obese vs. normal weight mothers was 3.19 (95% CI: 0.79, 12.95). After adjusting for confounding variables, obese women were at significantly higher risk for gestational diabetes (OR: 3.81; 95% CI: 1.29, 7.84; p=0.009;), as were overweight women (OR: 3.4; 95% CI: 1.49, 7.76; p=0.004). Among obese women, there was a trend for higher rates of maternal hypertension and c-section (p=0.2, p=0.055) when compared to normal weight women. Other

outcomes, including pre-eclampsia, NICU stay, and preterm birth, were not significantly different between groups.
Discussion: Among women with psychiatric disorders, obesity was associated with a significantly higher risk for major malformations in unadjusted analyses, as well as gestational diabetes compared to normal weight controls after controlling for confounding variables. The increased prevalence of obesity among psychiatrically ill women underscores the importance of developing interventions prior to and during pregnancy to reduce maternal and neonatal complications.

T10. THE IMPACT OF ADHERENCE INFORMATION ON PROVIDER DECISIONS IN TREATING BIPOLAR AND MAJOR DEPRESSIVE DISORDERS

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Abstract: Background: Adherence to antipsychotic medications is critical for treatment and relapse prevention in serious and persistent mental illness (SPMI). New technologies—such as ingestible event marker sensors embedded into medications—offer the opportunity for providers to review credible medication adherence information when making treatment decisions.
Objective: To estimate the impact of credible adherence information on provider prescribing patterns in the treatment of bipolar (BD) and major depressive (MDD) disorders using a provider survey.
Methods: Providers (N=180) who treat and prescribe antipsychotics to BD and MDD patients were randomized to two groups and completed a survey including five case vignettes that described patient demographics, treatment history, disease severity, and patient self-reported adherence to antipsychotic medication. The survey also included provider characteristics. Experimental condition vignettes included credible adherence information. Differences between the groups on prescribing patterns were compared within each disease state.
Results: Providers completed the BD (n=90) and MDD (n=90) surveys; 60.0% were female, 52.2% were ≤39 years of age, and 91.6% had a medical doctor (MD) degree. There were no demographic differences between groups, except respondents treating BD patients were less likely to have an MD versus other degrees ($p < 0.01$). BD providers were more likely to modify antipsychotic treatment as opposed to mood stabilizers. When presented with the vignettes describing non-adherent patients, BD providers in the experimental group were more likely to switch patients to an LAI than participants in the control group (69.6% vs. 22.7% $p < 0.001$). There were no group differences for vignettes describing adherent patients. Conversely, MDD providers were more likely to modify antidepressant treatment than antipsychotics. However, there was a nonsignificant trend toward experimental condition providers prescribing LAI formulation antipsychotic medications for non-adherent MDD patients.
Conclusions: Access to credible adherence information may help prescribers to identify non-adherent patients in an SPMI population, allowing them to make better (more informed) treatment decisions.
Sponsorship: Otsuka Pharmaceutical Development & Commercialization, Inc.

T11. A 52-WEEK, MULTICENTER, OPEN-LABEL STUDY TO EVALUATE THE EFFECTIVENESS OF ARIPIPRAZOLE ONCE-MONTHLY AS MAINTENANCE TREATMENT IN PATIENTS WITH BIPOLAR I DISORDER

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Abstract: The efficacy of oral aripiprazole in the maintenance treatment of bipolar I disorder (BP-I) has been well-established [1,2]. The objective of this study (NCT01710709) was to evaluate the effectiveness of long-acting injectable aripiprazole once-monthly 400 mg (AOM 400) as maintenance treatment in BP-I.

This study enrolled patients with a diagnosis of BP-I and at least one previous manic or mixed episode and patients who participated in a randomized, double-blind, placebo controlled study assessing the efficacy and safety of AOM 400 (NCT01567527). The study comprised a screening phase, a conversion phase to oral aripiprazole, an oral stabilization phase, and an open-label 52-week maintenance phase where AOM 400 was administered every 4 weeks. The subjects who completed trial NCT01567527 entered directly into AOM 400 maintenance phase.

A total of 464 subjects entered the maintenance phase. Of these, 63% (291/464) completed this trial. The most frequent reasons for discontinuation were withdrawal of consent (11%) and adverse events (10%). Weight increased (1.5%, 7/464) and bipolar I disorder (0.9% 4/464) were the most common reasons for discontinuations due to AEs. Overall, 88.9% of the patients who were stable (outpatient, YMRS or MADRS <12, and no suicidal ideation) at baseline were stable at the last visit. The improvements in mean YMRS, MADRS, CGI total scores, and functioning achieved in previous phases were maintained over 52-weeks. TEAEs experienced by >10% of the patients were akathisia (14.7%), weight increased (13.4%), nasopharyngitis (12.1%), insomnia (11.0%).

Long-term treatment with AOM 400 was safe and well tolerated, and maintained stability in patients with BP-I.

T12. TECHNOLOGY USE AMONG INDIVIDUALS WITH SERIOUS MENTAL ILLNESSES IN COMMUNITY SETTINGS

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Abstract: Introduction: Internet and mobile technologies provide a unique opportunity to deliver cost-effective interventions with on demand information to support health and wellness. Approximately nine-in-ten American adults use the internet, 93% own cell phones, 77% own smartphones, and 79% of adults who are online use popular social media sites such as Facebook [1-3]. Increasing mobile device ownership and internet use among lower-income adults is generating enthusiasm for the potential to reach millions of people with mental illness with potentially cost-effective and accessible interventions to advance physical and mental health

[4-7]. A first step in exploring the feasibility of intervening with digital health technologies is to understand how individuals with serious mental illness (SMI) access and use online and mobile technologies. Studies on the feasibility of providing mobile mental health interventions is an emerging area of study [8-11]. Mobile device access has been evolving rapidly, so the objective of this project is to assess current technology access in patients with SMI and their willingness to participate in health interventions.
Methods: Patients with SMI diagnoses from 4 community mental health centers (CMHCs), (2 in NH, 1 in RI, and 1 in MI) completed a 21-item questionnaire assessing their demographics, access to and use of technology and the internet, including social media, and willingness to try electronic health interventions. Data were analyzed using IBM SPSS software, version 25.
Results: 403 patients with SMI completed the survey. 207 (51.4%) were female, with average age 44.4 years (std dev 13.1 years). 43.9% of patients had a primary schizophrenia spectrum diagnosis, 14.6% had bipolar disorder, 18.6% had major depressive disorder (MDD), and 18.4% reported anxiety or another mental health disorder. 80.0% of patients with a schizophrenia spectrum disorder reported having a cell phone; 53.1% had a cell phone with Wi-Fi capability; 35.0% had a computer at home with internet access, and 27.1% had computer internet access outside the home. Among those with bipolar disorder, these proportions were 92.1%, 62.9%, 40.7%, and 35.6%; among people with MDD these proportions were 93.9%, 67.7%, 48.0% and 29.3%; for anxiety and other disorders these proportions were 92.9%, 84.9%, 43.2% and 33.8%, respectively. Of those surveyed, 67.5% use Facebook, 10.7% use Twitter, 13.6% use Snapchat, 16.9% use Instagram, and 5.7% use another form of social media. Most respondents indicated a willingness to participate in phone- or computer-delivered interventions for stress (72.5%), health (72.3%) or mental health (73.9%).
Conclusions: People with SMI receiving community mental health services reported substantial access to and use of mobile devices, comparable to existing national data. Almost 75% of those completing the survey expressed a willingness to participate in easy, technology-delivered interventions for health, mental health and stress, suggesting that mobile devices may be an increasingly useful tool for providing access to evidence-based care.

T13. NIMH FAST-MAS PHASE IIA STUDY OF THE EFFECTS OF THE SELECTIVE κ OPIOID ANTAGONIST JNJ-67953964 ON FMRI VENTRAL STRIATAL ACTIVATION DURING THE MONETARY INCENTIVE DELAY TEST IN ANHEDONIC PATIENTS WITH MOOD AND ANXIETY SPECTRUM DISORDERS

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Abstract: Introduction: A compelling body of preclinical research suggests that κ opioid receptor (KOR) antagonism has promise as treatment for anhedonia, a core symptom of mood and anxiety spectrum disorders. However, we lack data on the effects of selective KOR antagonists in humans. We carried out this Phase IIa study under the New Experimental

Medicine Studies: Fast-Fail Trials in Mood and Anxiety Spectrum Disorders (FAST-MAS) program to test the hypothesis that engaging this target with a highly selective KOR antagonist, JNJ-67953964 (formerly known as CERC-501 and LY2456302) modulates ventral striatal reward circuitry. This was intended to establish proof of concept (POC) that KOR antagonism has potential therapeutic effects on anhedonia and to serve as a model for the use of biomarker-based outcomes to establish POC in early phase drug development.
Methods: Subjects 21-65 years of age meeting DSM-5 criteria for either a mood disorder (Major Depressive Disorder or Bipolar I or II currently in a major depressive episode, N=70) or an anxiety disorder (Generalized Anxiety Disorder, Social Phobia, Panic Disorder or Post-Traumatic Stress Disorder, N=19) who had anhedonia (Snaith-Hamilton Pleasure Scale score $\geq$ 20), were randomized to 8 weeks of double-blind treatment with JNJ-67953964 10 mg (N=45) or placebo (N=44). A dose of 10 mg was selected based on prior positron emission tomography receptor occupancy data showing robust KOR antagonism. Primary outcome was assessed with fMRI in conjunction with a monetary incentive delay (MID) task that was administered at baseline and after 8 weeks of study drug administration. Analyses examined group activation differences during anticipation of monetary gain, contrasted with non-incentive trials. Mixed-model ANOVA queried average activation in an a priori bilateral accumbens area mask defined by the Harvard-Oxford Subcortical Atlas for each contrast of interest.
Results: A total of 67 subjects had data for the primary outcome measure both at baseline and during treatment and were included in the Intent to Treat sample. Mixed-model analyses revealed a significant Group x Time interaction in reward gain anticipation ($p < 0.01$) (a priori primary outcome), consistent with relatively greater change from baseline in ventral striatal activation during anticipation of gain with Study Drug vs placebo. JNJ-67953964 was not associated with any serious adverse events and was generally well tolerated. Side-effects of more than mild severity occurring more than 5% more frequently with JNJ-67953964 than placebo were pruritis (11.1%), depression exacerbation (6.7%), and rash (6.7%).
Conclusions: The results of this study establish that KOR antagonism has the hypothesized effect on neural function, thereby establishing POC that engaging this target is a promising means of treating anhedonia. The findings also specifically suggest the promise of JNJ-67953964 as an anhedonia therapy. This study provides the basis for carrying out larger trials with KOR antagonists powered for the use of clinical endpoints to determine the clinical impact of engaging this target. It also serves as a model for novel, RDoC-based, early phase drug development methodology incorporating rigorous testing of whether engaging a target has a hypothesized effect on neural function as a means of establishing POC before proceeding to trials with downstream clinical endpoints.

T14. CRCDS-MINISIM: A STANDARDIZED TEST FOR DRUG IMPAIRED DRIVING

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Abstract: In late 2017 the FDA published guidance for evaluating drug impaired driving (1). The guidance indicates when a dedicated driving study is required pre-approval.

This poster describes results obtained across a range of drugs evaluated with a standardized driving simulator and driving scenario. Results will be presented from 6 independent studies conducted for regulatory submission (2,3,4,5.6,7). The studies employed a double blind, randomized, placebo-controlled, crossover design. Subjects were dosed with drug, a matching placebo, and a positive control (to demonstrate assay sensitivity). The primary endpoint for these trials was the Standard Deviation of Lateral Position (SDLP), a measure of lane position control (e.g., "weaving"). SDLP is commonly utilized in driving studies submitted for regulatory review. Timing of the driving test post-dose was based upon whether the trial was being conducted to assess residual effects of nighttime dosing or determination of driving performance at T-max. Subjects were healthy male and female subjects between 21 and 55 years of age.

Studies were conducted with the CRCDS-MiniSim simulator which utilizes technology developed by the University of Iowa for the National Advanced Driving Simulator. The CRCDS-MiniSim simulator consists of a full-size driver's seat, steering wheel, pedals, dashboard display, and 108-degree view of the roadway. The driving scenario is the Country Vigilance Divided Attention drive (CVDA) modeled after the 100 km over-the-road drive historically used in driving studies conducted in the Netherlands (8).

Subjects were screened for simulator sickness and underwent standardized familiarization and training with the simulator. The CVDA scenario requires subjects to drive on a two-lane highway for approximately 1 hour. They were instructed to maintain constant lane position and speed. Subjects also perform a secondary vigilance task which requires monitoring for targets in the left and right-side mirrors.

Results:

Table 1 shows the change from placebo in SDLP for the 6 studies; results are arranged in terms of magnitude of the change in SDLP compared to placebo. For the CRCDS-MiniSim the increase in SDLP observed at 0.05% BAC, the commonly employed "safety threshold", is 4.4 cm. All of the drugs listed from zopiclone to alprazolam exceeded this safety threshold.

Table 1. Summary of SDLP Change from Placebo Studies

	Time Post-Dose	SDLP (cm) vs Placebo, (95% CI)
Flibanserin 100 mg (5)	8.0 hours	-2.47 (-3.9, -1.0)
Flibanserin 200 mg (5)	8.0 hours	-1.40 (-2.8, 0.0)
Tolperisone 450 mg (3)	3.0 hours	0.20 (-3.0, 3.4)
Gabapentin 250mg (4)	7.25 hours	0.55
Diphenhydramine Citrate 76mg (4)	7.25 hours	2.37 (1.0, 4.0)
Zopiclone 7.5mg (2)	8.0 hours	3.50 (2.5, 4.9)
ETOH .05 BAC (6)	N/A	4.40
ETOH .08 BAC (6)	N/A	5.80
Diphenhydramine HCl 50 mg (7)	3.0 hours	6.19 (4.8, 7.6)
ETOH .10 BAC (6)	N/A	7.90
Cyclobenzaprine 30 mg (3)	3.0 hours	8.80 (5.6, 12.0)
Triazolam 0.5mg (4)	7.25 hours	13.82 (10.9,17.4)
Alprazolam 1mg (7)	1.5 hours	22.71 (20.2,25.2)

Discussion:

Use of a standardized simulator and driving scenario with established sensitivity to low-dose alcohol facilitates development of objective information regarding the potential impairment of

driving caused by drugs. Results from dedicated driving studies can provide critically important information for labeling used by prescribers and consumers.

T15. AN OPTIMIZATION OF AGGREGATED N-OF-1 TRIAL DESIGN TO PREDICTIVE BIOMARKER VALIDATION

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Abstract: Background and Significance: Parallel-group randomized controlled trials (PG-RCTs) are the gold standard for detecting differences in mean improvement across treatment conditions. However, PG-RCTs are poorly optimized for quantifying the relationship of a biomarker measured at baseline to treatment response, or identifying subgroups of treatment response. They also require that many participants spend the full duration of the study on placebo, which can limit the enrollment of patients with particularly acute symptoms.
In N-of-1 trials, an individual subject moves between several treatment conditions, such as active treatment and placebo, in order to determine the individual's specific response to each treatment. In aggregated N-of-1 trials, a cohort of individuals moves through this same type of trial design, and their outcomes are analyzed to answer questions about e.g. patterns of treatment response. Aggregated N-of-1 trials can be designed to optimize both statistical power and clinical or logistical constraints, such as allowing all participants to begin with an open-label stabilization phase to facilitate the enrollment of more acutely symptomatic participants. Here, we describe a set of statistical simulation studies comparing the power of four different trial designs to detect a relationship between a predictive biomarker and subjects' specific response to the PTSD pharmacotherapeutic agent prazosin.
Methods: R statistical software was used to simulate the data from: (1) an open-label trial; (2) an open-label phase followed by a blinded discontinuation phase; (3) a traditional crossover trial; and (4) an open label phase, followed by a blinded discontinuation phase and a brief crossover phase. Each design was 20 weeks long, with 6 measurement timepoints. Response parameters were based on data from a PG-RCT of prazosin for PTSD, with response to prazosin and placebo modeled using modified Gompertz functions, and a carryover term describing an exponential decay of prazosin's effects following transitions to placebo. Each trial design was simulated 250 times, and results analyzed using a linear mixed effects model. The primary outcome analyzed for each trial was whether a statistically significant association between biomarker value and clinically significant response to prazosin was detected with 5% Type I error. This process was repeated while varying the correlation between biomarker and prazosin response, trial size, carryover term, and the parameter autocorrelations.
Results: Trial designs 3 & 4 had substantially higher power with fewer subjects than open label and open label plus blinded discontinuation designs. This pattern was maintained across a substantial number of permutations of the modeling assumptions.
Conclusions: These results suggest that both a cross-over trial design, and an aggregated N-of-1 trial design beginning with an open label titration phase, provide superior power over an open label or open label plus discontinuation design in detecting an association between a predictive biomarker and the clinical response to the PTSD pharmacotherapeutic prazosin. In addition, depending on the expected timecourse for symptoms to return after prazosin is discontinued, the aggregated N-of-1 trial design provides similar or minimally reduced power compared to a

traditional crossover design, while providing the substantial benefit of allowing all participants to spend the first 8 weeks of the trial on open-label active treatment.

T16. AXS-05 FOR NEUROPSYCHIATRIC DISORDERS: SCIENTIFIC RATIONALE AND CLINICAL DEVELOPMENT

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Abstract: Introduction: AXS-05 is a novel, oral, fixed-dose combination of dextromethorphan and bupropion currently in late-stage clinical development for treatment-resistant depression (TRD) and for agitation associated with Alzheimer's disease (AD). Dextromethorphan acts as an NMDA receptor antagonist, a sigma-1 receptor agonist and a reuptake inhibitor of both serotonin and norepinephrine. Due to extensive human metabolism of dextromethorphan, necessary plasma concentrations for proposed psychotherapeutic effects are not achievable in the absence of metabolic inhibition. Bupropion serves to inhibit the breakdown of dextromethorphan in humans via CYP2D6. Bupropion is also an established antidepressant which acts as a dopamine and norepinephrine reuptake inhibitor. Both dextromethorphan and bupropion are nicotinic acetylcholine receptor antagonists. Clinical evidence with antidepressants in several pharmacological classes, which individually share the mechanisms of action of AXS-05, support its development for TRD. Further, the NMDA receptor antagonist property of AXS-05 may hold the potential for rapid onset of action based on the clinical experience with the prototypical NMDA receptor antagonist ketamine. Clinical evidence also suggests glutamate transmission may play a role in the behavioral and cognitive changes in dementia. Clinical data with agents that, like AXS-05, target sigma-1 (e.g. fluvoxamine, donepezil) have shown effects in patients with behavioral disorders and AD. The role for the serotonergic properties of AXS-05 in AD patients with agitation is supported by clinical trial results with citalopram in this indication. Dextromethorphan has previously been reported, in the presence of metabolic inhibition, to reduce depressive symptoms in patients with TRD, AD and pseudobulbar affect, and to reduce agitation symptoms in patients with AD.
Methods: AXS-05 and it components have been evaluated in several Phase 1 pharmacokinetic trials involving over 100 patients. These studies examined the pharmacokinetics of dextromethorphan after AXS-05 dosing and assessed the safety and tolerability of AXS-05.
STRIDE-1 is a Phase 3, randomized, double-blind, active-controlled, 12-week trial of AXS-05 in subjects with TRD. This study consists of a 6-week open-label, bupropion lead-in period, and a 6-week, randomized, double-blind treatment period with AXS-05 or bupropion. The primary efficacy outcome measure is the Montgomery-Åsberg Depression Rating Scale (MADRS). ADVANCE-1 is a Phase 2/3, randomized, double-blind, placebo-controlled, 5-week trial of AXS-05 in subjects experiencing agitation associated with AD. The primary efficacy outcome measure is the Cohen-Mansfield Agitation Inventory (CMAI).
Results: Administration of AXS-05 resulted in substantial increases in dextromethorphan plasma concentrations in Phase 1 trials. AXS-05 was safe and generally well-tolerated. The STRIDE-1 study in patients with TRD is expected to enroll approximately 350 subjects. The ADVANCE-1 study in patients with AD is expected to enroll approximately 435 subjects. Both STRIDE-1 and ADVANCE-1 incorporate interim analyses.
Conclusions: AXS-05 is an innovative, oral, fixed-dose combination of dextromethorphan and bupropion. Increased dextromethorphan bioavailability has been demonstrated with AXS-05

administration. The mechanisms of action of both dextromethorphan and bupropion, and several lines of clinical evidence with agents that share these mechanisms, support the development of AXS-05 for neuropsychiatric symptoms. Late-stage clinical trials are assessing the efficacy and safety of AXS-05 in patients with TRD and in patients with agitation associated with AD.

T17. THE RELATIONSHIP BETWEEN COGNITION AND DEPRESSION IMPROVEMENT AMONG MDD PATIENTS BY NSI-189, A NEUROGENIC, PRO-COGNITIVE, ANTIDEPRESSANT COMPOUND

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Abstract: NSI-189 is a new chemical entity discovered based on its neurogenic activities on human hippocampal neural stem cells in vitro and in vivo mouse young normal hippocampus. Additionally, it has been found to stimulate synaptic remodeling of hippocampus in ischemic stroke model, reverse peripheral neuropathy in diabetic models, ameliorate cognitive impairment in radiation-induced brain injury model, and enhance LTP to supra-normal levels. The compound was recently tested for the treatment of major depressive disorder (MDD) in a Phase II double-blind trial as monotherapy in outpatients with MDD.

Using the sequential parallel comparison design (SPCD), 220 subjects were randomized to: NSI-189 40mg daily (n=44), NSI-189 80mg daily (n=44), or placebo (n=132) for 6 weeks (Stage 1). At the end of 6 weeks, placebo-treated subjects who were non-responders (defined as less than 50% reduction in Montgomery-Asberg Depression Rating Scale (MADRS)) with a MADRS score greater than 15 were re-randomized to 6 weeks treatment with NSI-189 40 mg daily (n=22), NSI-189 80 mg daily (n=22), or placebo (n=22) (Stage 2). Patients on NSI-189 who completed Stage 1 continued the same dose for another 6 weeks.

The primary and secondary endpoints on various depression scales were previously presented, which were not significant on MADRS or HAM-D17 but significant on SDQ, QIDS-SR (Stage 2 only), and CPFQ. We also noted that the compound showed statistically significant advantages on certain objective cognitive measures of attention and memory in CogScreen battery. We have further analyzed the correlation between changes in core symptoms of depression versus changes in individual CogScreen variables. Select variables show statistically significant correlation between improved MADRS-6 or SDQ-44 scores and increased cognitive performance in NSI-189 treated group, while showing significant correlation between worsening depression and worsening cognitive performance in placebo non-responders. By analyzing such associations, we hope to derive composite CogScreen indices that can detect cognitive improvement by NSI-189 in MDD patients, both dependent and independent of their depression status.

T18. EFFICACY OF INTRAVENOUS KETAMINE TREATMENT ON ANXIOUS VERSUS NON-ANXIOUS UNIPOLAR TREATMENT-RESISTANT DEPRESSION

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Abstract: Objective: In patients with major depressive disorder, anxious depression is more difficult to treat with traditional (i.e. monoaminergic) antidepressants than non-anxious depression (1). Ketamine, an N-methyl-D-aspartate (NMDA) receptor antagonist, results in an exceptionally fast and robust antidepressant response in patients with unipolar depression (2), though evidence for its efficacy in anxious depression remains scarce. Our group recently conducted a randomized placebo-controlled trial of intravenous ketamine in patients with unipolar treatment-resistant depression (TRD), where response to ketamine was found to be significantly better than placebo. Through secondary analysis of the same dataset, the present study examines the effect of a high baseline anxiety state on the response to ketamine in patients with unipolar TRD.
Methodology: In a multi-site, double-blind, placebo-controlled trial, 99 subjects with TRD were randomized to one of five treatment arms: a single dose of intravenous ketamine 0.1 mg/kg, 0.2 mg/kg, 0.5 mg/kg, 1.0 mg/kg, or midazolam 0.045 mg/kg (active placebo). The primary outcome measure was change in the 6-item Hamilton Rating Scale for Depression (HAM-D6) total score. Post-hoc analyses were conducted to examine the effect of anxious depression baseline status (defined by a Hamilton Depression Rating Scale Anxiety-Somatization (HDRS-AS) score ≥ 7) on response to ketamine vs. placebo one day post-infusion.
Results: Our sample consisted of 45 subjects with, and 54 subjects without anxious depression. Using a mixed effects model, while adjusting for baseline HAM-D6 scores and including study site as a covariate, we did not find a statistically significant interaction effect between treatment group assignment and anxious/non-anxious status on HAM-D6 score change at day one post-infusion, regardless of whether ketamine was analyzed as one pooled or four separate groups (p=0.8833 and 0.1788, respectively).
Conclusions: In contrast with what is observed with traditional antidepressants, response to ketamine was similar in both anxious and non-anxious treatment-resistant depression subjects. These results highlight the potential utility of ketamine in the treatment of unipolar anxious depression.

T19. ACUTE AND LONGER-TERM OUTCOMES USING KETAMINE AS A CLINICAL TREATMENT AT THE YALE PSYCHIATRIC HOSPITAL

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Abstract: Introduction: Ketamine has emerged as a rapid-acting antidepressant, though controversy remains regarding whether sufficient data exist to justify its use outside of research

protocols. In October 2014, our institution began providing off-label ketamine therapy for patients not able to participate in research protocols. Here we describe our experience over 39 months providing ketamine as a clinical treatment to participants with severe and treatment-resistant mood disorders.
Method: Initially, patients were treated with a single- or double-infusion protocol (0.5mg/kg over 40 minutes intravenously). We later transitioned to a 4-infusion protocol over two weeks and most recently to a 6-infusion protocol over three weeks.
Results: Overall, 72 severe and treatment refractory patients have received ketamine at our institution, with 849 total infusions performed. Overall, 48.6% of patients had a history of ECT, 68% had a history of psychiatric hospitalization, and 47% had a history of suicide attempt. Overall, 51.4% of patients with mood disorders (N=68) responded and 25.8% remitted to a protocol of infusions ranging from 1-6. A subsample (N=18) have received ketamine on a long-term basis, ranging from 12 to 60 total treatments, over a course of 14 to 163 weeks. We found no evidence of cognitive decline, increased proclivity to delusions, or emergence of symptoms consistent with cystitis in this subsample.
Conclusions: Overall, ketamine infusions have been tolerated well. The response and remission rates in our clinical sample were lower than those observed in some research protocols. The small number of patients who have been treated on a maintenance schedule limits the conclusions that can be drawn regarding long-term safety of ketamine, however no long-term adverse effects have been observed in our sample.

T20. KETAMINE NON-RESPONDERS EXHIBIT PATHOLOGICAL INCREASES IN EXTRACELLULAR FREE WATER FOLLOWING TREATMENT

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Abstract: Background: Major Depressive Disorder (MDD) is a pervasive and often chronically debilitating psychiatric disorder. MDD has been linked to alterations in neurotransmission, and symptoms are commonly alleviated by monoaminergic antidepressants. For patients that do not improve following treatment with multiple monoaminergics, ketamine, an NMDA receptor antagonist, has proven to be a fast-acting and efficacious treatment for 60-70% of individuals. Here, we investigate the relationship between clinical response to ketamine and changes in a sensitive in vivo diffusion imaging measure of extracellular water, called "Free Water" (FW), in the hippocampus. The hippocampus was chosen given its established role in neuroplasticity following antidepressant treatment.
Methods: Ten patients with MDD received an intravenous infusion of ketamine. T1 and diffusion weighted images (DWI) were acquired 1 hour prior to, and 4 hours after, the start of the infusion. T1 images were processed with the Freesurfer pipeline. Anatomical parcellations were registered to each subject's DWIs, which were then used to estimate average hippocampal FW. Paired t-tests were employed to analyze pre- to post-infusion FW changes. Pearson's correlations between delta-FW (post scan – pre scan FW) and percent improvement on the Hamilton Depression Rating Scale (HDRS) 24 hours post-infusion were conducted. Treatment response was defined as greater than 50% improvement on the HDRS at 24 hours.

Results: Ketamine treatment significantly increased FW in the right hippocampus in non-responders (N=3, p=0.039), but not responders (N=7, p=0.542). A negative correlation between right hippocampus delta-FW and HDRS percent improvement was found (r= -.64, p=0.046).
Discussion: Clinical non-response to ketamine was associated with a rapid, pathological increase in extracellular FW. This suggests that non-responders have an impaired ability to maintain water homeostasis after NMDA receptor blockade. Given the central role of astrocytic aquaporin 4 channels in regulating water homeostasis and synaptic plasticity, and post-mortem findings of astrocyte pathology in MDD, we hypothesize that astrocytes are involved in the neurobiology of ketamine's antidepressant mechanisms.

T21. CORTICAL EXCITABILITY IN PATIENTS WITH TREATMENT RESISTANT DEPRESSION RECEIVING KETAMINE

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Abstract: Introduction: Cortical inhibitory mechanisms, especially associated with the dysregulation of the gamma amino butyric acid (GABA)-ergic system, has been purported to play a role in the pathophysiology of major depressive disorder (MDD). This study aimed at assessing cortical excitability associated with treatment resistant depression (TRD) undergoing ketamine treatment, using transcranial magnetic stimulation (TMS) combined with motor evoked potential (MEP) and electroencephalographic (EEG) recordings. TMS is a noninvasive tool for investigating cortical inhibitory mechanisms associated with GABAergic neurotransmission. Using the paired-pulse TMS paradigm, short interval intracortical inhibition (SICI, a GABAA-dependent process) and intracortical facilitation (ICF, a glutamate dependent process) can be assessed. Studies investigating SICI and ICF suggest that there is a decreased SICI for MDD patients compared to healthy subjects, while no difference in ICF was observed. Little is known about cortical excitability specifically in the subgroup of depressed patients who are treatment resistant, the focus of this study, for whom the development of novel treatments is most urgently needed.
Methods: The study was approved by the Duke University School of Medicine Institutional Review Board. Ten depressed patients (7 female) and nine age-matched healthy volunteers (5 female) enrolled. Depressed patients met DSM-IV diagnostic criteria for MDD without psychotic features, and had an inadequate response to at least two antidepressants, one of which is in the current episode of depression. Subjects also had an Inventory of Depressive Symptomatology 30-item Clinician-rated (IDS-C30) total score $\geq$ 34. Single intravenous infusion of low-dose (0.5 mg/kg) ketamine was delivered to the patients. The cortical excitability assessment battery consisted of: 1) Resting motor threshold (RMT); 2) Resting EEG recording with eyes open for 5 minutes; 3) Somatosensory evoked potential (SEP); 4) Paired-pulse TMS with interstimulus intervals (ISI) of 2, 3, 15, and 25 ms; 5) simultaneous TMS-EEG.
Results: Resting EEG showed a significant suppression of alpha band power for the TRD group relative to controls at the parietal and occipital sites ($p < .05$), but not at the frontal cortex. The SEP recorded at CP3 (referenced to CP4) showed a diminution of the P30 component for TRD relative to healthy controls ($p < .05$). For paired-pulse TMS, there was a significant group-by-ISI interaction effect ($p < .05$); of interest, at 25 ms ISI, there was a significant reduction in MEP amplitude for the TRD group compared to controls ($p < .05$), which indicates a lack of

ICF. The TMS-evoked potential (TEP) showed an elevation of the P30 component for TRD relative to controls ($p < .05$). In ketamine responders, the time course of the P70 component of the TEP in the days following the infusion correlated with clinical response as measured by the Montgomery–Åsberg Depression Rating Scale.
Conclusions: Overall, TRD patients showed a general downregulation of cortical excitability in our battery of assessments. Although the direct neuronal underpinnings behind this phenomenon are unknown, we hypothesize that the diminution of response seen in TRD patients is related to deficiencies in plasticity mechanisms.

T22. ANTIDEPRESSANT EFFECTS ON THE PAIN NETWORK IN PATIENTS WITH DEPRESSION

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Abstract: Background: Depression is a common disorder affecting 9.5% of the population and conferring significant negative long-term sequela. Antidepressant medications offer an effective treatment, yet nearly 50% of patients either do not respond, or have side effects rendering them unable to continue the course of treatment. More effective and targeted treatments are needed. To advance the pharmacology of depression, mechanistic studies can help by examining the pathways by which treatment are effective. In this study, we aimed to identify pathways by which antidepressants exert their clinical effect and to test whether the identified pathways are reproducible across two independent datasets.
Methods: We conducted two independent antidepressant treatment studies with two different SNRI medications: duloxetine and desvenlafaxine. Both studies included a 10-week (duloxetine) or 12-week (desvenlafaxine) prospective, double-blinded, placebo-controlled trial with pre- and post-treatment MRI scans. The duloxetine cohort consisted of n=48 adults with depression, n=24 randomized to duloxetine, and n=24 to placebo. The desvenlafaxine cohort consisted of n=42 adults (n=20 desvenlafaxine; n=22 placebo). We utilized MVPA – a whole-brain, connectomic to examine FC. 18 MVPA-derived clusters showing significant treatment by time interactions. 12 of these 18 clusters were within the pain network, a previously identified network of 16 brain regions that co-activate during task-based fMRI studies of physical pain. In post-hoc analyses, we focused on the pain network. 16 region-of-interest (ROI) with 5mm radius were constructed.
Results: Three important findings emerged: 1) Across two independent studies, SNRI antidepressants significantly decease functional connectivity within the pain network; 2) Placebo had non-significant effects on pain network density; 3) Change in pain network density mediated the relationship between treatment and symptom improvement (reduction in the HAM-D summary score). The study findings raise intriguing questions about the relationship between pain, depression, and their interaction. The reduction in pain network density and its effects on depression may occur through direct or indirect routes – directly, reduction in pain network density may lead to improvement in depression; indirectly, reduction in pain network density may underlie an improvement in physical pain, which thereby gives rise to a reduction in depressive symptoms. This mechanistic question is particularly salient for SNRI medication which are effective treatments for both depression and physical pain and may be addressed in subsequent studies.

T23. RS10769025-ALX4 POLYMORPHISM PREDICTS SSRI RESPONSE: COMED TRIAL FINDINGS VALIDATED IN PGC CONSORTIUM GWAS DATASET

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Abstract: Background: COMED (Combination of Medications to Enhance Depression Outcomes) is a randomized, 3-arm clinical trial-comparing efficacy of monotherapy vs two antidepressant combinations. We recently found a potentially regulatory SNP rs10769025 in ALX4 gene on chromosome 11 with strong significance (p value= 9.85925E-08) in SSRI-responders (monotherapy). Haplotype analysis on ALX4 variants showed that a regulatory haplotype CAAACTG is significantly [OR (LCI-UCI) = 3.4 (1.7-7.0), p=2.00E-04] is strongly associated with SSRI-responders (monotherapy). In the present study, we tried to validate the findings from COMED trial using the Psychiatry Genomics Consortium (PGC) GWAS datasets, accessed from the open access domain link: http://psychiatry.som.jhmi.edu/metamoodics/gb/mdgwas.php?gene=ALX4

Methods: PGC Consortium datasets include meta-analyses results from nine different GWAS Studies. The total sample included 9,240 MDD cases and 9,519 controls all of European ancestry with data on ~1.2M genotyped and/or imputed SNPs. Once we had access to PGC GWAS datasets, we tried to validate rs10769025-ALX4 polymorphism our findings from the COMED trial using haplotype and linkage disequilibrium analyses. In addition, we investigated if the ALX4 gene is expressed in brain using human brain transcriptome mapping (courtesy: http://hbatlas.org/)

Results: PGC consortium datasets revealed 52 SNPs that are associated with ALX4 gene, the peak index SNP being rs897005, and we validated the same in COMED data sets. Our peak index SNP rs10769025-ALX4 polymorphism in PGC datasets showed a positive but moderate association with a p=3.00E-04. However, we found that ALX4 SNP rs897005 from PGC GWAS had a strong association in our genetic association studies from COMED with a p=3.00E-06. Overall this suggests that the two index SNPs has a good linkage disequilibrium with other variants in ALX4 gene suggesting that actual causal variant could be forming a haplotype with the index SNPs and other potentially functional variants associated with trait. Hence, there is a positive association of ALX4 variants in PGC GWAS datasets that does supports and validates our observations from COMED study. In addition, ALX4 is expressed in different regions of the brain such as cerebellar cortex, mediodorsal nucleus of the thalamus, striatum, amygdala, hippocampus and 11 areas of neocortex. (Courtesy, http://hbatlas.org/hbtd/images/wholeBrain/ALX4.pdf), suggesting its role in the brain.

Conclusions: Validating the GWAS association of rs10769025 and rs897005 ALX4 polymorphism in two different datasets from COMED and PGC GWAS studies suggest that there is a positive association of ALX4 polymorphism in Major Depression and SSRI-responsiveness in Caucasian ethnicity.

T24. PHARMACOGENOMICS AND DEPRESSION SYMPTOM IMPROVEMENT: TREATMENT BY PRIMARY CARE PHYSICIANS OR PSYCHIATRISTS

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Abstract: Background: Major depressive disorder (MDD) is a significant health burden worldwide. Multiple failed medication trials are associated with decreased probability of achieving remission, highlighting the need for optimizing treatment selection for depression. Among patients in psychiatric care settings, combinatorial pharmacogenomic (PGx) testing to guide medication choice has been associated with reduced depression symptoms, polypharmacy, medication costs, and healthcare utilization costs (Altar et al. 2015). Due to a lack of studies on PGx testing in primary care settings, the current investigation sought to compare the utility of a combinatorial PGx test in guiding treatment for patients with depression between primary care and psychiatric care settings.
Methods: We conducted a sub-analysis of a broader seven-year, naturalistic, un-blinded, prospective study examining PGx guidance in psychiatric medication prescription decisions (the IMPACT study, impact.camhx.ca/en/home.php) (Herbert et al. 2017). In a large patient sample (N=2025), selected for moderate-to-severe depression (Beck Depression Inventory, BDI, score >17) at baseline, who received the combinatorial PGx testing (Assurex Health, Inc), we compared symptom improvement, response, and remission between depressed patients treated by primary care physicians (PCPs) and psychiatrists. Symptom improvement was quantified based on the percent change in BDI score from baseline assessment to end of study, which occurred 8–12 weeks after baseline. Congruence of medication prescribing to the combinatorial PGx test guidance was also compared at the end of study between depressed patients treated by different healthcare providers.
Results: Psychiatrists were the prescribers for 57% of this patient sample. Symptom improvement was significantly greater at the end of study in patients treated by PCPs (32%) compared to psychiatrists (24%, $P<0.0005$). The same relationship between physician type and symptom improvement was observed for the subgroups of senior patients (≥65 years, $P=0.03$) and those younger than 65 ($P<0.001$). Response and remission rates were also higher in the PCP group, with patients treated by PCPs having 1.4 and 1.7 times greater odds of responding and remitting, respectively, compared to psychiatrists ($P<0.0005$). There was no significant difference in congruence with the combinatorial PGx test among PCPs and psychiatrists (88% and 85%, respectively) ($P>0.1$).
Conclusions and Significance: Following combinatorial PGx testing, patients with depression exhibited greater symptom improvement when treated by PCPs than psychiatrists. This study adds to findings from previous studies, including a large randomized controlled trial for depression, which have demonstrated that combinatorial PGx testing improves patient outcomes in psychiatric treatment settings. The current study supports the use of this treatment approach in a larger patient population and primary care treatment settings.

T25. CLINICAL EFFICACY AND SAFETY OF FLEXIBLY DOSED ESKETAMINE NASAL SPRAY IN A U.S. POPULATION OF PATIENTS WITH TREATMENT-RESISTANT DEPRESSION

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Abstract: Purpose: To evaluate efficacy and safety of flexibly dosed esketamine nasal spray plus a new oral antidepressant (AD) compared with placebo nasal spray plus a new oral AD (active comparator) to improve symptoms of depression among patients with treatment-resistant depression (TRD) living in the United States.
Content: Few options exist to reduce disease severity in patients with TRD, and treatment outcomes with esketamine nasal spray plus a new oral AD are not well characterized. This analysis evaluates response, remission, efficacy, and safety of esketamine nasal spray plus a new oral AD vs placebo nasal spray plus a new oral AD in US patients with TRD.
Methodology: In this double-blind (DB), flexibly dosed, multinational, multicenter study (NCT02418585), 91 US patients with TRD were randomly assigned 1:1 to esketamine nasal spray (56 or 84 mg) plus a new oral AD or to placebo nasal spray plus a new oral AD, twice weekly for 4 weeks. Response (defined as 50% decrease in Montgomery-Åsberg Depression Rating Scale [MADRS] baseline score) and remission (MADRS score ≤12) were assessed at 24 hours; on days 8, 15, and 22; and at the 4-week DB end point. The Clinical Global Impression of Severity (CGI-S) scale was assessed at baseline; on days 4, 8, 11, 15, and 22; and at 4 weeks post–initial dose. The Sheehan Disability Scale (SDS) and Patient Health Questionnaire-9 (PHQ-9) were assessed at baseline, on day 15, and at 4 weeks post–initial dose to capture changes in patient-reported symptoms of depression and functioning.
Results: In 90 US patients analyzed (1 did not dose), responses with esketamine plus a new oral AD vs placebo plus a new oral AD (active comparator) observed at ~24 hours postdose were 11/43 (25.6%) vs 9/40 (22.5%), respectively. Responses at 4 weeks postdose were 26/40 (65.0%) vs 15/38 (39.5%), respectively. Remission rates at ~24 hours postdose were 6/43 (14.0%) with esketamine plus a new oral AD vs 4/40 (10.0%) with placebo plus a new oral AD. Remission rates at 4 weeks postdose were 18/40 (45.0%) vs 9/38 (23.7%), respectively. Improvement in MADRS total score with esketamine plus a new oral AD vs placebo plus a new oral AD observed at ~24 hours postdose was (least squares [LS] mean difference [SE]) -1.6 [2.15; P=0.225] and at day 28 was -5.5 [2.58; P=0.017]. Analysis of covariance based on the ranks of change showed a statistically significant difference between the 2 treatment groups in improvement of severity of depressive illness as measured by the CGI-S at day 4 (P=0.015) and approached significance at day 28 (P=0.027). Differences in mean changes in SDS and PHQ-9 were (LS mean difference [SE]) -5.2 [2.13; P=0.009] and -3.1 [1.52; P=0.024], respectively, at day 28. Results for these analyses favored esketamine. The most common adverse events (>10%) for esketamine plus a new oral AD were dizziness, nausea, dysgeusia, headache, throat irritation, vertigo, nasal discomfort, feeling abnormal, dissociation, hypoesthesia, insomnia, and paresthesia. The incidence of these events was similar between the US patients and the total study population.
Importance: Esketamine nasal spray plus a new oral AD compared with placebo nasal spray plus a new oral AD provides evidence supporting meaningful reduction in symptoms of major depressive disorder as evaluated using MADRS response and remission rates among US patients with TRD. In addition, esketamine nasal spray plus a new oral AD was safe and well

tolerated. Safety and response/remission results of patients from the US treatment environment were similar to the total population studied.

T26. HIGH-FREQUENCY ASSESSMENT OF MOOD AND COGNITION IN MAJOR DEPRESSIVE DISORDER USING THE APPLE WATCH

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Abstract: Background: Cognitive problems, such as inattention and memory complaints, are commonly seen in major depressive disorder (MDD), and may offer a target for intervention.1 These are observed both in self-reports and in objective neuropsychological testing.2 However, tools to assess cognitive function, which can be used in an unsupervised setting, are required to support treatment and remediation of cognitive deficits in MDD.
Methods: This study examined compliance, feasibility, and validity of a wearable high-frequency cognitive and mood assessment tool over 6 weeks. Thirty patients (age 19-63; 19 women) with mild-moderate depression who were prescribed antidepressant monotherapy participated. Brief cognitive and mood tests were administered daily through the Cognition Kit application on Apple Watch in a single-arm, unblinded, 6-week observational study. The Cognition Kit application, delivered via the Apple Watch, provided a high-resolution display for task presentation and a touch screen for logging responses: cognition was assessed with the n-back task three times daily, and depressed mood with three short questions once daily. Selected tests sensitive to depression from the Cambridge Neuropsychological Test Automated Battery (CANTAB) and patient-reported measures of depression symptom severity, social function, and perceived cognitive difficulties were administered on four occasions (Training, Baseline, Week 3, and Week 6). At the first and final visit, a semi-structured interview was carried out assessing subjective motivation and barriers to adherence. Compliance was defined as participants completing at least one assessment daily.
Results: Mean baseline (BL) PHQ-9 was 9.13 [SD3.13]; 66% of subjects had comorbid anxiety and 67% of subjects at BL were currently treated with an SSRI. Compliance was excellent for both mood and cognitive assessments (95-96%), did not deteriorate over time, and was not influenced by depression symptom severity or cognitive function at study onset. Summary measures for daily mood assessment showed good correspondence with validated questionnaires of depression, and daily cognitive assessments showed good correspondence with CANTAB cognitive tests sensitive to depression.
Conclusions: Near-patient testing using wearable devices is feasible and well tolerated by patients with depression. Good correspondence with patient-reported outcomes and objective measures was shown, providing a novel, patient-centric methodology for frequent assessment of a range of symptoms.

T27. GOAL ACHIEVEMENT AFTER A SWITCH TO VORTIOXETINE IN ADULTS WITH MAJOR DEPRESSIVE DISORDER (MDD): INTERIM STUDY RESULTS

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Abstract: Background: Traditional measures of evaluating the response to treatment for patients with MDD involve the use of clinician- and patient–reported outcomes. As the symptoms of MDD may be different for each patient, these measures may not always capture meaningful changes in a patient's condition (1). The Goal Attainment Scale (GAS) (2) Adapted for Depression (GAS-D) provides a framework for development and measurement of progress on personalized treatment goals for each patient. This approach may better reflect functional improvement from a patient perspective. The GAS has been used in other settings; however, this is the first study to use the GAS as a primary outcome measure in MDD.

Methods: This is an ongoing Phase 4, open-label, multicenter clinical trial in the U.S. (ClinicalTrials.gov ID NCT02972632), evaluating the real-world effectiveness of a 12-week (wk) course of vortioxetine (10-20 mg) treatment on patient's goal achievement. Patients with MDD who enrolled in this trial were previously treated with an antidepressant but switched to vortioxetine because of inadequate response or tolerability issues.

The primary objective of this trial is to determine the proportion of patients who achieve their pre-identified goals as demonstrated by a GAS-D score of ≥50 at wk 12. Secondary outcome measures include change (Δ) from baseline (BL) measurements in total GAS-D scores and in other patient- and clinician-reported outcome measures at 6 and 12 wks. Patient-reported outcome measures include the Patient Health Questionnaire (PHQ-9), Perceived Deficits Questionnaire-Depression (PDQ-D), Quality of Life Enjoyment and Satisfaction Scale (Q-LES-Q), and World Health Organization Well-Being Index (WHO-5). Clinician-reported outcome measures include the Clinical Global Impression Scale-Severity (CGI-S) and Clinical Global Impression Scale-Improvement (CGI-I). Additional exploratory endpoints include the Digit Symbol Substitution Test (DSST), Lam Employment Absence and Productivity Scale (LEAPS), and Virtual Reality Functional Capacity Assessment Tool (VRFCAT).

Results: As of January 19, 2018, an interim analysis of the first 60 patients enrolled was available. Approximately 88% of patients (53/60) completed treatment; the full interim analysis set (FAS) included 56 patients. Of the 60 initially enrolled, 81.4% were women and 72.9% white; the mean age was 45 years.

For the primary outcome measure, 62.3% of patients achieved a GAS-D score of ≥ 50 at wk 12, with statistically significant ($p<.05$) changes from BL noted. Additional measures of depression severity, cognitive function, cognitive performance, and work functioning showed statistically significant improvements from BL at wks 6 and wk 12 for PHQ-9 (BL mean 15.5), PDQ-D (BL mean 38.9), DSST (wk 12 only, BL mean 46.7), and LEAPS (BL mean 13.9). For the VRFCAT, non-statistically significant improvements from BL to wk 12 were observed.

Statistically significant improvements in patient measures of well-being and quality of life were also observed at wk 12 for WHO-5 and Q-LES-Q. For the clinician-reported measures of patient global mental health, statistically significant improvements were shown with the CGI-S (BL mean 4.4), as well as a numerical improvement in CGI-I (wk 6 and wk 12).

Conclusion: Results from this study indicate that a significant proportion of patients treated with vortioxetine reached their personalized treatment goals, which may otherwise have been overlooked when using traditional patient and/or clinician-reported measures of clinical

success. Results for the GAS-D primary endpoint were reflective of improvements in many other areas, including mood, quality of life, and overall well-being.

T28. DEFINITIONS OF TREATMENT-RESISTANT DEPRESSION: A NARRATIVE AND SYSTEMATIC REVIEW

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Abstract: Objectives: As part of a review proposed by the Centers for Medicare & Medicaid Services and conducted for the Agency for Healthcare Research and Quality (AHRQ), we sought to:
1) inform future discussions and decisions about how to define treatment-resistant depression (TRD) and specify the important outcomes measured in research studies, and
2) clarify how trials or observational studies might best be designed and conducted to inform clinical practice and health policy.
Data Sources: To provide a comprehensive understanding of how experts and investigators have defined and studied TRD, we first performed a narrative review of relevant literature. We considered consensus statements, practice guidelines, government materials, and other literature published from 1/1/1995 through 8/18/2017, except for systematic reviews (limited to start 1/1/2005). Next, we performed a systematic review of published studies of TRD interventions (1/1/2005 through 8/18/2017) indexed in MEDLINE®, EMBASE, PsycINFO, and Cochrane Library.
Review Methods: Trained personnel dually reviewed all titles and abstracts for eligibility. Studies marked for possible inclusion by either reviewer and those with inadequate abstracts underwent dual full-text review. Disagreements were resolved by consensus discussion. One member of the research team abstracted data; a senior investigator reviewed abstractions for accuracy and completeness.
Results: Our narrative review indicated that no consensus definition existed for TRD. We identified four basic definitions for TRD (3 for major depressive disorder [MDD]; 1 for bipolar disorder). Based on frequency of reporting in the literature, the most common TRD definition for MDD required a minimum of two prior treatment failures and confirmation of prior adequate dose and duration. The most common TRD definition for bipolar disorder required one prior treatment failure. For all TRD definitions, no clear consensus emerged on defining adequacy of either dose or duration. Little agreement exists about the best approach to diagnose TRD or the preferred outcome measure, although the Hamilton Depression Rating Scale was the most used. We found general agreement about minimizing bias by using randomization; studies have not focused on minimizing placebo effects. Evidence about the risk factors (e.g., age, sex, number of prior failed treatments, and length of current depressive episode) associated with TRD and data to assess potential prognostic factors were limited.
Only 17 percent of intervention studies enrolled study populations that met frequently specified criteria for TRD. Most studies (88%) were randomized controlled trials; all studies applied some exclusion criteria to limit potential confounders. Depressive outcomes and clinical global impressions were commonly measured; functional impairment and quality-of-life tools were rarely used.

Conclusions: No agreed-upon definition of TRD exists; although experts may converge on two as the best number of prior treatment failures, they do not agree on definitions for adequacy of either dose or duration or outcomes measures. Critical to advancing TRD research are two key steps: (1) developing a consensus definition of TRD that addresses how best to specify the number of prior treatment failures and the adequacy of dose and duration; and (2) identifying a core package of outcome measures that can be applied in a standardized manner. Our recommendations about stronger approaches to designing and conducting TRD research will foster better evidence to translate into clearer guidelines for treating patients with this serious condition.

T29. DOES CHILDHOOD TRAUMA IMPACT OUTCOMES IN ADULTS RECEIVING KETAMINE FOR DEPRESSION?

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Abstract: Introduction: Repeated intravenous (IV) infusions of the rapidly-acting NMDA receptor antagonist ketamine improves depression in 40%-61% of adults with treatment-resistant depression (TRD). Childhood trauma is associated with inferior treatment response to conventional antidepressants. This relationship has not been extensively explored with ketamine. We compared antidepressant effects of repeated IV ketamine in adults with TRD who had low or high scores on self-reported childhood trauma scales who sought treatment at an outpatient ketamine clinic.
Methods: Fifty-seven (56% female; mean age=42.6, SD=14.8) TRD patients received up to 6 IV ketamine infusions (0.5-1 mg/kg over 40-60 min) over a 3-6 week period. All patients completed at least 3 infusions, outcomes of which are reported here. Depression severity was measured prior to each infusion with the Quick Inventory of Depression Scale-Self Report (QIDS-SR). Self-reported severity of total childhood trauma, and of physical, emotional and sexual abuse, and of physical and emotional neglect were assessed with the Childhood Trauma Questionnaire (CTQ) at baseline. Repeated measures general linear models (GLM) tested the effects of childhood trauma on QIDS-SR scores across 3 infusions of ketamine. Fisher exact tests compared response (≥50% change from baseline QIDS-SR score) and remission (QIDS-SR≤5) rates between patients with low and high CTQ scores.
Results: Ketamine lowered QIDS-SR scores (baseline=18.9, SD=4; pre-4th infusion=10.8, SD=6.2; $F(2.70,143.22)=68.3$, $p<.0001$) with 79% of patients meeting response and 58% meeting remission criteria at any time point between the 1st–4th infusion, with additive effects for each additional infusion. Total CTQ score did not associate with outcomes, but there was a main effect of emotional abuse (EA; $F(1,52)=8.5$, $p=.005$) due to higher QIDS-SR scores at baseline and throughout treatment for the high EA group. Analyses also showed an emotional neglect (EN) by time interaction ($F(2.77,143.97)=3.6$, $p=.018$), indicating a stronger antidepressant effect in the low versus high EN group. High EA scores were associated with similar response but lower remission rates (high EA=47% vs low EA=79%, $p=.045$). High EN scores were associated with lower response (high EN=70% vs low EN=95%, $p=0.04$) and remission rates (high EN=44% vs low EN=81%, $p=0.012$).

Conclusion: Emotional abuse and neglect were associated with higher depression scores at baseline and throughout treatment. Repeated ketamine improved depression irrespective of childhood trauma severity, although patients with high emotional neglect benefitted less from ketamine than patients with low emotional neglect. This is also reflected by lower response and remission rates with high emotional neglect. Findings are consistent with previously established relationships between childhood trauma and depression severity, and between childhood trauma and the efficacy of conventional antidepressants. However, ketamine's response and remission rates with high childhood trauma are comparable to conventional antidepressant response rates in patients without childhood trauma, suggesting increased efficacy of ketamine for patients with childhood trauma. Strengths of the study include the evaluation of sustained (3-7 days post-infusion) rather than acute (24 hrs post-infusion) effects of ketamine. Limitations of the study include non-randomization and its open label design.

T30. IMPROVING SCREENING, ACCESS, AND OUTCOMES THROUGH VIRTUAL BEHAVIORAL HEALTH INTEGRATION INTO PRIMARY CARE

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Abstract: Provider organizations have consistently struggled to meet the need for coordinated behavioral health services due to provider shortages and financial sustainability. Carolinas HealthCare System (CHS) designed and implemented an integrated, population health approach within primary care with proven success – both clinical and financial. Our presentation will provide attendees with a detailed look into the innovative design of our integrated model and the teams, tools, and processes utilized to achieve success. CHS Behavioral Health Integration steps away from the traditional model of specialist co-location to a unique and transformative virtual model within primary care. Working in collaboration with system physician leadership, mental health screening tools were identified and standardized screening processes were incorporated into the model. Through implementation of the virtual model, primary care providers have immediate access to behavioral health services via video technology and other resources. As a result, assessment and treatment planning can begin immediately, and follow-up care can be coordinated between the behavioral health team and medical providers all in one visit. This Collaborative Care model is designed to eliminate barriers to timely access, optimize provider skills, and leverage resources across a broad geography. Integrated collaborative care drives improvements in health outcomes and a decrease in utilization of high cost health resources. Most importantly, these improvements in care delivery are positively impacting patients, family members, primary care providers, and team members.

T31. EFFECT OF BREXPIPRAZOLE ON PROLACTIN: AN ANALYSIS OF SHORT- AND LONG-TERM TRIALS IN SCHIZOPHRENIA

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Abstract: Background: Hyperprolactinaemia is an undesirable effect of most antipsychotics, considered to be due to D2 receptor blockade. Brexpiprazole is a serotonin-dopamine activity modulator that is a partial agonist at 5-HT1A and dopamine D2 receptors, and an antagonist at 5-HT2A and noradrenaline alpha1B/2C receptors, all at subnanomolar potency. Brexpiprazole is approved in the US for use as adjunctive therapy to antidepressants for the treatment of MDD, and in the US, Canada and Australia for treatment of schizophrenia, including maintenance treatment. The effect of brexpiprazole on prolactin was assessed based on pooled data from three short-term, and two long-term extension studies in patients with schizophrenia.
Methods: In two fixed-dose studies (Vector [NCT01396421] and Beacon [NCT01393613]), patients with acute schizophrenia were randomized to 0.25, 1, 2, 4 mg brexpiprazole or placebo for 6 weeks. The third study (Lighthouse [NCT01810380]) randomized patients to flexible-dose brexpiprazole (2–4 mg/day) placebo or an active reference (quetiapine XR) for 6 weeks. The extension studies (Zenith; NCT01397786 and NCT01810783) were open-label, 52-week, flexible-dose (1–4 mg/day) studies enrolling de novo patients; or patients completing Vector, Beacon or Lighthouse studies. We report levels of prolactin by sex at baseline; at Week 6 of the short-term studies; at Week 52 of the long-term studies; the proportion of patients with post-baseline elevated (>3 x ULN) prolactin values at any visit; and prolactin-related treatment-emergent adverse events (TEAEs).
Results: Mean (median) baseline prolactin values in the brexpiprazole-treated patients in the short-term studies were: 21.07 (10.44) ng/ml for females, 11.67 (7.63) ng/ml for males; in placebo-treated patients: 22.45 (11.11) ng/ml for females, 11.43 (7.99) ng/ml for males. Mean (median) changes from baseline to Week 6 in the brexpiprazole-treated patients in short-term studies were: -1.08 (3.63) ng/ml for females, -1.58 (0.26) ng/ml for males; in placebo-treated patients: -8.07 (-2.15) ng/ml for females, -2.17 (-1.08) ng/ml for males.
In the long-term studies, mean (median) baseline prolactin values were: 17.29 (12.79) ng/ml for females, 9.64 (7.71) ng/ml for males, and mean (median) changes from baseline to Week 52 were 0.48 (0.60) ng/ml for females, 0.85 (0.18) ng/ml for males.
The proportion of brexpiprazole-treated patients with >3 x ULN post-baseline elevated prolactin values in the short-term studies were: 1.5% for females, 1.6% for males; in placebo-treated patients: 3.6% for females, 3.4% for males. The proportion of patients with >3 x ULN post-baseline elevated prolactin values in the long-term studies were 5.3% for females, 2.0% for males.
In the short-term studies, the incidence of prolactin-related TEAEs was 0.6% (5/882 patients) for brexpiprazole and 0.2% (1/529) for placebo. TEAEs comprised hyperprolactinaemia (0.3% vs 0.2%), blood prolactin increased (0.1% vs 0%) and breast tenderness (0.1% vs 0%). In the long-term studies, the incidence of prolactin-related TEAEs was 1.0% (13/1,240). TEAEs comprised hyperprolactinaemia (0.2%), blood prolactin increased (0.6%), galactorrhoea, gynaecomastia and hypomenorrhoea (each <0.1%).
Conclusions: In short- and long-term studies, small changes in prolactin levels, low proportions of patients with post-baseline elevated prolactin values, and low incidence of prolactin-related TEAEs were observed after treatment with brexpiprazole.

T32. EFFECT OF ADJUNCTIVE BREXPIPRAZOLE ON DEPRESSIVE SYMPTOMS IN ELDERLY PATIENTS WITH ANXIETY OR INSOMNIA: RESULTS FROM A POST-HOC ANALYSIS

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Abstract: Introduction: Depression in the elderly is associated with considerable burden, exacerbated comorbidities, and increased mortality. In MDD, high levels of anxiety are prevalent, associated with greater illness severity, suicidality, impaired functioning, and poor response to antidepressant treatment (ADT). Sleep disturbance predicts poorer outcomes, and is a risk factor for suicidal ideation/completed suicide. Residual insomnia predicts a greater risk for relapse.

Brexpiprazole is a serotonin-dopamine activity modulator that is approved in the US as adjunctive therapy to antidepressants for the treatment of MDD. Adjunctive treatment with long-term (26-week) open-label brexpiprazole 1–3 mg/day is well tolerated in elderly patients with MDD (Aquila; NCT02400346). This post-hoc analysis assessed the efficacy of adjunctive brexpiprazole in elderly patients with MDD and symptoms of anxiety or insomnia.

Methods: Elderly patients (≥65 years) with MDD, and inadequate response to ≥1 ADT received open-label, flexible-dose brexpiprazole (1–3mg/day) adjunctive to their current ADT for 26 weeks, including a 4-week titration period. In this post-hoc analysis, patients were categorized at baseline as having anxiety (score ≥3 on MADRS item 3 [inner tension]), and as having insomnia (score ≥3 on MADRS item 4 [reduced sleep]). The efficacy endpoint was the change in MADRS Total score from baseline to Week 6 in patients with/without anxiety or insomnia.

Results: 132 patients were treated, and 88 (66.7%) completed. The main reasons for withdrawal were adverse events (AEs) (18.2%), and lack of efficacy (6.8%). The mean age was 71.4 years (26.5% ≥75 years); 81.1% were women.

A total of 98 (74%) of patients met the criteria for having anxiety at baseline. Apart from baseline CGI-S and MADRS scores, baseline characteristics and demographics did not differ between patients with/without anxiety. The mean MADRS Total scores (SD) at baseline were 27.7 (4.6) and 24.5 (3.2) for patients with/without anxiety, respectively. At Week 26, the mean changes (SD) from baseline in MADRS Total scores were -17.06 (8.1) and -13.70 (6.57) for patients with/without anxiety, respectively.

A total of 88 (67%) of the patients met the criteria for having insomnia at baseline. Apart from baseline CGI-S and MADRS scores, baseline characteristics and demographics did not differ between patients with/without insomnia. The mean MADRS Total scores (SD) at baseline were 28.3 (4.4) and 24.1 (3.2) for patients with/without insomnia. At Week 26, the mean changes (SD) from baseline in MADRS Total scores were -16.97 (8.14) and -14.41 (6.94) for patients with/without insomnia, respectively.

Patients with anxiety at baseline had an overall higher incidence of treatment-emergent AEs (TEAEs) than patients without anxiety (80.6% vs. 67.6%); no such differences were seen for patients with/without insomnia at baseline (77.3% vs. 77.3%). TEAEs with an incidence ≥5% in the group with anxiety, and twice that of those without anxiety, comprised anxiety (10.2% vs. 0%); nasopharyngitis (8.2% vs. 0%); and insomnia (7.1% vs. 2.9%). TEAEs with an incidence ≥5% in the group with insomnia, and twice that of those without insomnia comprised akathisia (11.4% vs. 2.3%); anxiety (9.1% vs. 4.5%); and diarrhea (5.7% vs. 2.3%).

Conclusions: This post-hoc analysis suggests that adjunctive brexpiprazole may be efficacious in reducing depressive symptoms and is well tolerated in elderly patients with MDD with symptoms of anxiety or insomnia.

T33. MOVING BEYOND EFFICACY AND SAFETY TO REAL-WORLD USABILITY IN THE DIGITAL MEDICINE ERA

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Abstract: Background: A Digital Medicine System (DMS) has been developed to objectively measure and report a patient's medication ingestion. The DMS consists of a medication-embedded ingestible sensor, wearable sensor (adhesive patch), and mobile- and cloud-based software applications that enable the secure collection and sharing of objective medication adherence information with healthcare professionals (HCP), family members and friends.
Objective: Test the usability of the DMS in adult subjects with serious mental illness (SMI) consisting of schizophrenia (SCH), bipolar 1 disorder (BP1) or adjunctive treatment of major depressive disorder (MDD) who are treated with oral aripiprazole.
Methods: A series of usability (NCT02219009; NCT02722967) and human factors engineering (HFE) studies were completed in order to support approval of the system by the US FDA. Patients with SCH, BP1, or MDD stabilized on oral aripiprazole were enrolled in two 8-week usability studies, and a series of human factor studies were conducted in patients with SMI, as well as (HCPs) and caregivers. The outcomes of the usability studies were the proportion of time during the trial period when the subject wears their patch, and ingestion adherence defined as the total number of ingested events registered on the digital health server/number of treatment days in the trial with good patch coverage.
Results: 122 patients were screened and 116 enrolled in the 2 usability studies; 87/116 (75.0%) completed the study. Mean ingestion adherence was 86%and mean proportion of patch wear was 74% for all 116 patients over the course of the 8-week studies; no differences were observed among patients with SCH, BP1, or MDD. In the HFE validation study, 35 subjects with SMI successfully completed 783 of 803 (97.5%) tasks involving the use of DMS. Residual risks resistant to mitigation were found to be of low severity based on the US FDA HFE guidance. An additional pragmatic clinical study will soon be initiated to measure longer-term clinical outcomes associated with DMS use vs. standard-of-care in a naturalistic, real-world setting.
Conclusions: The results of the usability and HFE studies conducted with the DMS were sufficient for FDA-approval of the first DMS; additional real-world data is important to understand the place of the DMS in clinical practice.
Disclosure: Supported by Otsuka Pharmaceutical Development & Commercialization, Inc. All authors are full-time employees of Otsuka.

T34. ADHERENCE TO LOCAL MENTAL HEALTH CENTER FOLLOW-UP APPOINTMENTS AFTER DISCHARGE FROM AN ACUTE PSYCHIATRIC HOSPITALIZATION IN A RURAL AREA

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Abstract: Background: Patients with severe mental illnesses have high rates of nonadherence to medications and care, which may subsequently lead to poor quality of life and an increased risk of relapse and hospitalization. The transition from an acute hospitalization to outpatient care is a critical time for patients. Nonadherence after discharge from a psychiatric hospitalization, when patients are at risk for medication-related adverse effects and symptomatic destabilization, may lead to rehospitalization or relapse. Rates of nonadherence in patients with mental illness may be higher in rural populations based on previous studies, though it is unclear.
Objectives: The purpose of this study was to describe adherence to outpatient follow-up appointments and long-acting injectable antipsychotic care after discharge from an acute hospitalization in a rural area. Factors related to nonadherence were also examined.
Methods: A retrospective chart review was conducted among all adult patients discharged from an acute psychiatric unit at a community teaching hospital and the local mental health center (MHC) in the rural Southwest. The primary outcome was the number of patients discharged from the psychiatric unit attending the first scheduled follow-up appointment at the local MHC. A secondary outcome was the number of patients who attended their follow-up appointments for long-acting injectable antipsychotics that were initiated during their hospitalization. Descriptive statistics and logistic regression were used to analyze data.
Results: A total of 140 patients were included in the study. Approximately 25% of patients completed their scheduled follow-up appointments. Of the 26 patients initiated on a long-acting injectable antipsychotic (LAIA) during hospitalization, 11 (42.3%) received the next scheduled dose. The average number of subsequent injections over one year was 8.7. Results from the logistic regression analysis indicated that individuals with schizophrenia were more likely to be adherent to scheduled outpatient follow-up appointments (OR = 4.04, 95% CI: 1.24 to 13.14). Results also indicated that individuals with a greater number of discharged medications were less likely to be adherent to scheduled outpatient follow-up appointments (OR = 0.87, 95% CI: 0.76 to 0.99).
Conclusions: Many patients do not attend outpatient follow-up appointments or next LAIA injection appointments after discharge from a hospital in a rural area. Additional studies should be conducted to gain a better understanding of barriers impacting adherence to follow-up care and medication use. Potential interventions could reduce the burden of complex regimens (e.g., number of discharge medications) and/or adopt approaches used in transitional care provided to patients with schizophrenia.
Importance of Findings: Assessing the rates of adherence to mental health follow-up in a rural community is the first step to addressing the problem of nonadherence. Future research is needed to examine factors related to nonadherence in order to identify global strategies to improve utilization of services and transitions across various levels of care in patients with mental illness.

T35. PROJECT STARR 911: A MODEL FOR RESEARCHERS TO ENGAGE IN SUICIDE PREVENTION

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Abstract: Introduction: The STARR Coalition is a nonprofit organization consisting of thought leaders throughout the pharmaceutical industry, contract research organizations, clinical research sites and patient advocacy groups. The organization's mission of is to build unbiased, collaborative initiatives to reduce the stigma associated with central nervous system (CNS) disorders and promote research as an option for those seeking help.
A strong link exists between mental illness and suicide. Up to 20% of individuals with a diagnosis of mental illness die by suicide. 1) Approximately 90% of those who complete suicide experience mental illness. 2) People considering suicide usually seek help: approximately 64% of individuals who attempt suicide visit a doctor within a month before their attempt. 3) Having a chronic condition increases the odds of suicide by 363%. 4) Clinical research call centers field thousands of calls on a yearly basis. The purpose of project STARR 911 is to build collaboration between clinical research and suicide prevention. The first step is to identify current practices.
Methods: We surveyed clinical research sites to identify current practices for recognizing and taking action for callers who report suicidal ideation.
Results: Preliminary results indicated that some clinical research sites have scripts for their call centers and suicide hotline information readily available. It was generally agreed that national experts in suicide prevention are preferred referral sources over local resources that can be variable in accessibility and quality. Script suggestions included asking about intent to act and to determine how long the caller has felt suicidal, to determine the acuity. Creating a designated 'warm' line for call centers and sites to use to transfer individuals with potential suicidal ideations was discussed; a specific hotline for clinical research referrals would make tracking easier. Evaluation is ongoing, and an update on activities will be provided.
Discussion: In response to the limited process identified, Project 911 will identify intervention resources that could be provided to callers. A short script and best practices for recognition and de-escalation, and a brief training program that could be made widely available and implemented, will be developed. For example, a suicide prevention program can be disseminated at investigator meetings. A tracking system to record number of successful referrals or 'warm' hand-offs to suicide prevention specialists will be implemented, if possible.
Conclusions: Research can be a part of the solution to suicide prevention. Potential suicidal ideation or behavior can be identified through clinical research call centers and referred to national suicide prevention experts in a systematic way for broad-reaching impact.

T36. ARE DRUG INTERACTION WARNINGS INFLUENCED BY DRUG COMPANY PROMOTION?

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Abstract: Warning: lithium with an SSRI can cause the Serotonin Syndrome (SS), a "Major" Interaction. From whence does this warning derive? Lithium is not strongly serotonergic, and

has been widely used with antidepressants. Could companies promoting atypicals to augment antidepressants be playing a role?

The main organizations that warn about drug-drug interactions are Micromedex, Lexicomp, Clinical Pharmacology and Cernum Multum. All attempt and claim to be free of drug company bias. Only Micromedex provides somewhat detailed reviews with references. Deliberations are private and confidential.

Micromedex includes the SS as a major interaction between lithium and SSRI's, claiming "excellent" evidence; but the references list only one of the many controlled studies using lithium to augment antidepressants (none reported the SS). Several case reports are cited, mostly from the 1990's, of unclear significance: symptoms of the SS are non-specific; diagnosis is often uncertain. There are also case reports of the SS with aripiprazole and SSRI's, but no warnings.

Liu et al. reviewed psychiatric drug interactions in three of these drug databases and found much inconsistency. Of 2155 unique severe or major interactions, only 371 were included in all three databases and only 59 had "good" or "excellent" evidence supporting them. Of these 59, 38 involved MAO inhibitors, clonidine, Phenobarbital, carbamazepine or pimozide, leaving only 21 other consistent drug-drug interactions.

Reasons to think that drug company promotion has influenced these databases:

1) Lilly considered increasing attention to QT prolongation when Geodon was marketed (information from Lilly happens to be available, but other companies probably use the same strategies).
2) Sepracor, maker of Lunesta, funded a review of the efficacy of Trazodone for sedation, concluding that there was limited evidence of efficacy.
3) Drug companies target "thought leaders," formulary committee members, etc., for special promotional efforts. Board members of Micromedex, etc. would be in this group.
4) Drug companies can influence opinions about drugs, even among academic physicians.
5) The FDA recognizes that drug companies often report additional side effects after a drug goes generic.
6) Drug companies are known to unduly influence the drug compendia which create these drug interaction databases (McKinney et.al.).

Who should care?

1) Clinicians, who need objective information about risks.
2) Teachers of psychopharmacology.
3) Insurance companies (e.g., Medicare and Medicaid) who pay for medicine.
4) Patients.

<u>Solutions:</u>

Awareness helps. The FDA regulates drug promotion, and has recognized that criticism of a competitor drug constitutes promotion. The FDA could intervene, e.g., require all initiatives of any type regarding a competitor to be reported.

<u>Related Issues:</u>

Mirtazapine and SSRI's also trigger a warning about the SS, but atypical antipsychotics with similar 5HT 2A blocking effects don't.

Why does Trazodone with an SSRI trigger a warning, though articles promote its value for sedation (without mentioning the SS)?

Conclusions: current databases of drug-drug interactions seem of questionable value and may be influenced by drug companies seeking to promote patented drugs. Additional investigation and skepticism seem warranted.

T37. APPLICATION OF NOVEL APPROACHES FOR THE DESIGN OF PREDICTION ALGORITHMS FOR ANTIDEPRESSANT EFFICACY AND SIDE-EFFECTS

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Abstract: To date, the gold standard used to determine patient response to antidepressant treatment is a depression score improvement of 50% or greater from the initial score. However, this definition does not take into account the 'time to response' different individuals exhibit, therefore not allowing for any differentiation between response rates. By taking into consideration both depression scores, and time to response, new features can be identified that may serve as predictors. In addition, not necessarily a single polymorphism, but rather combinations of genetic variations may impact the efficacy to antidepressants. We applied novel methods, to design a prediction model of efficacy to antidepressant treatment. First, we designed a response model based on the raw data of the Sequence Treatment Alternatives to Relieve Depression (STAR*D) clinical trial. Second, we applied a genome- wide association approach for genetic feature selection, and then we developed a prediction model by applying machine learning algorithms to define combinations of parameters that predict response for antidepressant medications. The use of different response models and machine learning algorithms allowed us to design a highly accurate prediction models of response and side-effects. Applying new models and new algorithmic methods on currently available large datasets can lead to novel findings which will advance our understanding of psychiatric disorders, and advance the design of accurate prediction models for psychiatric medications.

T38. POPULATION PHARMACOKINETICS OF VALBENAZINE AND ITS ACTIVE METABOLITE

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Abstract: Background: Valbenazine (VBZ) is a vesicular monoamine transporter 2 (VMAT2) inhibitor approved in the US for the treatment of tardive dyskinesia and under development for the treatment of Tourette syndrome. A population pharmacokinetic (Pop PK) model was developed to enable determination of the effects of demographic and environmental variables on the PK of VBZ and its active metabolite, [+]-α-HTBZ (NBI-98782).
Methods: Plasma VBZ and [+]-α-HTBZ concentration data from 14 clinical studies were used for the analysis. VBZ and [+]-α-HTBZ PK were simultaneously fit to a joint parent-metabolite model using NONMEM (version 7.3). The base structural model was a 2-compartment disposition model with transit compartment (N=2) absorption and linear elimination for VBZ and a 2-compartment disposition model with linear elimination for [+]-α-HTBZ. A first-order transit absorption rate constant (ktr) was used to characterize the absorption process and was

dependent on formulation and meal status. Based on metabolism data from prior studies, the fraction of VBZ metabolized to [+]-α-HTBZ was set to 35%. The effect of demographic (age, gender, race, creatinine clearance, body weight, CYP2D6 genotype [poor metabolizer (PM) or non-PM]) and environmental (dose, formulation, food, concomitant potent CYP2D6 inhibitors [e.g., paroxetine, fluoxetine, bupropion]) variables on VBZ and [+]-α-HTBZ PK was evaluated.

Results: A joint parent-metabolite model including 2-compartment disposition, transit compartment absorption, and linear elimination for VBZ and 2-compartment disposition and linear elimination for [+]-α-HTBZ adequately described the plasma concentration-time profiles of both drug molecules. A sigmoid Emax model characterized the relationship between dose and relative bioavailability, with doses greater than 35 mg having approximately 30% higher bioavailability compared to a 1 mg dose. The relative bioavailability was similar for all doses above 35 mg. Increases in baseline body weight resulted in increases in clearance and central volume of distribution for both the parent and metabolite with subsequent decreases in steady-state Cmax and AUC. A 2.5-fold increase in body weight (from 40 kg to 100 kg) resulted in exposure decrease of 38% for VBZ and 34% for [+]-α-HTBZ. After accounting for body weight, age had no clinically-meaningful effect on VBZ or [+]-α-HTBZ exposure. CYP2D6 PM were predicted to have an approximate 50% reduction in [+]-α-HTBZ clearance, which resulted in approximately 2-fold increases in steady-state [+]-α-HTBZ AUC and Cmax. Sex, solution formulation, creatinine clearance, and fed meal status were not predicted to have a clinically-meaningful impact on VBZ or [+]-α-HTBZ exposure. Predicted [+]-α-HTBZ exposure was approximately 25% higher in patients receiving a concomitant potent CYP2D6 inhibitor.

Conclusions: A simultaneous Pop PK model of VBZ and [+]-α-HTBZ was developed. Although body weight and concomitant potent CYP2D6 inhibitors can affect predicted [+]-α-HTBZ exposure, no specific VBZ dose adjustments are required based on these variables. Dose reductions may be required in individual CYP2D6 PM based on tolerability.

T39. EFFECTS OF VALBENAZINE ON AIMS RESPONSE IN PATIENTS WITH TARDIVE DYSKINESIA: ANALYSES BY PSYCHIATRIC DIAGNOSIS SUBGROUPS

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Abstract: Background: Valbenazine (INGREZZA) is a novel and highly selective vesicular monoamine transporter 2 (VMAT2) inhibitor that is approved for the treatment of tardive dyskinesia (TD) in adults. While valbenazine clinical trials utilized a response threshold of ≥50% improvement from baseline in the Abnormal Involuntary Movement Scale (AIMS) total score (sum of items 1-7), other AIMS response criteria may also be clinically meaningful. Data from 2 valbenazine trials were analyzed post hoc to explore various AIMS response criteria in schizophrenia/schizoaffective disorder (SCZ) and mood disorder (MD) patients.

Methods: Data were pooled from two 6-week, double-blind, placebo-controlled trials: KINECT 2 (NCT01733121) and KINECT 3 (NCT02274558). Pooled valbenazine dose groups

were defined as follows: 40 mg group, included 50 mg (KINECT 2) and 40 mg (KINECT 3); 80 mg group, included 75 mg (KINECT 2) and 80 mg (KINECT 3). For AIMS total score, a range of response criteria was assessed, defined as ≥10 to ≥90% improvement from baseline to Week 6. Responses based on individual AIMS items (face, lips, jaw, tongue, upper extremities, lower extremities, trunk) were also assessed. Individual AIMS item response was defined as an improvement from a score ≥2 (mild to severe) at baseline to ≤1 (minimal to none) at Week 6, which is a stricter threshold than the shifts previously analyzed (≥3 [moderate or severe] at baseline to ≤2 [mild to none] at Week 6). All analyses were conducted in the SCZ and MD subgroups. The odds ratio (OR) and number needed to treat (NNT) were estimated for all response analyses (valbenazine dose vs. placebo).
Results: The SCZ subgroup included 204 participants (40 mg, n=54; 80 mg, n=70; placebo, n=80) and was larger than the MD subgroup (N=114; 40 mg, n=28; 80 mg, n=42; placebo, n=44). AIMS mean total scores at baseline were lower in the SCZ subgroup (40 mg, 8.8; 80 mg, 9.4; placebo, 8.6) than in the MD subgroup (40 mg, 11.4; 80 mg, 10.0; placebo, 10.2). In both subgroups, AIMS total score response rates at Week 6 were higher with valbenazine (40 and 80 mg) relative to placebo at all response thresholds (10%-90%). A clinically meaningful OR >2 and NNT <10 were found with valbenazine 80 mg for responses ≥10% to ≥80% in SCZ and for ≥10% to ≥60% in MD. For individual AIMS item responses, both valbenazine doses in the SCZ subgroup were more favorable than placebo in all body regions, except for jaw and lower extremities (both 40 mg). In the MD subgroup, AIMS item response rates were higher for both doses of valbenazine versus placebo in all regions. ORs >2 for valbenazine 80 mg were observed in the face (MD), lips (MD), jaw (MD), tongue (SCZ), upper extremities (MD), lower extremities (MD), and trunk (both subgroups). NNTs <10 for valbenazine 80 mg were found in the face (both), lips (MD), jaw (both), tongue (SCZ), upper extremities (both), lower extremities (MD), and trunk (both).
Conclusions: A clinically relevant reduction in abnormal movements was demonstrated with valbenazine in both psychiatric diagnosis subgroups, as evidenced by several measures of therapeutic response.

T40. THE EFFECT OF TREATMENT EXPECTATION ACROSS DIFFERENT CONDITIONS AND ON DRUG EFFICACY

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Abstract: Recent evidence suggests that patients' expectations can have a large influence on treatment outcomes and drug efficacy (1). The effectiveness of a pharmacological treatment is measured by its therapeutic benefit and adverse effects: However, it has been long recognized that an individual's beliefs and expectations can significantly influence the improvement (placebo effect) or worsening (nocebo effect) in response to even an inactive compound (2,3). This suggests that any drug treatment encompasses physiological and psychological components. For example, in Parkinson's disease, positive expectation induced release of dopamine in the striatum and changes of firing pattern of subthalamic nucleus neurons; in depression, placebo treatment caused metabolic changes in different brain region associated with clinical response; in pain, positive expectation induced activation of endogenous opioids. Furthermore, there have been reports on the positive and negative expectancy effects on the

analgesic efficacy of the opioid (4). For example, positive treatment expectancy substantially enhanced the analgesic benefit. In contrast, negative treatment expectancy abolished opioid analgesia. These subjective effects were substantiated by significant changes in the neural activity in the brain confirmed by fMRI. This review will provide an integrated model of patients' expectations in health outcomes and promote optimal patient-doctor interactions, and effective management of symptoms.

T41. IS THERE A RELATIONSHIP BETWEEN NICOTINE DEPENDENCE AND WITHDRAWAL WITH CURRENT AND PAST DIAGNOSIS OF ANXIETY AND DEPRESSIVE DISORDERS?

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Abstract: Background: Nicotine use and dependence are major public health concerns. Similarly data suggests that anxiety and depression are prevalent amongst nicotine users. We wanted to see if there was any relationship between nicotine dependence and withdrawal with current and past anxiety and or depression diagnosis. Literature suggests that there is high nicotine use and dependence in patients who suffer from anxiety and depression which may result in poorer outcomes in smoking cessation trials for these patients. Nicotine withdrawal symptoms worsen on quitting and represent a constellation of symptoms including dysphoria, anxiety, restlessness, poor sleep and irritability. Nicotine dependence and withdrawal are often measured by using Penn State Cigarette Dependence Index (PSCDI) and the Minnesota Nicotine Withdrawal Scale (MNWS).

Method: We recruited 188 current smokers who had no plans to quit smoking in the next 6 months to participate in a randomized clinical trial to observe the efficacy of reduced nicotine cigarettes in patients with anxiety and depressive disorders. Mini International Neuropsychiatric Interview (MINI) was used to screen and diagnose mental health conditions prior to the participants enrolling in our study. Only nicotine users/smokers with a current or past diagnosis of anxiety or depressive disorder were enrolled in our study. We used PSUCDI and MNWS to measure nicotine dependence and withdrawal symptoms at baseline, while participants were still smoking their usual number and brand of cigarettes. Kruskal-Wallis tests were used to test the differences in scores between those with current and those with past diagnoses of anxiety and depression.

Results: There was a pattern in which those participants who met the current diagnostic criteria for anxiety and depression (i.e. had current history only) had higher measures than those meeting past diagnostic criteria of anxiety and or depression. Both dependence scores (PSCDI: 14.2 for current versus 12.4 for past, $p=0.02$) and current withdrawal symptom scores (MNWS 19.8 for current versus 8.0 for past, $p=<0.01$) were significantly higher for those meeting current versus past diagnosis of anxiety and depression.

Discussion: Participants who met the diagnostic criteria for both current anxiety and depressive disorders had high scores on measures of nicotine dependence and withdrawal compared to those with a past history of anxiety and depression. It is possible that active smokers with current anxiety and depressive disorders have in particular difficulty in quitting smoking due to nicotine withdrawal (dysphoria, anxiety, restlessness, poor sleep, irritability etc.).

This suggests that adequate dose on smoking cessation medications (e.g. nicotine replacement therapy or varenicline) are particularly important for smokers with anxiety or depressive

disorder in addition to their appropriate psychotropic medications when attempting to quit smoking.

T42. MDMA-ASSISTED PSYCHOTHERAPY FOR TREATMENT OF CHRONIC POSTTRAUMATIC STRESS DISORDER (PTSD): FINDINGS FROM PHASE 2 CLINICAL RESEARCH TRIALS

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Abstract: Background: The Multidisciplinary Association for Psychedelic Studies (MAPS) recently completed FDA-regulated Phase 2 clinical trials of MDMA-assisted psychotherapy for the treatment of posttraumatic stress disorder (PTSD). MDMA stimulates release of serotonin, and to a lesser extent (nor)epinephrine and dopamine, with a subsequent enhancement of oxytocin and cortisol. The combined neurobiological effects of MDMA increases compassion for self and others, reduces defenses and fear of emotional injury, while enhancing communication and capacity for introspection, all of which may facilitate the therapeutic process.

Methods: Six double-blind, placebo-controlled studies were carried out to investigate the use of administering MDMA during 2-3 psychotherapy sessions spaced a month apart that were each accompanied by 3 non-drug integrative therapy sessions. Participants with chronic PTSD and a Clinician Administered PTSD scale (CAPS-4) Total Score of 50 were enrolled in the studies.

Results: The primary endpoint occurred after 3 preparatory non-drug sessions, 2-3 MDMA-assisted psychotherapy sessions spaced a month apart, and non-drug integrative sessions. When data was pooled across the 6 studies, a significant group effect was detected in change in CAPS-4 Total scores (n=103, placebo subtracted Cohen's d effect size 0.9, $p<0.001$). At the primary endpoint, 23% (n=31) for placebo/comparator group (0-40 mg MDMA) and 53% (n=72) of active MDMA group (75-125 mg) no longer met PTSD criteria. Significant improvements in depression (Beck Depression Inventory-II, $p<0.05$) and sleep quality (Pittsburgh Sleep Quality Index, $p<0.05$) were also measured in the active MDMA groups. The cause of PTSD, whether from war, childhood abuse, or sexual assault, did not impact the treatment outcomes. Remarkably, at the 12-month follow-up visit 67.7% (n=90) participants did not meet criteria for PTSD, demonstrating the long-term durability of this novel treatment. Mirroring study measure findings, participants reported extreme gains in life outcomes, such as enhanced relationships and increased effectiveness at their jobs or the ability to return to work. Physiological vital signs and adverse event rates support an acceptable risk/benefit ratio.

Conclusions: MDMA treatment was well-tolerated, with a good safety outcomes in these controlled clinical settings with limited administrations. FDA granted Breakthrough Therapy designation for MDMA-assisted psychotherapy for treatment of PTSD. Phase 3 trials at 15 sites in US, Canada, and Israel will commence in Spring 2018. If findings are replicated, MDMA-assisted psychotherapy could be a FDA-approved treatment for PTSD by 2021.

T43. A RANDOMIZED CLINICAL TRIAL USING AUDITORY-BASED COMPUTERIZED COGNITIVE TRAINING IN PATIENTS WITH CHRONIC SCHIZOPHRENIA IN RESIDENTIAL CARE: INTERACTION OF ANTICHOLINERGIC BURDEN ON TREATMENT EFFECTS

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Abstract: Background: Impairments in early auditory information-processing contribute to cognitive deficits in schizophrenia (SZ). Targeted cognitive training (TCT) is an emerging computerized intervention for remediating these deficits in SZ. TCT enhances "bottom-up" information processing through adaptive and intensive exercises designed to increase the fidelity of low-level auditory discrimination in SZ. TCT-associated gains in SZ are thought to depend on appropriate brain cholinergic signaling, but SZ patients are vulnerable to elevated anticholinergic load stemming from psychotropic medications. Reduced or abnormal brain cholinergic signaling is known to lead to cognitive deficits in other diseases (i.e., dementia), but the relationship between cholinergic signaling in the context of real-world TCT trials are not well characterized. Here we report preliminary findings from an ongoing randomized clinical trial investigating the effectiveness of TCT in SZ inpatients in a transitional care facility and the interaction of anticholinergic burden on treatment effects.

Methods: Patients with SZ were randomized to treatment as usual (TAU) or treatment as usual + TCT. The groups did not differ in demographic, clinical, or cognitive variables at baseline. Anticholinergic burden was calculated from medical records using the Anticholinergic Cognitive Burden Scale (ACCBS). Auditory discriminability, cognitive functioning, and symptom scores were assessed before and after a course of TCT. Data were analyzed using linear mixed effects models. No group differences in ACCBS scores were present at baseline or follow up.

Results: TCT was associated with significant improvements in auditory discriminability (d=0.63), verbal learning and memory (d=0.82), and positive symptoms (d=-0.62). Baseline ACCB negatively correlated with change in verbal learning (TAU, r=-.61, $p<0.02$; TCT, r =0.14, NS) and auditory discriminability (TAU, r=-.53, $p<0.05$; TCT, r = 0.41, NS) in TAU but not TCT group.

Conclusions: TCT improved auditory discrimination, cognitive functioning and symptoms in SZ patients in locked residential care. Anticholinergic burden negatively correlated with measures of auditory discrimination and cognition in the TAU group, but not in those receiving TCT. This pattern of results supports the idea that improving the fidelity of low-level auditory sensory processing can yield clinically meaningful outcomes, even in in SZ patients with a range of anticholinergic burden. These results also imply that TCT may protect from anticholinergic burden-associated impairment in SZ. Future studies are needed to identify strategies that optimize brain cholinergic signaling in SZ to better support cognitive training in SZ patients.

T44. DOES CULTURE AFFECT THE SEVERITY OF NEGATIVE SYMPTOMS IN SCHIZOPHRENIA?

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Abstract: Introduction: Norms for affective expression and social behavior are highly impacted by local culture. (1) Negative symptoms, which assess emotional expression and social behavior/occupational behavior are an enduring aspect of schizophrenia responsible for much of the illness's functional impairment. (2) Global clinical trials in schizophrenia pool data utilizing negative symptoms measurements derived from highly diverse cultures. We hypothesized that negative symptom measurement would be regionally impacted by cultural norms.
Methodology: Baseline data from 2,123 subjects participating in multiple phase 2 and phase 3 schizophrenia studies focusing on negative symptoms were analyzed. All raters received standardized interview and rater training for assessment of psychotic and negative symptoms. We used one-way analysis of variance (ANOVA) with post-hoc Bonferroni comparison tests to assess whether baseline differences between regions (Asia, Eastern Europe, Western Europe, North America, South America) exist on the PANSS total score, Marder Negative Factor score, PANSS expressive deficits subscale (N1, N3, N6, G5, G7 and G13) and PANSS avolition/apathy subscale (N2, N4 and G16).
Results: There were significant effects of region on all assessed variables, specifically the PANSS total score [$F(4, 2118) = 5.20$, $p < 0.001$]; Marder Negative Factor Score [$F(4, 2118) = 34.50$, $p < 0.001$]; PANSS expressive deficit subscale [$F(4, 2118) = 7.83$, $p < 0.001$] and PANSS avolition/apathy subscale [$F(4, 2118) = 35.78$, $p < 0.001$].
Discussion: In this post-hoc analysis there were modest, but statistically significant differences by region in PANSS totals and negative symptoms measured by the PANSS. All raters received similar standardized training in interview skills and measurement of psychotic and negative symptoms. The results suggest that expression and/or perception of negative symptoms is altered by local culture. If replicated in larger samples the potential psychometric influence of such differences may need to be considered in statistical plans for global negative symptom clinical trials.

T45. EXPLORING THE UTILITY OF MACHINE LEARNING FOR PREDICTING WITHIN-PANSS ERRORS IN SCHIZOPHRENIA CLINICAL TRIALS DATA

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Abstract: Introduction: Within-PANSS errors represent logical inconsistencies between individual PANSS items. The presence of within-PANSS discrepancies is frequent in schizophrenia data and varies considerably among different study types (1). We have previously identified a significant association between the presence of within-PANSS errors in the screening period with the presence of these errors after subject randomization (1) and demonstrated the detrimental effect of within-PANSS errors on placebo response (2). In the current analysis, we explore the utility of machine learning in using screening and baseline data to predict which subjects will be affected by within-PANSS errors after randomization.

Methods: Screening and baseline data collected from 8,544 subjects entering 21 schizophrenia clinical trials were randomly split into training and testing datasets of equal size. Using Weka (Weka 8.3.2), we trained seven different machine learning classification algorithms (OneR; J48; Random Forrest; Logistic Model Tree; Logistic; Support Vector Machine; Multilayer Perceptron) using the training data with 10-fold cross validation. We assessed the performance of these models with respect to sensitivity, specificity and correctly classified cases in predicting post-baseline within-PANSS errors in the testing dataset.
Results: At least one within-PANSS error was recorded in 27.3% of all collected visits. 3,812 (44.6%) subjects were affected by at least one error in the screening phase and 4,448 (52%) subjects after baseline. From the tested classifiers, the best performance with respect to sensitivity and specificity was observed in Random Forrest classifier with achieved sensitivity of 71.7% and specificity of 74.7%, correctly classifying 73.1% of cases.
Discussion: Our preliminary results suggest that machine learning algorithms applied on screening and baseline data have utility in predicting post-baseline occurrence of within-PANSS errors. The fact that post-baseline errors can be readily predicted from screening and baseline data with acceptable degrees of sensitivity and specificity offers unique opportunities to focus training and data monitoring resources to those raters and sites at highest risk of developing these post-baseline errors. Additionally, built into intelligent eCOA solutions, these algorithms could gate randomization of high at-risk subjects until the responsible raters are successfully remediated. Currently, we are validating these algorithms in several ongoing schizophrenia studies.

T46. PSYCHOPHARMACOLOGY AND PRODROMAL PSYCHOSIS: PRESCRIBING PATTERNS AND PHARMACOLOGICAL PREDICTORS IN A CLINICAL POPULATION WITH ATTENUATED PSYCHOSIS SYNDROME

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Abstract: Introduction: Conversion rates from the DSM-5-defined Attenuated Psychosis Syndrome (APS) to schizophrenia/schizoaffective disorder, and risk factors for conversion in this population, have previously been reported including identification that treatment with psychotropic medications in the period prior to APS was associated with decreased risk of conversion to full-scale schizophrenia. However, data on specific classes of medications have not been reported. The current study investigates psychopharmacological interventions used in a clinical population of individuals meeting diagnostic criteria for APS, both prior to the period of APS diagnosis, as well as during the monitoring period for conversion to schizophrenia.
Methods: A secondary analysis was conducted of a database of individuals meeting diagnostic criteria for APS to further examine psychopharmacological interventions in this population. Prescribing patterns, both pre-APS and during the period of monitor for conversion to full-scale psychotic disorders, are reported my medication class. Individual classes of medications were examined in relation to conversion to full-scale schizophrenia/schizoaffective disorder to identify risk factors for conversion, as well as in relation to suicide attempts (SA's). Chi-square analyses were used to analyze dichotomous variables to determine the association between each medication class and conversion to schizophrenia/schizoaffective disorder and SA's.

Results: 150 APS individuals were included in our sample. 57.3% had at least 1 trial with a psychotropic medication prior to the APS diagnosis. The most common medications prescribed were second generation antipsychotics (SGA's) (36.0%), antidepressants (28.7%), and ADHD medications (25.3%). During the period of monitoring for conversion, the vast majority of individuals received treatment with psychotropic medications (94.0%), with the most commonly prescribed classes being SGA's (86.0%), mood stabilizers (36.0%), benzodiazepines (30.7%) and antidepressants (30.7%). When analyzing predictors of conversion to schizophrenia, treatment with an SGA during the period prior to APS diagnoses was shown to be a protective factor against conversion to schizophrenia (p=0.048). In contrast, during the period of APS monitoring, treatment with a new SGA's (p=0.008) and benzodiazepines (p=0.006) were both associated with increased risk of conversion to schizophrenia; treatment with an ADHD medication was associated with decreased risk of conversion (p=0.009). In regards to predictors of lifetime SA's, in the pre-APS period treatment with antidepressants (p=0.002), mood stabilizers (p=0.017), and "other psychiatric medications" (p=0.020) were all associated with increased risk of lifetime SA's. During the APS monitoring period, no medication classes were shown to be either protective against, or risk factors for, suicide attempts.
Conclusions: Our study shows that APS individuals were prescribed a variety of psychotropic medications, both prior to the diagnosis of APS, as well as during the period of monitoring for conversion to schizophrenia. Certain classes of medications were shown to be either risks factors for, or protectors against, conversion to schizophrenia, as well as, SA's. Although these results are of interest, the data should be interpreted with caution, as due to methodological difficulties, a number of confounders may be presents such as co-occurring illnesses and illness severity.
More research in the area is warranted.

T47. LONG-TERM EFFECT OF BREXPIPRAZOLE ON SELECTED ITEMS AFFECTING SOCIAL FUNCTIONING AND QUALITY OF LIFE IN EARLY-EPISODE PATIENTS: RESULTS FROM A POST-HOC ANALYSIS IN PATIENTS WITH SCHIZOPHRENIA

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Abstract: Introduction: Treatment guidelines emphasize that maintaining or improving individual patients' level of functioning and quality of life should be one of the major goals for management of schizophrenia. It is critically important in early-episode schizophrenia, if patients are to return to premorbid functioning. Brexpiprazole is a serotonin–dopamine activity modulator that is a partial agonist at 5-HT1A and dopamine D2 receptors, and an antagonist at 5-HT2A and noradrenaline alpha1B/2C receptors, all with subnanomolar potency. Here, we describe the effects of brexpiprazole in early-episode schizophrenia on long-term social functioning and anxiety/depression factors based on pooled data from patients in two short-term, placebo-controlled studies (Vector; NCT01396421 [1] or Beacon; NCT01393613 [2]) who continued in the open-label extension of these studies (Zenith; NCT01397786).
Methods: In the two similarly designed short-term studies, patients with acute schizophrenia were randomly assigned to fixed once-daily doses of brexpiprazole 0.25 mg (Vector), 1 mg

(Beacon) 2 mg, 4 mg or placebo for 6 weeks. The long-term study was an open-label, 52-week, safety extension study with flexible-dose (1 to 4 mg/day) brexpiprazole. The early-episode group was defined as patients who were ≤40 years of age with ≤5 years' duration of illness and the analysis was conducted on patients who received brexpiprazole in the parent studies and continued in the open-label extension study. Social functioning was assessed by mean change from baseline on the PANSS Prosocial subscale (P03, P06, N02, N04, N07, G16), and on the Modified Prosocial subscale (N02, N04, N05, G16). The effect on anxiety/depression, which affects quality of life in patients with schizophrenia [3], was assessed by the mean change from baseline on the four items of PANSS Marder factor for anxiety and depression (G02, G03, G04, G06).
Results: A total of 442 patients treated with brexpiprazole in the short-term studies continued in the extension study. Of these, a total of 111 patients qualified as early-response and were included in the analysis (mean age 28). Over 43% (48/111) of patients completed 58 weeks of treatment with brexpiprazole.
Mean (standard deviation; SD) total score for the PANSS Prosocial subscale at baseline was 22.3 (3.9). Mean (SD) change from baseline in Prosocial subscale total score was -6.5 (4.1) at Week 6 (n=111); and -10.9 (4.4) at Week 58 (n=47). Mean (SD) total score for the PANSS Modified Prosocial subscale at baseline was 14.4 (3.1). Mean (SD) change from baseline in Modified Prosocial subscale total score was -2.9 (2.8) at Week 6; and -5.6 (3.0) at Week 58. Mean (SD) total score for the PANSS Marder factor Anxiety/Depression subscale at baseline was 11.3 (2.9). Mean (SD) change from baseline in Anxiety/Depression subscale total score was -3.9 (2.7) at Week 6; and -5.7 (3.0) at Week 58.
Conclusions: Patients with early episode schizophrenia receiving brexpiprazole for up to 58 weeks showed improvement in PANSS Prosocial, Modified Prosocial, and Marder factor scores for Anxiety/Depression indicating that brexpiprazole can improve early-episode patients' level of functioning and quality of life compared to baseline.

T48. GENETIC AND METABOLITE VARIABILITY IN FOLATE METABOLISM APPLIED TO AN INSULIN RESISTANCE MODEL IN PATIENTS WITH SCHIZOPHRENIA ON ATYPICAL ANTIPSYCHOTICS

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Abstract: Background: Our group has identified specific variants related to folate's pharmacogenomic metabolism (methylenetetrahydrofolate reductase gene MTHFR 1298 A>C, rs1801131; MTHFR 677 C>T, rs1801133), that are associated with the increased cardiovascular disease (CVD) risk in schizophrenia. However, the mechanistic underpinnings behind these association are unexplored. As folate metabolism is part of the network of cycles involved in one carbon metabolism, that include the kynurenine pathway, understanding the impact of disrupted folate metabolism on other metabolites in relation to CVD is critical. Therefore, this pilot study applied genetic and metabolite data to examine the relationship between folate pharmacogenomics, metabolomic markers, and insulin resistance (as measured using the homeostatic model of insulin resistance (HOMA IR) as a measure of CVD.

Methods: Participants in this pilot analysis were selected from an ongoing cross-sectional study on CVD risk in schizophrenia. Inclusion criteria for the parent study required a stable antipsychotic regimen for at least 6 months, and additional criteria for this pilot analysis included use of an atypical antipsychotic and no current diabetes diagnosis. Following DNA extraction from fasting whole blood, samples were genotyped for variants rs 1801131 and rs 1801133. Serum metabolite concentrations were obtained with NMR following extraction. A least squares regression model was used to identify associations with log(HOMA IR) values based on the following effects: serum glutamate, glycine, and serine concentrations, dietary folate intake, and carriers of the variant alleles for the selected genotypes (MTHFR 1298 A carriers and 677 T carriers).
Results: A total of 66 participants were included with an average age (± SD) of 46.5 (7.6) years, 33 % were female, 51 % were smokers, mean BMI (± SD) was 32.5 (7.8) kg/m2, median fasting insulin (IQR) 17.3 (10.6-26.8) mU/mL, mean fasting glucose (± SD) 94.8 (12.1) mg/dL, and mean log (HOMA IR) (± SD) was .63 (0.29). Folate variants followed Hardy Weinberg equilibrium. Overall, the model demonstrated an ability to predict log (HOMA IR) values with an adjusted R2 of 0.34 and a p value of 0.0003. Significant effects in the model were variant carriers of MTHFR 1298 (p = 0.0101), glutamate (p= 0.0011) and glycine (p= 0.0147). Presence of the MTHFR 677 variant allele approached significance (p= 0.0520). Glutamate and carriers of the MTHFR 1298 variant allele were correlated with log(HOMA-IR), whereas glycine concentrations trended inversely with log (HOMA-IR).
Conclusions: In agreement with our previous work, presence of pharmacogenomic variants that decrease the functional capacity of the MTHFR enzyme are associated with increased risk for cardiovascular disease, as measured in this instance by log (HOMA IR). Furthermore, glycine concentration trended inversely with HOMA-IR, suggesting that increased presence of methyl-donating groups is associated with lower measures of insulin resistance. Ultimately, these results will need to be replicated in a significantly larger population to identify predictive models with adequate power to be clinically useful.

T49. A LONG-TERM OPEN-LABEL, ROLLOVER PHASE 3B STUDY OF VALBENAZINE FOR TARDIVE DYSKINESIA

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Abstract: Background: Tardive dyskinesia (TD) is a persistent and potentially debilitating movement disorder associated with prolonged exposure to antipsychotics and other dopamine receptor blocking agents (DRBAs), and often requires long-term treatment. Valbenazine (INGREZZA), which is approved for the treatment of tardive dyskinesia (TD) in adults, has been evaluated in several clinical trials including randomized controlled (KINECT, KINECT 2, KINECT 3), long-term extension (KINECT 3 extension), and one-year open-label (KINECT 4) studies. The present rollover study (NCT02736955) was conducted to further investigate the long-term safety and effectiveness of valbenazine in participants who have completed the KINECT 3 and KINECT 4 studies.

Methods: Key eligibility criteria included: adult 18 to 85 years; completion of KINECT 3 or 4; maintenance medications (for schizophrenia, schizoaffective disorder, or mood disorder) at stable doses; psychiatrically stable (Brief Psychiatric Rating Scale score <50); and no risk of active suicidal ideation or behavior per Columbia-Suicide Severity Rating Scale scores. Participants received open-label valbenazine for up to 72 weeks or until valbenazine became commercially available. After initiation at 40 mg for 4 weeks, dosing was escalated to 80 mg based on the investigators' assessment of safety/tolerability and clinical assessment of TD; a subsequent reduction to 40 mg was allowed if 80 mg was not tolerated (80/40 mg group). Changes in TD were evaluated at baseline and at Weeks 12, 24, 48, 60, and 72 using the Clinical Global Impression of Severity-TD (CGIS-TD: a 7-point scale, ranging from 1=normal, not at all ill to 7=among the most extreme ill patient). CGIS-TD analyses included mean change from baseline and percentage of participants with a score of 1 (normal/not ill) or 2 (borderline ill). Safety assessments included treatment-emergent adverse events (TEAEs). All outcomes were analyzed descriptively.
Results: Preliminary topline results are available for 160 participants who received ≥1 dose of valbenazine and had ≥1 post-baseline efficacy or safety assessment (40 mg, n=35; 80 mg, n=117; 80/40 mg, n=8). The percentage of participants at Weeks 12, 24, 36, and 48 were 96.3%, 80.6%, 56.9% and 35.6%, respectively. Few participants reached Week 60 (n=4) or Week 72 (n=0) because valbenazine became commercially available during the study. Baseline characteristics in the overall population were as follows: men, 50.6%; white, 69.4%; black/African-American, 29.4%; schizophrenia/schizoaffective disorder, 65.0%. The mean CGIS-TD scores at baseline were 3.9 for both dose groups and the changes from baseline to Week 48 were -1.3 (40 mg) and -1.9 (80 mg). The percentage of participants with CGIS-TD score ≤2 (normal/not ill or borderline ill) increased from baseline (40 mg: 5.7%; 80 mg, 18.1%) to Week 48 (40 mg: 46.2%; 80 mg: 74.4%). The overall incidence of TEAEs was 53.1%; 10.0% of participants had a serious TEAE, and 5.6% had a TEAE leading to study discontinuation. Four deaths were observed during the study, none judged as treatment-related. The most commonly reported TEAEs were back pain and urinary tract infection (4.4% each).
Conclusions: Valbenazine was generally well tolerated and no new safety signals were observed. Clinician-based assessments indicated ongoing and meaningful TD improvements in participants who received valbenazine treatment for up to 60 weeks in the current study following 1 year of treatment in a previous study.

T50. EFFECTS OF BREXPIPRAZOLE ON LONG-TERM PERSONAL AND SOCIAL FUNCTIONING IN SCHIZOPHRENIA

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Abstract: Background: Brexpiprazole is a serotonin–dopamine activity modulator that acts as a partial agonist at 5-HT1A and dopamine D2 receptors, and as an antagonist at 5-HT2A and noradrenaline alpha1B/2C receptors, all with subnanomolar potency. Brexpiprazole is approved in the US as adjunctive therapy to antidepressants for the treatment of Major Depressive Disorder, and in the US, Australia and Canada as monotherapy for the treatment of schizophrenia. Here we evaluate the long-term effect of brexpiprazole on personal and social functioning in patients with schizophrenia, who participated in one of the two pivotal phase 3

randomized, placebo-controlled, 6-week studies in acute schizophrenia (Vector; NCT01396421 [1] or Beacon; NCT01393613 [2]) and continued in the 52-week open-label extension study (Zenith; NCT01397786), i.e., with up to 58 weeks of exposure to brexpiprazole.
Methods: The Personal and Social Performance (PSP) scale (a validated clinician-rated scale) was used to measure personal and social functioning in the domains of: socially useful activities (e.g., work and study); personal and social relationships; self-care; and disturbing and aggressive behaviors. Individual item scores range from 1 to 6 (1 = absent and 6 = very severe). Based on these assessments, the global score ranges from 1 to 100, where lower scores indicate poorer functioning (71–100, mild functional difficulty; 31–70, varying degrees of disability; 1–30, minimal functioning needing intense support and/or supervision). Changes from baseline in PSP Total score and individual items were analyzed using a mixed model repeated measures (MMRM) approach. Functional PSP response was defined as a ≥10-point category change from baseline to Week 58.
Results: Mean (standard deviation, SD) PSP Total score at baseline was 45.1 (11.5). Least squares (LS) mean (standard error, SE) change from baseline in PSP Total score was 16.9 (1.05) at Week 6 (n=403); 21.6 (1.15) at Week 32 (n=242); and 23.0 (1.17) at Week 58 (n=180), resulting in a mean (SD) PSP Total score of 68.5 (11.8) at Week 58. LS mean (SE) changes from baseline to Week 58 in individual PSP items were: -1.5 (0.09) for socially useful activities; -1.39 (0.09) for personal and social relationships; -1.09 (0.07) for self-care; and -0.55 (0.06) for disturbing and aggressive behaviors. At Week 58, 149/180 (82.8%) of patients were classified as functional responders, and 72/180 (40%) of patients had a mean PSP Total score ≥71.
Conclusions: Patients receiving brexpiprazole 1–4 mg/day over 58 weeks showed a mean improvement in PSP Total score of 23 points over the course of treatment, to a total of 68.5 points, representing a clinically meaningful improvement in their personal and social functioning.

T51. SUBMISSION WITHDRAWN

T52. ARIPIPRAZOLE LAUROXIL NANOCRYSTAL® DISPERSION: A POTENTIAL 1-DAY INITIATION REGIMEN FOR LONG-ACTING ARIPIPRAZOLE LAUROXIL

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Abstract: Background: Aripiprazole lauroxil (AL) is a long-acting injectable antipsychotic indicated for the treatment of schizophrenia. Currently, the first AL dose requires 21 days of oral aripiprazole supplementation. To provide a greater range of options for this critical initiation period, a 1-day initiation regimen has been developed utilizing a nano-crystalline milled dispersion of AL (ALNCD). The smaller nano-particle size enables faster dissolution, which is intended to yield rapid achievement of therapeutic levels of aripiprazole when ALNCD is given with the first AL dose. When starting AL in a hospital setting, a 1-day initiation regimen could serve as an important alternative to ensure therapeutic antipsychotic levels without oral medication at the time of discharge. Here, we report the findings of a

pharmacokinetic (PK) and safety study evaluating the 1-day initiation regimen for starting long-term AL therapy.
Methods: This was a blinded, randomized, phase 1, PK, safety, and tolerability study that compared the 1-day initiation regimen with a 21-day oral aripiprazole regimen. The 1-day initiation regimen consisted of a single injection of ALNCD and a single 30 mg dose of oral aripiprazole that, together, was hypothesized to achieve aripiprazole concentrations that are comparable with the 21-day regimen. Patients were randomized 1:1:1:1 to either the 1-day initiation regimen or the 21-day initiation regimen (15 mg/day oral aripiprazole), plus a dose of AL 441 or 882 mg.
Results: In total, 161 patients were enrolled and 133 patients completed the study. Each 1-day initiation regimen group had comparable aripiprazole exposure to each corresponding 21-day initiation regimen group. Overall, the most common adverse events (≥5.0%) were injection-site pain, headache, increased weight, insomnia, dyspepsia, and anxiety. In total, 9 akathisia events occurred (4 events in 4 patients and 5 events in 2 patients in the 1-day and 21-day initiation regimen groups, respectively; 8 of these were mild and none led to discontinuation).
Conclusions: The combination of ALNCD and 30 mg oral aripiprazole (as part of a 1-day initiation regimen with AL) was a well-tolerated, adequate substitute for 21 days of oral aripiprazole. ALNCD may offer an alternative AL starting regimen to ensure therapeutic levels of antipsychotic coverage throughout the initial 21 days of treatment. The ALNCD 1-day initiation regimen is currently under review by the FDA.

T53. A PHASE II, RANDOMIZED, DOUBLE-BLIND STUDY OF ALKS 3831 IN SCHIZOPHRENIA AND CO-OCCURRING ALCOHOL USE DISORDER

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Abstract: Background: Over a third of people with schizophrenia (SZ) have co-occurring alcohol use disorder (AUD), yet there is a dearth of randomized clinical trial (RCT) data evaluating possible efficacy of new pharmacologic treatments for this challenging comorbidity. ALKS 3831 is composed of a flexible dose of the antipsychotic olanzapine (OLZ) and a fixed dose of samidorphan (10 mg; a μ-opioid receptor antagonist). This phase 2 RCT compared the efficacy, safety and tolerability of ALKS 3831 in patients with SZ and active AUD.
Methods: Key inclusion criteria were adults (18–65) with a primary diagnosis of SZ complicated by AUD, with a recent exacerbation of SZ. Consenting patients received a 4 week open-label run-in of OLZ followed by 2 weeks of adding 10 mg SAM to OLZ to assess for safety and tolerability to both. Patients (N=234) were then randomized to double-blind ALKS 3831 vs OLZ+PBO and followed for at least 9 months and up to 15 months.
Primary outcome was time to event of exacerbation of disease symptoms (EEDS), estimated by Kaplan-Meier time-to-event adjusting for relevant covariates. An event was defined as the occurrence of at least one of eight pre-specified events of clinical worsening as judged by an Independent Adjudication Committee. Other outcomes included improvement in alcohol use (WHO criteria). Improvement in WHO drinking level was analyzed by a logistic regression model. Descriptive summary statistics were used for all safety measures.

Results: Of 229 randomized and dosed patients, 58 (49.6%) receiving OLZ+PBO completed the study compared with 53 (47.3%) receiving ALKS 3831. Mean age was 45.7 years and 78.6% of patients were males. The mean (± SD) dose of OLZ was 14.0 ± 6.6 mg for ALKS 3831 and 15.0 ± 6.8 mg in the OLZ+PBO group. For the primary endpoint, there was no significant group difference in time to first EEDS (hazard ratio [HR] 0.91; 95% confidence interval [95% CI]: 0.53, 1.56, p=0.75), or time to recurrent EEDS (HR 0.77; 95% CI: 0.43, 1.37, p=0.37). Alcohol use decreased in both groups during the study, but without differences between treatment groups. Patients treated with ALKS 3831 had numerically lower rates vs OLZ+PBO of hospitalization (3.6% [n=4] vs. 8.5% [n=10], p=0.14), emergency-room (ER) visits (1.8% [n=2] vs. 5.1% [n=6], p=0.16), aggression/suicide (8.9% [n=10] vs. 11.1% [n=13], p=0.57) and rescue medication (3.6% [n=4] vs. 9.4% [n=11], p=0.10. A similar proportion of patients met WHO criteria for >= 1 reduction in drinking level at Week 24 (40.5% [n=45] in the ALKS 3831 group and 37.9% [n=44] in the OLZ+PBO group). Treatment-emergent adverse events (AEs) were reported in 59.0% (n=69) of OLZ+PBO-treated patients vs. 57.1% (n=64) of ALKS 3831-treated patients. The most common AEs were weight increase, somnolence and dry mouth. The rates of serious AE's and AE-related discontinuations were similar between the two treatment groups.
Conclusions: Both OLZ+PBO and ALKS 3831 were generally well tolerated. Relative to OLZ+PBO, ALKS 3831 did not lower likelihood of, or delay the time until, an exacerbation of disease. ALKS 3831 treated patients had numerically lower rate of hospitalizations, ER visits, and rescue medication use. Both groups had a similar decrease in alcohol use during the study.

T54. A NOVEL APPROACH TO ADDRESS AN UNMET NEED IN THE TREATMENT OF SCHIZOPHRENIA AND DEPRESSION: LUMATEPERONE, AN INNOVATIVE MODULATOR OF DOPAMINE, SEROTONIN, AND GLUTAMATE

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Abstract: Schizophrenia is increasingly recognized to be associated with depression. As many as 40% of people with schizophrenia (SCZ) have a fully syndromal major depressive episode at some time in their lives with even more experiencing mild to moderate depression. Treatments designed to address both symptoms of SCZ and depression are lacking. An assessment of the relationships between depression and social cognition is provided. The effects of lumateperone (ITI-007), an investigational new drug, on psychosis, depression and social function in patients with SCZ was determined.
Methods: Two samples of patients with SCZ (n= 179, 218) were compared to samples of healthy controls (HC n= 104, 154) and were examined with measures of depression (Beck Depression Inventory-II; BDI), social cognition, and everyday functioning. Participants were examined for their speed of completion of the tasks and their confidence in their accuracy. Patients were also clinically rated with the Positive and Negative Syndrome Scale (PANSS).
In separate studies, the effects of ITI-007 60 mg were evaluated in two placebo-controlled SCZ trials [ITI-007-005 (ITI-007, n=84; Placebo, n=82) and ITI-007-301 (ITI-007, n=150; Placebo, n=149)]. Prospective analyses on the effects of lumateperone on symptoms of SCZ (PANSS),

depression (Calgary Depression Scale for Schizophrenia, CDSS), and social function (Personal and Social Performance Scale, PSP) were conducted. Additional post-hoc analyses were conducted.

Results: In both initial samples, SCZ patients were more depressed than HC (15, 15, vs 6, 6). In both samples of SCZ, BDI scores correlated positively with clinical ratings of depression (PANSS item 6: r's=.60 and .61). Performance on tests of emotion recognition and perception, social inference, and theory of mind were not correlated with BDI. Higher BDI were correlated with self-reports of more impaired everyday functioning, lower subjective impressions of social cognitive competence, and greater feelings of interpersonal sensitivity, combined with the impression that others were mistreating them. Depression in HC, but not patients, was associated with lower confidence while performing social cognitive tests, and depression in SCZ, but not HC, was associated with slower performance on these same tests.

In two positive clinical trials, lumateperone improved symptoms of schizophrenia compared to placebo [PANSS Total Score: Study 005, p=0.017; Study 301, p=0.022]. Symptoms of psychosis and/or symptoms of depression improved with lumateperone treatment in a subgroup of patients with co-morbid depression at baseline. Social function improved as evidenced by improvements on PSP (only measured in Study 301).

Discussion: Depressed mood impacts self-assessment of abilities and global world views. These impressions are not due to objective impairments in performance. In contrast, objective performance on social cognitive tests, like previous studies of the relationship of neurocognition and functional and depression, shows remarkably little overlap with subjective depression. Although the similarity of the relationships between depression, interpersonal sensitivity, and subjective quality of life are similar in HC and SCZ, the more severe depression in SCZ suggests that this is an area of considerable importance for clinical intervention. Lumateperone was shown to improve symptoms of SCZ and depression as well as social function in two positive, well-controlled trials and represents a potential novel approach to the treatment of multiple symptom domains. Together, the data suggest that lumateperone, by improving depression in SCZ, may improve self-assessment and global world views. Further research is warranted.

T55. A PROOF-OF-MECHANISM STUDY OF THE PDE10 INHIBITOR RG7203 IN PATIENTS WITH SCHIZOPHRENIA AND NEGATIVE SYMPTOMS PROBING REWARD FUNCTIONS WITH IMAGING AND BEHAVIORAL APPROACHES

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Abstract: Background: The enzyme phosphodiesterase 10A (PDE10A) is highly expressed in the striatum where it modulates both dopamine D2 and D1 dependent signaling. Its inhibition leads to a suppression of D2 mediated signaling –similar to effects of D2 antagonists - and an enhancement of D1 dependent signaling. D1-dependent signaling has been implicated in reward-based learning. Its deficient activation may be a key factor underlying deficient reward functions including reward anticipation and reward-based learning that have been implicated

as major drivers of negative symptoms of schizophrenia. Therefore inhibition of PDE10 could be a way to ameliorate such deficits and consequently negative symptoms. In healthy volunteers the PDE10 inhibitor RG7203 indeed enhanced performance in tasks that probed reward functioning suggestive of its potential utility to treat negative symptoms in schizophrenia. We therefore tested the hypothesis that it should enhance imaging and behavioral markers of reward functions in patients with moderate negative symptoms in order to establish mechanistic proof of its utility as treatment of negative symptoms.
Methods: In a three-way cross-over study we investigated the effects of two doses of RG7203 (5 mg and 15 mg) and placebo given as adjunctive treatment to stable background antipsychotic treatment on reward functioning and reward-based effortful behavior using the monetary incentive delay (MID) task during fMRI and the effort choice task in patients with chronic schizophrenia and moderate levels of negative symptoms (PANSS negative symptom factor score ≥ 18 points). Each treatment period lasted three weeks followed by a 2-week washout period. fMRI and behavioral tasks were administered at the end of each treatment period. Key outcome measures were the differential BOLD during reward anticipation and overall BOLD activity during the MID task and the percentage of high-effort high-reward choices when the probability of reward was 100% during the effort choice task.
Results: Thirty-three patients with schizophrenia (30 male; 21 B, 9 W, 3 A; mean age 36.6±7 y; PANSS NSFS = 22.8 (±1.4) at screening) were recruited at three study centers in the US. Twenty-four subjects finished the entire study. RG7203 at 5 mg significantly increased differential BOLD activity during reward anticipation in the MID task. However, this enhancement occurred in the context of a significant decrease of BOLD activity across all conditions during the MID task under treatment with RG7203 . RG7203 significantly worsened reward-based effortful behavior in the effort choice task (the high-effort high-reward choice: 67% for both doses of RG7203 versus 73% for placebo). Multiple regression revealed that the decrease in effortful behavior was significantly related to the decrease in overall BOLD activity during the MID task and not related to the difference of BOLD activity during reward anticipation versus the control condition.
Conclusions: In contrast to our expectation and previous results in healthy volunteers, RG7203 worsened indices of reward functions which we hypothesize may be due to a further enhancement of D2 antagonistic activity. The results do not support the utility of a PDE10 inhibitor as adjunctive treatment for negative symptoms in patients with schizophrenia. Given the previous observation that RG7203 enhanced reward functions in healthy volunteers who were not treated with D2 antagonist, the results of our study point to potentially deleterious effects of D2 blockade on reward functions and by extension on negative symptoms of schizophrenia. They raise the question if the presence of D2 antagonistic treatment curtails the potential effects of any adjunctive treatment for negative symptoms.

T56. REAL LIFE ASSESSMENT OF ABILIFY MAINTENA (RELIAM): FINAL ANALYSIS FROM A CANADIAN NATURALISTIC STUDY OF ARIPIPRAZOLE LONG-ACTING INJECTABLE IN PATIENTS WITH SCHIZOPHRENIA

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Abstract: Objectives: In patients with schizophrenia, non-adherence to treatment with oral antipsychotics contributes to suboptimal management of the disorder through increased rates of relapse, reduced time in remission, and eventually poor functional outcomes. With the objective of increasing the utility of findings from controlled clinical trials to real-life clinical settings, ReLiAM (Real Life Assessment of Abilify Maintena) was designed as a naturalistic, prospective, non-interventional, Canadian study, with functioning and illness severity as the main outcomes, for patients with schizophrenia treated with aripiprazole once-monthly 400 mg (AOM) in routine clinical environments.
Methods: Canadian patients with schizophrenia, prescribed AOM prior to screening, were initiated for treatment with once-monthly AOM and followed for 24 months. Study assessments were recommended, but not imposed for the purpose of the study, to occur every 3 months. The primary endpoint was functional status, assessed by the Global Assessment of Functioning (GAF) Scale at 12 months. Secondary measures included changes in the Brief Psychiatric Rating Scale (BPRS), the 7-item Quality of Life Scale (QLS), relapse/remission rates, and safety and tolerability. The final results of the pre-planned 12-month interim analysis are presented here; all data presented are observed cases (OC).
Results: 199 eligible patients at 18 sites in Canada were enrolled, with 169 patients (84.9%) having at least one post-baseline assessment. Patients were classified as early psychosis (≤5 years from original diagnosis; 63.9%, n = 108) or later (>5 years; 34.9%, n = 59). The pre-planned interim analysis at 12 months showed mean increase in GAF score from baseline of 12.3 (n = 113; 95% CI 9.35, 15.23; p<0.001). Early-phase patients showed a mean increase in GAF score from baseline of 14.1 (n = 71; 95% CI 10.02, 18.21; p<0.001), and later-phase patients of 8.8 (n = 41; 95% CI 4.96, 12.70; p<0.001). The mean change from baseline in total BPRS score was -10.5 (n = 113; 95% CI -12.50, -8.42; p<0.001); -11.8 for early-phase (n = 71; 95% CI -14.58, -9.06; p<0.001), and -8.1 for later-phase (n = 41; 95% CI -11.05, -5.15; p<0.001). Improvements were also seen in each item of the QLS from baseline to 12 months. In addition, 54.4% of patients achieved remission (n = 92/169), and 26.1% had a relapse (n = 24/92). No new safety signals were observed, and safety and tolerability were consistent with the Canadian Product Monograph of AOM.
Conclusions: In this first study of naturalistic data for AOM in Canadian patients with schizophrenia, significant improvements in overall patient functioning, symptom severity, and quality of life were observed over 12 months of treatment, with more pronounced improvements observed in those patients earlier in the course of their illness. In addition, remission rates were high and relapse rates were low, and AOM was well tolerated.

T57. SUSTAINED REMISSION AND SYMPTOMATIC STABILITY AMONG PATIENTS WITH SCHIZOPHRENIA RECEIVING ARIPIPRAZOLE ONCE-MONTHLY IN A 52-WEEK, OPEN-LABEL, MAINTENANCE STUDY

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Abstract: Background: Therapeutic success in schizophrenia is typically defined as symptomatic improvement; however, sustained remission according to criteria that include duration may be more clinically relevant as a long-term treatment objective [1].

Aims: We report secondary efficacy endpoints of an open-label extension study (NCT00731549) [2] assessing the sustained remission and symptom stability during 52 weeks maintenance treatment of schizophrenia with aripiprazole once-monthly 400 mg (AOM 400), a long-acting injectable antipsychotic.
Methods: Enrolled patients were 18 to 65 years of age with a current diagnosis of schizophrenia (DSM-IV-TR), who were previously randomized in one of two controlled trials assessing the efficacy and safety of AOM 400 (NCT00705783 and NCT00706654), or were naïve to AOM 400 treatment. Patients were cross-titrated to oral aripiprazole (if needed), then stabilized on oral aripiprazole; those meeting predefined stabilization criteria continued to 52 weeks of AOM 400 maintenance treatment. Sustained remission was defined as scores ≤3 simultaneously on 8 items from the Positive And Negative Syndrome Scale (PANSS), maintained for ≥6 months [1].
Proportion of patients in remission was reported using descriptive statistics. Symptomatic stability was assessed by the mean changes from the beginning of maintenance treatment in PANSS positive and negative subscale scores at each visit (Last Observation Carried Forward method).
Results: Of 1,178 patients enrolled, 1,081 (91.8%) entered maintenance treatment and 858/1,081 (79.4%) completed the study. Of 937/1,081 (86.7%) evaluable patients who received AOM 400 for ≥6 months, 51.7% met remission criteria. Both positive and negative PANSS subscale scores showed small but continued improvements.
Conclusions: Approximately 50% of patients achieved sustained remission during 52 weeks of AOM 400 treatment. Positive and negative symptoms remained stable, thus highlighting the efficacy of AOM 400 for the long-term maintenance treatment of schizophrenia.

T58. THE NEUROIMAGING EFFECTS OF SINGLE-SESSION TDCS ON BRAIN REGIONS IMPLICATED IN IMPAIRED INSIGHT IN SCHIZOPHRENIA

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Abstract: Background: Schizophrenia is a devastating disorder that affects approximately 1% of the world's population. Impaired insight, described as having lack of awareness of one's illness and the need for treatment, is a common feature of schizophrenia that negatively contributes to treatment outcomes. Currently, there are no established intervention strategies to improve insight in patients with schizophrenia. Findings from functional neuroimaging studies suggest that impaired insight is attributable to interhemispheric imbalance, resulting from overactivation of the left posterior parietal area (PPA). Thus, the PPA may be a suitable target for neuromodulation with transcranial direct current stimulation (tDCS) to restore interhemispheric balance and improve insight into illness. The objective of this randomized sham-controlled pilot study was to investigate the effects of single-session tDCS on: 1) blood oxygen level-dependent (BOLD) response to an insight-task, and 2) regional cerebral blood flow in patients with schizophrenia.

Methods: Participants with schizophrenia with moderate-to-severe insight impairment (≥3 PANSS G12 Lack of judgement & insight item) and healthy controls were recruited. A crossover design was employed, where each participant received both active and sham stimulation in random order separated by at least one week. A single-session 20-min bi-parietal tDCS was administered inside the scanner. The anode was placed over the P4 (right-hemisphere) and the cathode was placed over P3 (left-hemisphere). Each participant completed a task-based functional MRI pre- and post-tDCS to measure changes in BOLD response to an insight-task. During stimulation, participants received serial 5-min arterial spin labelling (ASL) scans to measure regional cerebral blood flow.
Results: Eleven participants with schizophrenia and 10 healthy controls were included. Consistent with findings from our previous work, higher BOLD response was observed in the left-PPA at baseline in patients with schizophrenia compared to healthy controls. During stimulation, active tDCS increased regional cerebral blood flow beneath the anode in the right-PPA in all participants compared to sham stimulation ($F(4,80)=4.39$, $p=0.003$). No changes in regional cerebral blood flow were observed beneath the cathode. Post-tDCS, BOLD response in the left- and right-PPA were normalized. Exploratory regression analyses showed an interaction effect of chlorpromazine equivalent antipsychotic dose and cerebral atrophy on changes in regional cerebral blood flow.
Discussion: The results of this pilot study provide mechanistic justification to trial tDCS as an adjunctive treatment to improve insight in patients with schizophrenia. We showed that single-session bi-parietal tDCS transiently modulates the PPA, a brain region associated with impaired insight. Further studies are needed to investigate if serial tDCS can lead to sustained improvement in insight in patients with schizophrenia.

T59. REAL-WORLD PATIENT EXPERIENCE WITH TREATMENT-EMERGENT SEXUAL DYSFUNCTION (TESD) IN DEPRESSION

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Abstract: Introduction: Despite the prevalence of treatment-emergent sexual dysfunction (TESD) in antidepressant treatment, little is known about patients' related real-world experiences (1,2).
Design: A cross-sectional survey (N=483) was developed and fielded to members from PatientsLikeMe, an online data-driven patient network, self-reporting Major Depressive Disorder. Sexual functioning was assessed using the Changes in Sexual Functioning Questionnaire-short form (CSFQ-14) and a patient attribution question. Survey measures also included the Patient Health Questionnaire Depression Scale (PHQ8) and the Couples Satisfaction Index-4 (CSI-4).
Results: Based on CSFQ scores, 56% of patients taking antidepressants reported sexual dysfunction. Sexual dysfunction was associated with greater depression severity for both women and men, and with lower relationship satisfaction (CSI-4) among women currently taking antidepressants. Based on patient attribution, less than half with TESD mentioned it to their doctor, and a minority (ranging 20%-36%) indicated that their doctor subsequently switched them to another antidepressant after disclosure of this issue. In response to issues with sexual functioning, 48% stated that they continued taking their current antidepressant(s) until

sexual side effects went away; 36% adjusted their dosing (lower dose, skipped dose); and 11% took another medication to improve sexual functioning.
Conclusion: Sexual dysfunction is associated with greater depression severity and relationship dissatisfaction. Despite various actions taken by patients to ameliorate sexual dysfunction, over half currently taking antidepressants still experience TESD.

T60. BREMELANOTIDE FOR HYPOACTIVE SEXUAL DESIRE DISORDER IN THE RECONNECT STUDY: ANALYSIS OF CO-PRIMARY ENDPOINTS ACCORDING TO BASELINE FSFI TOTAL SCORES

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Abstract: Objective: Bremelanotide (BMT) is a melanocortin-4 receptor agonist, an analog of the endogenous neuropeptide α-melanocyte stimulating hormone, which is taken as-desired to improve sexual desire and decrease personal distress in premenopausal women diagnosed with hypoactive sexual desire disorder (HSDD). Clinical studies indicate that BMT has greater efficacy than placebo for treatment of HSDD. The objective of this analysis was to determine whether BMT demonstrated a treatment benefit in women with HSDD regardless of baseline FSFI total scores.
Materials and Methods: The population (N=1202) in this analysis consisted of premenopausal women from two phase 3 studies (RECONNECT) who were divided into subgroups according to female sexual function index (FSFI) total score (sum of multiple domains) at screening. For inclusion in the studies, participants needed either FSFI total score ≤26 (if diagnosed with HSDD with/without symptoms of decreased arousal) or FSFI desire domain (FSFI-D) score of ≤5 (if diagnosed with HSDD without decreased arousal) regardless of total FSFI score. The FSFI-D and female sexual distress scale – desire arousal orgasm (FSDS-DAO) Item 13 were patient-reported outcomes (PROs) that served as co-primary endpoints of RECONNECT.
Results: For subjects with the lowest baseline FSFI total score, <16.5 (BMT n=275; placebo n=262), the difference (BMT-placebo) in mean changes in FSFI-D from baseline was 0.32. For subjects with baseline FSFI total scores of 16.5-20.49 (BMT n=171; placebo n=190) and 20.5-25.49 (BMT n=131; placebo n=131), differences in mean changes in FSFI-D from baseline were 0.38 and 0.43, respectively. For the small number of subjects with baseline FSFI total scores of ≥25.5 (BMT n=19; placebo n=23), differences in mean changes in FSFI-D from baseline were 0.07. In the total integrated population (BMT n=596; placebo n=606), the difference in mean change in FSFI-D from baseline was 0.36. In the analysis of FSDS-DAO Item 13, the differences in mean change from baseline for those with baseline FSFI total scores of <16.5, 16.5-20.49, 20.5-25.49, and ≥25.5 were -0.4, -0.3, -0.4, and -0.2, respectively. In the total integrated population, the difference in mean change in FSDS-DAO Item 13 was -0.3. For both endpoints, the estimated differences between treatment groups were statistically significant ($P<0.05$) for all baseline FSFI score ranges except for the ≥25.5 subgroup, which was limited by a small sample size.

Conclusions: This placebo-controlled RECONNECT subgroup analysis demonstrated that the treatment benefit with BMT was independent of baseline total scores for FSFI in women with HSDD.

T61. SUICIDAL IDEATION AMONG NEWLY ADMITTED NURSING HOME RESIDENTS IN THE U.S.

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Abstract: Introduction: Rates of suicide are alarmingly high among older adults in the U.S. Older nursing home residents experience many risk factors for suicide, making nursing homes an important but often neglected healthcare setting in which suicide risk needs to be addressed and reduced. Understanding the extent of suicidal ideation in these facilities is important as ideation is associated with substantial distress and suffering and can be an important predictor of suicide death. Improving our knowledge of the prevalence and correlates of suicidal ideation in this population is imperative for developing effective interventions for suicide prevention. The objectives of this study were to: 1) describe the prevalence of suicidal ideation among newly admitted nursing home residents; and 2) describe the psychopharmacological and psychological therapy received by these residents.
Methods: We used data on older adults newly admitted to U.S. nursing homes from the 2011-2012 national Minimum Data Set (MDS) 3.0. Federally-mandated for all residents of Medicare/Medicaid-certified nursing facilities, MDS 3.0 is a comprehensive assessment containing validated assessments of active clinical diagnoses, pharmacological and non-pharmacological treatments, physical functioning, and cognitive impairment. We identified 706,828 long-stay residents who were aged ≥ 65 years, not comatose, and did not have cancer at admission. Suicidal ideation experienced during the prior two weeks was measured using the ninth item of the PHQ-9. Psychotherapeutic treatment was documented as receipt of antidepressants, antianxiety medication, antipsychotics, hypnotics, and psychological therapy at any time in the seven days before the assessment.
Results: At admission, 16,488 residents screened positive for suicidal ideation as assessed by the ninth item of the PHQ-9. Of those with suicidal ideation, 46.9% had an active diagnosis of major depression and 26.0% had an active anxiety disorder. Of those without suicidal ideation, 32.1% had a diagnosis of depression and 18.8% had an anxiety disorder. Frequencies of other comorbidities, functional limitations, cognitive impairment, and pain were similar between those with and without ideation. Among residents with depression, those with ideation were more likely than those without to endorse the other eight depressive symptoms on the PHQ-9, e.g., insomnia/hypersomnia was reported by 50.1% with ideation compared to 26.5% of those without ideation. Approximately 56% of residents with ideation did not receive any psychotherapeutic treatment. Almost half (48.7%) of those with ideation and a documented diagnosis of depression did not receive antidepressants. Of those without ideation, 20.8% received antidepressants and 10.4% received antianxiety medications.
Conclusions: The results of this work illustrate that although suicidal ideation is present among older adults upon nursing home admission, management of suicide risk factors such as psychiatric disorders is often lacking. Additional research on suicide risk and protective factors at admission and throughout the nursing home stay is necessary to improve efforts to identify

residents at high risk for suicide and inform tailored suicide prevention efforts in this healthcare setting.

T62. DOES CITALOPRAM INCREASE THE FREQUENCY OF UP-SWITCHES OF IMPULSIVE SUICIDALITY IN A SUBJECT WITH IMPULSE ATTACK SUICIDALITY DISORDER? A CASE STUDY

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Abstract: Background: This case study reports the effect of the SSRI citalopram in causing up-switches of impulsive suicidality.
Methods: A 29-year-old female subject who experienced suicidality almost daily for over 20 years prospectively collected a self-report data series over 248 days using the computerized versions of the Suicidality Modifiers Scale (SMS) and the Sheehan - Suicidality Tracking Scale (S-STS), covering a timeframe before, during and after a 116 day trial of citalopram. The S-STS data was mapped into the C-CASA 2010 and FDA-CASA 2012 categories and compared to the scores for the severity of impulsive suicidality from the SMS.
Results: The SMS data show a 39% increase in up-switches in suicidal impulsivity while the subject was taking the citalopram. The data show the C-CASA 2010 and FDA-CASA 2012 categories were unable to detect this signal of increased up-switches in suicidal impulsivity. The data in some of these C-CASA 2010 and FDA-CASA 2012 categories suggest that the subject's suicidality was improving while these danger signals were worsening.
Conclusions: The SSRI citalopram is associated with an increase in up-switches in suicidal impulsivity in a non-Bipolar Disorder subject. That the existing safety detecting classification algorithms used by the US Food and Drug Administration (2010 and 2012) can fail to detect a serious suicidal adverse event such as the one described above is a cause for serious concern and needs to be corrected. Any rating instrument or classification "algorithm" used to detect safety signals of suicidality needs to include an item on impulsive suicidality.

T63. SLEEP DISTURBANCES PREDICT SUICIDAL IDEATION DURING AND AFTER INPATIENT TREATMENT

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Abstract: As death by suicide has increased 24% over the past 15 years, understanding the risk factors for suicide is critical for reversing this alarming trend. This study investigates one modifiable suicide risk factor: sleep disturbance. Sleep disturbances are commonly reported in generalized anxiety disorder (GAD) and major depressive disorder (MDD). Patients with both disorders are at high risk for suicide. Evidence shows the most effective treatment of sleep disturbance should integrate both psychotherapy and pharmacological approaches. We hypothesized sleep disturbance would be greatest in those with comorbid MDD/GAD,

followed by those with MDD or GAD, relative to patient controls (e.g., bipolar). Across all groups, greater sleep disturbance at discharge was expected to predict more suicidal ideation post-discharge and those prescribed medication only for sleep disturbance would not experience improvement in suicidal ideation.
Participants were 2,703 inpatients at a psychiatric hospital (1,400 male, 1,303 female; mean age = 34.90, range = 17-89). Psychiatric diagnoses were determined using the Structured Clinical Interview for DSM-IV Axis I and Axis II Disorders, Research Version. The mean duration of inpatient hospitalization was 43.31 days, range = 1-238 days). Patients received pharmacological and psychotherapy treatments. 5% took hypnotics and 71% were on anti-depressants. No sleep psychotherapy protocol was implemented at the hospital. Self-reported sleep disturbance was assessed using the Patient Health Questionnaire-9 (PHQ-9; "trouble falling or staying asleep, or sleeping too much") and suicidal ideation on the Columbia Suicide Severity Rating Scale (CSSRS). The PHQ-9 and CSSRS were administered at admission, 2 weeks, and 4 weeks during hospitalization, and at follow-up after 2 weeks, 3 months, 6 months, and 1 year post-discharge. The Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) was completed at admission to assess substance use. Analyses controlled for gender, age, and substance use.
Repeated measures analysis of covariance (ANCOVA) was completed to examine change of self-reported sleep disturbance over time during treatment by group. There was an effect for diagnostic group, $F(1,3) = 30.926$, $p < 0.001$, but no main effect of time nor group-by-time interaction. The MDD/GAD group demonstrated more sleep disturbance relative to patient control ($p < 0.001$), MDD ($p = 0.002$), and GAD ($p = 0.038$). Across all groups, increased frequency of sleep disturbance at discharge was significantly correlated with more suicidal ideation at the 2 week ($r(574) = 0.218$, $p < 0.001$), 3 month ($r(485) = 0.140$, $p = 0.002$), and 6 month ($r(387) = .139$, $p = 0.006$) follow-up, but not at 1-year follow-up ($p > 0.400$). Those who were received combined anti-depressant and hypnotic treatment reported the highest sleep disturbance across follow-up relative to those not prescribed either or those only prescribed one (p's = 0.002-0.030). The hypnotics treatment group reported the second highest.
The comorbid MDD/GAD group self-reported the greatest sleep disturbance across inpatient treatment relative to all other groups, irrespective of gender, age, and substance use. Greater sleep disturbance at discharge was correlated with more suicide ideation up to 6 months after inpatient psychiatric treatment and those prescribed anti-depressants/hypnotics combined or hypnotics alone reported the most sleep disturbance across the follow-up period. This highlights the importance of using combined evidence-based psychotherapy for sleep and pharmacological intervention, especially for those with comorbid MDD/GAD. Integrated intervention may decrease risk of suicide during and after treatment.

T64. THE GRAPHIC DISPLAY OF QUANTITATIVE SUICIDALITY DATA: S-PLOTS

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Abstract: Background: Regulatory agencies, pharmaceutical companies, clinical research organizations, data safety monitoring boards, medical directors of health care organizations, and medical safety officers are challenged with the difficulty of summarizing the suicidality

status of patients under their care in a simple, clear manner. Currently, data collected using a dimensional scale are reduced to the categorical system at the completion of a study. Suicidality data is currently organized and reviewed in complex tables, reflecting these categories, with a resultant loss of sensitivity and the risk of delayed detection, or of detection errors. Linking such data to study stopping rules is a complex multistep series of tasks, fraught with potential errors. In the interest of reducing error, speeding detection, protection of patients, clarity of data presentation and display, there is a need for a more efficient, clear, and simple system to display suicidality data.
Methods: We explored and reviewed graphic displays of quantitative data in other medical and scientific disciplines to find suitable models. The selection criteria included simplicity, clarity, the ease of interpretation of the data, and how appropriate the displays would be for suicidality data, collected using a dimensional suicidality tracking scale. We applied a variety of graphic displays to a prospectively collected dataset using the Sheehan-Suicidality Tracking Scale (S-STS). The final displays are the result of this iterative process.
Results: Suicidality-Plots (S-Plots) display the data for groups of patients and for individual patients over time. Interpretation of these S-Plots can quickly identify patients at higher risk, and provide a method to monitor the status of patients within a large sample over time. Interpretation of S-Plots can quickly identify the overall status of suicidality in the study over time in relation to the study stopping rules. Graphic display of quantitative suicidality data can be used to quickly visually identify individual patients at high risk, the disposition of all patients in a healthcare setting or clinical trial, and whether a clinical trial should be halted because of treatment-emergent suicidality. These S-Plots are customizable for the needs of different clinical trials and settings. A computer-generated version of these S-Plots is available. It can also generate e-mails or phone alerts to site investigators and sponsors for subjects deemed at imminent risk, and who need immediate attention.
Conclusions: Use of S-Plots may reduce the potential medico-legal hazards from either the delayed analysis or delayed detection of suicidality in safety data, and the risk to patients in research trials and clinical settings.

T65. RATIONALE AND DESIGN OF FOUR PHASE 3 RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDIES EVALUATING THE EFFICACY AND SAFETY OF EXTENDED-RELEASE VILOXAZINE (SPN-812) FOR ADHD IN CHILDREN AND ADOLESCENTS

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Abstract: Background: Although stimulants are the most common treatment for attention-deficit/hyperactivity disorder (ADHD), approximately 10–30% of patients have an inadequate response, experience intolerable side effects or have comorbidities that prevent stimulant use. Thus there is a need for effective nonstimulant options, with improved safety and faster onset of action. Extended-release viloxazine (SPN-812), a nonstimulant, is currently in development for the treatment of ADHD in children and adolescents. SPN-812 is a structurally distinct, bicyclic norepinephrine reuptake inhibitor with selective serotonergic activity. Results of the Phase 2 program demonstrated efficacy (improved mean ADHD-RS-4 total score) and safety of SPN-812 in the pediatric population (ages 6–12 years), as well as an onset of action within 1–2 weeks.

Methodology: Four ongoing Phase 3 randomized, double-blind, placebo-controlled, multicenter studies are investigating the efficacy and safety of once-daily SPN-812 as monotherapy for the treatment of ADHD in children and adolescents. Two studies (P301, P303) are enrolling children (6–11 years) and two (P302, P304) are enrolling adolescents (12–17 years). Eligible children/adolescents are required to have minimum baseline scores of ≥28 for ADHD-RS-5 and ≥4 for CGI-S. The studies compare placebo with SPN-812 100, 200, and 400 mg (in children) or 200, 400, and 600 mg (in adolescents). In total, the four studies will randomize approximately 1200 children/adolescents with ADHD, with approximately 800 subjects receiving SPN-812. Titration periods for the studies range from 1 to 3 weeks; all studies have a 5-week maintenance period. The primary endpoint in all studies is the mean change from baseline to end of study in the ADHD-RS-5 total score for SPN-812 vs. placebo. Secondary endpoints include change from baseline to end of study in 30% Responder Rate (% change; ADHD RS 5); Hyperactivity/Impulsivity and Inattention ADHD-RS-5 subscale scores; Conners 3 Rating Scale (parent and self-report); CGI-S/I; Weiss Functional Impairment Rating Scale (parent report); Parenting Stress Index (children); and Stress Index for Parents of Adolescents (adolescents) after 6–8 weeks of treatment. Safety is assessed using adverse events, clinical laboratory tests, vital signs, ECGs, physical examinations, and the Columbia-Suicide Severity Rating Scale. Phase 3 completers will be offered enrollment in an open-label extension study (up to 3 years) with a starting dose of 100 mg (children) or 200 mg (adolescents). Data will be summarized with descriptive statistics and analyzed using appropriate statistical methods such as ANOVA and nonparametric or chi-square tests.
Enrollment Update: As of March 2018, ~41% of planned subjects are enrolled in the Phase 3 studies; ~18% have completed Phase 3 and are entered into the open-label extension study.
Summary: There is an unmet need for nonstimulant ADHD treatment for children and adolescents that is effective, long-acting, and well tolerated. SPN-812 is being investigated in four Phase 3 randomized, placebo-controlled studies for the treatment of children and adolescents with ADHD, based on demonstrated efficacy and safety in the Phase 2 program.

T66. DISCOVERY AND DEVELOPMENT OF EMB-001 FOR THE TREATMENT OF SUBSTANCE USE DISORDERS: READY FOR PHASE 2 CLINICAL TRIALS IN TOBACCO AND COCAINE USE DISORDERS

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Abstract: Background: EMB-001 is a combination of two FDA-approved drugs: metyrapone, a cortisol synthesis inhibitor, and oxazepam, a benzodiazepine. Both have been approved by the FDA and other regulatory authorities for five decades; oxazepam for various anxiety disorders (acute and chronic use) and metyrapone, administered at 3000 – 4500 mg for one day only as a test for hypothalamic-pituitary ACTH (adrenocorticotropic hormone) function.
There is a complex relationship between stress, anxiety, the HPA (hypothalamo-pituitary-adrenal) axis and reinforcement. The hypothesis we have been exploring is whether a combination of drugs working by different stress-related mechanisms may have the potential to reduce substance use disorders, at low doses that minimize the risks (safety, tolerability, abuse potential) of each individual drug.

Methods: We summarize here a range of preclinical and clinical data demonstrating the potential utility of EMB-001 for the treatment of substance use disorders.
Results: (Preclinical) We have shown (Goeders, 2008) that metyrapone and oxazepam together (EMB-001) is effective at doses of each component that are ineffective when given alone. We have also reported that EMB-001 reduces nicotine self-administration in rats Goeders 2012), and that EMB-001 attenuates cocaine and methamphetamine cue reactivity (animal model of relapse) in rats (Keller, 2013).
(Clinical) A pilot human clinical study of EMB-001 in cocaine dependence (Kablinger, 2012) showed a significant reduction in cocaine use at the higher dose tested (1500 mg/d metyrapone, 20 mg/d oxazepam). The combination in this clinical trial was generally safe and well-tolerated. Other published studies have supported the safety of metyrapone given for 2-8 weeks at 500-4000 mg/day (O'Dwyer 1995; Murphy 1998; Eriksson, 2001; Jahn, 2004; Rogoz 2004; McAllister-Williams, 2016). A Phase 1 combined single- and multiple rising-dose study with doses up to 1440 (MET) and 48 (OX) mg/d showed that EMB-001 was well-tolerated, and no new safety signals were identified. PK results suggested that twice-daily dosing may provide appropriate duration of exposure for efficacy. Exploratory efficacy measures on smoking were encouraging for a small study that was not powered for efficacy. Subsequently, in a Phase 1b crossover study of potential interaction of EMB-001 and cocaine, in non-treatment-seeking patients with cocaine use disorder, EMB-001 was well-tolerated, and again no new safety signals were identified. No clinically significant interactions between EMB-001 and cocaine were observed in PK, safety or exploratory efficacy measures. Cortisol findings supported the underlying hypothesis.
Discussion: Preclinical data demonstrate that EMB-001 is effective and well-tolerated in animal models of drug addiction. A pilot human study also showed efficacy in cocaine dependence. Phase 1 studies supported safety, PK, and exploratory efficacy in smoking, as well as an important biomarker. To our knowledge, this is one of very few drugs advanced into clinical development that has the potential to treat many addictions – including non-chemical addictions such as gambling, sex and internet addictions. And to our knowledge, it is among the furthest advanced in clinical testing for cocaine use disorder, for which there are no approved pharmacotherapies. We plan to begin Phase 2 studies in both tobacco and cocaine use disorders this year.

T67. LONG-TERM SAFETY OF INTRANASAL ESKETAMINE PLUS ORAL ANTIDEPRESSANT IN PATIENTS WITH TREATMENT-RESISTANT DEPRESSION: PHASE 3, OPEN-LABEL, SAFETY AND EFFICACY STUDY (SUSTAIN-2)

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Abstract: Objective: This long-term safety study evaluated intranasal esketamine (ESK, 28, 56 or 84 mg) plus a newly initiated oral antidepressant (AD) in patients with treatment-resistant depression (TRD).
Methods: In this phase 3, open-label, 52-week safety study, patients (≥18 years) were directly enrolled or transferred from another phase 3 study of elderly (≥65 years) patients. Eligible patients entered a 4-week induction (IND) followed by a 48-week optimization/maintenance (OP/MAINT) phase and a 4-week follow-up. Safety evaluations (primary outcome) included treatment-emergent adverse events (TEAEs), vital signs, clinical laboratory tests, physical examination, nasal tolerability and cognitive tests. Efficacy evaluations (secondary outcome) included mean Montgomery–Åsberg Depression Rating Scale (MADRS) total score, response rate and remission rate over time.
Results: Of the total 802 enrolled patients, 691 (86.2%) were direct-entry and 111 (13.8%) were transfer-entry. Discontinuation rates due to AEs were 6.7% during IND and 4.1% during OP/MAINT phases. The most common TEAEs (≥10% patients) were: dizziness (33.0%), nausea (25.1%), headache (24.9%), dissociation (22.4%), somnolence (16.7%), dysgeusia and hypoaesthesia (11.8% each), vertigo and vomiting (10.8% each), and viral upper respiratory tract infection (10.2%). No clinically meaningful changes in cognition were noted. Fifty-five (6.9%) patients experienced 68 serious TEAEs and 2 deaths were reported in the treatment phase. Laboratory tests, physical examination, and nasal tolerability revealed no trends of clinical concern. The mean (SD) change in MADRS total score from IND baseline to endpoint was −16.4 (8.76) and from OP/MAINT baseline to endpoint was 0.3 (8.12). At IND endpoint, the response rate was 78.4% and remission rate was 47.2%; of the responders proceeding to the OPT/MAINT phase, 76.5% were responders and 58.2% were remitters at endpoint.
Conclusions: Long-term treatment with intranasal ESK plus oral AD was tolerable and no new safety concerns emerged; improvement in depressive symptoms appeared to be sustained in TRD patients.

T68. EXPLORING FEMICIDE STATISTICS IN LATIN AMERICA - ECUADOR

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Abstract: Femicide is a violent crime against women. It is the final consequence of gender violence. Femicide has been considered for a long time a psychosocial question, a silent problem. Nowadays femicide is a relevant concern not only in Mental Health but also a political dilemma for the Justice Department in different countries. For instance, Ecuador just in 2014 determined femicide as a felony murder. The aim of this study is to analyze the ecuadorian femicide data. Information was collected from the police department (ministry of interior), INEC (Ecuadorian National Institute of Statistics and Census), Human Rights, Foundations and national press media, the latter frequently display gender violence and Femicide cases. Therefore, we consider it an important tool in this study.
Results: 2014 human rights: no information, public prosecution 19; ministry of interior no info, Telegrafo press 92. 2015 H R no info, public p 55, ministry interior no info, telegrafo press 60. 2016 H R no info, public p 74, ministry of interior no info, telegrafo no info. 2017 H R 151,

public p 96, ministry of interior 90, telegrafo no info. There is a wide disparity between the government database, Human Rights and press media. we also must establish that it was very difficult to obtain government information. There must be a transparent communication in order to develop programs to prevent Femicide.

T69. CLINICAL EFFICACY AND SAFETY OF FLEXIBLY DOSED ESKETAMINE NASAL SPRAY IN U.S. GERIATRIC PATIENTS WITH TREATMENT-RESISTANT DEPRESSION

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Abstract: Purpose: To evaluate the efficacy and safety of flexibly dosed esketamine nasal spray plus a new oral antidepressant (AD) compared with placebo nasal spray plus a new oral AD (active comparator) to improve symptoms of depression among geriatric patients with treatment-resistant depression (TRD) living in the United States.
Content: Treatment outcomes with esketamine nasal spray plus a new oral AD are not well characterized in geriatric patients. This analysis evaluates efficacy and safety of esketamine nasal spray plus a new oral AD vs placebo nasal spray plus a new oral AD in US geriatric patients with TRD.
Methodology: In this double-blind (DB), flexibly dosed, multinational, multicenter study (NCT02422186), a subset of 70 US geriatric patients with TRD were randomly assigned 1:1 to flexibly dosed esketamine nasal spray 28/56/84 mg plus a new oral AD or to placebo nasal spray plus a new oral AD twice weekly for 4 weeks. The primary efficacy endpoint was the difference between treatment groups on Montgomery-Åsberg Depression Rating Scale (MADRS) scores on change from baseline to week 4. Response (defined as a 50% decrease in MADRS baseline score) and remission (MADRS score ≤12) were measured at intervals until the 4-week DB endpoint. Secondary efficacy measures included changes on the Clinical Global Impression of Severity (CGI-S) scale, the Sheehan Disability Scale (SDS), and the Patient Health Questionnaire-9 (PHQ-9), which measure changes in general clinical condition and function.
Results: In this subpopulation of 70 US geriatric patients, statistically significant improvement in MADRS total score was observed with esketamine plus a new oral AD vs placebo plus a new oral AD at DB (active comparator) end point (least squares [LS] mean difference [SE]: -5.4 [2.48]; 95% CI, -10.36 to -0.45). At 4 weeks, response rates in patients treated with esketamine plus a new oral AD vs patients treated with placebo plus a new oral AD were 8/30 (26.7%) vs 5/34 (14.7%), respectively. Remission rates were 5/30 (16.7%) vs 1/34 (2.9%), respectively. Analysis of covariance based on ranks of change between the 2 groups in improvement of severity of depressive illness as measured by the CGI-S achieved significance at DB endpoint (1-sided P=0.005). Differences in mean changes in SDS and PHQ-9 were (LS mean difference [SE]) -7.6 [2.68; 1-sided P=0.004] and -4.4 [1.68; 1-sided P=0.006], respectively, at Day 28. All results favored esketamine. The most common adverse events (AEs) for esketamine plus oral AD were dysphoria, fatigue, headache, insomnia, nausea, abdominal discomfort, cough, dizziness, erythema, nasal congestion, urinary tract infection,

and vomiting. The incidence of AEs in these geriatric US patients was similar to that observed in the overall study population and in studies with younger patients.
Importance: In this subpopulation of US geriatric patients with TRD, almost twice as many patients showed a 50% response and approximately 5-fold greater remission rates when treated with esketamine nasal spray plus a new oral AD vs placebo nasal spray plus a new oral AD. After 4 weeks of treatment, esketamine nasal spray plus a new oral AD compared with placebo nasal spray plus a new oral AD provides evidence supporting a clinically meaningful, statistically significant reduction of depressive symptoms and an improvement in clinical condition and functioning. The safety, response, and remission results of US patients were similar to those found in the total population studied and in younger patients treated with esketamine in phase 2 and 3 studies.

T70. FEASIBILITY ASSESSMENT OF AN OPIOID OVERDOSE EMERGENCY TEXTING SERVICE DESIGNED TO REDUCE OVERDOSE DEATHS

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Abstract: In Philadelphia and other major cities across the country, opioid related deaths have dramatically increased. According to the Philadelphia Department of Public Health, overdose deaths rose from approximately 700 in 2016 to 900 in 2017. Of these 900 deaths, 80% were due to opioid intoxication. This public health issue is especially devastating neighborhoods like El Campamento in Kensington, which according to the DEA is, "the East Coast's largest heroin market." Vigilantidote intends to increase public access to the opioid overdose reversal drug by creating a community of trained naloxone carriers willing to respond in an opioid overdose emergency, ancillary to local EMS. Vigilantidote is an SMS group text service where trained naloxone carriers may be alerted of an overdose. Through partnerships with local naloxone training programs, Vigilantidote will recruit naloxone carrier volunteers to register with the service. To measure overall feasibility, preliminary surveys will be conducted at local community centers. Efficacy will be measured by tracking amount of time for responder text back and arrival, and number of overdose revivals. Currently, Vigilantidote has recruited 20-25 trained naloxone carrier responders. One live incident has been reported with a successful overdose revival. The responder texted back in two minutes and arrived with naloxone in nine minutes. Vigilantidote may provide greater access to trained naloxone carriers and reduce overdose related deaths in the area. This is a step towards decreasing mortality from opioid overdose in Philadelphia and may eventually be utilized in other high density opioid overdose areas throughout the United States.

T71. SIMPLIFIED NEGATIVE AND POSITIVE SYMPTOMS INTERVIEW (SNAPSI): AN ABBREVIATED ASSESSMENT TECHNIQUE FOR SCHIZOPHRENIA STUDIES

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Abstract: Methodological question: Can the PANSS be modified to be useable in clinical settings as well as in research?

Overview/Aims: There are numerous barriers practical problems associated with using the full 30-item PANSS in clinical practice. The abbreviated, 6-item version of PANSS (PANSS-6) was derived empirically from the full PANSS-30. PANSS-6 ratings, guided by the newly developed, 15-minute stand-alone Simplified Negative and Positive Symptoms Interview (SNAPSI), may help bridge the measurement gap between research and clinical care in schizophrenia.
Methods: Valid PANSS-6 ratings may be obtained by means of the SNAPSI; data on this question is currently being collected. The SNAPSI and its utility is being studied with inpatients with schizophrenia, evaluated and compared to the SCI-PANSS as conducted by two independent raters. One rater will conduct the SCI-PANSS and subsequently rate the patient on the full 30-item PANSS. The other will conduct SNAPSI and rate on PANSS-6. Sensitivity to change in severity of illness will be taken into account and ratings may be compared at admission and discharge points during treatment.
Conclusion/Summary: The full 30-item PANSS is often used in research studies, but is too time consuming to allow for routine clinical use. The much briefer PANSS-6 is a psychometrically valid measure of core symptoms of schizophrenia and is sensitive to symptom improvement following pharmacological treatment. Our current research program may help to address the question as to whether the SNAPSI will help bridge the measurement gap between research and clinical care in schizophrenia.