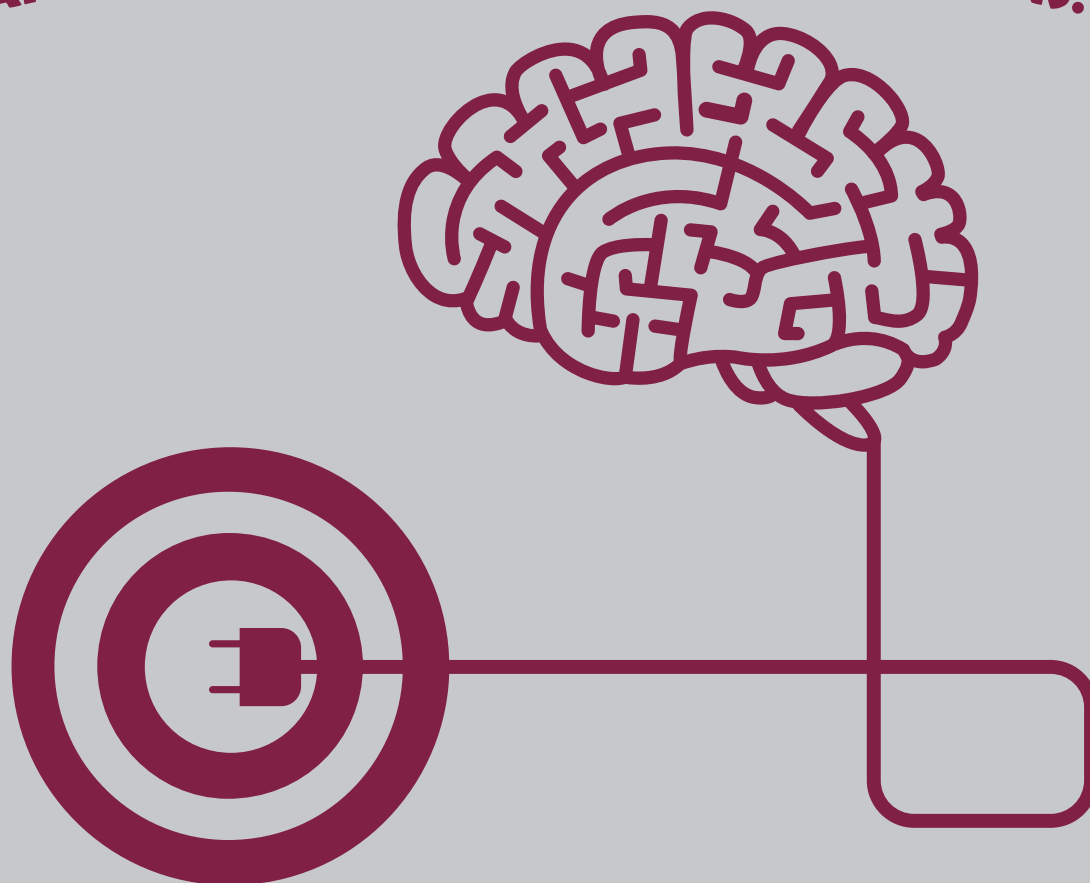


POSTER ABSTRACT BOOK

ASCP ANNUAL MEETING
FAIRMONT SCOTTSDALE PRINCESS
MAY 30-JUNE 3, 2016

ANTICIPATING FUTURE INTERVENTIONS:



**DISCOVERING NEW TARGETS,
INTEGRATIVE BIOMARKERS, AND BEYOND**



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Wednesday, June 1, 2016

Poster Session I with Lunch

W1. HLD200, A NOVEL DELIVERY SYSTEM OF METHYLPHENIDATE, IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER

Floyd Sallee¹, Sharon Wigal², Ann Childress³, Mary Ann McDonnell⁴, Scott Kollins⁵, Norberto DeSousa⁶

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Abstract: Introduction: HLD200 is an investigational drug that incorporates methylphenidate (MPH) in a novel delayed-release and extended-release micro-bead technology. Dosed in the evening, HLD200 delays initial release of MPH approximately 8-hours, targeting onset of clinically meaningful treatment effect immediately upon awakening and throughout the day and early evening. Clinical data from an exploratory study: a 6-week open-label, treatment optimization phase followed by a 1-week randomized, double-blind, placebo-controlled, parallel-group test phase to assess HLD200 safety and efficacy in pediatric subjects with attention-deficit/hyperactivity disorder (ADHD), will be discussed. This presentation will report results for the ADHD Rating Scale (ADHD-RS-IV), early morning ADHD symptoms and functioning for the Before School Functioning Questionnaire (BSFQ), and results of Daily Parent Rating of Evening and Morning Behavior, Revised (DPREMB-R [AM/PM]), for the dose optimization period, as well as safety endpoints for the open-label and double-blind phases.

Methods: Boys and girls (N=43) with ADHD, ages 6-12 at study entry, were enrolled following informed consent. At baseline (Visit 2 [V2]), the start of the open-label phase, subjects took HLD200 at their previous MPH dose equivalent (or approx. 1.4mg/kg HLD200 at investigator discretion) for 1 week. Five subsequent weekly dose adjustments were permitted to achieve an optimal daily dosage and evening administration time, prior to the start of the double-blind phase (V8). Optimal dose was defined as safe and well tolerated, allowing for improvement from baseline of $\geq 30\%$ on the ADHD-RS-IV. Similarly, the optimal evening dosage administration time was defined as one that is well tolerated, allowing for improvement from baseline of $\geq 30\%$ on the BSFQ. At V8, subjects were randomly assigned (1:1 ratio; n=22 and 21 subjects on HLD200 and placebo (PBO), respectively) to double-blind HLD200 or PBO treatment for a period of 1 week.

Results: Twenty girls and 23 boys were included in this analysis. The mean HLD200 starting dose was 33 mg, and the mean optimal dose achieved was 66 mg. Modal evening administration time was 9 p.m. Mean baseline ADHD-RS-IV scores ($\pm$ SD) at V2 were 38.2 ± 8.9 compared to mean V8 scores of 12.5 ± 6.6 ($p < 0.0001$). Mean BSFQ scores ($\pm$ SD) at V2 were 36.2 ± 13.3 compared to mean V8 scores of 10.1 ± 7.3 ($p < 0.0001$). DPREMB-R AM and PM scores ($\pm$ SD) also showed statistically significant differences, with an AM mean of 4.9 ± 2.4 at V2 and 1.2 ± 1.2 at V8 ($p < 0.0001$) and a PM mean of 15.1 ± 5.9 at V2 and 7.7 ± 5.7 at V8 ($p < 0.0001$).

There were no reports of treatment emergent adverse events (TEAEs) leading to early withdrawal and no treatment emergent serious AEs during the course of the study. During the open-label phase, 121 TEAEs were reported in 38 subjects (88%). The most commonly reported TEAEs (>10% of subjects) included: decreased appetite (35%), headache (16%), insomnia (16%), abdominal pain upper (14%) and irritability (12%). In the double-blind phase, a total of 7 HLD200-(32%) and 7 PBO-treated subjects (33%) reported a TEAE. The most commonly reported TEAE was headache (HLD200: 9%; PBO: 10%) with no other TEAE reported more than once in any subject.

Conclusions: HLD200, which delivers MPH via a novel micro-bead technology designed for nighttime dosing, demonstrated a favorable tolerability and safety profile in pediatric ADHD subjects. Control of ADHD symptoms was achieved immediately upon awakening and throughout the day.

W2. CENTANAFADINE SR (CTN-SR) DEMONSTRATES BRAIN OCCUPANCY AT NOREPINEPHRINE TRANSPORTER (NET), SEROTONIN TRANSPORTER (SERT) AND DOPAMINE TRANSPORTER (DAT) USING SINGLE PHOTON EMISSION TOMOGRAPHY (SPECT) IN HEALTHY VOLUNTEERS (HVS)

*Anthony McKinney*¹, Danna Jennings², Olivier Barret³, Gary Wisniewski³, Kenneth Marek³, Catherine O'Brien⁴, Gary Maier⁵, Connie Reininger⁶, Gilles Tamagnan³, David Alagille³, John Seibyl³*

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Abstract: Background: Central modulation of serotonin, norepinephrine and dopamine appears to underlie the efficacy for a variety of psychiatric therapeutics. CTN-SR is an investigational monoamine transport inhibitor in development for treatment of attention deficit hyperactivity disorder (ADHD) and its comorbidities, such as mood and anxiety disorders. The purpose of this study was to determine brain occupancy of CTN-SR at NET, SERT and DAT in HVs. In addition, occupancy studies utilizing methylphenidate (MPH) and atomoxetine (ATX) as agents with expected DAT and NET occupancy, respectively, were performed using the same methodology for comparison.

Methods: [¹²³I]INER was the radiotracer used to measure NET, while [¹²³I]β-CIT was the radiotracer used for imaging SERT and DAT. Oral dosing with CTN-SR, MPH-LA and ATX was titrated for post dose imaging at steady state. For NET target occupancy studies, HVs received CTN-SR 500 mg (n=3) or ATX 80 mg and post-dose [¹²³I]INER SPECT imaging. For SERT and DAT target occupancy evaluation, HVs received CTN-SR and post-dose [¹²³I]β-CIT SPECT imaging at 200 (n=3), 500 (n=6) and 800 mg (n=6). Additional HVs (n=3) received MPH-LA 40 mg and post-dose [¹²³I]β-CIT SPECT.

NET occupancy of CTN-SR and ATX was calculated as percent reduction in BPND between baseline and post-dose SPECT imaging for applicable ROI (brainstem). SERT and DAT occupancy of CTN-SR and MPH was calculated as percent reduction in binding potential (BPND) between baseline and post-dose SPECT imaging for applicable regions of interest (ROI for SERT: thalamus, midbrain and brainstem; ROI for DAT: putamen and caudate). Correlation analyses were completed to evaluate the relationship between target occupancies and plasma concentrations.

Results: Oral CTN-SR (200-800 mg) was safe and well tolerated. CTN-SR penetrated the brain demonstrating dose-related occupancy on NET, SERT and DAT. NET occupancy was 14.6% for CTN-SR 500 mg and 16.0% for ATX 80 mg. SERT occupancy for CTN-SR was 1.8%, 12.8% and 30.0% for 200, 500 and 800 mg respectively; SERT occupancy for MPH-LA, as expected, was 4.3%. DAT occupancy for CTN-SR was 8.0%, 12.8% and 25.0% for 200, 500 and 800 mg respectively. DAT occupancy for MPH-LA 40 mg was 20.7%. SERT and DAT occupancy increased with dose and significantly correlated with plasma concentrations ($r^2 = 0.70$, $p = 0.0001$; $r^2 = 0.53$, $p = 0.003$, respectively for SERT and DAT).

Conclusions: These results provide evidence for dose-related brain occupancy for CTN-SR on NET, SERT and DAT suggesting a central mechanism of action via norepinephrine, serotonergic, and dopaminergic pathways for CTN-SR in HV subjects. In addition, NET occupancy at an equivalent level to that of a typical dose ATX and CTN-SR demonstrates similar DAT occupancy to that of a typical dose of MPH-LA. This data provides valuable information comparing CTN-SR to currently available therapeutics and to aid dose selection for future clinical trials.

W3. DASOTRALINE: A NOVEL DRUG CANDIDATE BEING EVALUATED FOR THE TREATMENT OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AND BINGE EATING DISORDER

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Abstract: Dasotraline is being evaluated by Sunovion Pharmaceuticals as a novel drug candidate for treating symptoms of Attention Deficit Hyperactivity Disorder (ADHD) in children, adolescents, and adults, and Binge Eating Disorder (BED) in adults.

Numerous stimulant and non-stimulant medications are available to treat ADHD, but their limited duration of effect may lead to inadequate symptom control before morning dosing and after the drug effect wears off later in the day. PK spikes that occur with each dosing interval can result in symptom rebound, while rapid surges in catecholamines induce effects that may be associated with drug abuse liabilities. Dasotraline may be a potential new therapeutic option for ADHD. It is a potent inhibitor of human dopamine (DA) and norepinephrine (NE) transporters. The PK profile in adults demonstrates slow absorption (t_{max} , 10-12 h) and elimination ($t_{1/2}$, 47-77 h), with continuous, 24-hour steady-state plasma concentrations achievable within 2 weeks. A phase 2, double-blind, fixed-dose study of 331 adults with ADHD receiving once-daily dasotraline (4 mg/d [$n=114$] or 8 mg/d [$n=107$]) or placebo ($n=110$) demonstrated significant LS-mean improvement in the primary endpoint (ADHD Rating Scale, Version IV total score) at Week 4 with 8-mg/d dasotraline vs placebo (-13.9 vs -9.7; $P=0.019$) and trend-level significance with 4 mg/d (-12.4; $P=0.076$). The most frequently reported adverse events (AE) were insomnia, decreased appetite, nausea, and dry mouth. Consistent with its PK profile, a single-dose human abuse liability study in healthy adult recreational stimulant users showed no significant difference between 3 dasotraline doses (8, 16, and 36 mg) vs placebo for the primary endpoint (Drug Liking Visual Analog Score at time of peak effect [DL-VAS E_{max}]), and for most secondary endpoints. All dasotraline doses were associated with significantly lower DL-VAS E_{max} compared with methylphenidate (40 and 80 mg). Both 8- and 16-mg dasotraline doses demonstrated an

incidence of AEs similar to placebo, with the exception of insomnia (higher with 8- and 16-mg dasotraline doses) and headache (higher with 16-mg dose). AE incidence was higher with the 36-mg dose, though this is higher than the anticipated maximum therapeutic dose. For pediatric patients with ADHD, a single-dose study of 105 patients (6-17 y) showed a PK profile similar to adults, with slow absorption (median t_{max} 9.6-12 h) and elimination ($t_{1/2}$ 56-84 h). Further, 2-4 mg/d doses in pediatric patients would yield exposures equivalent to 4-8 mg/d doses in adults. Studies assessing dasotraline at an additional dose in adults and dasotraline efficacy/safety in pediatric patients are underway.

Dasotraline may also be a potential new therapeutic option for BED. Non-clinical and clinical studies implicate dysregulated DA and NE circuitry as contributing to the BED etiology. Given the overlap between dasotraline DNRI pharmacology and BED neurobiology, studies are underway to evaluate once-daily dasotraline (4-8 mg/d) as a potential treatment option for moderate-to-severe BED in adults.

In summary, dasotraline provides continuous inhibition of DA and NE reuptake and has a low potential for abuse based on the human abuse liability study. Available clinical data add to the growing evidence of dasotraline as a potential new therapeutic option for the treatment of ADHD in children, adolescents, and adults, and moderate-to-severe BED in adults.

W4. A RANDOMIZED PLACEBO-CONTROLLED MULTICENTER TRIAL OF A LOW-DOSE BEDTIME SUBLINGUAL FORMULATION OF CYCLOBENZAPRINE (TNX-102 SL*) FOR THE TREATMENT OF MILITARY-RELATED PTSD

Gregory Sullivan¹, Judith Gendreau¹, R. Michael Gendreau², Amy Schaberg³, Bruce Daugherty¹, Heather Jividen¹, Ashild Peters¹, Perry Peters¹, Seth Lederman¹

¹Tonix Pharmaceuticals, Inc., ²Gendreau Consulting, ³Schaberg Consulting

Abstract: Background: With only two agents, both selective serotonin reuptake inhibitors (SSRIs), FDA-approved for the treatment of posttraumatic stress disorder (PTSD), and no clear evidence of efficacy of any SSRI in clinical studies of US military personnel or veterans, there is a need for improved pharmacotherapy interventions for the disorder. TNX-102 SL is a low dose formulation of the tricyclic molecule cyclobenzaprine that has been designed for bedtime administration and sublingual absorption, with bypass of first-pass hepatic metabolism. Based on the multifunctional activity of cyclobenzaprine, which has with 5-HT_{2A} serotonergic, α 1-adrenergic, and H₁-histaminergic receptor blocking properties, TNX-102 SL is hypothesized to improve global symptoms of PTSD through therapeutic effects on sleep disturbance and hyperarousal. Study TNX-CY-P201 (the 'AtEase Study') is being conducted in order to assess for the efficacy, safety, and tolerability of TNX-102 SL in the treatment of PTSD in a population with primarily military-related traumas. Methods: In this multicenter, 12-week, double-blind study, adults meeting a DSM-5 diagnosis of PTSD as assessed by the Clinician Administered PTSD Scale for DSM-5 (CAPS-5) were recruited by advertisement and randomized to TNX-102 SL 2.8 mg, 5.6 mg, or Placebo in a 2:1:2 ratio. Patients were enrolled at 24 sites in the US. Eligible participants (males and females) were 18-65 years of age, had experienced DSM-5 PTSD Criterion A-qualifying trauma(s) during military service since 2001, had at least a moderate level of PTSD severity as indicated by a CAPS-5 score > 28, and were free of antidepressants for at least 2 months and free of or washed off other psychotropic medications. Exclusion criteria

included serious suicide risk, unstable medical illness, substance use disorders within the prior 6 months, and lifetime history of bipolar 1 or 2, psychotic disorders, obsessive compulsive disorder, or antisocial personality disorder. The primary efficacy endpoint is the mean change from baseline in the CAPS-5 severity score between the TNX-102 SL 2.8 mg and placebo groups. Secondary endpoints include the PTSD Checklist for DSM-5 (PCL-5), Montgomery-Asberg Depression Rating Scale, Clinical and Patient Global Impression scales (CGI-I, PGIC), PROMIS Sleep Disturbance, CAPS-5 symptom cluster scores, and the Sheehan Disability Scale (SDS). A dynamic randomization procedure was employed to minimize trial-wide imbalances between the three treatment arms by site, sex, and presence (yes/no) of current comorbid major depressive disorder. CAPS-5 raters were MA-level or above in mental health fields who underwent a rigorous training and certification process. Sample size was powered to detect a 10-point difference between the Placebo and the TNX-102 SL 2.8 mg groups on the CAPS-5, considered a clinically relevant difference.

Results: A total of 245 participants were enrolled between January 2015 and December 2015. The results of primary topline analyses, including safety and tolerability information, will be presented.

Discussion: It is hypothesized that TNX-102 SL is a potentially effective, well-tolerated pharmacological intervention for the treatment of PTSD that works via effects on sleep disturbance and hyperarousal. The implications of the study results on further drug development and clinical practice in PTSD will be discussed.

Trial Registration

NCT02277704 Safety and Efficacy Study of TNX-102 SL in Subjects with Military-Related PTSD and Related Conditions

*TNX-102 SL is an Investigational New Drug and has not been approved for any indication.

W5. AN OPEN LABEL PILOT STUDY OF ADJUNCTIVE ASENAPINE FOR THE TREATMENT OF POSTTRAUMATIC STRESS DISORDER

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Abstract: Background: The selective serotonin reuptake inhibitors (SSRI) sertraline and paroxetine are the only FDA-approved medications for the treatment of posttraumatic stress disorder (PTSD). In spite of mixed results, especially in Veterans, SSRIs remain the first-line treatment for PTSD. However, prominent residual PTSD symptoms lead many clinicians to choose combination pharmacotherapy that often includes an atypical antipsychotic medication. Asenapine (Saphris) is an atypical antipsychotic that is currently FDA approved for the treatment of schizophrenia and bipolar disorder. The unique receptor profile of asenapine involves a high serotonin (5-HT_{2A}) to dopamine (D₂) affinity ratio and alpha-1 adrenergic antagonism. These potent receptor properties of asenapine address many of the disturbances underlying the pathophysiology of PTSD. The primary objective of this study was to determine the feasibility of recruitment, assessments, and intervention, with some initial evaluation of therapeutic effect and tolerability of adjunctive asenapine in Veterans with unremitting PTSD despite an adequate dose and duration of a serotonergic antidepressant.

Methods: This pilot study was a single-site, prospective, open label, 12-week trial of adjunctive asenapine in the treatment of PTSD in Veterans who had not responded to an adequate course of treatment with an SSRI, selective serotonin norepinephrine reuptake inhibitor (SNRI), or the noradrenergic/serotonergic antidepressant, mirtazapine. After signed informed consent and meeting eligibility criteria, participants continued the antidepressant medication and started 5 mg sublingual asenapine at bedtime. Asenapine was gradually titrated as tolerated to a maximum dose of 10 mg twice a day. The primary PTSD outcome was assessed by the Clinician Administered PTSD Scale (CAPS).

Results: Eighteen Veterans with PTSD were eligible, enrolled, and started on asenapine. Fifteen finished at least four weeks and eleven completed 12 weeks. There was a clinically meaningful decrease in CAPS from baseline (77.56 ± 14.48) to week 4 (48.7 ± 30.6) and to week 12 (35.3 ± 19.7). The PTSD Checklist, Quick Inventory of Depressive Symptoms – self report, and Clinical Global Impression scales also showed clinically meaningful improvements. Six participants experienced adverse events possibly related to asenapine; however only three participants discontinued early due to related adverse events.

Significance: In spite of conventional treatments, such as antidepressants, many Veterans with PTSD continue to experience significant symptomatology and non-remission. The primary role of this pilot study was to examine the feasibility of recruitment, intervention, and assessments, which were all successful. This study also demonstrated that asenapine is helpful in treating PTSD in Veterans who are not fully responding to an antidepressant. Although fairly well-tolerated, a few participants experienced adverse side effects. A placebo-controlled study is needed to better understand efficacy and tolerability in the treatment of PTSD. **Limitations:** open-label; small sample size; single-site; Veterans only.

Learning Objectives:

- Understand limitations of treatment with antidepressants in patients with posttraumatic stress disorder and the alternatives of augmentation strategies.
- Understand the potential therapeutic and side effects of asenapine in the treatment of posttraumatic stress disorder.

Literature References:

- Leon AC, Davis LL, Kraemer HC: The role and interpretation of pilot studies in clinical research. *J Psychiatr Res* 2011; 45(5):626-9.
- Shahid M, Walker GB, Zorn SH, Wong E: Asenapine: a novel psychopharmacologic agent with a unique receptor signature. *J Psychopharmacol* 2009; 23: 65-73.

W6. LURASIDONE IN THE TREATMENT OF BIPOLAR DEPRESSION: EFFECT OF BASELINE DEPRESSION SEVERITY ON CLINICAL OUTCOME

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Abstract: Objective: The aim of this post-hoc analysis was to evaluate the effect of baseline depression severity on clinical response in patients with bipolar depression treated with lurasidone.

Methods: Patients with bipolar I depression in 2 registration trials were randomized to 6 weeks of once-daily, double-blind, placebo-controlled treatment with lurasidone

monotherapy (20-60 mg/d or 80-120 mg/d; N=499); or with lurasidone adjunctive to lithium or valproate (20-120 mg/d; N=345). Two baseline depression severity groups were defined post-hoc: a moderate (Montgomery-Asberg Depression Rating Scale [MADRS] total score: 20-29) and a high (MADRS $\geq$ 30) severity group. For each group, changes in MADRS total and Clinical Global Impression, Bipolar Severity (CGI-BP-S) scores were analyzed using a mixed model for repeated measures analysis. Additional efficacy outcomes included the 16-item Quick Inventory of Depressive Symptomatology, self-report (QIDS-SR16).

Results: In the monotherapy study, 42.9% of patients were in the moderate severity group (mean MADRS total score: 26.0) and 57.1% were in the high severity group (MADRS: 33.9); in the adjunctive therapy study, 39.7% of patients were in the moderate severity group (mean MADRS: 25.7) and 60.3% were in the high severity group (MADRS: 34.0). In the monotherapy study, lurasidone effect sizes (d) for MADRS change at week 6 in the high severity vs. moderate severity groups were d=0.60 (P<0.001) vs. 0.40 (P=0.035) for the 20-60 mg/d dose range, and d=0.55 (P=0.002) vs. 0.50 (P=0.008) for the 80-120 mg/d dose range. Monotherapy with lurasidone was associated with significantly greater week 6 improvement for both severity groups on the CGI-BP-S (with effect sizes ranging from 0.42-0.68), and on the QIDS-SR16 (with effect sizes ranging from 0.39-0.59). In the adjunctive therapy study, lurasidone effect sizes for MADRS change in the high severity vs. moderate severity groups were d=0.25 (P=0.10) vs. d=0.41 (P=0.033); effect sizes for CGI-BP-S change were d=0.21 (P=0.18) vs. d=0.60 (P=0.002); and effect sizes for QIDS-SR16 change were d=0.32 (P=0.026) vs. d=0.73 (P<0.001). Lurasidone was well-tolerated in both studies, regardless of depression severity subgroup.

Conclusions: In this post-hoc analysis, the magnitude of endpoint improvement in depressive symptoms (as measured by endpoint change in the MADRS, CGI-BP-S, and QIDS-SR16) was similar-or-greater for patients with high (vs moderate) baseline depression severity during both monotherapy and adjunctive therapy with lurasidone. These results found that severity of depressive symptoms had no clinically meaningful effect on treatment response to lurasidone, a finding that was confirmed by the lack of a significance on a treatment by severity interaction test.

Clinicaltrials.gov identifier: NCT00868699, NCT00868452.

Sponsored by Sunovion Pharmaceuticals Inc.

Learning Objectives:

- After completion of this presentation, the reader will have a better understanding of the effect of baseline depression severity on response to lurasidone in patients with bipolar disorder.
- After completion of this presentation, the reader will have a better understanding of the effect of whether baseline depression severity influences tolerability and adherence to lurasidone during short-term therapy.

Literature References:

- Loebel A, Cucchiaro J, Silva R, et al. Lurasidone monotherapy in the treatment of bipolar I depression: a randomized, double-blind, placebo-controlled study. *Am J Psychiatry* 2014;171:160-8.
- Loebel A, Cucchiaro J, Silva R, et al. Lurasidone as adjunctive therapy with lithium or valproate for the treatment of bipolar I depression: a randomized, double-blind, placebo-controlled study. *Am J Psychiatry* 2014;171:169-77.

W7. A RETROSPECTIVE STUDY OF TRANSCRANIAL MAGNETIC STIMULATION (TMS) IN THE TREATMENT OF BIPOLAR DEPRESSION

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Abstract: Background: Treatment options are limited for patients with bipolar depression. Data from the STEP-BD support the notion that antidepressants added to mood stabilizers provide no improvement in outcome but may carry the risk of precipitating a mixed or manic episode. Neurostimulation may provide an option for bipolar depressed patients.

Methods: The database from the TMS Service at Sheppard Pratt Health System was reviewed to identify 45 patients clinically diagnosed with bipolar type I or 2 depression who were treated with TMS. Records were analyzed to capture response and remission rates based on MADRS scores, length of treatment to achieve response, and if treatment was stopped due to an adverse event. All had failed at least two prior treatments for their depression and were currently on at least one mood stabilizing agent.

Results: 45 patients with bipolar depression were identified which represented 15% of the total TMS population. Four patients stopped due to switching to ECT, five patients had their courses completed at a different facility and two did not have complete data leaving 34 patients whose data was analyzed. 26 patients (75%) met MADRS response criteria and 12 (35%) met remission criteria. This is superior to the rates seen at this center for treatment resistant unipolar depression (62% response, 31% remission). Time to response was quicker than seen in unipolar depression. No patients demonstrated treatment emergent mania.

Conclusion: TMS and other neurostimulation interventions may prove particularly effective in the bipolar depressed population where episode focused intervention can be effectively offered.

Learning Objectives:

1. Participants will be able to review the current options for somatic treatment of bipolar depression.
2. Participants will be able to discuss the risks and benefits for using TMS in patients with bipolar depression.

Literature References:

- Nierenberg AA, McIntyre RS, Sachs GS. Improving outcomes in patients with bipolar depression: a comprehensive review. *J Clin Psychiatry*, 2015, 76(3):e10.
- Woźniak-Kwaśniewska A, Szekely D, Harquel S, Bougerol T, David O. Resting electroencephalographic correlates of the clinical response to repetitive transcranial magnetic stimulation: A preliminary comparison between unipolar and bipolar depression. *J Affect Disord*. 2015 Sep 1;183:15-21

W8. DISCREPANCY BETWEEN SUBJECTIVE AND OBJECTIVE SLEEP PARAMETERS IN SYMPTOMATIC AND EUTHYMIC BIPOLAR DISORDER COMPARED TO HEALTHY CONTROLS

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Abstract: Objectives: Sleep disturbances are a cardinal feature of BD and are an important clinical target for treatment¹. Our main objective was 1) to investigate discrepancy between objective and subjective sleep measures of sleep latency, total sleep time (TST) and sleep efficiency in symptomatic (SBD) and euthymic (EBD) BD compared to healthy controls (HC), 2) to explore the correlation between subjective and objective sleep variables of sleep latency, total sleep time (TST) and sleep efficiency in the SBD, EBD as well as HC, 3) the effect of mood on the discrepancy between objective and subjective sleep variables in the above three groups.

Methods: 32 SBD, 11 EBD and 30 HC were involved in this study. Subjective sleep was measured by Pittsburgh sleep Quality Index² (PSQI) and objective sleep measured by actigraphy for one week. Discrepancy variables were calculated by subtracting objective sleep latency, duration, and sleep efficiency on actigraphy from respective subjective variables on the PSQI.

Results: 1) The SBD group had significantly higher discrepancy between objective and subjective measures of sleep latency (SBD=60.1±54.3, EBD=15.8±12.9, HC=11.5±12.7, $p<0.01$), TST (SBD=2.3±1.3, EBD=1.1±0.6, HC=1±0.8, $p<0.01$) and sleep efficiency (SBD=26.8±26.5, EBD=13.9±11.8, HC=11.1±6.4, $p<0.01$) as compared to the euthymic BD and HC group. There was no statistically significant difference between EBD and HC group for the above sleep variables, 2) The proportion of the BD group that inaccurately estimated sleep latency (SBD=59%, EBD=18%, HC=7%, Chi-square=20.9, $p<0.01$) and TST (SBD=81%, EBD=54%, HC=40%, Chi-square=11.2, $p<0.01$) was significantly higher in the symptomatic group followed by the euthymic group as compared to the controls. 3) TST as measured by actigraphy did not correlate with the subjective TST measured by PSQI for the SBD group ($r=0.15$, $p=0.4$), but significantly correlated for the EBD ($r=0.7$, $p=0.02$), and the HC group ($r=0.42$, $p=0.02$). On multi variate regression analysis, depression measured by Hamilton Depression Rating Scale (HDRS) predicted the discrepancy between objective and subjective TST in SBD group.

Conclusion: Subjective sleep misperception is common in symptomatic BD group as evidenced by significantly higher discrepancy between objective and subjective sleep variables as well as a higher proportion of SBD subjects inaccurately estimating their sleep. Objective measures of sleep like actigraphy can be helpful in evaluation of sleep in such subjects. Behavioral interventions directed to address sleep misperception in symptomatic BD may be helpful. Depression can lead to sleep misperception in SBD and studies evaluating the effect of treatment of depression on sleep misperception need to be considered.

Learning Objectives:

- Subjective sleep misperception is common in symptomatic BD group. Objective measures of sleep like actigraphy can be helpful in evaluation of sleep in such subjects.
- Depression can lead to sleep misperception in SBD and studies evaluating the effect of treatment of depression on sleep misperception need to be considered.

Literature References:

- Krystal, A. D., Thakur, M., & Roth, T. (2008). Sleep disturbance in psychiatric disorders: effects on function and quality of life in mood disorders, alcoholism, and schizophrenia. *Annals of Clinical Psychiatry*, 20(1), 39-46.

- Buysse, D. J., Reynolds, C. F., Monk, T. H., Berman, S. R., & Kupfer, D. J. (1989). The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry research*, 28(2), 193-213.

W9. TREATING PEDIATRIC ANXIETY: THE USE OF SSRIS AND OTHER PRESCRIPTION MEDICATIONS

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Abstract: Background: Based on randomized controlled trial (RCT) evidence, selective serotonin reuptake inhibitors (SSRIs) are the recommended initial pharmacotherapy for pediatric anxiety (Birmaher, 2007). However several pharmacotherapies for anxiety exist. With the exception of select SSRIs for pediatric obsessive-compulsive disorder, no pharmacotherapies are FDA approved to treat pediatric anxiety. It is unknown if medications are prescribed concordant with the evidence that supports SSRI use.

Objective: To describe the initial medication classes used to treat pediatric anxiety and the proportion of children with an SSRI as their initial medication. Also, to examine initiation of SSRI and of non-SSRI medication classes across the study period and by patient characteristics.

Methods: Our population included children (3-17 years) initiating prescription medication to treat anxiety from 2004-2013 with a diagnosis of an anxiety disorder (ICD-9-CM=293.84, 300.0x, 300.2x, 300.3x, 309.21, 309.81, 313.23) ≤ 30 days prior to the filled prescription. We used Truven Health's MarketScan Commercial Claims and Encounters database and restricted to children with continuous insurance enrollment with mental health and prescription coverage. Initial medication regimens were assessed using records of dispensed prescriptions. Provider type was defined using the provider associated with the most recent inpatient or outpatient claim with an anxiety diagnosis before the initial prescription. We examined initial medication use over time and used adjusted polynomial logistic regression to evaluate factors associated with initiation of 1) SSRI alone, 2) non-SSRI medication, and 3) SSRI + a non-SSRI medication.

Results: Of 66,902 children beginning medication for anxiety, 69% initiated with an SSRI (62% SSRI alone, 6% SSRI in combination), with variation by anxiety disorder: 57-84%. Twelve-percent of children initiated with a benzodiazepine (9% alone, 3% with an SSRI). Additional mono-therapies included: 8% non-SSRI antidepressants, 4% hydroxyzine, 3% atypical antipsychotic, 2% buspirone, 1% beta-blockers, 1% anticonvulsants, and 3% other anti-anxiety; 1% initiated non-SSRI combination therapy. Across the study period, SSRI use alone or in combination remained stable in the youngest children aged 3-5 years (2004: 51% to 2013: 52%) and increased in older children (10-13 years: 66% to 74%, 14-17 years: 61 to

73%). In children aged 14-17, the proportion initiating on a benzodiazepine decreased (19% to 12%) across the study period.

Compared with initiation on an SSRI alone, initiation on a non-SSRI medication was more common in males (OR=1.3, 1.2-1.3), children with PTSD (OR: 1.9, 1.7-2.0), panic disorder (OR: 2.2, 2.0-2.4), or unspecified anxiety diagnosis (OR=1.3, 1.3-1.4) versus generalized anxiety disorder diagnosis, and children recently seen for anxiety in an inpatient setting (OR=1.3, 1.2-1.4). Age, provider type, prior psychotherapy use, and region were also associated with non-SSRI initiation. Various patient characteristics were associated with initiation on an SSRI + a non-SSRI medication compared with SSRI alone.

Conclusions: In concordance with recommendations and RCT evidence, SSRIs are the most commonly used first-line medication for pediatric anxiety. Still, 1/3 of children began therapy on a non-SSRI medication, for which there is limited evidence of effectiveness for pediatric anxiety (Ipser, 2010).

Learning Objectives:

- To determine the initial pharmacotherapy children with anxiety receive and whether it corresponds with recommendations for SSRIs.
- To examine factors that influence the initial medication class prescribed for pediatric anxiety.

Literature References:

- Birmaher B, Brent D, AACAP Work Group on Quality Issues: Practice parameter for the assessment and treatment of children and adolescents with depressive disorders. *J Am Acad Child Adolesc Psychiatry* 2007; 46:1503-1526
- Ipser JC SD, Hawkrigde S, Hoppe L: Pharmacotherapy for anxiety disorders in children and adolescents (Review) *Cochrane Libr.* 2010

W10. VIRGIL INVESTIGATIVE STUDY PLATFORM: IMPROVING SIGNAL DETECTION IN PSYCHIATRY CLINICAL TRIALS

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¹*MedAvante*

Abstract: Background: Clinical trials of major depressive disorder (MDD) suffer from high placebo response rates that lead to inconclusive results¹. The very high failure rate in these trials is in part due to inconsistent and inefficient psychiatric assessments, which add noise around the signal. Clinical outcome assessments (COA) with traditional paper-based administration, already recognized as cost- and time-inefficient, also contribute to human error, creating more variability in measurement. The Virgil digital platform for electronic assessments (eCOA) provides clinicians with tablet devices in place of paper to collect source data with real-time clinical guidance in order to help standardize measurements and improve data quality.

The Hamilton Depression Rating Scale (HAM-D) is one of the most widely used endpoints in clinical trials of major depression². While the structured interview guide for HAM-D (SIGH-D) has helped standardize the scale, paper-based assessments are still prone to administration and scoring errors which contribute to poor interrater reliability. In the present study, we compared paper-based administrations of the SIGH-D against Virgil administrations to

determine the extent to which the use of eCOA minimizes scoring errors to improve data quality.

Methods: Paper-based assessments of the seventeen-item SIGH-D administered in a MDD trial were compared against eCOA administrations of the same scale in a separate MDD trial. Score discrepancies were identified via review of audio recordings and worksheets by the same cohort of expert calibrated reviewers. The percentage of reviews with discrepancies was compared between paper-based and eCOA administrations. Item-level discrepancies were also examined.

Results: The percentage of reviews with two or more discrepancies was significantly lower in eCOA administrations compared to paper-based. Virgil administrations also resulted in fewer discrepancies on the item level compared to paper-based assessments.

Conclusions: Paper-based administrations create unnecessary variability around endpoint measurements, which contribute to inconclusive results in psychiatry trials. An eCOA platform with real-time clinical guidance, auto-calculation of scores, and prompts for missing data and out-of-range errors can help standardize scale administration and scoring, thereby improving signal detection.

Learning Objectives:

- To compare scoring discrepancies between traditional paper-based administrations and a digital platform that uses electronic Clinical Outcome Assessments (eCOA) in the administration and scoring of SIGH-D in Major Depressive Disorder trials.
- To compare item discrepancies between paper-based and electronic administrations of SIGH-D in Major Depressive Disorder trials.

Literature References:

- Walsh BT, Seidman SN, Sysko R, et al. Placebo response in studies of depression: variable, substantial, and growing. *JAMA*. 2002;287:1840–7
- Williams JB. A structured interview guide for the Hamilton Depression Rating Scale. *Arch Gen Psychiatry*. 1988 Aug;45(8):742-7

W11. ACCESS TO INFORMATION ON SCHIZOPHRENIA PATIENTS' MEDICATION ADHERENCE CAN CHANGE PRESCRIBER'S TREATMENT PRACTICES

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Abstract: Background: For patients with schizophrenia, antipsychotic (AP) medication non-adherence harms health and increases costs for the health care system, but credible data on patient medication adherence is scarce. New technologies—such as ingestible event monitors embedded into medications—offer credible information on adherence. Such information may facilitate more effective treatment decision making, with the potential for improving outcomes and reducing cost of care. To assess this hypothesis, we conducted a survey to determine how healthcare providers' treatment decisions would be influenced by the presence of credible AP medication adherence information.

Methods: A convenience sample of physicians, physician assistants and nurse practitioners that prescribe AP medications for schizophrenia patients was recruited via email, mail and fax. Respondents were randomized to one of two groups. Both groups received 6 patient vignettes describing patient demographics, history of symptoms and treatment (Tx), current disease severity and co-morbid conditions. The experimental group vignettes included AP medication adherence information reported from a credible source (i.e., collected using MEMS caps or blood plasma level). This adherence information was omitted from the control group vignettes. Three of the six vignettes for both groups described patients who were truly adhering to their medication and the other three described non-adherent patients. In both arms, respondents were asked to select their preferred pharmaceutical and non-pharmaceutical treatment recommendations based on characteristics of cases presented. The primary outcome was the share of prescribers that selected an adherence-remediation related Tx (i.e., long-acting injectable or adherence-related motivational interviews) for each case. Between group Tx differences were tested using χ^2 test of proportions.

Results: 221 prescribers completed the survey. Of these 44% were male, 50% were ≤ 39 years of age and 76% had an MD. Provider demographic and practice characteristics were well-balanced across groups (p-values: 0.11 to 0.98 across all characteristics). When presented with the three vignettes describing non-adherent patients, providers in the experimental group were more than twice as likely to choose an adherence-remediation related Tx option compared to the control group (87.2% vs. 41.4%; $p < 0.001$ for all cases). For the one vignette where patients were adherent to their medication but symptoms were well-controlled, we found no statistically significant difference in adherence-remediation related Tx across groups (3.7% vs. 6.3%, $p = 0.370$). However, for the two cases where the patient was adherent, but not well controlled, unnecessary prescribing of adherence-remediation related Tx was 84% lower in the treatment group with adherence information than the control group (3.7% vs. 23.0%, $p < 0.001$).

Conclusions: In this study, access to credible AP medication adherence information more than doubled the use of adherence-remediating interventions for non-adherent patients and decreased the use of these interventions among patients that were already adherent but poorly controlled. The absence of credible information on AP adherence may contribute to suboptimal treatment choices, which may in turn increase the relapse risk, inpatient utilization, and cost. Future research should explore how access to adherence information affects real-world patient health and economic outcomes.

Learning Objectives:

- Describe how physicians currently treat patients with schizophrenia that may be at risk of nonadherence to their antipsychotic medication.
- Understand how access to accurate, real-time information on medication adherence to antipsychotics would affect the decision making of providers treating patients with schizophrenia.

Literature References:

- Stephenson, J. J., et al. (2012). "Adherence to oral second-generation antipsychotic medications in patients with schizophrenia and bipolar disorder: physicians' perceptions of adherence vs. pharmacy claims." *Int J Clin Pract* 66(6): 565-573.
- Lindenmayer, J.-P., et al., Medication nonadherence and treatment outcome in patients with schizophrenia or schizoaffective disorder with suboptimal prior response. *The Journal of clinical psychiatry*, 2009(70): p. 990-6.

W12. THE ECOA AND PAPER REVISED NEGATIVE SYMPTOM ASSESSMENT-16 (NSA-16) INSTRUCTION MANUAL AND SEMI-STRUCTURED INTERVIEW–VERSION 3.0

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Abstract: Background: The purpose of the Negative Symptom Assessment -16 is to permit the reliable rating of reduction or absence of emotional expression and volitional behaviors commonly associated with the concept of negative symptoms in schizophrenia. (Axelrod BN, Goldman, RS, Alphas, LD, 1993) The NSA-16 Instruction Manual includes a semi-structured interview and detailed instructions to enhance the accuracy and reliability of assessment. In Version 3.0, revised June 22, 2015, we have revised the NSA-16 Manual to include additional instructions and a more detailed semi-structured interview. Version 3.0, June 22, 2015, has been adapted for either paper or electronic capture (eCOA) on a tablet or desk top computer.

Method: Principles for revision of the NSA-16 Instruction Manual and Semi-structured interview included:

- enhanced clarity of sources of information, reference population, time frame and factors considered in rating the global score.
- additional details and probes in the structured interview to enhance the consistency and thoroughness of assessment.

Principles guiding the creation of an eCOA version included:

- rapid acquisition of data,
- lack of need for transcription from paper to eCRF,
- capacity for real time edit checks for logical inconsistencies in scoring prior to data submission and
- the capacity for alerts for disqualifying scores after data submission at screening and baseline.

Results: Examples of Updated Text in Version 3.0 (additions to previous text are enclosed in brackets below)

Reference Population: The 'normal' reference population against which the subject is to be compared is a young person in their twenties [without schizophrenia]. It is not (1) the same person at another point in time; (2) a healthy person of similar age, living under similar circumstances; or (3) another hospitalized person.

Semi-Structured Interview: Are you employed now? What do you do? Do you work full time? If not, how many hours per week? Is your employer satisfied with the work that you do?

[Do you go to school? If so, how many hours per week? What types of grades do you receive?]

[Are you responsible for cooking, cleaning or other housework where you live?][What are your responsibilities? Have you been able to perform this work as expected?]

[Do you attend a day program, vocational rehabilitation or a sheltered workshop? If so, how many hours per week do you attend? Do attend as required?]

7. Starting with the time you get up; could you tell me how you have spent a typical day during the past week? [What do you do next? Follow up on ambiguous statements.] [For example, if the patient says, “I eat breakfast,” ask what he or she eats and who makes it. If the patient says, “I take my medication”, you may want to ask if she takes it herself or if someone reminds her.]

Discussion: The revisions in Version 3.0 of the NSA-16 Instruction Manual are expected to provide further enhancement of thoroughness of interview technique and accuracy and reliability of ratings. The eCOA version permits paperless data acquisition with incorporation of ratings quality edit checks prior to data submission and disqualification alerts at screening and baseline after data submission. The eCOA version will be piloted in an upcoming global clinical trial.

Learning Objectives:

- Familiarity with the purpose and content of the revisions to the NSA-16.
- Understanding of the potential effects on data quality of an electronic version of the NSA-16.

Literature References:

- Axelrod BN, Goldman, RS, Alphas, LD: Validation of the 16 Item NSA Assessment. J Psychiatr Research, 27: 253-258, 1993
- Alphas LD: NSA-16 Instruction Manual Version 3, 2006, Revised June 22, 2015

W13. A RETROSPECTIVE ANALYSIS OF THE EFFECTS OF SUBJECT CHARACTERISTICS ON COMPLETION RATES IN PHASE 1 STUDIES IN SUBJECTS WITH STABLE SCHIZOPHRENIA

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Abstract: Introduction: Subject attrition from randomized Schizophrenia trials is a significant problem and has been found in a meta-analysis to be as high as 76% (Robinowitz et al., 2005). The problem of drop-out is sometimes not addressed until the statistical analysis stage of a study which can decrease the validity of the results increasing the likelihood of a failed trial.

The authors have previously conducted a retrospective analysis of the effects of protocol design on completion rates in Phase 1 studies with subjects with stable Schizophrenia or Schizoaffective Disorder. (Krefetz et al., 2015). That analysis showed that decreased inpatient confinement, longer outpatient phase, and more frequent outpatient visits had significant positive impact on study completion.

While trial design features can increase attrition for various reasons, there is growing evidence that subject-level variables also have a significant impact on retention in Schizophrenia trials.

The authors now study the impact of specific subject characteristics on study completion in Phase 1 studies in subjects with stable Schizophrenia or Schizoaffective Disorder and discuss how the results of the present analysis can inform future subject selection to improve completion rates.

With the recent refinement of mechanisms for unbiased external review of individual subjects prior to randomization, it is important to identify which subject variables are most likely to lead to improved retention to capitalize on this knowledge during recruitment and screening.

Methods: The authors examined the effect of 7 subject-level independent variables on completion rates in 12 Phase I trials with subjects with stable Schizophrenia or Schizoaffective Disorder. These 12 trials were conducted at two clinical trial sites from 2009-2015. The sites enrolled 343 subjects and had an overall completion rate of 84%.

The variables studied include age, gender, geographical distance from study site, length of current stability period, number of previous trials, overall length of psychotic illness, and previous history of substance abuse. Variables are analyzed via a stepwise linear regression analysis to assess the predictive value of each variable with regard to study completion.

Results: We present significant variables and discuss conclusions that can be drawn to inform subject selection that will lead to studies with better retention which will increase the information gained from these clinical trials.

Learning Objectives:

- Identify subject variables that are associated with improved study completion rates in Phase 1 clinical trials in subjects with stable Schizophrenia or Schizoaffective Disorder.
- Understand how to best utilize the knowledge of variables associated with increased subject completion when establishing eligibility criteria and selecting subjects for participation.

Literature References:

- Rabinowitz J, Levine SZ, Barkai O, Davidov O. Dropout Rates in Randomized Clinical Trials of Antipsychotics: A Meta-analysis Comparing First- and Second-Generation Drugs and an Examination of the Role of Trial Design Features. *Schizophrenia Bulletin*. 2009; 35(4):775-788.
- Krefetz DG et al. A Retrospective Analysis of the Effects of Protocol Design on Completion Rates in Phase 1 Studies in Subjects with Stable Schizophrenia. Poster presented at CNS Summit. 2015 Oct 9; Boca Raton, FL.

W14. REDUCED INHIBITORY CONTROL MEDIATES THE RELATIONSHIP BETWEEN CORTICAL THICKNESS IN THE RIGHT SUPERIOR FRONTAL GYRUS AND BODY MASS INDEX

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Abstract: Background: Unhealthy eating behaviors often develop in the setting of inadequate inhibitory control, a function broadly ascribed to the prefrontal cortex (PFC). Regulation of inhibitory control by the PFC and its anatomical components and their contribution to increasing body mass index (BMI) are poorly understood.

Methods: To study the role of PFC in the regulation of inhibitory control and body weight, we examined measures of cortical thickness in PFC sub-regions, inhibitory control (color-

word interference task, CWIT), and BMI in 91 healthy volunteers. We tested the predictive effect of PFC sub-regional cortical thickness on BMI and mediation by inhibitory control measured with CWIT. Measures of depression (BDI-II), anxiety (STAI-T) and trauma-related symptoms (TSC-40) were collected; the disinhibition scale of the three-factor eating questionnaire (TFEQ) was used to assess disinhibited eating. We then tested the relationship between BDI-II, STAI-T, TSC-40, TFEQ, CWIT and BMI with correlation analyses.

Results: Right superior frontal gyrus cortical thickness significantly predicted BMI ($\beta = -.91$; $t = -3.2$; $p = .002$). Mediation analysis showed a significant indirect effect of cortical thickness on BMI mediated by inhibitory control (95% CI = -6.1, -.67). BMI was unrelated to BDI-II, STAI-T, TSC-40 or TFEQ scores.

Conclusions and importance of the findings for the field: We found an inverse relationship between cortical thickness in the right superior frontal gyrus and BMI, which was fully mediated by inhibitory control neurocognitive performance. Our results suggest possible targets for neuromodulation in obesity (i.e. superior frontal gyrus) and a quantifiable mediator of their effects (i.e. inhibitory control). Furthermore, these findings suggest that psychotropic drugs which are known to increase PFC function (like lisdexamfetamine, recently approved for the treatment of binge eating disorder by the Food and Drug Administration) might hold promise for weight reduction through the facilitation of inhibitory control.

Learning Objectives:

- Studying the relationship cortical thickness in the prefrontal cortex and body mass index.
- Testing whether this relationship is mediated by inhibitory control.

Literature References:

- Alonso-Alonso M: Translating tDCS into the field of obesity: mechanism-driven approaches. *Frontiers of Human Neuroscience* 2013; 7: 512.
- Bari A, Robbins TW: Inhibition and impulsivity: behavioral and neural basis of response control. *Prog Neurobiol* 2013; 108: 44–79.

W15. ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AND DEPRESSION: SEQUENTIAL AND CONCURRENT DISORDERS

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Abstract: Background: Depression and suicide have become major public health concerns as rates continue to increase and have become among the leading causes of disability and death respectively. Research suggests that more than 11% of adolescents experience depression and that depressed adolescents are 6-times more likely to attempt suicide compared to non-depressed individuals. As well, adolescents with a history of attention deficit hyperactivity disorder (ADHD) are significantly more likely to develop depression by adulthood. A core symptom of depression, anhedonia, is present in a subset of patients with ADHD and associated with poorer treatment response in patients treated with traditional antidepressants. Thus, the aim of this study was to determine predictive factors and clinical features associated with the development of treatment-resistance depression (TRD) and suicidality in patients with mood and anxiety disorders.

Method: Data was collected from consecutive referrals to a tertiary-care mood and anxiety clinic between 2011 and 2015. Only patients that provided informed consent and were new referrals were included in the analysis (n=160). Diagnosis was established by using the Mini International Neuropsychiatric Interview Plus 5.0.0 and a semi-structured interview by the treating physician. One-way analysis of variance and t-tests were performed to examine predictive factors related to the development of TRD and factors that may suggest an increased risk for suicidality.

Results: Results indicated that 34% of patients referred for TRD had untreated ADHD with more than 48% of these patients presenting with chronic anhedonia. The number of failed psychiatric medications ($p<0.001$), SSRI failures ($p<0.020$), and number of past SSRI failures ($p<0.032$) was predictive of ADHD in patients with TRD. The most predictive factor of SSRI failure within this group was the presence of anhedonia ($p<0.002$). Moreover, the presence of chronic anhedonia was predictive of increased reports of suicide ideation ($p<0.05$) and attempts ($p<0.000$).

Conclusions: These results support previous findings that ADHD is a significant risk factor for the development of TRD. This study demonstrated that the presence of chronic (trait) anhedonia or low hedonic tone may be a link between TRD and ADHD, which may predict poorer treatment outcomes in a subset of patients treated with SSRIs. Moreover, low hedonic tone may increase the risk of suicidality. These findings suggest that it is imperative to assure safety and optimal outcomes in patients presenting with depression, by ensuring accurate screening in patients that fail SSRI treatment, for concurrent ADHD, as well as low hedonic tone.

Learning Objectives:

- Examine the role of ADHD as a potential precursor and predictor of treatment-resistant depression.
- Identify clinical clues and treatment implications of concurrent ADHD and depression.

Literature References:

- Meinzer, MC, Lewinsohn, PM, Pettit, JW, Seeley, JR, Gau, JM, Chronis-Tuscano, A and Waxmonsky, JG. Attention-Deficit/Hyperactivity Disorder In Adolescence Predicts Onset Of Major Depressive Disorder Through Early Adulthood. *Depress. Anxiety*. 2013;30:546–553. doi: 10.1002/da.22082
- Nock MK, Green J, Hwang I, McLaughlin KA, Sampson NA, Zaslavsky AM, Kessler RC. Prevalence, Correlates, and Treatment of Lifetime Suicidal Behavior Among Adolescents: Results From the National Comorbidity Survey Replication Adolescent Supplement. *JAMA Psychiatry*. 2013;70(3):300-310. doi:10.1001/2013.jamapsychiatry.55.

W16. IMPROVING ALZHEIMER'S DISEASE DATA QUALITY THROUGH VIDEO MONITORING

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Abstract: The development of effective drugs in Alzheimer's disease has been challenging. Measurements at baseline and during the study to assess the efficacy of the drug depend on

consistent, standard administration of scoring instruments. However, when the interviews and assessments of subjects during a clinical study are independently monitored, administration and scoring errors by the persons performing the assessments (the “raters”) are frequently detected.

In a large, global clinical trial, 4327 screening visits were video-recorded. The videos were reviewed by doctoral-level clinicians for scoring and administrative accuracy. Fifty-seven percent of the visits were found to have at least one administrative or scoring error in the application of the measurement instrument. Thirty percent of these errors would not have been detected through traditional Data Surveillance methodologies. Twenty-five percent of the errors that were detected were scoring errors that led to a recommended scoring change. Scoring errors impacted eligibility conclusions in 20% of the screening visits with errors had subjects being approved for inclusion or potentially excluded based on erroneously scored and administered Mimi-Mental Status Exams (MMSE). If efficacy in a clinical trial is defined as a 3-point change in the ADAS-Cog, correcting 25% of screening measurement scoring errors committed by raters will drastically improve the quality of the data.

Video monitoring was effective at identifying administration and scoring errors, retraining raters and correcting erroneous scores resulting in improved data quality and confirmed eligibility of subjects. Future training programs should be informed by the lessons learned on most frequently occurring scoring and administrative errors.

Learning Objectives:

- Reviewing errors committed on standard Alzheimer’s disease endpoints which can improve the accuracy of enrolling eligible subjects reduce error variance in data.
- Identify training opportunities which can improve trial data accuracy.

Literature References:

- Gaur, R, Bullock, R, Geetika, N, Kakati, R, and Santi, S. Are we adequately evaluating and monitoring rater performance in clinical trials with dementia? *Alzheimer’s and Dementia*, 5(4), 240.
- Kobak, K, Kane, J, Thase, M, Nierenberg, A. Why do clinical trials fail? *Journal of Clinical Psychopharmacology*, 2007(27), 1-5.

W17. OPEN BOARD

W18. CATEGORICAL IMPROVEMENTS IN DISEASE SEVERITY IN MDD PATIENTS TREATED WITH VILAZODONE: POST HOC ANALYSIS OF 4 RANDOMIZED, PLACEBO-CONTROLLED TRIALS

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Abstract: Background: Vilazodone (VLZ) is a serotonin reuptake inhibitor and 5-HT1A receptor partial agonist that is approved for the treatment of major depressive disorder (MDD) in adults. Three 8 week studies of VLZ 40 mg/d or placebo (PBO) (NCT00683592, NCT00285376, NCT01473394) have been conducted in MDD patients, as well as one 10-week study of VLZ 20 mg/d, 40 mg/d, or PBO (NCT01473381). In all 4 studies, treatment with either dose of VLZ versus PBO led to significantly greater improvements from baseline in depression symptoms (Montgomery-Åsberg Depression Rating Scale [MADRS] total

score) and global disease severity (Clinical Global Impression of Severity [CGI-S] score). However, interpreting these between-group differences in mean score changes can be difficult--for example, determining whether mean improvements with VLZ or PBO were due to large changes in a few patients or moderate changes in many patients. Therefore, a post hoc analysis of the 4 studies was conducted to examine categorical shifts in disease severity using CGI-S scores at baseline and end of treatment (EOT).

Methods: Analyses were conducted in the pooled intent-to-treat (ITT) population (N=2251), with VLZ dose groups combined. EOT was defined as the last available post-baseline assessment in the double-blind treatment period. Categorical improvement in disease severity was based on the proportion of patients who met either of the following sets of criteria: 1) CGI-S score ≥ 4 (moderately ill or worse) at baseline and CGI-S score ≤ 2 (normal or borderline ill) at EOT; or 2) CGI-S score ≥ 5 (markedly ill or worse) at baseline and CGI-S score ≤ 2 at EOT. Odds ratios (ORs) for VLZ versus PBO were analyzed using logistic regression models adjusted for study and baseline CGI-S values, with these category shifts as the outcome variable.

Results: At baseline, 2217 patients were moderately ill or worse (CGI-S score of 4, 5, or 6; PBO=964, VLZ=1253), 979 were markedly ill or worse (score of 5 or 6; PBO=435, VLZ=544), and 43 were severely ill (score of 6; PBO=13, VLZ=30); no patient was rated as "among the most extremely ill patients" (score of 7). In patients with baseline CGI-S score ≥ 4 , the proportion who improved to CGI-S score ≤ 2 at EOT was significantly higher with VLZ than with PBO (39.9% vs 27.9%, OR=1.7, $P<.0001$). In patients with baseline CGI-S score ≥ 5 , the proportion who improved to CGI-S score ≤ 2 at EOT was also significantly higher with VLZ than with PBO (36.8% vs 25.5%, OR=1.7, $P=.0002$).

Conclusions: Categorical shift analyses using baseline and EOT CGI-S scores showed that treatment with VLZ versus PBO resulted in a significantly greater proportion of adult MDD patients achieving improvements in global disease severity categories. Clinicians may find it easier to interpret these shifts from greater severity to lesser severity categories than mean changes in rating scores.

Learning Objectives:

- To explain how shifts in global disease severity may be used to ascertain overall symptom improvements in adults with major depressive disorder.
- To understand the effects of vilazodone on patients with varying degrees of global disease severity at baseline (eg, moderately ill or worse, markedly ill or worse).

Literature References:

- McCormack PL: Vilazodone: a review in major depressive disorder in adults. *Drugs* 2015;75:1915-1923
- Culpepper L, Mathews M, Ghorri R, Edwards J: Clinical relevance of vilazodone treatment in patients with major depressive disorder: categorical improvement in symptoms. *Prim Care Companion CNS Disord* 2014;16:e1-e7

W19. ADJUNCTIVE BREXPIPIRAZOLE (OPC-34712) IN PATIENTS WITH MDD AND ANXIETY SYMPTOMS: Results FROM POST-HOC ANALYSES OF TWO PIVOTAL STUDIES

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Abstract: Background: Symptoms of anxiety are prevalent in major depressive disorder (MDD) and are associated with greater illness severity, suicidality, impaired functioning, and poor response to antidepressant treatment (ADT). The presence of anxiety symptoms in MDD can be assessed using different definitions, e.g., anxious depression (score ≥ 7 on the HAM-D anxiety/somatization factor, as defined by the STAR*D investigators), or using the new DSM-5 specifier ‘anxious distress.’ Brexpiprazole is a serotonin-dopamine activity modulator that acts as a partial agonist at 5-HT_{1A} and dopamine D₂ receptors, and as an antagonist at 5-HT_{2A} and noradrenaline α _{1B/2C} receptors, all at similar potencies. The efficacy, tolerability, and safety of brexpiprazole adjunctive to ADT in the treatment of patients with MDD were evaluated in two pivotal randomized, double-blind, placebo-controlled studies (NCT01360645 and NCT01360632). The objective of this post-hoc analysis of the pivotal studies was to assess the efficacy of brexpiprazole adjunctive to ADT in patients with MDD and anxiety symptoms using two definitions: 1) anxious depression; 2) anxious distress.

Methods: Patients with MDD and an inadequate response to 1–3 ADTs were enrolled and received single-blind ADT for 8 weeks. Patients with inadequate response throughout this prospective phase were randomized to ADT+brexpiprazole or ADT+placebo for 6 weeks. Both studies included fixed doses of brexpiprazole (2 mg [Study 1]; 1 mg or 3 mg [Study 2]). Patients with anxious depression were identified from scores on specific items of the HAM-D anxiety/somatization factor at randomization. Patients with anxious distress were identified using proxies: ≥ 2 symptoms of tension (MADRS item 3 score ≥ 3), restlessness (IDS item 24 score ≥ 2), concentration (MADRS item 6 score ≥ 3), or apprehension (HAM-D item 10 score ≥ 3) at randomization. The efficacy endpoint was change in MADRS total score over the 6 weeks of treatment, analyzed using a Mixed Model Repeated Measure approach with pooled placebo groups.

Results: Of the 987 patients who had an inadequate response to 8 weeks of prospective ADT, anxious depression or anxious distress criteria were met by 49.0% and 55.6% of patients, respectively. Mean MADRS total score was similar for patients with anxious depression (28.8) or anxious distress (29.1). Adjunctive brexpiprazole showed greater improvement than placebo in MADRS total score over the 6 weeks of the study for both patients with anxious depression (least square mean differences for adjunctive brexpiprazole vs. adjunctive placebo [n=187]: 1 mg [n=97]: -1.42, p=0.1531; 2 mg [n=84]: -2.10, p=0.0461; 3 mg [n=112]: -2.05, p=0.0324), or anxious distress (vs. adjunctive placebo [n=209]: 1 mg [n=119]: -1.74, p=0.0583; 2 mg [n=103]: -2.95, p=0.023; 3 mg [n=112]: -2.81, p=0.0027). The presence of anxiety symptoms was not associated with an increased incidence of activating adverse events (akathisia, restlessness, agitation, anxiety, or insomnia).

Conclusion: Results show that after 8 weeks of treatment with ADT monotherapy, approximately 50% of patients with an inadequate response meet criteria for either anxious depression or anxious distress. The present data suggest that adjunctive brexpiprazole may be efficacious in reducing depressive symptoms in patients with anxious depression or anxious distress, which is an important finding as symptoms of anxiety with MDD suggests a more severe course of illness.

Learning Objectives:

- Half of patients with MDD in 2 studies of brexpiprazole adjunctive to antidepressants, who had demonstrated an inadequate response to 8 weeks of antidepressant monotherapy, met predefined criteria for symptoms of anxious depression or anxious distress.
- Brexpiprazole, administered adjunctively with antidepressants, may be efficacious in reducing depressive symptoms in MDD patients with symptoms of anxious depression or anxious distress.

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W20. OPEN BOARD

W21. A POST HOC SUBGROUP ANALYSIS OF THE IMPACT OF VORTIOXETINE ON FUNCTIONAL CAPACITY, AS MEASURED BY UPSA, IN MDD PATIENTS WITH SUBJECTIVE COGNITIVE DYSFUNCTION

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Abstract: Objective: To evaluate the effect of vortioxetine on functional capacity, as assessed by the UCSD Performance-Based Skills Assessment (UPSA), in patients with major depressive disorder (MDD) who report cognitive symptoms.

Methods: NCT01564862 was an 8-week, double-blind, placebo-controlled study designed to evaluate the effect of flexible-dose vortioxetine (10–20mg) in patients with moderate-to-severe MDD (18–65 yrs, Montgomery-Åsberg Depression Rating Scale [MADRS] ≥ 26) and self-reported cognitive symptoms [1]. Primary outcome was change in cognitive functioning (measured by the Digit Symbol Substitution Test), with change in functional capacity measured by the UPSA as an additional endpoint [2]. Duloxetine 60mg was included as active reference. These post hoc exploratory analyses investigated change from baseline to Week 8 in the UPSA composite score (comprising the full UPSA or UPSA-B at English- and non-English-speaking sites, respectively; possible range, 0–100) in patient subgroups based on: number of previous major depressive episodes (MDEs), duration of current MDE, baseline MADRS and Clinical Global Impressions–Severity [CGI-S] scores, response rate (MADRS improvement $\geq 50\%$), remission rate (MADRS ≤ 10), sex, age, education, and work status.

Results: This analysis was conducted in 602 randomized patients (vortioxetine, n=198; placebo, n=194; duloxetine, n=210). At 8 weeks, vortioxetine showed a significant improvement in functional capacity versus placebo (vortioxetine, n=175, $\Delta +8.0$; placebo, n=166, $\Delta +5.1$; $p < 0.001$). The improvement in functional capacity with vortioxetine versus placebo was similar across all patient subgroups based on baseline disease severity (MADRS < 30 , n=63, $\Delta +3.5$, $p = 0.014$; MADRS ≥ 30 , n=112, $\Delta +2.5$, $p = 0.015$; CGI-S ≤ 4 , n=84, $\Delta +2.8$, $p = 0.010$; CGI-S > 4 , n=91, $\Delta +3.0$, $p = 0.020$), number of previous MDEs (≤ 2 , n=108, $\Delta +2.7$,

p=0.011; >2, n=67, Δ +3.3, p=0.020), duration of current MDE ($\leq$ 22 weeks, n=89, Δ +3.7, p=0.003; >22 weeks, n=86, Δ +2.4, p=0.031), sex (male, n=54, Δ +3.2, p=0.023; female, n=121, Δ +2.9, p=0.005), age (<55, n=134, Δ +2.5, p=0.009; $\geq$ 55, n=41, Δ +5.6, p=0.003) or education level (< high school education, n=32, Δ +3.2; p=0.209; high school education, n=69, Δ +2.8, p=0.026; post-high school education, n=74, Δ +2.7, p=0.049). Improvement in functional capacity was also seen for patients who responded to vortioxetine treatment (n=89, Δ +3.7, p=0.004), those in remission (n=53, Δ +5.2, p=0.003), and working patients (n=78, Δ +2.8, p=0.015). Duloxetine did not significantly improve functional capacity versus placebo in the total population (n=187, Δ +0.2, p=0.637) or in any of the subgroups.

Conclusions: Vortioxetine offers clinical improvements across all the different patient subgroups included here in performance-based functional capacity in MDD patients with self-reported cognitive symptoms at baseline, as demonstrated by this post hoc analysis of the UPSA in NCT01564862.

Learning Objectives:

- Evaluate the efficacy of vortioxetine 10–20mg (versus placebo) on performance-based functional capacity (using the UCSD Performance-Based Skills Assessment [UPSA]) in patients with major depressive disorder and subjective cognitive dysfunction.
- Describe the effects of vortioxetine 10–20mg (versus placebo) on functional capacity in clinically relevant subgroups of these patients, determined by depression history, baseline disease severity, treatment response, depression remission, sex, age, education level, and work status.

Literature References:

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W22. PERSEVERE: A STUDY OF ESKETAMINE FOR THE RAPID REDUCTION OF THE SYMPTOMS OF MAJOR DEPRESSIVE DISORDER, INCLUDING SUICIDAL IDEATION, IN SUBJECTS ASSESSED TO BE AT IMMINENT RISK FOR SUICIDE

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Abstract: Background: Major depressive disorder (MDD) is associated with an elevated rate of mortality, primarily due to suicide. The risk of suicide in those with MDD is about 20 times that of the general population, with over half of all suicides occurring in depressed individuals. While conventional antidepressants are often effective in treating depressive symptoms including suicidal ideation (SI), their delayed onset of action significantly limits their utility in the treatment of patients with MDD who are at imminent risk of suicide.

Recently, several studies of ketamine and esketamine have demonstrated that these agents can improve symptoms of depression in individuals with MDD within hours of administration. Additionally, preliminary studies of ketamine suggest it may have a similarly rapid effect in significantly reducing SI in subjects with MDD. As such, Janssen R&D is developing intranasal esketamine for the rapid reduction of the symptoms of MDD, including SI, in patients who are assessed to be at imminent risk for suicide.

Methods: PeRSEVERe is a recently completed 12-week, randomized, double-blind, placebo-controlled, multicenter Phase 2 study of intranasal esketamine in 68 adult subjects with MDD who are assessed to be at imminent risk for suicide. Included subjects had active SI and intent, and were in need of inpatient psychiatric hospitalization. The primary objective is to evaluate the efficacy of intranasal esketamine 84 mg compared with intranasal placebo in reducing the symptoms of MDD, including SI, as measured by the change from baseline on the MADRS total score at 4 hours post-dose on Day 1. Secondary efficacy objectives include the assessment of single and repeated doses of intranasal esketamine compared with intranasal placebo on the clinician's assessment of suicide risk as measured by the Suicide Ideation and Behavior Assessment Tool, and the subject's report of the severity in SI as measured by the Beck Scale for Suicide Ideation, through the end of the double-blind (DB) treatment and follow-up phases. Safety objectives include the assessment of transient perceptual changes, sedation, nasal tolerability, vital signs and suicidal thinking and behavior.

The study consists of a 24-48 hour screening evaluation performed prior to the Day 1 intranasal dose, immediately followed by a 25-day DB treatment phase, and a 56-day follow up phase. Given the vulnerability of the patient population, the study was conducted in the context of standard clinical care, with all subjects receiving standard antidepressant medication and initial in-patient hospitalization.

Results: PeRSEVERe is the first multi-center, prospective, placebo-controlled trial of a rapidly acting antidepressant in subjects with MDD who are assessed to be at imminent risk for suicide. The study, which was conducted at 11 centers in the United States, recently completed enrollment. Preliminary efficacy and safety results from the DB treatment phase will be available for presentation.

Conclusion: PeRSEVERe is the first multi-center placebo-controlled study of a potential rapidly acting antidepressant in patients with MDD who are assessed to be at imminent risk for suicide. Should study results be positive, esketamine may offer hope and a new paradigm of treatment for depressed patients at risk for suicide.

W23. MODERATING FACTORS AFFECT SIGNAL DETECTION WITH MSI-195 VS. PLACEBO IN A MAJOR DEPRESSIVE DISORDER AUGMENTATION TRIAL

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Abstract: The focus of most antidepressant clinical trial research is on the relation between the independent (contingent) primary variable assessed at baseline and the same variable assessed at the study endpoint (outcome). However, within the confines of a short term trial, moderating factors such as demographics (e.g., age, weight) or clinical history (e.g., premorbid anxiety, previous treatment response) may substantially affect the relation between the independent and outcome variable, and thus signal detection.

Methylation Sciences is developing a novel formulation of S-Adenosyl-L-Methionine (MSI-195) for the treatment of depression. The effect of age, weight, clinical history, symptom severity, comorbidities, and symptom fluctuation between visits as potential moderating variables (factors) that might enhance or impede signal detection in a recently completed phase II double-blind, placebo controlled clinical trial: Methylation Sciences Inc., NCT # NCT01912196: A double-blind, placebo-controlled, randomized add-on study of MSI-195 (S-Adenosyl-L-Methionine, SAME) for patients with Major Depressive Disorder (MDD) who have had an inadequate response to current antidepressant therapy.

The study randomly assigned 234 subjects who had failed to respond to an adequate dose of antidepressant medication, to either MSI-195 (800 mg QD) plus ongoing antidepressant or placebo plus ongoing antidepressant over a 6-week treatment interval. The study failed to achieve a significant signal (HAMD17 treatment difference of -0.2 points favoring MSI-195 over placebo (n= 227; MMRM)). However, exclusion of subjects with a number of specific moderating factors using MADRS (BMI $\geq$ 40, high symptom fluctuation during a placebo lead-in) resulted in a -3.2 MADRS point difference favoring MSI-195 over placebo (n= 143; MMRM, p= 0.04)

While this post-hoc analysis is limited by multiplicity considerations, as an exploratory analysis the information demonstrates the attributes of consistency across scales, correlations in response within value ranges for the moderating variables, biological and clinical plausibility and external validation.

These findings support the inclusion of pre-specified moderating factors (variables) in the statistical analysis plan of exploratory clinical trials. Further, assessment of these variables as part of clinical trial design, with a view toward striking a balance between generalizability and the establishment of an assay sensitive population, is an important consideration in future clinical development.

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Learning Objectives:

- To understand the importance of moderating variables affect on clinical trial outcomes.
- To explore trial data examining the impact of specific moderating factors on signal detection in a clinical trial of MDD.

W24. LURASIDONE FOR MAJOR DEPRESSIVE DISORDER WITH MIXED FEATURES: EFFECT OF CONCURRENT ANXIETY SEVERITY

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Abstract: Objective: Major depressive disorder (MDD) with mixed features is recognized as a diagnostic subtype in DSM-5. Compared with “pure” MDD, MDD with mixed features is associated with higher rates of anxiety comorbidity and/or symptom severity [1]. The aim of this post-hoc analysis of patients with a diagnosis of MDD with mixed features was to evaluate the impact of anxiety on response to lurasidone.

Methods: Patients meeting DSM-IV-TR criteria for unipolar MDD, with a Montgomery-Asberg Depression Rating Scale (MADRS) total score ≥ 26 , who presented with 2 or 3 protocol-defined manic symptoms, were randomized to 6 weeks of double-blind treatment with either lurasidone 20-60 mg/d (N=108) or placebo (N=100). Anxiety severity was evaluated using the Hamilton Anxiety Rating Scale (HAM-A). To evaluate the effect of baseline anxiety on response to lurasidone, the following 3 anxiety groups were defined: mild anxiety (HAM-A ≤ 14), moderate anxiety (HAM-A, 15-23), and severe anxiety (HAM-A ≥ 24) [2]. Changes in HAM-A total score (ANCOVA-LOCF) and MADRS total score (MMRM) were analyzed for patients with mild, moderate, and severe levels of anxiety at study baseline.

Results: Mild anxiety was present at baseline in 43.3% of patients (mean HAM-A, 11.6; mean MADRS, 31.9), moderate anxiety in 42.3% (HAM-A, 18.1; MADRS, 33.7), and severe anxiety in 14.4% (HAM-A, 29.0; MADRS, 36.1). Baseline HAM-A and YMRS scores were minimally correlated ($r=0.17$). Treatment with lurasidone was associated with significant week 6 change vs. placebo in MADRS total score for both the mild anxiety group (-18.4 vs. -12.8 ; $P<0.01$; effect size [ES], 0.59) and the moderate anxiety group (-22.4 vs. -12.4 ; $P<0.001$; ES, 1.05), but not the severe anxiety group (-21.1 vs. -16.0 ; $P=0.18$; ES, 0.55). A treatment by anxiety severity group interaction test was not significant. Week 6 improvement in the HAM-A total score was observed in the mild (-7.6 vs. -4.0 ; $P<0.01$; ES, 0.62; LOCF), moderate (-11.6 vs. -5.9 ; $P<0.0001$; ES, 0.98) and severe (-12.6 vs. -9.1 ; $P=0.12$; ES, 0.60) anxiety groups, but did not achieve significance in the severe group. Lurasidone was associated with significant week 6 improvement (vs. placebo) in the YMRS score for both the moderate anxiety group (-8.0 vs. -4.8 ; $P<0.0001$; ES, 0.91), and the severe anxiety group (-6.5 vs. -3.7 ; $P<0.05$; ES, 0.83), but not the mild anxiety group (-6.4 vs. -5.5 ; $P=0.21$; ES, 0.28). The mean daily dose of lurasidone was 37.8 mg, 36.7 mg, and 31.4 mg in the mild, moderate, and severe anxiety groups, respectively.

Conclusions: In this post-hoc analysis of an MDD-mixed population, treatment with lurasidone was associated with improvement in depressive and anxiety symptoms (in the mild and moderate anxiety groups for both outcomes), and in manic symptoms (in the moderate and severe anxiety groups). The presence of manic symptoms appeared to be independent of baseline levels of anxiety. The lack of significance on an interaction test suggests that baseline severity of anxiety does not reduce the antidepressant effect of lurasidone in this population, however, further studies with larger sample sizes are needed to confirm this.

Clinicaltrials.gov: NCT01421134

Sponsored by Sunovion Pharmaceuticals Inc.

Learning Objectives:

- After completion of this presentation, the reader will have a better understanding of the clinical presentation of patients with MDD with mixed features who present with high levels of anxiety.
- After completion of this presentation, the reader will have a better understanding of the effect of lurasidone on depressive symptoms and symptoms of anxiety in patients with MDD with mixed features who present with high levels of anxiety.

Literature References:

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W25. EFFECT OF ADJUNCTIVE BREXPIRAZOLE AND ADJUNCTIVE ARIPIRAZOLE ON WEIGHT: AN ANALYSIS OF LONG-TERM TRIALS IN MAJOR DEPRESSIVE DISORDER

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Abstract: Background: Brexpiprazole is a serotonin-dopamine activity modulator that acts as a partial agonist at 5-HT_{1A} and dopamine D₂ receptors, and as an antagonist at 5-HT_{2A} and noradrenaline α _{1B/2C} receptors, all at similar potencies. Brexpiprazole was approved in 2015 by the FDA for use as an adjunctive therapy to antidepressants (ADT) for the treatment of major depressive disorder (MDD) and for treatment of schizophrenia. Compared with aripiprazole, brexpiprazole is more potent at 5-HT_{1A} receptors and displays less intrinsic activity at D₂ receptors. Here we evaluate the long-term effect of adjunctive brexpiprazole and adjunctive aripiprazole, respectively, on weight in patients with MDD and inadequate response to antidepressant treatments, based on a comparison between pooled data from two open-label extension studies with brexpiprazole (NCT01447576; NCT01360866) and one open-label extension study with aripiprazole [1].

Methods: The studies with adjunctive brexpiprazole were flexible dose, open-label, 52-week (Study 1: [NCT01447576] 0.25 to 3mg/day) and 26-week (Study 2: [NCT01360866; 0.5 to 3mg/day) studies. Study 1 enrolled de novo patients and patients completing one of the two phase II studies (NCT00797966; NCT01052077) while study 2 enrolled patients completing one of the two pivotal phase III studies (NCT01360645 [2]; NCT01360632 [3]). Study 2 is still ongoing and brexpiprazole data presented are based on a data-cut from 15-May-2015.

The aripiprazole study [1] was a flexible-dose (2 to 30 mg/day), open-label, 52-week study, enrolling patients completing one of two 14-week double-blind studies of aripiprazole augmentation, as well as de novo patients.

Results: In the brexpiprazole studies, 2084 patients were enrolled (697 [rollover, n=454; de novo, n=243] from study 1 and 1387 from study 2); 48.8% of patients (1016/2084) completed 52 weeks of treatment. Mean brexpiprazole dose was 1.6 mg/day. The mean change in

weight (observed cases) from baseline to week 26 was 2.9 kg (n=1259) and 3.2 kg at week 52 (n=1015). A total of 30.3% (629/2077) of patients had a weight increase that was $\geq 7\%$ in body weight at any time during the studies. In the aripiprazole study, 1002 patients entered the open-label treatment phase (rollover, n=706; de novo, n=296); 32.2% of patients (323/1002) completed 52 weeks of treatment. The mean dose of aripiprazole was 10.1 mg/day. The mean change in weight (observed cases) from baseline to week 26/32 was 3.6 kg (n=491) and 4.4 kg at week 52/58 (n=303). A total of 28.0% of patients had a weight increase that was $\geq 7\%$ in body weight based on LOCF analysis.

Conclusion: A comparable moderate weight increase was observed after adjunctive treatment with either brexpiprazole or aripiprazole.

Learning Objectives:

- To understand the long term effects of adjunctive brexpiprazole on weight in patients with MDD.
- To understand the long term effects of adjunctive aripiprazole on weight in patients with MDD.

Literature References:

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W26. VALIDATION AND DETERMINATION OF MINIMAL CLINICALLY IMPORTANT DIFFERENCES AND TREATMENT RESPONSE FOR THE UCSD PERFORMANCE-BASED SKILLS ASSESSMENT (UPSA) IN MAJOR DEPRESSIVE DISORDER

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Abstract: Objective: The UCSD Performance-Based Skills Assessment (UPSA) has been extensively utilized in patients with schizophrenia and bipolar disorder to measure functional capacity. This post hoc analysis of NCT01564862 [1] reports the psychometric properties of the UPSA in outpatients with major depressive disorder (MDD) and self-reported cognitive symptoms.

Methods: Patients with recurrent MDD (18–65 years, Montgomery-Åsberg Depression Rating Scale [MADRS] ≥ 26) reporting cognitive symptoms were enrolled in an 8-week, randomized, double-blind, placebo-controlled, multicenter study. Clinical parameters included cognitive performance (Digit Symbol Substitution Test [DSST]), subjective cognitive functioning (Perceived Deficits Questionnaire [PDQ]), workplace productivity (Work Limitations Questionnaire [WLQ]), mood (MADRS), and functional capacity (UPSA). Construct validity was examined via baseline correlation analyses (Pearson's r) of the UPSA composite score ("UPSA," possible range: 0–100) with various baseline clinical parameters. Anchor-based (Clinical Global Impressions–Improvement [CGI-I] score ≤ 2) and distribution-based (one-half standard deviation [SD]) analysis methods were used to establish a responder definition and minimal clinically important difference (MCID) threshold.

Results: A total of 602 MDD patients (randomized to placebo, vortioxetine, or duloxetine) were included in this analysis. The mean UPSA composite score at baseline was 77.8 (SD = 12.88; range: 29–100). Statistically significant baseline correlations ($p < 0.05$) were observed between the UPSA and duration of the current major depressive episode (MDE; $r = 0.10$), age ($r = -0.13$), education ($r = 0.29$), DSST ($r = 0.36$), and WLQ ($r = -0.17$), but not the number of previous MDEs ($r = -0.06$), MADRS total score ($r = 0.02$), or the PDQ ($r = -0.02$). The MADRS was only correlated ($p < 0.05$) with the duration of the current MDE ($r = 0.13$) and the PDQ ($r = 0.32$). The anchor-based approach resulted in an estimate of $\Delta +6.7$ for the MCID on the UPSA, which was supported by the distribution-based approach (one-half SD = +6.44).

Conclusion: At baseline, the UPSA was positively correlated with cognitive performance and workplace productivity, but not mood or subjective cognitive functioning, supporting the construct validity of the UPSA for functional capacity in MDD, independently of mood symptom severity. Both the distribution-based and anchor-based approaches suggest defining the MCID of treatment response on the UPSA composite score as a change of approximately +6 to +7 points.

Learning Objectives:

- Determine the minimal clinically important difference (MCID) threshold for functional treatment response in patients with major depressive disorder and subjective cognitive dysfunction using the UCSD Performance-Based Skills Assessment (UPSA).
- Describe correlations between functional capacity (as assessed with the UPSA) and other baseline clinical parameters of depression (e.g., objective and subjective cognitive functioning, workplace productivity, and mood symptoms).

Literature References:

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W27. SYMPTOMATIC AND FUNCTIONAL REMISSION AS A THERAPEUTIC OBJECTIVE IN MAJOR DEPRESSIVE DISORDER: VORTIOXETINE COMPARATIVE DATA IN WORKING POPULATION

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Abstract: Introduction: Major depressive disorder (MDD) is associated with significant functional impairment in different dimensions (e.g., work). Optimally, the goal of antidepressant treatment should not only be the symptomatic remission but also the restoration of normal functioning.

Objective: To evaluate the efficacy of vortioxetine, an antidepressant with a multimodal mechanism of action, in achieving symptomatic and/or functional remission in the working

population using data from 2 active comparator studies: SOLUTION (NCT01571453) and REVIVE (NCT01488071).

Methods: SOLUTION was an 8-week double-blind, randomized, fixed dose study comparing vortioxetine (10mg) to venlafaxine XR (150mg) in MDD patients in Asia. REVIVE was a 12-week double-blind, randomized, flexible dose study comparing vortioxetine (10–20mg) to agomelatine (25–50mg) in patients who switched treatment due to an inadequate response to previous antidepressant treatment of their current depressive episode. Post hoc analyses of SOLUTION and REVIVE considered 3 levels of treatment success: symptomatic remission on the Montgomery-Åsberg Depression Rating Scale (MADRS total score ≤ 10), functional remission on the Sheehan Disability Scale (SDS total score ≤ 6) and combined symptomatic/functional remission (MADRS total score ≤ 10 and SDS total score ≤ 6) at each assessment visit. These analyses (using observed cases) were performed on the sub-group of working patients, based on SDS item 1 and based on patients who have both a MADRS and a SDS total score at all visits assessed.

Results: In SOLUTION, ~70% of patients were employed (vortioxetine n=154; venlafaxine n=141). The proportion of patients achieving each level of treatment success was numerically greater for vortioxetine than venlafaxine at week 8. For the combined outcome (MADRS and SDS), the remission rate was 29.9% vs 26.2% for vortioxetine and venlafaxine respectively. In REVIVE, ~50% of patients were employed (vortioxetine n=134, agomelatine n=123). The proportion of patients achieving each level of treatment success was also numerically greater for vortioxetine than agomelatine. The rate of the combined symptomatic and functional remission increased over time and was higher in the vortioxetine arm than the agomelatine arm: 19.4% vs 11.4%; 29.9% vs 24.4%; and 47.8% vs 38.2% at weeks 4, 8, and 12, respectively.

Conclusions: These post hoc analyses suggest that vortioxetine provides benefit vs venlafaxine XR and agomelatine in achieving symptomatic, functional, or both symptomatic and functional remission, with clinically relevant differences of more than 5 percent points from week 4 onwards in the REVIVE study. These results should be interpreted with respect to the reduced sample size focusing on the working population.

Learning Objectives:

- Compare the treatment success (symptomatic remission, functional remission, and combined symptomatic/functional remission) of vortioxetine 10 mg versus venlafaxine XR 150 mg in working patients with major depressive disorder living in Asia.
- Compare the treatment success (symptomatic remission, functional remission, and combined symptomatic/functional remission) of vortioxetine 10–20 mg to agomelatine 25–50 mg in working patients with major depressive disorder who switched treatment due to an inadequate response to previous antidepressant treatment of their current depressive episode.

Literature References:

- Wang G, Gislum M, Filippov G, Montgomery S: Comparison of vortioxetine versus venlafaxine XR in adults in Asia with major depressive disorder: a randomized, double-blind study. *Curr Med Res Opin* 2015; 31(4):785-94.
- Montgomery SA, Nielsen RZ, Poulsen LH, Häggström L: A randomised, double-blind study in adults with major depressive disorder with an inadequate response to a single course of selective serotonin reuptake inhibitor or serotonin-noradrenaline

reuptake inhibitor treatment switched to vortioxetine or agomelatine. Hum Psychopharmacol 2014; 29(5):470-82.

W28. A POPULATION DOSE-RESPONSE ANALYSIS OF LURASIDONE IN THE TREATMENT OF MAJOR DEPRESSIVE DISORDER WITH MIXED FEATURES

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Abstract: Objective: Major depressive disorder (MDD) with mixed features is newly recognized by DSM-5 as a variant of MDD that is associated with subthreshold hypomanic symptoms. A recently completed placebo-controlled trial investigated the efficacy of lurasidone in this patient population. The objective of this pharmacometric analysis was to characterize the dose-response profile of lurasidone in patients with MDD with mixed features.

Methods: Population PK/PD modeling was performed based on data derived from a randomized, 6-week, double-blind, placebo-controlled, flexible-dose study (20–60 mg/d of lurasidone as monotherapy) in patients with MDD with mixed features [1]. Data included 1405 Montgomery-Åsberg Depression Rating Scale (MADRS) observations from 208 patients who had received lurasidone or placebo treatment. Potential covariates that might influence response to lurasidone (ie, body weight, age, race, gender, psychiatric history, country, US vs non-US residency, use of concomitant medications) were evaluated in the models. Simulations were performed to reconcile the underlying linear dose-response relationship and the apparent flexible dose design-induced flat dose-response relationship. To incorporate the non-random nature of dose escalation in the current flexible dose design, the observed pattern of dose escalation depending on the weekly MADRS score improvement was stochastically accounted for.

Results: The time course of placebo effect on the MADRS score was adequately described by an exponential asymptotic placebo model. A linear dose-response model best described the effect of lurasidone across the therapeutic dose range of 20-60 mg/d. There were no significant covariates for all placebo and treatment effect parameters; therefore, no adjustment on the basis of demographic covariates, background, or concomitant medications is likely to be necessary. The observed placebo-adjusted means from the study by modal dose were -7.2, -7.8, and 7.5 for doses of 20, 40, and 60 mg/d, respectively. However, based on the model (without dose escalation), the mean net reduction in MADRS total score at Week 6 (after adjusting for placebo) was estimated to be -2.9 (for lurasidone 20 mg/d), -5.8 (40 mg/d), and -8.8 (60 mg/d). This difference was reconciled by simulations incorporating the non-random nature of the dose-escalation (ie, patients with less improvement tended to have dose escalation). A flexible-dose study simulation yielded placebo-adjusted mean MADRS score reductions of -5.3, -6.5, and -7.7 for lurasidone doses of 20, 40, and 60 mg/d, respectively, thus confirming the underlying dose-response relationship for lurasidone in the treatment of MDD with mixed features that may be obscured due to the flexible dose design.

Conclusion: A dose-response relationship for lurasidone in the treatment of MDD patients with mixed features was suggested based on the current pharmacometric analysis. The

current findings suggest that higher lurasidone doses in the 20-60 mg/d range may be associated with larger treatment effects. Current results are consistent with a previous lurasidone dose-response analysis in patients with bipolar depression [2].

Learning Objectives:

- After completion of this presentation, the reader will have a better understanding of the effect of daily dose on the antidepressant efficacy of lurasidone in patients with major depressive disorder with mixed features.
- After completion of this presentation, the reader will have a better understanding of the effect of demographic variables (sex, age) and concomitant medications on the dosing of lurasidone in patients with major depressive disorder with mixed features.

Literature References:

- Suppes T, Silva R, Cucchiaro J, et al. Lurasidone for the Treatment of Major Depressive Disorder With Mixed Features: A Randomized, Double-Blind, Placebo-Controlled Study. *Am J Psychiatry*. 2015 Nov 10. [Epub ahead of print].
- Chapel S, Chiu YY, Hsu J, et al. Lurasidone Dose Response in Bipolar Depression: A Population Dose-Response Analysis. *Clin Ther*. 2015 Dec 22. [Epub ahead of print].

W29. VILAZODONE EFFICACY IN SUBGROUPS OF PATIENTS WITH MDD: POST HOC ANALYSIS OF 4 RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIALS

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Abstract: Background: Demographics, disease history, and symptom severity are variables that may affect treatment outcomes in patients with major depressive disorder (MDD). Since response to antidepressant treatment can vary widely among individual patients, identifying medications that can effectively reduce depression symptoms across different populations remains an important area of research. Vilazodone (VLZ) is currently approved for the treatment of MDD at doses of 20-40 mg/day. In three 8-week studies of VLZ 40 mg/d (NCT00285376, NCT01473381, NCT01473394) and one 10-week study of VLZ 20 and 40 mg/d (NCT01473381), treatment with VLZ (20 or 40 mg/d) versus placebo (PBO) resulted in significantly greater ($P < .05$) mean improvements in Montgomery-Åsberg Depression Rating Scale (MADRS) total score. A post hoc analysis of these 4 randomized, double-blind, PBO-controlled studies was conducted to evaluate the effects of VLZ across different patient subgroups.

Methods: VLZ dose groups were pooled for the post hoc analysis. Mean changes from baseline (BL) to Week 8 were analyzed in the pooled intent-to-treat (ITT) population and patient subgroups defined as follows: sex (men, women); age (<45 , ≥ 45 to <60 , ≥ 60 years); MDD duration (<2 , ≥ 2 years); recurrent episodes (yes, no); current episode duration (≤ 6 , >6 to ≤ 12 , >12 months); and baseline MADRS total score (<30 , ≥ 30). A subgroup of very severely depressed patients (BL MADRS total score ≥ 35) was also included. Treatment effect sizes for MADRS improvements were estimated using the Cohen's d calculation. Additional analyses included MADRS response ($\geq 50\%$ total score improvement from baseline) and

remission (total score ≤ 10) at Week 8 in the ITT population, with number needed to treat (NNT) calculated from the rate difference between VLZ and PBO.

Results: In the pooled ITT population (VLZ=1254, PBO=964), the mean changes from BL to Week 8 in MADRS total score was significantly greater with VLZ vs PBO (-15.2 vs -11.7, $P<.0001$), with an effect size of 0.37. In the subgroups, effect sizes for MADRS total score change ranged from 0.29 (age ≥ 45 to <60 years, BL MADRS total score <30) to 0.82 (age ≥ 60 years), with most subgroups having a treatment effect size of ~ 0.3 to 0.4; the difference between VLZ and PBO was statistically significant in all subgroups (all $P<.001$). Significant results favoring VLZ vs PBO were found for both MADRS response (49.0% vs 34.4%, $P<.0001$, NNT=7) and MADRS remission (33.7% vs 23.1%, $P<.0001$, NNT=9).

Conclusions: In a post hoc analysis of data pooled from 4 clinical trials, VLZ showed consistent efficacy across various patient subgroups. These subgroup results, along with NNTs <10 for response and remission in the ITT population, suggest that VLZ may be an appropriate treatment option for many adults with MDD.

Learning Objectives:

- To become familiar with the effects of vilazodone in adults with major depressive disorder who were categorized by sex, age, disease history, and baseline symptom severity.
- To identify the various subgroups of patients who might most benefit from treatment with vilazodone provide, based on clinically relevant information such as effect sizes and numbers needed to treat.

Literature References:

- McCormack PL: Vilazodone: a review in major depressive disorder in adults. *Drugs* 2015; 2015;75:1915-1923
- Citrome L: Vilazodone for major depressive disorder: a systematic review of the efficacy and safety profile for this newly approved antidepressant - what is the number needed to treat, number needed to harm and likelihood to be helped or harmed? *Int J Clin Pract* 2012; 66:356-68

W30. EFFICACY OF VORTIOXETINE ON COGNITIVE FUNCTIONING IN WORKING SUBJECTS WITH MAJOR DEPRESSIVE DISORDER

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⁴University of British Columbia, Canada

Abstract: Objective: Vortioxetine is an antidepressant with a multimodal mechanism of action and has demonstrated positive effects on cognitive functioning in patients with major depressive disorder (MDD). Most MDD patients are working and even a small degree of cognitive dysfunction can cause substantial disability [1]. The aim of this study was to examine the effect of vortioxetine (10 and 20 mg) in working patients with MDD on measures of cognitive functioning and depressive symptoms using a post hoc secondary analysis of data from the FOCUS trial (NCT01422213) [2].

Methods: Patients with MDD (N=602) were randomized 1:1:1 to 8 weeks of treatment with vortioxetine 10 mg, vortioxetine 20 mg, or placebo. The Digit Symbol Substitution Test–

number of correct symbols (DSST), Trail Making Test A/B (TMT-A/B), and Stroop (congruent / incongruent) were applied to objectively assess the cognitive performance of the patients. The effect on cognitive functioning as perceived by the patients was assessed by the Perceived Deficits Questionnaire (PDQ). The effect on depressive symptoms, as assessed by the Montgomery-Åsberg Depression Rating Scale (MADRS) total score, was performed as a sensitivity analysis using data from three additional short-term placebo-controlled studies (2 of which included duloxetine as an active reference) and one relapse prevention study. Analyses were made in a modified intent-to-treat set of patients who were working/taking an education at baseline. Additionally, outcomes as a function of workplace position were analyzed. All analyses were made versus placebo.

Results: In FOCUS, the mean difference to placebo on the DSST was 5.6 for 10 mg (n=108, $p<0.001$) and 5.0 for 20 mg (n=117, $p<0.001$) in working patients (57% of total study population) while it was 4.0 ($p<0.001$) for both 10 mg (n=193) and 20 mg (n=204) in the total study population. The effect remained significant after adjusting for the change from baseline in the MADRS total score. In patients with “professional” (i.e., manager/administrator and professional) positions, the effect was 9.2 for 10 mg (n=31, $p=0.006$) and 9.0 for 20 mg (n=38, $p=0.001$). A similar pattern of results was also observed for the TMT-A/B, Stroop, PDQ, and MADRS total score. In the sensitivity analysis, the efficacy (as assessed by MADRS) of duloxetine was not significantly different versus placebo ($p>0.05$) in any of the populations (i.e., total, working, and working as “professional”).

Conclusions: These results indicate that the beneficial effects of vortioxetine on objective and subjective measures of cognitive function are greater in patients with MDD who are currently working and/or engaged in educational pursuits than in the total MDD population. In addition, overall depressive symptom reduction was greater in working patients than in the total MDD population. The observed benefits on cognitive functions were independent of the improvement in depressive symptoms. This greater symptom reduction was not observed for duloxetine in working patients.

Learning Objectives:

- To compare the effects of vortioxetine 10–20 mg (versus placebo) in patients with major depressive disorder versus the subset of these patients who were working on measures of cognitive functioning, both subjective and objective.
- To compare the effects of vortioxetine 10–20 mg (versus placebo) in patients with major depressive disorder versus the subset of these patients who were working on measures of depressive symptoms.

Literature References:

- Buist-Bouwman MA, Ormel J, de Graaf R, de Jonge P, van Sonderen E, Alonso J, Bruffaerts R, Vollebergh WA; ESEMeD/MHEDEA 2000 investigators: Mediators of the association between depression and role functioning. *Acta Psychiatr Scand* 2008; 118(6):451-8.
- McIntyre RS, Lophaven S, Olsen CK: A randomized, double-blind, placebo-controlled study of vortioxetine on cognitive function in depressed adults. *Int J Neuropsychopharmacol* 2014; 17(10):1557-67.

W31. MEASUREMENT OF ADHERENCE TO ANTIDEPRESSANTS AND OUTCOMES AMONG PATIENTS WITH BOTH MAJOR DEPRESSIVE DISORDER AND TYPE 2 DIABETES

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Abstract: Purpose: Major depressive disorder affects an estimated 20% of patients with diabetes (1). Patients with depression have been shown to have difficulty with adherence to their diabetes medications (2). The objective of this study is to evaluate the association between adherence to antidepressants and an effect on clinical outcomes and healthcare costs in patients with type 2 diabetes (T2D) and comorbid major depressive disorder (MDD).

Methods: This retrospective cohort study used MarketScan® claims databases from January 2012 to March 2014. Study entry was the first claim for an antidepressant indicated for MDD, along with a diagnosis of T2D (ICD-9-CM 250.x0 and 250.x2) and MDD (ICD-9-CM 296.2x and 296.3x) 6 months prior. Adherence was defined as a medication possession ratio (MPR) of $\geq 80\%$. Persistence was measured by length of therapy (LOT) with no gaps ≥ 15 days during the 6 months after the index date. T2D control (HbA1c $< 7\%$) and health care costs were measured for 12 months after index. Chi-square and t-tests were used to determine the significance of differences in categorical and continuous variables between adherent and non-adherent patients as well as persistent and non-persistent patients.

Results: The study sample consisted of 1,361 patients. The mean age was 59 years, 55% were women and 71% had a commercial insurance plan. The mean MPR for antidepressants was 40% with 36% of patients (n=489) being adherent (MPR $\geq 80\%$). The average LOT was 100 days and 32% of patients (n=435) were persistent. Total costs were lower for adherent and persistent patients, but the results were not significant ($p > 0.05$). Among patients adherent or persistent to their antidepressants, 71% and 72%, respectively, were also adherent to their oral antidiabetic agents. Of those with HbA1c data, a significantly higher proportion of antidepressant adherent (n=26/42) versus non-adherent patients (n=27/79) had controlled HbA1c levels (62% versus 34%; $p = 0.0034$).

Conclusion: Our study found that patients with better antidepressant adherence had better adherence to oral diabetes medications and better HbA1c control in a subset of patients. Additionally, adherent patients had no increase in health care costs when compared with the non-adherent patients. In this analysis, MDD severity was not accounted for due to the limited reporting of severity in claims databases. Also, because claims do not include lifestyle or counseling interventions, their impact on adherence could not be evaluated. Furthermore, as this was a descriptive cross-sectional study of adherence, further research is needed to extend the study period to assess longitudinal adherence.

Learning Objectives:

- To evaluate the scope of the relationship of adherence and persistence to antidepressants and oral agents for diabetes.
- To assess the clinical impact on diabetes control of adherence and persistence to antidepressants among adults with T2D and MDD.

Literature References:

- Andersen RJ et al. The prevalence of comorbid depression in adults with diabetes. *Diabetes Care* 2001;24:1069–1078.

- Lin EHB et al. Relationship of depression and diabetes self-care, medication adherence, and preventive care. *Diabetes Care* September 2004 vol. 27 no. 9 2154-2160.

W32. THE DSM-5 ANXIOUS DISTRESS SPECIFIER INTERVIEW: RELIABILITY AND VALIDITY

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Abstract: Objective: During the past 20 years the clinical significance of co-existing anxiety disorders and anxiety symptoms in depressed patients has been increasingly recognized. Prevalence is high, and co-occurring anxiety has been associated with increased suicidality, greater impairment in functioning, worse health-related quality of life, poorer longitudinal course, greater number of depressive episodes, and poorer response to treatment. To acknowledge the clinical significance of anxious features in depressed patients, DSM-5 included criteria for an anxious distress specifier for major depressive disorder. In the present report from the Rhode Island Methods to Improve Diagnostic Assessment and Services (MIDAS) project we describe the development, reliability, and validity of the DSM-5 Anxious Distress Specifier Interview (DADSI).

Methods: The DADSI is a brief, clinician-administered, interview that assesses the DSM-5 anxious distress criteria in both a dichotomous and continuous fashion. Thus, the DADSI determines if a depressed patient meets the DSM-5 subtype, and quantifies the severity of the anxious distress specifier features and thus can be used to monitor outcome. Depressed patients were interviewed with the SCID, DADSI, Hamilton Depression Rating Scale (HAMD), and Hamilton Anxiety Rating Scale (HAMA). The patients also completed self-report measures of anxiety, depression, psychosocial functioning, and quality of life.

Results: The interrater reliability of the DSM-5 anxious distress subtyping and DADSI total scores was high. Likewise, the internal consistency of the DADSI was high and all item-scale correlations were significant. DADSI scores were more highly correlated with the HAMD than the HAMA, and more highly correlated with self-report measures of anxiety than depression and anger. Depressed patients with anxiety disorder diagnoses had significantly higher DADSI scores than depressed patients without an anxiety disorder. Patients who met the anxious distress specifier reported more impairment in psychosocial functioning and poorer quality of life than patients who did not meet the anxious distress specifier.

Conclusion: The results of the present study indicate that the DADSI is a reliable and valid measure of the DSM-5 anxious distress specifier.

Learning Objectives:

At the conclusion of the session, the participant should be able:

- To recognize the clinical significance of anxiety in depressed patients.
- To become familiar with the DSM-5 criteria for the anxious distress specifier.
- To learn about a new interview measure that evaluates the DSM-5 anxious distress specifier (DADSI).
- To become familiar with the psychometric properties, reliability and validity of the DADSI.

Literature References:

- Zimmerman M, McDermut W, Mattia J. The frequency of anxiety disorders in psychiatric outpatients with major depressive disorder. *Am J Psychiatry*. 2000;157:1337-1400.
- Fava M, Rush AJ, Alpert JE, et al. Difference in treatment outcome in outpatients with anxious versus nonanxious depression: a STAR*D report. *Am J Psychiatry*. 2008;165:342-351.

W33. ETHICS OF MEDICAL MARIJUANA: MEDICALIZATION OF TREATMENT WITH PAUCITY OF PROOF

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Abstract: Currently, 23 states and the District of Columbia have laws allowing for the use of medical marijuana for numerous and varied medical and behavioral health conditions. Between these states, there are no standards for what conditions are prescribed medical marijuana, there is little proof for the efficacy of marijuana for conditions prescribed for, and no trials have established dosage or safety. Adding to this complexity, more than half of states in the United States do not have laws allowing for medical marijuana use, and further have laws against recreational possession. This model does not follow any previously defined model of medication dispensation. This poster will explore the numerous and unique issues involved with the medical marijuana movement in the United States.

Learning Objectives:

- Ethics of medicalization of marijuana with paucity of information regarding its efficacy for wide array of conditions.
- Issues for patients prescribed medical marijuana that occur across state lines due to inconsistent state laws.
- Federal laws often contrary to state law.
- Addressing these complexities with patients receiving medical marijuana.

Literature References:

- Clark PA, Capuzzi K, Fick C. Medical marijuana: medical necessity versus political agenda. *Med Sci Monit* 2011; 17 (12): RA249-261.
- Grotenherman F, Muller-Vahl K. The therapeutic potential of cannabis and cannabinoids. *Deutsches Arzteblatt International* 2012; 109 (29-30): 495-501.
- Whiting PF, Wolff RF, Deshpande S, Di Nisio M, Duffy S, Hernandez AV, Keurentjes JC, Lang S, Misso K, Ryder S, Schmidtkoer S, Westwood M, Kleijnen J. Cannabinoids for medical use a systematic review and meta-analysis. *JAMA* 2015; 313 (24): 2456-2473.

W34. A CLASSIFICATION OF SUICIDALITY DISORDER PHENOTYPES

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Abstract: Background: The view that suicidality is trans-nosological and that all forms of suicide are the same, is not consistent with response to pharmacological treatment evidence.

For example, antidepressants make suicidality better in some patients, worse in others, and are no better than placebo for a third group. This suggests that there may be more than one type of suicidality.

Methods: We used a phenomenological approach by observing in detail and directly communicating with subjects over time about their suicidality.

Results: We developed diagnostic criteria and a related structured diagnostic interview for 9 distinct suicidality disorder phenotypes. These include 1) Impulse Attack Suicidality Disorder, 2) Psychotic Suicidality Disorder, 3) Obsessive-Compulsive Suicidality Disorder, 4) PTSD Induced Suicidality Disorder, 5) Substance Induced Suicidality Disorder, 6) Medical Illness / Neurological Condition Induced Suicidality Disorder, 7) Mood Disorder Induced Suicidality Disorder, 8) Life Event Induced Suicidality Disorder, and 9) Suicidality Disorder, Not Elsewhere Classified. Among these phenotypes the description of Impulse Attack Suicidality Disorder is new and has never been described from the prospective presented. This disorder is associated with unexpected, unprovoked attacks of an urgent need to kill oneself.

Conclusion: We offer 9 distinct suicidality disorder phenotypes. Because these phenotypes may have a different response to treatment, each phenotype should be investigated separately when investigating anti-suicidality treatments and when investigating the relationship between genetic and other biomarkers in suicidality.

Learning Objectives:

Following this presentation, participants will be better able to:

- Identify the different phenotypes of suicidality disorders.
- Appreciate that not all clinical phenotypes of suicidality disorders have the same clinical features, natural history, response to life events, prognosis, or response to treatment.

Literature References:

- Sheehan, DV and Giddens, JM. Suicidality Disorders Criteria. In: Sheehan, DV and Giddens, JM. 2015. Suicidality: A Roadmap for Assessment and Treatment. p. 82-126. Available from: <http://www.HarmResearch.org>
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W35. CHIME (CHILDHOOD IMPULSIVE AGGRESSION AND MOLINDONE ER): DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF SPN-810 ADDED TO STANDARD ADHD THERAPY IN CHILDREN WITH IMPULSIVE AGGRESSION AND ADHD

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Abstract: Background: Because impulsive aggression (IA) comorbid with childhood ADHD markedly increases the risk of poor outcomes, including adult antisocial disorders, effective treatment strategies with early onset are needed. As yet, no medication is specifically FDA-approved for IA-targeted therapy in children with ADHD. Empirical evidence does not

support the current practice in which antipsychotics are added to ADHD therapy. Molindone is a medium-potency D2/D5-receptor antagonist with +30-yr clinical history as an immediate-release (IR) formulation to treat schizophrenia. Extended-release (ER) molindone (SPN-810, Supernus Pharmaceuticals, Inc.) is designed to deliver more constant plasma drug concentrations with longer dosing intervals vs. IR molindone in order to improve tolerability and adherence. In a Phase 2B double-blind placebo-controlled dose-ranging study in children with ADHD and IA receiving standard ADHD therapy, SPN-810 (12-36 mg/day) was significantly superior to Placebo in reducing IA behaviors (effect size: 0.60). SPN-810 was better tolerated than similar total daily dosages of IR molindone evaluated in a Phase 2A study. The first Phase 3 study in the CHIME Clinical Development Program, which was recently initiated, will be summarized. Study Design: Multicenter, randomized, double-blind, placebo-controlled study with 1:1:1 randomization to Placebo, 18 mg SPN-810 (Dose I), and 36 mg SPN-810 (Dose II). After 2-wk Baseline period to determine IA behavior episode frequency and eligibility, subjects will enter the 5-wk double-blind treatment phase: 2-wk titration period and 3-wk maintenance period. Study Population: Planned: 291 randomized subjects (97 per treatment arm). Key inclusion criteria: Otherwise healthy subjects, 6-12 yrs (inclusive) at Screening with a primary diagnosis of ADHD and currently receiving monotherapy with an optimized FDA-approved ADHD medication for ≥ 1 month before Screening (dose to be unchanged throughout Baseline and Treatment periods); R-MOAS (Retrospective-Modified Overt Aggression Scale) score ≥ 24 at Screening; CGI-S score of at least moderately ill at both Screening and Randomization; Vitiello Aggression Scale score -2 to -5 at Screening; free of antipsychotic medication for ≥ 2 wks at Baseline; 80% compliant during Baseline period. Key exclusion criteria: Current or past diagnosis of epilepsy, major depressive disorder, bipolar disorder, schizophrenia or related disorder, personality disorder, Tourette's disorder, or psychosis not otherwise specified; currently meeting DSM-5 criteria for autism spectrum disorder, pervasive developmental disorder, obsessive compulsive disorder, post-traumatic stress disorder, or any other anxiety disorder as primary diagnosis; IQ < 70; suicidality. Primary Efficacy Evaluation: IA behaviors will be monitored. Primary endpoint: Median percent change in IA behavior frequency per 7 days in the Maintenance period corrected for Baseline in the Intent-to-Treat population. Secondary endpoints: Severity and improvement of IA behaviors (CGI-S/CGI-I); quality-of-life scales (CHQ-PF28 and PSI-4-SF). Safety/Tolerability Assessments: Adverse events; EPS scales; clinical laboratory tests; ECGs; vital signs; Columbia Suicide Severity Rating Scale; Infrequent Behaviors Checklist.

W36. LOST IN TRANSLATION: TRANSLATABILITY OF PSYCHIATRIC TERMS - THE EXAMPLE OF THE MINI-INTERNATIONAL NEUROPSYCHIATRIC INTERVIEW (M.I.N.I.)

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Abstract: Objectives. The Mini-International Neuropsychiatric Interview (M.I.N.I.) is a short, structured diagnostic interview, developed jointly by psychiatrists and clinicians in the United States and Europe, for DSM-IV and ICD-10 psychiatric disorders. The objectives of our study were: (1) To evaluate if the psychiatric terms used in the M.I.N.I. are translatable

worldwide, especially in non-western countries; and (2) To review strategies used to culturally adapt psychiatric terms.

Methods. We reviewed the records of all linguistic validation projects involving the M.I.N.I. performed by Mapi Language Services.

Results. We retrieved 67 language versions, representing 47 countries. The analysis of the translations' content showed that three strategies were used, depending on the existence (or not) of corresponding psychiatric terminology in the target languages. The standard methodology (forward/backward and clinician review) was used in all countries and adapted, depending on the context. In all western and westernized countries (e.g., Europe, Russia; in total, 50 languages), the psychiatric terms used in the M.I.N.I. were easily translated (i.e., existence of an agreed-upon corresponding terminology). In languages where psychiatric terms do not exist (e.g., certain Sub-Saharan languages; in total, 5 languages), all the clinician-directed parts (titles, clinician-directed instructions/algorithms), which are capitalized in the original instrument, were left in English, and the patient-directed parts were translated in the target languages. In languages where there is a partially agreed-upon terminology (e.g., Thai, Indian languages; in total, 12 languages), the titles as well as the algorithms were translated with corresponding English equivalents between brackets, when necessary. Moreover, in order to follow the typographical conventions of the M.I.N.I., in languages with no capital letters (such as Kannada or Malayalam), the translations used bigger font size.

Conclusion. This review showed that terms used to describe psychiatric disorders had no equivalents in some countries, especially in Africa. Translation was not always possible and was even judged to be culturally and linguistically irrelevant in countries where psychiatry is, for now, only taught in English.

Learning Objectives:

- To understand the challenges faced by researchers involved in international clinical research.
- To describe the translation methodologies used to ensure that the translations of the M.I.N.I. are conceptually equivalent to the original.

Literature References:

- Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, Hergueta T, Baker R, Dunbar GC: The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry* 1998; 59(Suppl 20):22-33.
- Wild D, Grove A, Martin M, Eremenco S, McElroy S, Verjee-Lorenz A, Erikson P; ISPOR Task Force for Translation and Cultural Adaptation: Principles of Good Practice for the Translation and Cultural Adaptation Process for Patient-Reported Outcomes (PRO) Measures: report of the ISPOR Task Force for Translation and Cultural Adaptation. *Value Health*. 2005; 8(2):94-104.

W37. HUMAN FACTORS EVALUATION OF A NOVEL DIGITAL HEALTH FEEDBACK SYSTEM IN PSYCHIATRY

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Abstract: Background: Poor medication adherence is a common problem in patients with serious mental illness (SMI). The Digital Health Feedback System (DHFS) is a novel class of combination drug-device developed for patients with SMI comprising a sensor-embedded medication, wearable sensor, and software applications. The DHFS offers a new opportunity to objectively measure patient's medication ingestion, help patients stay on track with therapy, and share the data with healthcare professionals (HCPs) to inform medical decisions. The absence of directly applicable user experience from a comparable existing product highlights the importance of applying human factors (HF) methods to analyze use-related risks and optimize the system. HF engineering is recommended in the FDA guidance to assess the safe and effective use of a system by the intended users for the intended uses. This is particularly critical for patients with SMI who may have cognitive impairments associated with poor functional skills.

Objective: To design the DHFS to be safe and effective by using HF methodology to identify steps in the use process that may result in use-related risks, understand the root cause of performance problems, and iteratively mitigate risks by redesigning the product to ensure usability in SMI patients with potential cognitive limitations.

Methods: Three successive formative HF studies were conducted. Each study tested use in the intended user group which included patients with schizophrenia, major depressive disorder, and bipolar disorder. Both objective and subjective qualitative data was gathered for all tasks considered critical to safety or essential for effective use. The root cause for errors was assessed and risks to the users were identified. A use risk analysis was performed before and after each study to identify remaining user risks associated with the system and inform iterations of product design. With this methodology, use-related hazards were iteratively mitigated throughout the design process, while also improving effective use by the intended users.

Results: Feedback from the formative HF studies of the patient interface was used to implement further design modifications to the patient app and electronic instructions for use. The modifications were designed to reduce cognitive effort needed to effectively use an app for persons with SMI, including: minimizing the number of the application levels (hierarchy), simplifying content (sentences, composition, reading level), using explicit wording, and avoiding information overload. There were no distinguishable differences in performance observed among patients with different diagnoses. Risk analysis performed after the final iterative study showed further reduction in the risk levels and improved effectiveness of the system.

Conclusion: Analysis of results from iterative studies of the patient interface of the DHFS demonstrated that the system was safe and effective for its intended users, intended uses, and use environments, in addition to being responsive to the cognitive characteristics of patients with SMI.

Disclosure: Otsuka Pharmaceutical Development & Commercialization, Inc.

Learning Objectives:

- To assess the use-related risks and effective use of a novel digital health feedback system, which objectively assesses adherence by measuring actual medication ingestion, in patients with serious mental illness (SMI).

- To understand how potential use-related risks were iteratively mitigated and effectiveness improved by understanding root causes and then modifying the design, thereby increasing the safety and effectiveness of digital health feedback system and ensuring usability in SMI patients with potential cognitive limitations.

Literature References:

- Sajatovic M, Velligan DI, Weiden PJ, Valenstein MA, Ogedegbe G. Measurement of psychiatric treatment adherence. *J Psychosom Res.* 2010;69(6):591-599
- US Department of Health and Human Services. HE75/ISO 10485, 2011

W38. INVOLVING THE CAREGIVERS IN DIGITAL HEALTH-ENHANCED CARE OF PATIENTS WITH SERIOUS MENTAL ILLNESS: RECOMMENDATIONS FROM AN EXPERT CONSENSUS SURVEY

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Abstract: Background: Patients with serious mental illness (SMI), including schizophrenia, bipolar disorder, and major depressive disorder, often rely on caregivers for support, care, and encouragement with their treatment plans. Thus, if digital health tools (DHT) are included in a treatment plan, engagement of caregivers with these tools may play an important role in optimizing outcomes.

Objective: To assess expert opinion on factors affecting use of DHT by caregivers of patients with SMI.

Methods: This survey followed the expert consensus methodology that was developed to quantify and report expert opinion to inform areas where literature is scant and/or for areas not well-covered by definitive research. A panel of leading experts, who met criteria for participation by having contributed to literature on development and evaluation of DHT in psychiatric disorders and behavioral health, completed a 2-part survey containing 19 questions and rated predefined responses on a 9-point Likert scale. In responding, the experts were asked to consider the tool(s) and technology with which they had most experience. Consensus was determined using Chi-square test of score distributions across the 3 ranges (1–3, 4–6, 7–9). Categorical ratings of first-, second-, or third-line were designated based on the lowest category in which the confidence interval of the mean ratings fell, with a boundary of >6.5 for first-line. We describe results from 4 questions on various caregiver-related factors that could impact the use of DHT (n = 40 respondents).

Results: Among 13 predefined characteristics that might enable caregivers to successfully participate in a patient's digital health-enhanced care, all experts rated a positive attitude towards the healthcare professional's decision to incorporate DHT in the patient's regimen as first-line (mean, 8.1; SD, 0.8). Among potential benefits that could motivate caregivers to participate in use of DHT, improvement in patient functioning and reduction in number of hospitalizations were given the highest rating by at least 50% of experts. In terms of potential barriers to or unintended consequences of caregiver involvement with a patient's use of DHT, the experts' main concerns were related to family members breaching patient confidentiality or being invasive or overly involved. When asked about training and resources for caregivers, more than three-fourths of the experts gave a first-line rating (average ≥ 7.6) to: (i) providing

a clear rationale about the usefulness of the device, (ii) in-person training sessions with the patient and a member of treatment team, and (iii) a simple-to-use platform.

Conclusions: Experts identified important characteristics of caregivers and resources they would need to actively engage in use of DHT for patients with SMI. These results can guide the clinicians in operationalizing the use of DHT.

Disclosure: Supported by Otsuka Pharmaceutical Development & Commercialization, Inc.

Learning Objectives:

- To understand expert opinion on caregiver factors that would promote their acceptance of digital health tools for patients with serious mental illness.
- To understand expert opinion on potential barriers to caregiver involvement with a patient's use of digital health tools.

Literature References:

- Kahn DA, Docherty JP, Carpenter D, Frances A: Consensus methods in practice guideline development: a review and description of a new method. *Psychopharmacol Bull* 1997; 33(4):631-639
- Rotondi AJ, Anderson CM, Haas GL, Eack SM, Spring MB, Ganguli R, Newhill C, Rosenstock J: Web-based psychoeducational intervention for persons with schizophrenia and their supporters: one-year outcomes. *Psychiatr Serv* 2010; 61(11):1099-1105

W39. FACTORS AFFECTING THE USE OF DIGITAL HEALTH TOOLS BY HEALTHCARE PROFESSIONALS FOR PATIENTS WITH SERIOUS MENTAL ILLNESS: AN EXPERT CONSENSUS SURVEY

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Abstract: Background: While digital health technology (DHT) is increasingly being used to deliver and enhance healthcare in other areas, factors affecting use of DHT by healthcare professionals (HCP) for patients with serious mental illness (SMI) are not clear. Development of DHT that HCPs can successfully use with SMI patients requires consideration of HCP characteristics, training, and resources to facilitate DHT use.

Objective: To assess expert opinion on HCP-related factors affecting the use of DHT in patients with SMI.

Methods: A panel of leading experts who met criteria for participation by having contributed to literature on development and evaluation of DHT in psychiatric disorders completed a 2-part survey containing 19 multi-part questions and rated predefined responses on a 9-point Likert scale. In responding, the experts were asked to consider the tool(s) and technology with which they had most experience. Consensus was determined using Chi-square test of score distributions across 3 ranges (1–3, 4–6, 7–9). Categorical ratings of first-, second-, or third-line were designated based on the lowest category in which the confidence interval of the mean ratings fell, with a boundary of >6.5 for first-line. We describe results from 4 questions on HCP-related factors relevant to acceptability of DHT for use in clinical practice (n=40 respondents).

Results: Experts agreed with a high degree of consensus (average rating ≥ 8.2) that to successfully incorporate DHT in their practice, HCPs should be enthusiastic about the tool, and have staff and equipment available to support its use. Reimbursements by payers for time spent training patients and reviewing data from DHT; improved patient adherence and functioning; and reduced symptomatology were rated first-line by over 90% of the experts as benefits extremely likely to motivate HCPs to use DHT. In terms of barriers that might interfere with an HCP using DHT in patients with SMI, the experts' main concerns related to liability, reimbursement, patients' access to and ability to use technology, and uncertainty about how to incorporate DHT into practice and use the generated data. In considering what would help HCPs prescribe and engage with DHT, the experts stressed the importance of giving HCPs a clear rationale about how DHT would improve outcomes (95% first-line). Although the majority of experts agreed that HCPs would need to be trained and also train patients, 56% suggested that training patients would be somewhat difficult for HCPs.

Conclusions: The experts identified factors that affect acceptance of DHT by HCPs who treat patients with SMI. Appropriate training, availability of necessary resources, and reimbursement for time spent were considered most likely to support DHT use. These results may be used as guidance for facilitating the use of DHT in clinical practice.

Disclosure: Supported by Otsuka Pharmaceutical Development & Commercialization, Inc.

Learning Objectives:

- To understand expert opinion on characteristics of healthcare professionals relevant to acceptability of digital health tools to healthcare professionals for patients with serious mental illness.
- To understand expert opinion on the training and resources that healthcare professionals would need for optimizing their use of digital health tools for patients with serious mental illness.

Literature References:

- Kahn DA, Docherty JP, Carpenter D, Frances A: Consensus methods in practice guideline development: a review and description of a new method. *Psychopharmacol Bull* 1997; 33(4):631-639
- Gagnon MP, Ngangue P, Payne-Gagnon J, Desmartis M: m-Health Adoption by Healthcare Professionals: A Systematic Review. *J Am Med Inform Assoc* 2015 [Epub ahead of print]

W40. WEB-BASED CURRICULUMS FOR TEACHING PSYCHOPHARMACOLOGY: REVISION OF THE RESIDENT, MEDICAL STUDENT, AND PRIMARY CARE CURRICULUMS

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Abstract: Started by the ACNP training committee in 1984, the ASCP Psychopharmacology Committee has developed unique and widely disseminated curricula for teaching clinical psychopharmacology to psychiatric residents, medical students and primary care physicians. It has increasingly had global penetration. We present here the 8th edition of the resident curriculum, the 3rd edition for medical students and the 2nd edition for primary care. The ASCP Curriculum Committee composed of directors of both resident education as well as medical student education educators have developed materials related to the “what, why, and

how” to teach and evaluate. In addition, for each curriculum, we included both a core series of lectures as well as optional lectures developed by experts in their fields. We have done follow-ups on all three curriculums within the last 2 years. We describe here the process of revising, updating, and moving to a web-based curriculum. We present the content for the three curriculum. Based on the follow up of all three curriculums, we have revised every lecture and updated the pedagogy. Depending on the size/resources of the program, teachers use the curriculum in its entirety or in parts. It works even in non-English speaking countries as committee members work with users to adapt/translate to local conditions and teaching strategies. It has been difficult to connect with primary care training programs.

For residents, the curriculum is now in its 8th edition and has 88 lectures and over 4,000 slides. For teaching medical students and primary care physicians, there has never been a generally accepted curriculum or set of teaching materials specifically designed for them. There is a great deal to teach in the four-year curriculum and medical students have widely divergent career paths. This curriculum has 22 lectures. Having the curriculum web-based has improved availability although some programs globally still need a hard copy version.

Learning Objectives:

- At the conclusion of this presentation, the student will be aware of recent advances in psychopharmacology for medical students.
- At the conclusion of this presentation, the student will be aware of recent advances in psychopharmacology for primary care physicians.

Literature References:

- American Society of Clinical Psychopharmacology Model Psychopharmacology Curriculum, for Psychopharmacology Teachers for Primary Care Clinicians, 2nd Edition, 2015, ASCP, 5034A Thoroughbred Lane, Brentwood, TN 37027.
- American Society of Clinical Psychopharmacology Model Psychopharmacology Curriculum, for Directors of Medical Student Education and Teachers of Psychopharmacology in Medical Student Programs, 3rd Edition, 2015, ASCP, 5034A Thoroughbred Lane, Brentwood, TN 37027.

W41. PREDICTORS OF MEDICATION ADHERENCE EVALUATED BY URINE DRUG MONITORING IN PATIENTS PRESCRIBED ANTIPSYCHOTIC AGENTS

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Abstract: Objective: To assess the relationship between patient characteristics and potential medication nonadherence in patients prescribed antipsychotic agents.

Methods: Urine samples from patients prescribed antipsychotic medications were analyzed for the presence of antipsychotics using liquid chromatography/tandem mass spectrometry. Samples were classified as positive for the antipsychotic if parent drug and/or metabolite(s) were confirmed and negative if neither were detected. Adjusted odds ratio (aOR) and 95% confidence interval (CI) predicting nonadherence were calculated using multiple logistic regression analysis with the following independent variables: sex, age decade, primary payor, prescribed antipsychotic, geographic region, and year tested.

Results: A total of 15,847 samples were analyzed; 25.9% tested negative for a prescribed antipsychotic. Potential nonadherence was observed in a similar proportion of samples from men versus women (24.6% vs 27.1%; aOR, 0.93; 95% CI, 0.86-1.00). Relative to patients aged 20 to 29 years, potential nonadherence was less common among samples from patients aged 10 to 19 years (23.9% vs 27.9%; aOR, 0.80; 95% CI, 0.66-0.97) and those 50 to 79 years (16.1%-23.2%; aOR range, 0.58-0.78). Compared with samples from uninsured/indigent patients, potential nonadherence rates were lower in samples from patients with Medicare (20.0% vs 32.0%; aOR, 0.52; 95% CI, 0.47-0.58), commercial insurance (25.0%; aOR, 0.68; 95% CI, 0.59-0.79), or Medicaid (27.8%; aOR, 0.82; 95% CI, 0.74-0.90) as the primary payor.

Conclusions: Potential nonadherence was common among patients prescribed antipsychotic medications, with some variation based on patient characteristics. Urine drug monitoring may be valuable for identifying patients in whom addressing medication nonadherence could improve treatment outcomes.

Sponsored by Ingenuity Health, a service of Ameritox Ltd.

Learning Objectives:

- Identify factors driving medication nonadherence.
- Assess the role of urine medication adherence monitoring as part of the treatment plan.

Literature References:

- Sajatovic M, Valenstein M, Blow FC, et al. Treatment adherence with antipsychotic medications in bipolar disorder. *Bipolar Disord.* 2006;8(3):232-241.
- Offord S, Lin J, Mirski D, et al. Impact of Early Nonadherence to Oral Antipsychotics on Clinical and Economic Outcomes Among Patients with Schizophrenia. *Adv Ther.* 2013;30(3):286-297

W42. PREVENTION OF DRUG INTERACTIONS INVOLVING PSYCHOTROPIC DRUGS

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Abstract: Background: Psychiatric patients often present with a number of medical comorbidities, requiring concurrent non-psychotropic pharmacological treatment, which may increase the risk for drug interactions (DI). In addition to interactions with other prescribed drugs, psychotropic agents may also interact with over the counter (OTC) medications, herbal supplements, alcohol, tobacco products and certain types of food. A thorough understanding of the basis of drug interactions is crucially important for physicians to prevent toxicity and maximize efficacy of the prescribed treatment.

Purpose: This study was to categorize and classify pharmacodynamic and pharmacokinetic DI for providing clinical guidance to the physician. We also developed recommendations to minimize potential interactions between psychotropic drugs and other prescription or OTC drugs.

Methods: We searched the National Library of Medicine from 1985 to 2015 for original studies and review articles. The search terms were: psychotropic, drug-drug interaction, Cytochrome P450, pharmacokinetics.

Results: Based on the clinical intensity of outcomes, we classified the types of drug interactions as severe, moderate or mild. Severe interactions may lead to serious life-threatening complications and should be avoided. Moderate interactions include efficacy issues and should be closely monitored. Mild interactions include non-serious side effects, like somnolence. The following guidelines are recommended for avoiding clinically significant drug interactions.

- The patient should be requested to prepare a list of medications (and doses), including prescription medications, over-the-counter medications and herbal supplements. Information regarding food items, use of alcohol, recreational drugs, and tobacco products should also be collected. The physician should then revise the list and, if possible, change therapeutic regimens to avoid the occurrence of clinically significant DIs.
- Since most of the severe DIs result in cardiovascular complications, screening for known cardiac risk factors and regular monitoring of ECG changes from baseline are very important.
- Medication regimens should be simplified, weighing the potential clinical benefits and risks for pharmacological interactions. The number of prescribed medications, over-the-counter medications and herbal supplements should be kept as few as possible.
- Ascertain if drugs involved in the DIs could be substituted by other drugs with similar spectrum of efficacy but with lower potential for interactions.
- New medications being added to existing pharmacotherapy regimens should be started at low doses and titrated slowly.
- Continuous monitoring of newly developed side effects and changes in clinical response when a medication is prescribed concomitantly with either an inhibitor or an inducer of its metabolism, or when the inhibitor or inducer is discontinued.
- Clinicians should utilize available resources such as updated textbooks, electronic databases, reviews, and updated drug interactions websites, to learn about the DIs. Furthermore, the use of pharmacogenetic tests should be considered in selected clinical situations.

Conclusions: Most drug interactions are predictable and preventable. Physicians should be continuously educated about the various mechanisms of drug interactions, and follow appropriate recommendations.

Learning Objectives:

- To learn about drug interactions with psychotropics.
- How to minimize the drug interactions.

Literature References:

- Madhusoodanan, S., Velama, M., Parmar, J., Goia, D., Brenner, R. 2014. A current review of cytochrome P450 interactions of psychotropic drugs. *Ann Clin Psychiatry*. 26 (2): 120-138
- Madhusoodanan, S., Tsoy-Podosenin, M., Steinberg, L., Tandan, N. Drug interactions involving psychotropic drugs. In *Textbook Mental Disorders in Primary Care: A Guide to their Evaluation and Managing*, edited by Roger S. McIntyre, Andre F. Carvalho and Sloan Manning. Oxford University Press, In Print.

W43. PSYCHIATRIC COMORBIDITY IN PATIENTS WITH PSEUDOBULBAR AFFECT

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Abstract: Background: Pseudobulbar affect (PBA) is characterized by frequent, sudden and involuntary laughing and/or crying episodes occurring secondary to neurological disorders affecting the brain. Studies suggest PBA is under-recognized in clinical practice. Patients with PBA may have comorbid psychiatric conditions that can pose challenges for differential diagnosis; however, the presence of psychiatric comorbidity has not been well described across different neurologic conditions that cause PBA, and clinical trial populations often exclude patients with significant psychiatric comorbidity. This analysis evaluates the presence of psychiatric comorbidity across different neurological conditions from a large US online survey designed to measure aspects of PBA-associated burden.

Methods: The survey was conducted by Harris Interactive using online registrants (or their caregivers) previously diagnosed with traumatic brain injury (TBI), Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), Parkinson's disease (PD), or stroke. Recruitment methods have been reported in full.² The "PBA-group" was defined as those with a score ≥ 13 on the Center for Neurologic Study Lability Scale (CNS-LS). The survey utilized a matched sample design, first recruiting the PBA-group, then recruiting a demographically-matched Control group (CNS-LS < 13) within each neurologic condition. Weighting was applied to control for between-group differences in primary neurological disease severity. Participants were asked about the presence of specific psychiatric diagnoses; additionally, all respondents completed a Center for Epidemiologic Studies depression scale 10-item short form.

Results: A total of 1,052 respondents completed the survey (n=399 PBA group; n=653 non-PBA controls). Psychiatric diagnoses were reported by 72% of the PBA-group respondents vs 45% controls ($P < .05$). Individual psychiatric diagnoses were reported by significantly more PBA-group respondents vs controls ($P < .05$ for all), including depression (52% vs 28%), anxiety/panic attacks (43% vs 17%), PTSD (20% vs 11%), bipolar disorder (13% vs 4%), psychotic disorder (9% vs 1%), and schizophrenia/delusional disorder (5% vs 2%).

Differences between PBA-group and controls respondents were also seen within each neurologic condition for all psychiatric conditions evaluated. For example, depression was reported by (PBA-group vs controls) 56% vs 31% with TBI, 49% vs 32% with AD, 33% vs 7% with ALS, 45% vs 18% with MS, 41% vs 25% with PD, and 55% vs 16% with stroke. Presence of anxiety/panic attacks were reported by 51% vs 23% with TBI; 45% vs 16% with AD, 36% vs 7% with ALS, 25% vs 5% with MS, 21% vs 5% with PD, and 30% vs 11% with stroke. PTSD was most often reported by those with TBI (29% vs 23%). Bipolar disorder, psychotic disorder, and schizophrenia/delusional disorder were generally more commonly reported for those with AD (PBA-group: 18%, 15% and 12%, vs controls: 0%, 1%, 5%).

Conclusion: Regardless of the primary neurological condition, PBA-group respondents reported a higher incidence of comorbid psychiatric diagnoses compared with non-PBA-group controls. The degree to which the greater frequency of psychiatric diagnoses in the PBA-group may represent a misdiagnosis of PBA symptoms or difficulties in distinguishing PBA from psychiatric conditions on the basis of the CNS-LS alone is unclear. Studies using structured diagnosis of PBA and psychiatric conditions are needed.

Learning Objectives:

- To evaluate the potential presence of psychiatric comorbidities in persons with PBA across neurologic conditions based on estimates from a large online survey (Colamonic et al 2012).
- To improve understanding of the clinical presentation of persons with PBA and distinguishing characteristics from psychiatric conditions.

Literature References:

- Miller A, Pratt H, Schiffer RB. Pseudobulbar affect: the spectrum of clinical presentations, etiologies and treatments. *Expert Rev Neurother*. 2011 Jul;11(7):1077-88.
- Colamonic J, Formella A, Bradley W. Pseudobulbar affect: burden of illness in the USA. *Adv Ther*. 2012 Sep;29(9):775-98.

W44. INTRANASAL OXYTOCIN MODULATES NEURAL RESPONSES TO INCENTIVE STIMULI IN HUMANS

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Abstract: Oxytocin is a neuropeptide widely recognized for its role in regulating social and reproductive behavior. Increasing evidence from animal models suggests that oxytocin also modulates reward circuitry in non-social contexts, but evidence in humans is lacking. Here we examined the effects of oxytocin administration on reward circuit function in 18 healthy men as they performed a monetary incentive task. The blood oxygenation level dependent (BOLD) signal was measured using functional magnetic resonance imaging in the context of a randomized, double-blind, placebo-controlled, crossover trial of intranasal oxytocin. We found that oxytocin enhanced the BOLD signal in the midbrain (substantia nigra and ventral tegmental area) during the late phase of the hemodynamic response. This late enhancement was more prominent for reward stimuli than for loss stimuli. Oxytocin's effects on midbrain responses correlated positively with its effects on positive emotional state. We did not detect an effect of oxytocin on responses in the nucleus accumbens. Whole-brain analyses revealed that oxytocin attenuated medial prefrontal cortical deactivation specifically during anticipation of monetary loss. Our findings demonstrate that intranasal administration of oxytocin has valence-specific effects on human midbrain and medial prefrontal function during motivated behavior. These findings suggest that endogenous oxytocin is a neurochemical mediator of reward behaviors in humans – even in a non-social context – and that the oxytocinergic system is a potential target of pharmacotherapy for psychiatric disorders that involve dysfunction of reward circuitry.

Learning Objectives:

- Understand the influence of oxytocin administration on reward circuitry in humans.
- Appreciate the potential of the oxytocinergic system as a target of pharmacotherapy for psychiatric disorders that involve dysfunction of reward circuitry.

Literature References:

- Boccia ML, Petrusz P, Suzuki K, Marson L, Pedersen CA (2013) Immunohistochemical localization of oxytocin receptors in human brain. *Neuroscience* 253:155-164.

- Sarnyai Z, Kovács GL (2014) Oxytocin in learning and addiction: From early discoveries to the present. *Pharmacol Biochem Behav* 119:3-9.

W45. EFFICACY OF LURASIDONE IN PATIENTS WITH SCHIZOPHRENIA WITH PROMINENT POSITIVE SYMPTOMS: A POOLED ANALYSIS OF SHORT-TERM PLACEBO-CONTROLLED STUDIES

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Abstract: Introduction: Acute schizophrenia is characterized by the presence of active positive symptoms, which may be disruptive to the patient and increase the risk of behavioral disturbance and hospitalization. This post hoc analysis evaluated the efficacy of lurasidone in patients with acute schizophrenia with prominent positive symptoms.

Methods: Patient-level data were pooled from 5 similarly designed, multiregional, randomized, double-blind, placebo-controlled, 6-week studies of fixed-dose lurasidone (40, 80, 120, or 160 mg/d) conducted in adult patients (age 18-75 years) with acute schizophrenia. Prominent positive symptoms were defined as baseline Positive and Negative Syndrome Scale (PANSS) positive subscale score > baseline PANSS negative subscale score. Change from baseline in PANSS total score was evaluated using mixed-model repeated-measures analysis (MMRM). Treatment response was defined as $\geq 30\%$ decrease in PANSS total score at week 6 (last observation carried forward [LOCF]). The number needed to treat (NNT) to obtain one additional responder was calculated as the reciprocal of the difference in response rates between lurasidone and placebo groups.

Results: This analysis included 919 patients with prominent positive symptoms (mean age, 38.5 years; male, 72.3%) and 613 patients without prominent positive symptoms (mean age, 38.3 years; male, 74.1%). Study discontinuation rates were 39.5% for lurasidone and 48.7% for placebo in patients with prominent positive symptoms, and 29.5% for lurasidone and 36.2% for placebo in patients without prominent positive symptoms. Based on change from baseline to week 6 in PANSS total score (MMRM), effect sizes for the lurasidone 40, 80, 120, and 160 mg/d dose groups were 0.51, 0.65, 0.44, and 1.09, respectively, for patients with prominent positive symptoms (all $P < 0.001$) and 0.29, 0.46, 0.55, and 0.67, respectively, for patients without prominent positive symptoms ($P < 0.05$ for 40 mg/d, all other $P < 0.001$). In patients with prominent positive symptoms, treatment response ($\geq 30\%$ improvement in PANSS total score) at week 6 LOCF was observed in 29.3% of patients in the placebo group and 48.3%, 46.6%, 43.2%, and 64.4% of patients in the lurasidone 40, 80, 120, and 160 mg/d dose groups, respectively (with associated NNT of 6, 6, 8, and 3, respectively). In patients without prominent positive symptoms, treatment response at week 6 LOCF was observed in 35.7% of patients in the placebo group and 50.0%, 52.1%, 54.5%, and 60.4% of patients in the lurasidone 40, 80, 120, and 160 mg/d dose groups, respectively (NNT of 7, 7, 6, and 5, respectively).

Conclusions: In adult patients with schizophrenia presenting with prominent positive symptoms, lurasidone therapy was associated with medium to large treatment effects sizes. Larger effect sizes were observed in patients with prominent positive symptoms compared with patients without prominent positive symptoms. These results may inform the design of future clinical trials in schizophrenia.

ClinicalTrials.gov identifiers: NCT00088634, NCT00549718, NCT00615433, and NCT00790192. One study was completed prior to the requirement to register trials.

Supported by Sunovion Pharmaceuticals Inc.

Learning Objectives:

- Assess the efficacy of lurasidone for the treatment of patients with an acute exacerbation of schizophrenia with prominent positive symptoms.
- Compare the treatment response to lurasidone in patients with and without prominent positive symptoms of schizophrenia.

Literature References:

- Chen L, Johnston JA, Kinon BJ, Stauffer V, Succop P, Marques TR, Ascher-Svanum H. The longitudinal interplay between negative and positive symptom trajectories in patients under antipsychotic treatment: a post hoc analysis of data from a randomized, 1-year pragmatic trial. *BMC Psychiatry* 2013; 13:320
- Lee J, Takeuchi H, Fervaha G, Sin GL, Foussias G, Agid O, Farooq S, Remington G. Subtyping schizophrenia by treatment response: antipsychotic development and the central role of positive symptoms. *Can J Psychiatry* 2015; 60:515-522

W46. EFFECTS OF ARIPIPRAZOLE ONCE-MONTHLY AND PALIPERIDONE PALMITATE ON WORK READINESS IN PATIENTS FROM THE QUALIFY STUDY STRATIFIED BY AGE

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Abstract: Background: The QUALIFY (QUALity of LIfe with AbiliFY Maintena) study compared treatment effectiveness of aripiprazole once-monthly 400 mg (AOM 400), a dopamine D2 receptor partial agonist, to paliperidone palmitate once-monthly (PP), a D2 antagonist. The primary outcome showed superior improvements with AOM 400 vs PP on health-related quality of life and functioning (Naber et al. 2015). As an additional endpoint with relevance for quality of life, the patients' functional capacity to work was assessed with the clinician-rated Readiness for Work Questionnaire (WoRQ, Potkin et al. 2014). Increasing work readiness could be of particular importance in younger, higher functioning patients with schizophrenia. Here we present age-stratified analysis of effect of AOM 400 and PP on capacity to work and work readiness.

Methods: QUALIFY was a 28-week, randomized, open-label, rater-blinded, head-to-head study (NCT01795547) of 2 atypical long-acting injectable anti-psychotics (LAIs), AOM 400 and PP (flexible dosing per label, 50-150 mg/month as paliperidone [EU and Canada], 78-234 mg/month as paliperidone palmitate [US]) in patients with schizophrenia. Included patients were age 18-60 years needing a change from current oral antipsychotic treatment. The QUALIFY protocol pre-specified effectiveness analyses in patients ≤35 years and >35 years and therefore recruitment targeted 30% of patients ≤35 years. WoRQ was rated at baseline and at week 28 (end of study) and consists of 7 statements rated on a 4-point scale:

total scores range from 7-28 with lower scores indicating better functioning. In the final item 8, the clinician indicates if the patient is ready for work (Yes/No). Analyses of covariance were applied to changes after AOM 400 and PP treatment in WoRQ total scores, while logistic regression was used to estimate odds ratios for work readiness at week 28, adjusted for work readiness status at baseline.

Results: At baseline, WoRQ total scores and frequencies of work readiness were similar between AOM 400 and PP treatment groups in patients ≤ 35 years ($n=54$) and >35 years ($n=154$). In patients ≤ 35 years, significantly greater improvements with AOM 400 vs PP were found in WoRQ total scores at week 28 (least squares mean [LSM] treatment difference: -2.70; 95%CI: [-4.41; -0.99], $p=0.0026$). Similarly, shifts from No to Yes in work readiness were more frequent after AOM 400 (38% [12/32]) vs (9% [2/22]) PP treatment, and the odds of being rated as ready for work at week 28 were significantly better for AOM 400 vs PP treatment (adjusted odds ratio: 14.7; 95%CI: [2.48, 87.2], $p=0.0031$). In patients >35 years, numerically larger improvements were seen after AOM 400 vs PP treatment on WoRQ total score (LSM treatment difference: -0.70; 95%CI: [-1.60; 0.19], $p=0.12$) and on work readiness at week 28 (22% [17/78] of AOM 400 and 13% [10/76] of PP patients shifted from No to Yes, with an adjusted odds ratio: 1.93; 95% CI: [0.92; 4.06], $p=0.083$).

Conclusions: Significantly greater improvements on WoRQ total scores and work readiness in patients ≤ 35 years from the QUALIFY study support increased functional capacity after AOM 400 vs PP treatment. Numeric improvements with AOM 400 vs PP were observed in patients >35 years. These results indicate that increased capacity to work and work readiness are attainable treatment goals in schizophrenia, and may be of particular importance in younger patients.

Supported by Otsuka Pharmaceutical Development & Commercialization, Inc. and H. Lundbeck A/S.

Learning Objectives:

- To understand the effects the two different atypical LAIs on functional capacity to work and work readiness in a randomized, head-to-head study in schizophrenia.
- To understand the effects of aripiprazole once-monthly and paliperidone palmitate on work readiness as an important measure of functioning in schizophrenia in young patients, and that treatment-related improvements in work readiness are possible.

Literature References:

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W47. PRECLINICAL AND INITIAL CLINICAL CHARACTERIZATION OF APN1125, AN $\alpha 7$ NICOTINIC ACETYLCHOLINE RECEPTOR AGONIST FOR THE TREATMENT OF COGNITIVE DISORDERS

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Abstract: APN1125 is an $\alpha 7$ nicotinic acetylcholine receptor (nAChR) agonist. The $\alpha 7$ nAChR is a rapidly desensitizing, ligand-gated ion channel and is abundantly expressed in neuroanatomical structures linked to cognition, attention processing and memory formation. Partial agonist activation by APN1125 of the $\alpha 7$ nAChR was observed (EC₅₀ of 1.16 mM, E_{max} 41%) measured using voltage-clamp recordings in *Xenopus laevis* oocytes expressing recombinant human $\alpha 7$ nAChRs. An improvement in cognition was observed following APN1125 administration in a natural forgetting Novel Object Recognition (NOR) task in rats, over a broad range of doses (1-30 mg/kg). In addition, APN1125 demonstrated favorable drug-like properties including evaluations of absorption and metabolism. A deficit in gating of sensory stimuli, similar to that observed in schizophrenic patients, in a mouse strain naturally deficient in expression of $\alpha 7$ nAChR, was alleviated by APN1125 as measured by electroencephalography (EEG) recordings.

A first-in-human Phase 1 clinical study of APN1125 has been initiated. The double-blind, placebo-controlled, single ascending dose study was designed to evaluate the safety, tolerability and pharmacokinetics of APN1125 in healthy normal subjects. An update on this study will be provided.

Learning Objectives:

- The reader should be able to understand the pharmacology of $\alpha 7$ nicotinic receptors.
- The reader should be able to understand the potential application of $\alpha 7$ nicotinic receptors in the treatment of disorders of cognition.

Literature References:

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W48. A PHASE 1 SINGLE- AND MULTIPLE-RISING DOSE STUDY OF THE SAFETY & PK OF EMB-001, A POTENTIAL TREATMENT FOR SUBSTANCE USE DISORDERS, WITH EXPLORATORY EFFICACY MEASURES IN TOBACCO USE DISORDER

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Abstract: Introduction: EMB-001 is a combination of two FDA-approved drugs: metyrapone (MET), a cortisol synthesis inhibitor, and oxazepam (OX), a benzodiazepine. MET is approved for only one day of use as a test of pituitary function; OX is approved for

acute and chronic treatment of various anxiety disorders. EMB-001 reduced cocaine and nicotine self-administration and attenuated cocaine and methamphetamine cue reactivity in rats. In a human study in cocaine-dependent subjects, EMB-001 significantly reduced cocaine use.

Methods: This was a single- and multiple-rising dose study. Healthy volunteers who were daily cigarette smokers aged 18-65 were recruited; this population is relevant for studying both tobacco use disorder and cocaine use disorder, as 75-80% of the latter also smoke cigarettes. They received a single am dose on Day 1, BID dosing on Days 3-9 and a single am dose on Day 10. Three sequential dose cohorts of 8 subjects (6 drug, 2 placebo) received the following doses of MET and OX, respectively: 270 and 12 mg; 540 and 24 mg; and 720 and 24 mg. Total daily doses were double these amounts on BID dosing days, which were still low relative to FDA-approved maximum daily doses of both drugs. Primary outcomes were safety and the pharmacokinetics of MET, its active metabolite metyrapol, and OX. Safety measures included vital signs, ECGs and standard safety labs. Cortisol and other HPA axis parameters were monitored closely throughout the study. In addition, exploratory measures of efficacy in smoking cessation were assessed. Cigarettes smoked, breath CO and urine cotinine were assessed. The Smoking Urges Questionnaire and the Minnesota Nicotine Withdrawal Symptoms scales were administered prior to the start of BID dosing on day 3, and on the last day of BID dosing after a 12-hr enforced abstinence from smoking. The study was not powered for these efficacy assessments.

Results: The most frequent adverse event was somnolence. Most AEs were mild; all were mild or moderate. There were no SAEs and no discontinuations due to AEs. Serum cortisol was reduced 2-4 hours after the first dose, consistent with the known pharmacology of MET, but had returned to baseline on subsequent mornings and at follow-up; there were minimal to no symptoms suggesting adrenal insufficiency and ACTH stimulation tests were normal. There were no clinically significant changes in vital signs, ECGs or other safety labs. The half-lives of MET, OX and metyrapol were approximately and respectively 2, 7.5 and 8 hr. Exposure increased with increasing dose and there was modest accumulation with repeated dosing. There were reductions in cigarettes smoked, smoking urges and withdrawal symptoms, and although there was large variability, few systematic dose-related effects and most findings did not reach statistical significance in this small study, the Cohen's d effect sizes were moderate, ranging from .31 - .47.

Conclusions: EMB-001 was well-tolerated in this study and no new safety signals were identified. These findings are generally consistent with MET and OX approved labeling and with safety data in 6 published studies in which MET doses of 500-4000 mg/day were given for 2-8 weeks. PK results suggest that twice-daily dosing may provide appropriate duration of exposure for efficacy. Effects on smoking were encouraging for a small study that was not powered for efficacy. Future plans include Phase 1b and 2 studies in cocaine use disorder and/or tobacco use disorder.

W49. SYMPTOM STABILITY IN A 52-WEEK SCHIZOPHRENIA EXTENSION STUDY OF TREATMENT WITH LONG-ACTING INJECTABLE ARIPIRAZOLE LAUROXIL

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¹*Alkermes*

Abstract: Introduction: Aripiprazole lauroxil (AL; ARISTADA™, Alkermes, Inc.), a long-acting injectable antipsychotic, is approved for the treatment of schizophrenia. Clinical stability is a highly-desirable treatment outcome, as it may help predict better long-term outcomes. We assessed symptom stability in schizophrenia patients treated with AL in an efficacy study as well as the long-term safety extension study.

Methods: Enrolled subjects (n=478, safety population): de novo subjects with chronic stable schizophrenia who could benefit from switching to a LAI and, rollover subjects who had completed a double-blind, 12-week, placebo-controlled study. De novo subjects received monthly injections of AL 882 mg, and rollover (placebo or AL) subjects received monthly injection with either AL 441 mg or AL 882 mg depending on their assigned treatment in the preceding placebo-controlled study. Subjects who were first assigned to active AL also received daily oral aripiprazole (15 mg) for 3 weeks. The exploratory analysis of the 1-year extension study included subjects who met two stability criteria: Positive and Negative Syndrome total Score (PANSS) ≤ 80 and PANSS ≤ 4 on each of items P2, P3, P6 and G9 simultaneously for 12 continuous weeks. For subjects who were stabilized, remission and relapse rates were assessed using the Schizophrenia Working Group remission criteria (SWGRC). Remission was defined as a PANSS ≤ 3 for each of items P1, G9, P3, P2, G5, N1, N4, and N6 for ≥ 6 continuous months. Relapse criteria was defined as an increase of 10 points or more in PANSS total score from the end of the stabilization period.

Results: The full analysis set contained data from 462 subjects; 396 (86%) subjects reached stabilization within a median time of 85 days, while 66 subjects never met stability criteria. Among 396 stabilized subjects, 383 (97%) remained stable for the entire study, only 39 (10%) relapsed after achieving stabilization, and 233 (60%) achieved symptom remission. Among the 66 subjects who did not meet stability criteria, 30 subjects were not treated for a sufficient period as they discontinued before day 85. For the other 36 subjects, treatment emergent adverse events included schizophrenia (17%) and insomnia (11%). Overall, 318 subjects completed the entire study and 313 (98%) stayed stable after achieving stabilization.

Conclusion: The majority of subjects with schizophrenia who were treated with AL achieved response and remained stable for ≥ 52 weeks. Safety extension studies may have the limitation of selecting for treatment responders, but about half of our study subjects were treated de novo. Nonetheless, over half of the study subjects achieved remission.

Learning Objectives:

- Awareness of long-term treatment outcomes with aripiprazole lauroxil, a recently-approved long-acting injectable antipsychotic for the treatment of schizophrenia.
- Awareness of results from an aripiprazole lauroxil extension study regarding response, symptom stability, and remission.

Literature References:

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W50. ADDRESSING ADHERENCE CHALLENGES AMONG RECENTLY DIAGNOSED SCHIZOPHRENIA PATIENTS: Results FROM AN RCT COMPARING A PSYCHOEDUCATION-BASED VS. A CBT-BASED BRIEF PSYCHOSOCIAL INTERVENTION

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Abstract: Background: Patients with first-episode schizophrenia usually respond well to antipsychotic medication but do not usually stay on medication for very long. This is a vexing problem, and no single intervention has been uniformly successful. Psychoeducation (PE) is considered to be a universal starting point for newly diagnosed patients, but many newly diagnosed patients do not accept the underlying concept of mental illness and need for medication. We therefore tested divergent psychosocial treatment with a study randomizing recently diagnosed patients to one of two kinds of brief individual psychotherapy. The experimental intervention developed for this study is known as the Health Dialogue Intervention (HDI) and was based on the platform of CBT principles of goal setting based on patient priorities, along with an open-ended dialogue about the pros and cons of medication within the context of a developmental narrative.

Methods: Subjects were recruited from the UIC First Episode Psychosis service. Potential subjects entered an initial screening phase with the objectives of stabilization and establishing a research diagnosis. Subjects meeting diagnostic criteria of schizophrenia with 1st psychotic symptom ≤ 5 years ago and willing to be randomized to a course of individual psychotherapy were re-consented. Study interventions consisted of randomization to one of two forms of individual therapy, with up to 15 sessions flexibly delivered in 6 months and a planned maximum of 22 sessions over a maximum of 2 years. The HDI therapists were trained as per Treatment Manual of the CBT for Psychosis Insight program, which was modified to a focus on health related recovery goals that included an adherence interview. The PE intervention consisted of therapists trained in the widely used psychoeducation known as Team Solutions modules modified for first-episode patients and administered in a flexible manner as per therapist judgment. Therapists differed and both received ongoing supervision. The primary outcome was time until 1st medication gap defined as no antipsychotic for ≥ 1 week.

Medication adherence assessment used the All Source Verification (ASV) that integrated multiple sources of adherence information into a single composite score. Secondary outcomes included number of therapy sessions attended, therapeutic alliance, medication adherence attitudes, and symptoms over time.

Results: Between 2009 and 2012, a total of 47 “first-episode” patients entered the diagnostic assessment phase, 34 met criteria for randomization to the psychosocial intervention study. Of those, 18 were randomized to Team Solutions psychoeducation (PE) and 16 to the CBT-based approach (HDI). The mean age was 24 (range: 17 to 43), 68% were men, with schizophrenia N=17 (50%) as the most common diagnosis. All subjects had lifetime exposure to antipsychotic medication for mean of 26.5 weeks (range: 1.4 to 130), and all were prescribed a first-line oral antipsychotic at time of randomization, with none of these variables differing between randomized groups. The mean number of individual psychotherapy sessions was 13.1 (SD 7.4), with significant differences in retention favoring HDI over PE (17.6 vs 9.2 sessions, respectively, $p < .001$). The HDI group stayed on medication longer than the PE group (mean time until first medication gap ≥ 1 week was the

primary outcome), as time until first medication gap, was 46.7 weeks [95%CI 27.3-66.1] compared to 22.5 [95%CI 9.6-35.5] weeks for the PE subjects (Log Rank (Mantel-Cox) chi-square=3.7121, df=1, p=.054).

Conclusion: Medication nonadherence is an enormous challenge in young adults recently diagnosed with schizophrenia. Our preliminary findings are consistent with the hypothesis that psychosocial interventions based on CBT principles are more acceptable than illness-based psychoeducation during the first 5 years, and that moving away from a disease-based orientation may actually facilitate acceptance of antipsychotic medication.

Learning Objectives:

- The presentation will review the background of the problem: the epidemiology of nonadherence to maintenance antipsychotic medication in young adults who have recently been diagnosed with schizophrenia, and the theoretical limitations of standard psychoeducation in addressing the problem in this patient population, as well as the need to consider alternate psychosocial approaches given the relative failure of current psychosocial interventions in addressing the problem.
- We will present new research results from a pilot RCT comparing a course of psychoeducation-based individual psychotherapy with an alternative approach based on a CBT platform.

Literature References:

- Turkington D, Kingdon D, Weiden PJ. Cognitive behavior therapy for schizophrenia. *The American Journal of Psychiatry* 2006;163(3):365-373.
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W51. THE EFFICACY OF LURASIDONE IN IMPROVING COGNITION

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Abstract: Background: Cognitive impairment involving working memory and attention domains are core features of schizophrenia. These deficits significantly impair functionality, medication compliance, and frequent hospitalizations. Addressing the cognitive deficits is crucial to improving long-term treatment outcomes. Lurasidone is an FDA approved novel antipsychotic medication for the treatment of schizophrenia in adults. Animal models have established that lurasidone reverses MK-801-induced memory and learning impairment. Some evidence indicated that the drug at 80mg or higher can improve cognitive outcomes, however, the consensus remains unclear.

Objective: The primary objective of this study is to assess if lurasidone at a dose 80mg or higher improves cognitive measures using the Montreal Cognitive Assessment (MOCA) before and after treatment compared to controls.

Methods: The design is a sample of 20 patients diagnosed with schizophrenia or schizoaffective disorder. They will be randomly selected from two board certified psychiatrists' caseloads at Paradise Valley Hospital/Baview Behavioral Health. Within this group, criteria for selection will include 10 patients who are prescribed Lurasidone at a dose of 80-160 mg. An additional 10 patients will be selected based on receiving a therapeutic dose of other antipsychotic medications and will serve as the control group. Within 48 hours of admission, all subjects will be pretested through administration of the MOCA scale.

MOCA post-test measures will be conducted 3 days after a full therapeutic dose.

Demographic characteristics for all subjects will be collected to include age, sex, compliance/motivation and history of/current positive drug screen.

Analysis: An analysis of the Lurasidone, and the control group will be conducted utilizing a One-Way ANOVA with subsequent Independent T-tests to determine differences between means. Primary analysis will use MOCA Total Scores as the dependent variable. A secondary analysis will be conducted using MOCA subtest scores to determine trends within overall cognitive functioning.

Results: The results from the study could provide some signal and direction for addressing the cognitive deficits in patients with schizophrenia.

Learning Objectives:

- To better understand cognitive deficits in patients with schizophrenia.
- Further understanding of the role that novel antipsychotics have on cognition of patients with schizophrenia and schizoaffective disorder.

Literature References:

- Bowie, C, Harvey, P: Cognitive Deficits and functional outcome in schizophrenia. *Neuropsychiatric Disease and Treatment*, 2006; 4:531-536.
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W52. OLFACTORY DEFICITS IN 22Q11.2 DELETION SYNDROME ARE SIGNIFICANT COMPARED TO NON-DELETED INDIVIDUALS WITH CLINICAL RISK AND SCHIZOPHRENIA

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Abstract: Background: 22q11.2 deletion syndrome (22q11DS) is an important model of genetic risk for psychosis and affects genes regulating dopamine and craniofacial development. Olfactory deficits are well established in schizophrenia, and implicate both dopaminergic pathways and embryonic development. Few studies have examined olfactory function in 22q11DS. This is the first to include psychosis-spectrum controls.

Methods: Olfactory identification, discrimination, and detection sensitivity were assessed in 22q11DS (n=31) and compared to non-deleted controls at low risk (LR; n=77), clinical risk for psychosis (CR; n=50), and schizophrenia (SZ; n=42). Age affected odor identification and discrimination and was regressed out of both measures prior to analyzes. Scores were normalized to controls for intuitive comparison. The Structured Interview for Prodromal Syndromes was administered to assess psychosis spectrum symptoms.

Results: Olfactory identification (p=0.004) and discrimination (p=0.0001) were impaired in 22q11DS, CR, and SZ compared to LR. There were no significant differences between CR (mean = -0.6 for both identification and discrimination) and SZ (mean = -0.4 for both identification and discrimination), but 22q11DS (means: identification=-1.0; discrimination=-1.2) performed worse than SZ. All three clinical groups exhibited impaired sensitivity to the odorant lylal, but only 22q11DS additionally showed impaired sensitivity to citralva. Odor discrimination deficits were related to increased negative symptoms in the overall sample (p=0.01) and within 22q11DS (p=0.03).

Conclusions: Individuals with 22q11DS experience significant impairment in olfactory identification, discrimination, and sensitivity. Deficits are more pronounced than those of non-deleted individuals with clinical risk and schizophrenia, and may reflect more diffuse involvement of olfactory structures and pathways.

Learning Objectives:

- Demonstrate olfactory deficits in individuals with 22q11.2 deletion syndrome.
- Compare deficits to individuals without genetic deletion but meet criteria for schizophrenia or have subthreshold psychosis symptoms.

Literature References:

- Kamath V, Turetsky BI, Calkins ME, Kohler CG, Conroy CG, Borgmann-Winter K, Gatto DE, Gur RE, Moberg PJ: Olfactory processing in schizophrenia, non-ill first degree family members and young people at-risk for psychosis. *World Journal of Biological Psychiatry* 2014; 15:209-218.
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W53. MAINTENANCE ELECTROCONVULSIVE THERAPY (ECT) FOR CLOZAPINE-RESISTANT SCHIZOPHRENIA

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Abstract: Background: Clozapine is indicated for the treatment of medication-resistant schizophrenia. Nonetheless, up to 70% of patients who tolerate an adequate trial of clozapine fail to benefit from or partially respond to this drug. Historically, response to clozapine is defined as 20 or 30% reduction in the 4 psychosis items (delusions, hallucinations, disorganization and paranoia) in the Brief Psychiatric Rating Scale (BPRS-PS). In a randomized, controlled, single-blind, NIMH-sponsored study we evaluated the efficacy of electroconvulsive therapy (ECT) as an augmentation strategy for the treatment of clozapine-resistant schizophrenia. Patients with schizophrenia on stable clozapine dose with serum levels > 250 meq/ml for at least 8 weeks, with persistent psychotic symptoms (> 12 in the BPRS-PS) and no current mood symptoms were included in the acute phase. Patients were randomized to receive 8 weeks of ECT in addition to clozapine or to continue with clozapine for 8 weeks. Patients in the pharmacotherapy arm, who did not respond after 8 weeks, crossed over to the ECT arm and received the combination treatment for another 8 weeks. Using as response criterion 40% reduction in the BPRS-PS, we reported response rates of 50% in the single blinded phase and 48% in the cross-over phase of the study. We report here the results for the open-label follow-up study with maintenance ECT for up to 6 months.

Methods Patients who completed either the blinded or open label phases of the above mentioned study and met the a priori set response criterion of 40% reduction in the BPRS psychosis subscale (BPRS-PS) were included in the study. The continuation phase lasted for up to 24 weeks during which patients received bilateral ECT with the same treatment parameters as in the acute phase. We followed a tapered schedule of 4 weekly ECT, followed by 4 ECT every 2 weeks and 2 monthly ECT for a total of 10 treatments in 6 months. Medications, including clozapine, remained the same as in the acute phase. Psychopathology ratings were performed at baseline (end of acute phase) before each ECT and at the end of the study.

Results: Nineteen patients who met the aforementioned response criteria were offered maintenance ECT for up to 6 months. Thirteen patients agreed to participate. For these patients the mean BPRS-PS was 16.0 (+ 6.94) before the acute course of ECT. Their mean BPRS-PS at maintenance baseline was 7.69 (+ 3.66) and at the end of the study 9.2 (+ 4.32). Six of the 13 patients (46.1%) completed the 6-month study (10 maintenance ECT). Seven patients (53.9%) received maintenance treatments for 1- 2 months (4-7 maintenance treatments, but opted to discontinue before the completion of 6 months. None of the 13 patients had relapsed at the time they exited the study. For those who completed the 6-month period the mean BPRS-PS was 7.83 (+ 3.6) at baseline and 7.66 (+ 2.48) at the exit. For those who received 4-7 maintenance ECT BPRS-P was 8.0 (+ 3. 83) at baseline and 8.5 (+3.96) at the exit. All 7 patients who received maintenance ECT for less than 6 months stated that they felt well and there was no further need for ECT, or could not continue for practical reasons (mostly lack of social support as outpatients). No patient discontinued the treatment because of side effects or worsening of psychotic symptoms.

Learning Objectives:

- To understand the role of ECT as an augmentation strategy in clozapine-resistant schizophrenia.
- To understand the role of maintenance treatments for relapse prevention in clozapine resistant schizophrenia.

Literature References:

- Petrides G, Malur C, Braga RJ, Bailine SH, Schooler NR, Malhotra AK, Kane JM, Sanghani S, Goldberg TE, John M, Mendelowitz A. Electroconvulsive Therapy Augmentation in Clozapine-Resistant Schizophrenia: A Prospective, Randomized Study. *Am J Psychiatry*. *Am J Psychiatry* 172:1, January 2015 52-58. doi: 10.1176/appi.ajp.2014.13060787.

W54. METABOLIC SYNDROME IN PATIENTS WITH SCHIZOPHRENIA RECEIVING LONG-TERM TREATMENT WITH LURASIDONE, QUETIAPINE XR, OR RISPERIDONE

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Abstract: Introduction: Patients with schizophrenia are at high risk for developing metabolic syndrome, which may be exacerbated by treatment with antipsychotic agents. Lurasidone has demonstrated low propensity for metabolic disturbance in adult patients with schizophrenia in short-term, 6-week studies. This analysis evaluated metabolic syndrome occurrence during long-term treatment of schizophrenia with lurasidone or other antipsychotic agents.

Methods: Metabolic syndrome rates (as defined by the US National Cholesterol Education Program-Adult Treatment Panel III without using drug treatment criteria) were evaluated in adult patients with schizophrenia treated with lurasidone in 2 long-term, active-controlled studies (quetiapine XR or risperidone). In the quetiapine XR-controlled study, patients completing a 6-week, double-blind, placebo-controlled, fixed-dose trial of lurasidone (80 mg/d or 160 mg/d) or quetiapine XR (600 mg/d) continued on double-blind, flexibly dosed lurasidone (40-160 mg/d) or quetiapine XR (200-800 mg/d) for up to 12 months. In the risperidone-controlled study, patients received double-blind, flexibly dosed lurasidone (40-120 mg/d) or risperidone (2-6 mg/d) for up to 12 months.

Results: Among patients without metabolic syndrome at baseline in the quetiapine XR-controlled study, 2.4% (2/84) of patients treated with lurasidone and 7.4% (2/27) of patients treated with quetiapine XR developed metabolic syndrome at month 12 (P=NS). Of patients without metabolic syndrome at baseline in the risperidone-controlled study, 10.3% (12/117) of patients treated with lurasidone and 23.2% (16/69) of patients treated with risperidone developed metabolic syndrome at month 12 (P=0.02).

Conclusion: Long-term treatment with lurasidone was associated with lower rates of metabolic syndrome in patients with schizophrenia compared with treatment with quetiapine XR or risperidone.

ClinicalTrials.gov identifiers: NCT00789698 and NCT00641745.

Sponsored by Sunovion Pharmaceuticals Inc.

Learning Objectives:

- Evaluate the effect of long-term treatment with lurasidone on metabolic syndrome in patients with schizophrenia.
- Compare the rates of metabolic syndrome in patients with schizophrenia receiving long-term treatment with lurasidone, quetiapine XR, or risperidone.

Literature References:

- Mitchell AJ, Vancampfort D, Sweers K, van Winkel R, Yu W, De Hert M. Prevalence of metabolic syndrome and metabolic abnormalities in schizophrenia and related disorders: a systematic review and meta-analysis. *Schizophr Bull* 2013; 39:306-318
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W55. EFFECTS OF PALIPERIDONE PALMITATE 3-MONTH AND 1-MONTH FORMULATIONS ON PERSONAL AND SOCIAL PERFORMANCE SCALE DOMAIN SCORES IN PATIENTS WITH SCHIZOPHRENIA

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Abstract: Purpose: Evaluate treatment effect of paliperidone palmitate 3-month (PP3M) vs paliperidone palmitate 1-month (PP1M) on functional status of patients with schizophrenia as measured by the change in Personal and Social Performance (PSP) scale score during a long-term, randomized, multicenter, double-blind (DB) noninferiority study (NCT01515423).

Content: Improving patient function is a long-term treatment goal for patients with schizophrenia. This analysis evaluates the impact of treatment with PP3M or PP1M on total PSP total scores and on individual PSP domains.

Methodology: Subjects with schizophrenia were treated with PP1M in a 17-week open-label (OL) phase. Upon meeting clinical stabilization criteria, patients were randomized 1:1 to PP3M or PP1M in a 48-week, DB, relapse-prevention phase. The modified intent-to-treat (DB) analysis set included 995 patients (PP3M, n=483; PP1M, n=512). Functioning was evaluated using the PSP scale (4 domains: socially useful activities, personal/social relationships, self-care, and disturbing/aggressive behaviors). PSP total score (based on domain assessments) was scored from 1–100; scores >70 indicate good functioning. Each PSP domain was assessed on a 6-point severity scale, with 1=absent and 6=very severe. Categorical changes from OL baseline (BL) in PSP scores were examined using McNemar's test. Comparisons of PSP domain scores in the DB period were conducted using a chi-square test. No adjustments were made for multiplicity.

Results: At OL BL, the mean (SD) PSP total score was 53.5 (12.20). During the OL phase, mean (SD) PSP total scores increased from OL BL to OL endpoint (DB baseline) by 11.6 (10.5) points with PP1M treatment. Mean (SD) change in PSP total score from DB BL to DB endpoint showed a similar improvement for PP3M (1.3 [10.22]) and PP1M (1.9 [9.21]). A shift in PSP category scores was observed during OL PP1M treatment, with the proportion of subjects with good functioning (>70) increasing from 5.1% at OL BL to 27.9% at OL endpoint (P<0.001). In the DB phase, the proportion of patients with good functioning (>70) in the PP3M and PP1M groups was similar at DB BL (28.8% and 27.1%; P=0.567) and increased similarly at DB endpoint (37.8% and 37.8%; P=0.996). PSP domain scores showed substantial levels of dysfunction in all 4 domains at OL BL, particularly in socially useful activities and personal/social relationships. Improvements in each domain were observed from OL BL to OL endpoint (DB BL) in the proportion of patients with absent/mild dysfunction in socially useful activities (12.6%–37.1%), personal/social relationships (12.8%–43.3%), self-care (68.7%–87.4%), and disturbing/aggressive behaviors (88.1%–99.0%) (P<0.001, all domains). In the DB phase, improvements in self-care and

disturbing/aggressive behavior were maintained in both PP3M and PP1M groups. Further improvements in socially useful activities and personal/social relationships were observed at DB endpoint with numerically similar improvements for the PP3M and PP1M groups: socially useful activities (PP3M, 47.0%; PP1M, 45.9%) and personal and social relationships (PP3M, 51.7%; PP1M, 52.3%).

Importance: Overall functioning as measured by the PSP scale improved during OL treatment and remained stable during DB treatment with no significant difference between PP3M and PP1M. The improvement observed in all 4 PSP domains support the value of continued administration of long-acting injectable antipsychotic medication.

Learning Objectives:

- Understand the treatment effect of paliperidone palmitate long-acting injectables on the functional status of patients with schizophrenia as measured by the change in PSP score.
- Understand the treatment effects of PP3M vs PP1M on each functioning domain of the PSP scale.

Literature References:

- Berwaerts J, Liu Y, Gopal S, Nuamah I, Xu H, Savitz A, Coppola D, Schotte A, Remmerie B, Maruta N, Hough DW. Efficacy and safety of the 3-month formulation of paliperidone palmitate vs placebo for relapse prevention of schizophrenia: a randomized clinical trial. *JAMA Psychiatry* 2015;72(8):830-839.
- Nasrallah H, Morosini P, Gagnon DD. Reliability, validity and ability to detect change of the Personal and Social Performance scale in patients with stable schizophrenia. *Psychiatry Res* 2008;161:213-224.

W56. EFFICACY OF CARIPRAZINE IN NEGATIVE, COGNITIVE, AND SOCIAL FUNCTION SYMPTOMS IN SCHIZOPHRENIA: A POST HOC ANALYSIS OF A RANDOMIZED, CONTROLLED TRIAL

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Abstract: Introduction: Antipsychotics are generally effective in treating the positive symptoms of schizophrenia, but negative symptoms and cognitive deficits are difficult to treat and may contribute to poor social functioning. Cariprazine, a potent dopamine D2/D3 receptor partial agonist with preferential binding to D3 receptors, is approved for the treatment of schizophrenia. It has shown efficacy in a broad range of schizophrenia symptoms in clinical trials. This post hoc analysis of a Phase 3 placebo- and active-controlled trial (NCT01104766) evaluated cariprazine on Positive and Negative Syndrome Scale (PANSS)-derived subscales related to negative symptoms, cognition, and social functioning in patients with acute exacerbation of schizophrenia.

Methods: A total of 604 patients were randomized to 6 weeks of double-blind treatment (placebo=149, cariprazine 3 mg/d=151, cariprazine 6 mg/d=154, aripiprazole 10 mg/d=150). Efficacy was analyzed using change from baseline in PANSS negative subscale score and PANSS-derived cognitive (P2, N5, N7, G10, G11) and prosocial (P3, P6, N2, N4, N7, G16) factor scores.

Results: The least squares mean difference (LSMD) was statistically significant in favor of cariprazine over placebo in PANSS negative (3 mg/d=-1.4 [95% CI: -2.4, -0.4], P=.0068; 6 mg/d=-1.7 [95% CI: -2.7, -0.7], P=.0009), cognitive (3 mg/d=-1.2 [95% CI: -1.9, -0.5], P=.0005; 6 mg/d=-1.2 [95% CI: -1.9, -0.6], P=.0004), and prosocial (3 mg/d=-1.4 [95% CI: -2.5, -0.4], P=.0070; 6 mg/d=-2.2 [95% CI: -3.2, -1.1], P<.0001) scores. In PANSS negative score, significant improvement was seen for both cariprazine doses versus placebo by Week 1 (P<.05). In PANSS cognitive score, significant improvement was seen by Week 2 for cariprazine 6 mg/d (P<.05) and Week 3 for 3 mg/d (P<.01). In PANSS prosocial score, significant improvement was seen by Week 1 for cariprazine 6 mg/d and Week 3 for 3 mg/d (P<.05 for both). Early significant differences from placebo for both cariprazine doses on PANSS negative, cognitive, and prosocial scores were maintained through Week 6. LSMDs for aripiprazole versus placebo were statistically significant on PANSS negative (-1.2 [95% CI: -2.2, -0.2], P=.0152), cognitive (LSMD=-1.0 [95% CI: -1.6, -0.3], P=.0047), and prosocial (LSMD=-1.3 [95% CI: -2.4, -0.3], P=.0099) scores. Significant improvement was seen by Week 3 on PANSS cognitive scores (P<.001) and by Week 2 on negative (P<.05) and prosocial (P<.01) scores; significant differences were maintained through Week 6.

Conclusion: Cariprazine 3 and 6 mg/d versus placebo demonstrated significant and sustained efficacy within 1 to 3 weeks of treatment initiation across PANSS negative, cognitive, and prosocial domains. Results suggest that cariprazine may be beneficial in improving negative and cognitive symptoms as well as social functioning in patients with acute exacerbation of schizophrenia.

Learning Objectives:

- At the conclusion of this session, participants should be able to identify several difficult-to-treat symptom domains that are associated with the clinical presentation of schizophrenia.
- At the conclusion of this session, participants should know that cariprazine demonstrated significant and sustained efficacy when compared with placebo across negative, cognitive, and prosocial symptom domains in patients with schizophrenia.

Literature References:

- Durgam S, Cutler AJ, Lu K, Migliore R, Ruth A, Laszlovszky I, Németh G, Meltzer HY: Cariprazine in acute exacerbation of schizophrenia: A fixed-dose, phase III randomized, double-blind, placebo- and active-controlled trial. *J Clin Psychiatry* 2015; 76:e1574-1582
- Citrome L: Cariprazine in schizophrenia: clinical efficacy, tolerability, and place in therapy. *Adv Ther* 2013; 30:114-126

W57. RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PHASE 3 STUDY OF ENCENICLINE AS PRO-COGNITIVE TREATMENT IN PATIENTS WITH SCHIZOPHRENIA ON CHRONIC STABLE ATYPICAL ANTIPSYCHOTIC THERAPY

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Abstract: Background: Patients with schizophrenia suffer from cognitive impairments [1], which significantly affect quality of life, even when positive and negative symptoms are optimally treated. Encenicline is a selective $\alpha 7$ nicotinic receptor agonist. Phase 2 studies

were positive, leading to two follow-up Phase 3 studies [2]. The primary objective of this Phase 3 study was to assess the efficacy and safety of once-daily encenicline tablets as a pro-cognitive treatment versus placebo in stable patients with schizophrenia.

Methods: NCT01716975 was a randomized, double-blind, placebo-controlled, parallel-dosing, 26-week, Phase 3 study to evaluate the efficacy and safety of once-daily encenicline tablets (0.9 and 1.8 mg) versus placebo. Eligible male and female subjects aged 18–50 years with a diagnosis of schizophrenia of at least 3 years' duration were assigned to treatment in a 1:1:1 ratio, after successful completion of a 14-day single-blind placebo run-in period. The co-primary efficacy endpoints were cognitive function, as measured by the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB) Neurocognitive Composite Score, and patient function, as measured by the interview-based Schizophrenia Cognition Rating Scale (SCoRS). Both tests were administered during the screening visit (Day -14, which preceded the placebo run-in period), and on Days 1 (pre-dose), 28, 56, 84, and 182. The Day 1 MCCB and SCoRS scores represent the baseline for each of the efficacy evaluations. Safety and tolerability were determined by clinical and laboratory assessments.

Results: 1147 subjects were screened and 766 subjects were randomized; 46.2% of subjects were enrolled from sites located in the United States. The effects of encenicline versus placebo on cognition (as measured by the MCCB Neurocognitive Composite Score) and function (as measured by SCoRS), as well as safety and tolerability results, will be presented.

Learning Objectives:

- To review the efficacy, determined by improved cognition and patient function, of two doses of once-daily encenicline as a pro-cognitive treatment when added to chronic, stable atypical antipsychotic therapy in subjects with schizophrenia in the NCT01716975 study.
- To understand the safety and tolerability of encenicline as a pro-cognitive treatment when added to chronic, stable atypical antipsychotic therapy in subjects with schizophrenia.

Literature References:

- Kraus MS, Keefe RS: Cognition as an outcome measure in schizophrenia. *Br J Psych* 2007;50(Suppl):s46-51.
- Keefe RS, et al: Randomized, double-blind, placebo-controlled study of encenicline, an $\alpha 7$ nicotinic acetylcholine receptor agonist, as a treatment for cognitive impairment in schizophrenia. *Neuropsychopharmacology* 2015;40:3053-3060.

W58. LONG-TERM CARIPRAZINE TREATMENT FOR THE PREVENTION OF RELAPSE IN PATIENTS WITH SCHIZOPHRENIA: ANALYSIS OF ADDITIONAL EFFICACY OUTCOMES

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Abstract: Introduction: Cariprazine, a potent dopamine D3/D2 receptor partial agonist that binds preferentially to D3 receptors, is approved for the treatment of schizophrenia. Cariprazine has demonstrated efficacy in 6-week, randomized, placebo-controlled trials in

patients with acute exacerbation of schizophrenia. This study was conducted to evaluate the efficacy, safety, and tolerability of cariprazine versus placebo in the prevention of relapse in patients with schizophrenia (NCT01412060).

Methods: This was a multinational, randomized, double-blind, placebo-controlled, parallel-group study in adult patients with schizophrenia. Schizophrenia symptoms were stabilized during 2 open-label phases: an 8-week, flexible-dose, run-in phase and a 12-week, fixed-dose, stabilization phase with cariprazine (3-9 mg/d). Patients completing the 20-week open-label treatment phases were randomized to continue cariprazine (3, 6, or 9 mg/d) or switch to placebo for up to 72 weeks of double-blind treatment. The primary efficacy parameter was time to relapse, defined as worsening of symptom scores, psychiatric hospitalization, aggressive/violent behavior, or suicidal risk. Additional efficacy parameters included score changes in Positive and Negative Syndrome Scale (PANSS; total and subscales), Clinical Global Impression-Severity (CGI-S), Negative Symptom Assessment (NSA-16), and Personal and Social Performance Scale (PSP).

Results: A total of 264/765 (35%) patients completed open-label treatment; mean improvements from baseline were observed in PANSS total (-22.8), PANSS Positive subscale (-7.4), PANSS Negative subscale (-4.9), CGI-S (-1.1), NSA-16 (-8.2), and PSP (+11.1) scores. At the end of open-label treatment, 200 patients met eligibility criteria and were randomized to double-blind treatment with placebo (n=99) or cariprazine (n=101). The time to relapse was significantly longer in patients who continued cariprazine than in patients who switched to placebo ($P=.0010$, log-rank test). Relapse occurred in nearly twice as many placebo- (47.5%) as cariprazine-treated (24.8%) patients; the hazard ratio [95% CI] was 0.45 [0.28, 0.73]. At the end of the double-blind treatment period, a greater mean worsening of symptoms was seen in placebo- versus cariprazine-treated patients on all efficacy parameters: PANSS total (+13.2 vs +5.0), PANSS Positive subscale (+4.3 vs +1.3), PANSS Negative subscale (+2.4 vs +1.4), CGI-S (+0.7 vs +0.1), NSA-16 (+4.1 vs +0.6), and PSP score (-7.2 vs 0.0).

Conclusion: Long-term cariprazine treatment was significantly more effective than placebo for the prevention of relapse in patients with schizophrenia. Mean change in scores on additional efficacy parameters suggested improvement of symptoms during open-label cariprazine treatment; during the subsequent double-blind treatment period, patients randomized to cariprazine experienced less worsening of symptoms than placebo-treated patients.

Learning Objectives:

- At the conclusion of this session, participants should recognize the importance of effective long-term maintenance treatment in patients with schizophrenia.
- At the conclusion of this session, participants should know that cariprazine was significantly better than placebo in preventing relapse in patients with schizophrenia.

Literature References:

- Citrome L: Cariprazine in schizophrenia: clinical efficacy, tolerability, and place in therapy. *Adv Ther* 2013; 30:114-126
- Leucht S, Tardy M, Komossa K, Heres S, Kissling W, Salanti G, Davis JM: Antipsychotic drugs versus placebo for relapse prevention in schizophrenia: a systematic review and meta-analysis. *Lancet* 2012; 379:2063-2071

W59. THE EFFECT OF TROPISETRON ON THE IMPROVEMENT OF P50 DEFICITS AND ASPECTS OF COGNITIVE PERFORMANCE IN PATIENTS WITH SCHIZOPHRENIA

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Abstract: Background: Cognitive impairment is an import target for treatment due to the prime cause of significant disabilities in schizophrenia. However, current treatment has minimal effect on the improvement of cognitive function in schizophrenia (Kantak et al., 20011). $\alpha 7$ nicotinic acetylcholine receptor is associated with cognitive and auditory P50 gating deficits in schizophrenia (Olincy et al., 2007) and $\alpha 7$ nAChR agonists can potentially reverse these deficits. Tropisetron is a high-affinity partial agonist of the $\alpha 7$ nAChR . Our study is to test the effect of Tropisetron on the improvement of P50 deficits and aspects of cognitive performance in nonsmoking patients with schizophrenia.

Methods: A. Patient and Healthy control groups: 1). Patient group: a total of 200 first-episode and drug-naïve patients with schizophrenia were enrolled. Subjects were randomly assigned to a fixed titration of tropisetron (10 mg/day) plus risperidone (n=100) or placebo plus risperidone (n=100) in a 12-week double-blind trial. 2). Control groups: 405 psychiatrically and medically healthy controls, matched to patients for sex, age and educational levels have completed the MATRICS (Measurement and Treatment Research to Improve Cognition in Schizophrenia) and P50 gating testing. B. Positive and Negative Syndrome Scale (PANSS), the MATRICS Cognitive Battery, and nicotine Dependence (ND), including weekly self-reported number of cigarettes/day, and the Fagerstrom test for ND (FTND), as well as P50 gating test were measured.

Results: The results showed that tropisetron improved the negative subscore and the PANSS total score at week 6 and week 12, as well as P50 and some aspects of cognitive deficits at week 12 in schizophrenic patients. Furthermore, administration of tropisetron significantly decreased the number of cigarettes smoked per day and the FTND score in these patients .

Discussion/Significance: Cognitive dysfunction is a major problem in schizophrenia. Current psychotropic medications including novel antipsychotics appear more focusing on the treatment of positive symptoms and there is very little data shown the improvement of cognitive function. Our data has shown the effectiveness of tropisetron significantly improved overall cognitive deficits in schizophrenic patients. It should also be noticed that the improvement of cognitive function is limited to certain functions. Some deficits of cognitive function is more persistent, which needs further studies

Learning Objectives:

- Understand the effect of administration of tropisetron on the cognitive deficits in schizophrenic patients.
- Understand that the administration of tropisetron significantly decreased the number of cigarettes smoked per day and the FTND score in schizophrenic patients.

Literature References:

- Kantak KM, Hofman SG. Cognitive Enhancers for the Treatment of Neuropsychiatric Disorders: Clinical and Preclinical Investigations. *Pharmacol Biochem Behav.* 2011 Aug;99(2):113-115.
- Olincy A, Stevens KE: Treating schizophrenia symptoms with an alpha7 nicotinic agonist, from mice to men. *Biochem Pharmacol.* 2007 Oct 15; 74(8): 1192–1201.

W60. PSYCHOPHARMACOLOGICAL TREATMENT OF SEVERELY AGGRESSIVE INPATIENTS IN A STATE PSYCHIATRIC HOSPITAL

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Abstract: Violent behaviors of severely mentally ill inpatients interfere with treatment, endanger staff, and are a barrier to discharge. Thus, finding effective treatments for these behaviors is highly important. As violence and aggression are not considered psychiatric conditions, there are no medications with FDA indications for their treatment. However, psychotropic medications are frequently used in combination to manage these behaviors in psychiatric inpatients, and the neurobiology of violence involving several neurotransmitter systems supports this practice. A small percentage of psychiatric inpatients have been shown to be responsible for a large percentage of violent episodes in psychiatric hospitals. In this study, we examined the medication regimens used in the treatment of such severely aggressive inpatients in a state-run psychiatric hospital via a retrospective chart review. Patients with more than two violent episodes (16% of the patients, responsible for 89% of assaults) were identified and characterized based on diagnostic information and demographic information. Their medication regimens were recorded and compared. Weekly number of violent episodes leading to seclusion or restraint and weekly average scores on the Modified Overt Aggression Scale (MOAS) and the Nurses' Observation Scale for In-patient Evaluation (NOSIE) for these patients were used to demonstrate the trajectory and timeline of changes in violence and hostility during the inpatient stays of this severely aggressive cohort of patients. There was widespread use of typical and atypical antipsychotics, mood stabilizers, benzodiazepines, non-benzodiazepine anxiolytics, and antidepressants for various diagnoses in this cohort. The most common list of medications administered included a typical and atypical antipsychotic, a mood stabilizer, and a benzodiazepine (26% of the cohort). The second most common list was this combination plus a non-benzodiazepine anxiolytic (16% of the cohort). The third most common was the same as the most common with the addition of an antidepressant (7% of the cohort). Results of this study indicate that current clinical practice endorses the use of a combination of antipsychotics, mood stabilizers, and benzodiazepines for aggression. Prospective comparisons of these regimens for the indication of aggression and violence are needed to further inform clinical care.

Learning Objectives:

- Describe medication regimens of severely aggressive inpatients in a state-run psychiatric hospital.
- Characterize severely aggressive inpatients diagnostically and demographically.

Literature References:

- Mauri MC, Rovera C, Paletta S, De Gaspari IF, Maffini M, Altamura AC: Aggression and psychopharmacological treatments in major psychosis and personality disorders during hospitalisation. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 2011; 35:1631–1635
- Comai S, Tau M, Pavlovic Z, Gobbi G: The Psychopharmacology of Aggressive Behavior. *J Clin Psychopharmacol* 2012; 32:237–260

W61. PALIPERIDONE PALMITATE 3-MONTHLY VS. 1-MONTHLY INJECTABLE IN SCHIZOPHRENIA PATIENTS WITH OR WITHOUT PRIOR EXPOSURE TO ORAL RISPERIDONE OR PALIPERIDONE

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Abstract: Purpose: A post-hoc subgroup analysis was performed to compare outcomes following administration of paliperidone palmitate 3-monthly (PP3M) versus 1-monthly (PP1M) injectable in patients with schizophrenia previously treated/not treated with oral risperidone/paliperidone (RIS/PALI) before study entry.

Methods: Patients received PP1M (50, 75, 100, or 150 mg eq.) during 17-week open-label (OL) phase, randomized (1:1) to PP3M (175, 263, 350, or 525 mg eq.) or PP1M (50, 75, 100, or 150 mg eq.) during 48-week double-blind (DB) phase. Based on prior RIS/PALI exposure, outcomes were compared between two subgroups: recent=at least 28 days of RIS/PALI exposure with last dose within 14 days before study entry; no=no RIS/PALI exposure within 60 days before study entry.

Results: 452 patients had received recent RIS/PALI (n=323 [71%]) randomized to PP3M=166; PP1M=157), and 709 did not receive RIS/PALI (n=506 [71%]) randomized to PP3M=254; PP1M=252). Improvements in PANSS scores following OL PP1M were similar in recent RIS/PALI (mean [SD] of -18.3 [17.96]) and no prior RIS/PALI (-21.1 [16.40]) subgroups at OL endpoint. Relapse-free rates during DB phase were comparable across recent RIS/PALI (PP3M: 89.7%; PP1M: 87.1%, 95% CI for difference: [-4.7; 10.0]) and no RIS/PALI subgroups (PP3M: 91.6%; PP1M: 90.8%, 95% CI for difference: [-4.5; 6.0]). Incidences of extrapyramidal symptom-related adverse events were: recent RIS/PALI (OL PP1M:12.4%; DB: PP3M:7.8% vs. PP1M:7.0%) and no RIS/PALI (OL PP1M: 11.4%; DB: PP3M: 7.1% vs. PP1M: 6.7%).

Conclusion: This exploratory analysis suggests comparable treatment outcomes and tolerability following PP3M or PP1M administration in patients with schizophrenia, irrespective of prior treatment with/without oral RIS/PALI.

Learning Objectives:

- This post hoc analysis will provide insights into the treatment outcomes and safety profile following administration of PP1M vs. PP3M long acting injectable in patients with schizophrenia who had been pretreated with oral risperidone or paliperidone.
- The results will help the clinicians and psychiatrists in clinical decision making while using this formulation in patient population with prior exposure to risperidone or paliperidone.

Literature References:

- Gopal S, Vermeulen A, Nandy P, Ravenstijn P, Nuamah I, Buron Vidal JA, Berwaerts J, Savitz A, Hough D, Samtani MN. Practical guidance for dosing and switching from paliperidone palmitate 1 monthly to 3 monthly formulation in schizophrenia. Current medical research and opinion. 2015 Nov 2;31(11):2043-54.
- Berwaerts J, Liu Y, Gopal S, Nuamah I, Xu H, Savitz A, Coppola D, Schotte A, Remmerie B, Maruta N, Hough DW. Efficacy and Safety of the 3-Month Formulation of Paliperidone Palmitate vs Placebo for Relapse Prevention of Schizophrenia: A Randomized Clinical Trial. JAMA psychiatry. 2015 Mar 29.

W62. PHASE 2 STUDY OF BREMELANOTIDE IN PREMENOPAUSAL WOMEN WITH FEMALE SEXUAL DYSFUNCTIONS: RESPONDER ANALYSES BASED ON MINIMUM CLINICALLY IMPORTANT DIFFERENCES DERIVED FROM RECEIVER OPERATING CHARACTERISTIC CURVES

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Abstract: Background: Bremelanotide (BMT) is a novel cyclic heptapeptide known to act as a melanocortin-receptor-4 agonist and is in development to treat women with female sexual dysfunctions (FSDs).

Objectives: Post hoc responder analyses using receiver operating characteristic (ROC) curves were conducted to evaluate key efficacy outcomes in a large phase 2 study of BMT in premenopausal women with FSDs. The 5 key efficacy endpoints included the 4-week number of satisfying sexual events (SSEs), the total score and desire subscore on the Female Sexual Function Index (FSFI), and the total score and desire subscore on the Female Sexual Distress Scale–Desire/Arousal/Orgasm (FSDS-DAO).

Material and Methods: All patients were premenopausal, nonpregnant women ≥ 21 years old with hypoactive sexual desire disorder, female sexual arousal disorder, or both. Patients completing a 4-week baseline period of single-blinded subcutaneous (SC) placebo self-administration were then randomized to a 12-week treatment period of double-blind SC placebo or BMT 0.75-, 1.25-, or 1.75-mg dose for at-home, as-needed self-administration. The change from baseline to the end of the study of the key efficacy endpoints were calculated from patient responses to a questionnaire, which included an item asking: “To what degree do you think you benefited from taking the study drug?” The questionnaire used a 7-point Likert scale with choices ranging from 1 (“very much worse”) to 4 (“no change”) to 7 (“very much better”). A rating of 5 to 7 indicated a responder (i.e., patient-reported global benefit).

The minimum clinically important difference (MCID) was computed as the value simultaneously maximizing the endpoint’s sensitivity and specificity for predicting a rating of 5 to 7 using an ROC curve for each of the 5 efficacy endpoints. The MCIDs were the anchors for the responder analyses.

Results: Responses from 327 patients provided data (for SSEs, n=324). The computed MCIDs were +1.0 for number of SSEs, +2.1 for FSFI total score, +0.6 for FSFI desire subscore, –7.0 for FSDS-DAO total score, and –1.0 for FSDS-DAO desire subscore. Using these cut-offs, the SSE responder rate was 37% for placebo versus 38%, 48%, and 55% for BMT 0.75, 1.25, and 1.75 mg, respectively. The FSFI responder rate was 46% versus 45%, 61%, and 69%, respectively, for total score and 53% versus 46%, 60%, and 77%, respectively, for the FSFI desire subscore. The FSDS-DAO responder rate was 45% versus 49%, 60%, and 69%, respectively, for total score and 45% versus 48%, 57%, and 72%, respectively, for FSDS-DAO distress subscore. For all 5 endpoints, the difference from placebo was statistically significant for the BMT 1.75-mg dose ($P < 0.05$, Cochran-Mantel-Haenszel test).

Conclusions: There was a dose-dependent increase in responder rates of patients who self-administered SC BMT. The MCIDs for multiple FSD measures, which are widely used and clinically relevant, attained statistical significance in patients who self-administered the BMT 1.75-mg dose compared with placebo. Phase 3 studies to further evaluate SC BMT for the treatment of premenopausal women with FSD are in progress (ClinicalTrials.gov identifiers NCT02338960 and NCT02333071).

Study supported by: Palatin Technologies, Inc.

W63. HEMODYNAMIC AND PHARMACOKINETIC INTERACTIONS OF INTRANASAL BREMELANOTIDE AND ETHANOL IN A PHASE 1, RANDOMIZED, PLACEBO-CONTROLLED, DOUBLE-BLIND, THREE-PERIOD, THREE-WAY CROSSOVER STUDY

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¹Palatin Technologies, Inc., ²University of Virginia, Charlottesville, VA, ³Maryland Center for Sexual Health

Abstract: Objectives: A phase 1 study of bremelanotide (BMT) to evaluate the safety and tolerability of BMT when co-administered with ethanol in healthy participants.

Materials and Methods: A randomized, placebo-controlled, double-blind, three period, three-way crossover study was employed. After meeting the inclusion/exclusion criteria, participants were enrolled and received BMT or placebo with or without ethanol at the research facility for 7 consecutive days. Participants were randomized to one of six treatment paths: intranasal, single doses of 20 mg BMT or placebo administered with or without 0.6 g/kg ethanol on day 1, 4, and 7. The intranasal, 20-mg dose of BMT has an exposure equivalent to approximately 1 to 2 times the subcutaneous dose currently being evaluated in a phase 3 study. The hemodynamic effect of co-administration of BMT and ethanol was examined using orthostatic vital sign checks. At baseline and on day 7 a physical examination and a resting 12-lead ECG were performed. Vital signs, self-rated sedation scores, nursing and medical observations, and spontaneous reporting by participants provided the basis for evaluation of adverse events (AEs). Pharmacokinetic evaluation included collection of blood samples at designated time points. Blood and urine were obtained for clinical safety laboratory tests.

Results: Twenty-four participants were enrolled and all completed the study (12 men; 12 women). The intranasal, 20-mg dose of BMT administered with or without 0.6 g/kg ethanol was found to be safe and generally well tolerated. No significant drug-related hypotensive or orthostatic hypotensive effects were noted. There was no increase in frequency of treatment-related AEs with BMT and no discontinuations due to AEs or serious AEs.

Conclusions: Female sexual dysfunction is a multifactorial condition including anatomical, physiological, medical, psychological, and social components. BMT, is a synthetic peptide analog of the naturally occurring hormone alpha-melanocyte stimulating hormone and a melanocortin agonist that is being developed for the treatment of hypoactive sexual desire disorder. The BMT mechanism of action involves activation of endogenous melanocortin hormone pathways involved in the sexual desire and arousal response. This phase 1 study demonstrates that BMT administered with or without ethanol is generally well tolerated, can be safely co-administered with ethanol, and had no reports of drug-related serious AEs. Phase

3 studies to further evaluate subcutaneous BMT for the treatment of premenopausal women with female sexual dysfunctions are in progress (ClinicalTrials.gov identifiers NCT02338960 and NCT02333071).

Study supported by: Palatin Technologies, Inc.

W64. EFFECT OF ASENAPINE ON MEASURES OF HOSTILITY IN ADULTS WITH BIPOLAR I DISORDER OR SCHIZOPHRENIA

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Abstract: Introduction: Patients with bipolar I disorder and schizophrenia may experience hostility during acute episodes (1,2). Hostility requires effective management to ensure patient safety and prevent harm to others. Asenapine (ASN) is currently indicated for the acute treatment of both schizophrenia and manic or mixed episodes associated with bipolar I disorder with or without psychotic features, in adults.

Objective: To investigate the effect of ASN on hostility symptoms in patients with bipolar I disorder (experiencing manic or mixed episodes) or schizophrenia.

Methods: Data were pooled from randomized, double-blind, placebo (PBO)-controlled trials (4 schizophrenia, 3 bipolar trials); patients who received ≥ 1 dose of trial medication with ≥ 1 baseline and postbaseline Positive and Negative Symptom Scale (PANSS) total score measurement were included. Mean changes in the PANSS hostility item score (P7) from baseline to day 21 (bipolar I disease) or baseline to day 42 (schizophrenia) were assessed. For bipolar I disorder, mean changes in the Young Mania Rating Scale (YMRS) total score and individual items (including the hostility items, disruptive-aggressive behavior and irritability) were also assessed from baseline to day 21. A mixed model for repeated measures (MMRM) analysis was used to assess the least-squares (LS) mean change from baseline and the difference in LS mean change between treatment groups.

Results: Patients with bipolar I disorder who received ASN 5 mg or 10 mg twice daily (BID) (n=605) or PBO BID (n=324) for up to 3 weeks and patients with schizophrenia who received ASN 5 mg BID (n=380) or PBO BID (n=373) for up to 6 weeks were included.

In patients with bipolar I disorder, the LS mean change in total YMRS score was -9.4 and -13.8 for PBO and ASN groups, respectively, resulting in a significant between-group difference of -4.5 (95% confidence interval [CI] -6.05, -2.86; $P < .0001$). All individual YMRS items were significantly improved for ASN, with most effect sizes between 0.26 and 0.39. The LS mean change in both YMRS hostility items remained significantly greater for ASN- than PBO-treated patients after adjustment for the other YMRS items (both $P < .05$). Improvement in the PANSS hostility item was significantly greater with ASN than PBO at days 7 and 21 (but not 14), with a LS mean difference of -0.3 ($P = .001$) at day 21. After adjustment for PANSS positive symptoms and sedation, the differences remained significant at days 7 and 21, but not day 14.

In patients with schizophrenia, improvement in the PANSS hostility item was significantly greater with ASN 5 mg BID than with PBO at all time points after day 7, with a LS mean difference of -0.2 ($P < .05$) at day 42. After additional adjustment for PANSS positive symptoms and sedation, the differences remained significant at some time points, but not at day 42.

Conclusion: In this pooled analysis of randomized trials, ASN was superior to PBO in reducing hostility symptoms in patients with bipolar I disorder and in patients with schizophrenia. These effects remained significant after adjusting for covariates, suggesting the effects are independent of sedation and are partially independent of PANSS positive symptom items. Results of these post hoc analyses suggest that ASN may be an effective treatment for hostility in patients with bipolar I disorder or with schizophrenia.

Learning Objectives:

- To understand the effect of ASN on hostility symptoms in patients with bipolar I disorder experiencing a manic or mixed episode.
- To understand the effect of ASN on hostility symptoms in patients with schizophrenia.

Literature References:

- Volavka J, Van Dorn RA, Citrome L, Kahn RS, Fleischhacker WW, Czobor P: Hostility in schizophrenia: An integrated analysis of the combined Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) and the European First Episode Schizophrenia Trial (EUFEST) studies. *Eur Psychiatry* 2016; 31:13-19
- Citrome L, Volavka J: The psychopharmacology of violence: making sensible decisions. *CNS Spectr* 2014; 19(5):411-418

W65. VORTIOXETINE FOR MAJOR DEPRESSIVE DISORDER: NUMBER NEEDED TO TREAT, NUMBER NEEDED TO HARM, AND LIKELIHOOD TO BE HELPED OR HARMED

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Abstract: Background: Vortioxetine is approved for the treatment of major depressive disorder and differs from other antidepressants in terms of its pharmacodynamic profile. Given the limited number of head-to-head studies comparing vortioxetine with other antidepressants, indirect comparisons using standardized effect sizes observed in other trials can be helpful to discern potential differences in clinical outcomes.

Methods: Data sources were the clinical trial reports for the pivotal randomized short-term double-blind trials for vortioxetine and from publicly available sources for the pivotal short-term double-blind trials for two commonly used generic serotonin specific reuptake inhibitor antidepressants (sertraline, escitalopram), two commonly used generic serotonin-norepinephrine reuptake inhibitor antidepressants (venlafaxine, duloxetine), and two recently introduced branded antidepressants (vilazodone, levomilnacipran). Response, defined as a $\geq 50\%$ reduction from baseline on the Montgomery-Asberg Depression Rating Scale or Hamilton Depression Rating Scale, was the efficacy outcome of interest. The tolerability outcome of interest was discontinuation due to an adverse event. Number needed to treat (NNT) and number needed to harm (NNH) for these outcomes versus placebo were calculated, as well as likelihood to be helped or harmed (LHH) to contrast efficacy versus tolerability.

Results: The analysis included 8 duloxetine studies, 3 escitalopram studies, 5 levomilnacipran studies for, 1 sertraline study, 4 venlafaxine studies, 2 vilazodone studies, and 11 vortioxetine studies. NNTs for response versus placebo were 6 (95% CI 5-8), 7 (5-11), 10 (8-16), 6 (4-13), 6 (5-9), 8 (6-16), and 9 (7-11), respectively. NNHs for discontinuation because of an adverse

event versus placebo were 25 (17-51), 31 (19-92), 19 (14-27), 7 (5-12), 8 (7-11), 27 (15-104), and 43 (28-91), respectively. LHH values contrasting response versus discontinuation due to an adverse event were 4.3, 4.6, 1.8, 1.2, 1.4, 3.3, and 5.1 respectively.

Limitations: Subjects were all participants in randomized controlled trials and may not necessarily reflect patients in clinical settings who may have complex psychiatric and non-psychiatric comorbidities. The measured outcomes come from different studies and thus comparisons are indirect.

Conclusions: Vortioxetine demonstrates similar efficacy to that observed for duloxetine, escitalopram, levomilnacipran, sertraline, venlafaxine, and vilazodone; however, there is a difference in overall tolerability, as measured by discontinuation due to an adverse event. Vortioxetine is 5.1 times more likely to be associated with response than discontinuation because of an adverse event when compared to placebo.

Learning Objectives:

- To place vortioxetine into clinical perspective by indirect comparison with other antidepressants, specifically by examining number needed to treat (NNT) for response and number needed to harm (NNH) for discontinuation due to an adverse event.
- To further explore the likelihood to be helped or harmed (LHH) metric when assessing benefit and risk.

Literature References:

- Citrome L, Ketter TA: When does a difference make a difference? Interpretation of number needed to treat, number needed to harm, and likelihood to be helped or harmed. *Int J Clin Pract* 2013;67:407-411.
- Citrome L: Vortioxetine for major depressive disorder: a systematic review of the efficacy and safety profile for this newly approved antidepressant - what is the number needed to treat, number needed to harm and likelihood to be helped or harmed? *Int J Clin Pract* 2014;68:60-82.

W66. SYMPTOMATIC REMISSION STATUS IN PATIENTS WITH SCHIZOPHRENIA TREATED WITH PALIPERIDONE PALMITATE (1-MONTH AND 3-MONTH FORMULATIONS)

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Abstract: Background: In this double-blind (DB), parallel-group, multicenter, phase-3 study (EudraCT no: 2011-004889-15), symptomatic remission was analyzed in patients (age 18-70 years) with schizophrenia following treatment with paliperidone palmitate (1-month [PP1M] and 3-month [PP3M] formulation).

Methods: Patients previously stabilized on PP1M and treated with fixed doses of PP3M (175, 263, 350, or 525 mg eq. deltoid/gluteal) or PP1M (50, 75, 100, or 150 mg eq. deltoid/gluteal) for 48 weeks were included in this analysis. Symptomatic remission was assessed according to Andreason's criteria (≤ 3 score on all positive and negative symptom score [PANSS] items: P1, P2, P3, N1, N4, N6, G5, and G9 for the last 6 months of DB treatment, with no excursion allowed). Functional remission was also assessed.

Results: Consistent with the primary efficacy endpoint with similar relapse rates in both treatment groups (PP3M: n=37, 8%; PP1M: n=45, 9%; difference in relapse-free rate: 1.2% [95% CI:-2.7%; 5.1%]), the percentage of patients who showed symptomatic remission was similar and >50% in both groups (PP3M: n=243/483, 50%; PP1M: n=260/512, 51%; relative risk of remission [95% CI]: 0.98 [0.87, 1.11]). Among the remitters at entry into DB phase, percentage of patients who met the symptomatic remission criteria was similar in both groups across 48 weeks. Proportion of patients who maintained symptomatic remission and functioning remission (PSP score >70 during the last 6 months of DB treatment) was similar between both groups (PP3M: n=121/483, 25%; PP1M: n=136/512; 27%).

Conclusion: Patients treated with PP demonstrated higher symptomatic remission compared with remission rates published elsewhere¹ with similar rates in both treatment groups across all 48 weeks. PP3M can thus be considered as a unique option for symptomatic remission in patients with schizophrenia previously stabilized on PP1M.

¹ Beitinger, R., et al. Progress in Neuro-Psychopharmacology and Biological Psychiatry, 2008. 32(7): p. 1643-1651.

Learning Objectives:

At the conclusion of the session, the participant should be able to:

- Recognize the symptomatic remission and functional recovery in patients with schizophrenia following treatment with paliperidone.
- Assess the function/dysfunction of the patient as an important component of recovery in schizophrenia treatment.
- Identify the benefits of symptomatic remission and functional recovery within schizophrenia and psychiatry clinics and aid to better coordinate mental health care.

Literature References:

- Berwaerts, J., Liu, Y., Gopal, S., Nuamah, I., Xu, H., Savitz, A., Coppola, D., Schotte, A., Remmerie, B., Maruta, N., Hough, D. W. (2015). Efficacy and Safety of the 3-Month Formulation of Paliperidone Palmitate vs Placebo for Relapse Prevention of Schizophrenia: A Randomized Clinical Trial. JAMA Psychiatry.
- Savitz, A., Xu, H., Gopal, S., Nuamah, I., Ravenstijn, P., Janik, A., Schotte, A., Hough, D., Fleischhacker, W.W. Efficacy and safety of paliperidone palmitate 3-month formulation for patients with schizophrenia: A randomized, multicenter, double-blind, noninferiority study (2016). accepted for publications at Int J Neuropsychopharmacol.

W67. LURASIDONE IN THE TREATMENT OF SLEEP DISTURBANCE ASSOCIATED WITH BIPOLAR DEPRESSION: POST-HOC ANALYSIS OF A PLACEBO-CONTROLLED TRIAL FOLLOWED BY A LONG-TERM EXTENSION STUDY

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Abstract: Background: Sleep disturbance, which is common in depression, has a significant impact on treatment outcomes and functioning (1). This post-hoc analysis evaluates the effect of lurasidone on sleep disturbance in patients with bipolar depression.

Methods: Outpatients meeting DSM-IV-TR criteria for bipolar I depression received once-daily lurasidone 20-60 mg, 80-120 mg, or placebo in a 6-week acute treatment study, followed by lurasidone 20-120 mg/d in a 6-month, open-label extension study (2). Montgomery Asberg Depression Rating Scale (MADRS) and Quick Inventory of Depressive Symptomatology–Self Report (QIDS-SR) were assessed at baseline and weeks 1 - 6 of the acute study. MADRS and the Sheehan Disability Scale (SDS) were also assessed at months 3 and 6 of the extension study. Sleep disturbance was assessed using the QIDS-SR sleep domain score defined a priori as the highest score on any of the 4 sleep items (initial, middle, late insomnia or hypersomnia): 0 (for no symptoms) to 3 (for insomnia symptoms more than half of the time, or sleeping longer than 12 hours in a 24 hour period). Recovery was defined as meeting criteria for combined symptomatic (MADRS ≤ 12) and functional remission (all SDS domain scores ≤ 3) at both months 3 and 6. Analysis of covariance and logistic regression methods were applied in the analyses.

Results: A majority of patients (78.5%) had sleep disturbance at baseline (QIDS-SR sleep domain score > 2), while 19.1% and 2.1% of patients had QIDS-SR sleep domain scores of 1 and 0, respectively. Improvement in sleep disturbance as assessed by mean change from baseline to week 6 in QIDS-SR sleep domain score was significantly greater for lurasidone 80-120 mg/d ($p < 0.05$) compared with placebo. Consistent trends were observed for lurasidone 20-60 mg/d ($p = 0.059$, vs. placebo). Acute improvement in sleep disturbance (reduction in QIDS-SR sleep domain score from baseline to week 6) was significantly associated with greater likelihood of attaining combined symptomatic and functional remission at week 6 in the acute study (NNT=4, $p < 0.05$, adjusted for treatment and site effects). Acute improvement in sleep disturbance also significantly predicted longer-term recovery in the continuation study ($p < 0.05$, odds ratio=0.747, 95% CI 0.559, 0.998).

Discussion: In this randomized double-blind, placebo-controlled study, once-daily lurasidone 20-60 mg or 80-120 mg significantly reduced sleep disturbance, assessed using the QIDS-SR sleep domain score, in patients with bipolar depression. Improvement in sleep disturbance at week 6 increased the likelihood of longer-term recovery.

Learning Objectives:

- To evaluate the effect of lurasidone on improvement of sleep disturbance in patients with bipolar depression.
- To evaluate the impact of improved sleep disturbance on symptomatic and functional recovery in bipolar depression.

Literature References:

- Harvey AG, Talbot LS, Gershon A: Sleep disturbance in bipolar disorder across the lifespan. *Clin Psychol* 2009; 162:56-277.
- Loebel A., Cucchiaro J., Silva R., et al.: Lurasidone monotherapy in the treatment of bipolar I depression, a randomized, double-blind, placebo-controlled study. *Am. J. Psychiatry* 2014; 171:160-168.

W68. DIRECT AND INDIRECT EFFECTS OF LEVOMILNACIPRAN ER ON FUNCTIONAL IMPAIRMENT IN ADULTS WITH MDD: POST HOC PATH ANALYSES

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Abstract: Background: In patients with major depressive disorder (MDD), some of the symptoms that can contribute to functional deficits are associated with decreased serotonergic activity (anxiety, irritability); others are more related to deficits in noradrenergic (NA) activity (fatigue, decreased energy, lack of motivation, concentration difficulties). Levomilnacipran extended-release (LVM-ER) is a serotonin and norepinephrine reuptake inhibitor approved for the treatment of MDD. In clinical trials, LVM-ER significantly improved functional impairment relative to placebo (Sambunaris, Int Clin Psychopharmacol 2014; Cutler, Prim Care Companion CNS Disord 2015). Path analyses were conducted to assess the direct/indirect effects of LVM-ER on functional impairment, focusing on how certain symptom improvements (motivation/energy, NA symptoms, anxiety symptoms) may affect functional outcomes.

Methods: Two path models were constructed using regression analyses, both of which included LVM-ER treatment as the fixed effect and change from baseline in Sheehan Disability Scale (SDS) total score as the functional impairment outcome. Model 1 analyzed data from LVM-ER–treated patients in a Phase 3 clinical trial (NCT01034462) that included the Motivation and Energy Inventory (MEI) as an efficacy measure. Mediating factors tested in Model 1 were changes from baseline in Montgomery-Åsberg Depression Rating Scale (MADRS) and MEI total scores. Model 2 analyzed data from LVM-ER–treated patients in 5 randomized, double-blind, placebo-controlled trials (NCT00969709, NCT01377194, NCT00969150, NCT01034462, EudraCT:2006-002404-34). Mediating factors tested in Model 2 were the changes from baseline in “NA Cluster” and “Anxiety Cluster” scores, defined as sum scores of individual items from the MADRS and 17-item Hamilton Rating Scale for Depression (HAM-D) as follows: NA Cluster (MADRS items 6 [Concentration Difficulties], 7 [Lassitude], 8 [Inability to Feel]; HAM-D items 7 [Work/Activities], 8 [Retardation], 13 [General Somatic Symptoms]); and Anxiety Cluster (MADRS item 3 [Inner Tension]; HAM-D items 9 [Agitation], 10 [Psychic Anxiety], 11 [Somatic Anxiety]).

Results: In Model 1, the direct effect of LVM-ER on SDS total score was 2%. The indirect effects of treatment on SDS total score, as mediated through changes in MADRS and MEI total scores, were 26% and 48%, respectively. In Model 2, the direct effect of LVM-ER on SDS total score was 3%. The indirect effects of treatment on SDS total score, as mediated through changes in NA and Anxiety Cluster scores, were 59% and 12%, respectively.

Conclusions: These path analyses indicated that in adults with MDD, the favorable effects of LVM-ER on functional impairment were mostly mediated (>70%) through improvements in overall depression, motivation/energy, NA symptoms, and anxiety symptoms.

Learning Objectives:

- To familiarize participants about the types of symptoms that might affect functional ability in adults with major depressive disorder.
- To identify the extent to which improvements in functional impairment may be attributable to the direct treatment effects of levomilnacipran ER, and to the indirect effects of treatment through improvements in various symptom domains (ie, overall depression severity, motivation/energy, noradrenergic-related symptoms, anxiousness).

Literature References:

- Sambunaris A, Gommoll C, Chen C, Greenberg WM: Efficacy of levomilnacipran extended-release in improving functional impairment associated with major depressive disorder: pooled analyses of five double-blind, placebo-controlled trials. *Int Clin Psychopharmacol.* 2014;29:197-205
- Cutler AJ, Gommoll CP, Chen C, Greenberg WM, Ruth A: Levomilnacipran extended-release treatment in patients with major depressive disorder: improvements in functional impairment categories. *Prim Care Companion CNS Disord* 2015;17:doi 10.4088/PCC.14m01753

W69. COMPARATIVE EVALUATION OF VORTIOXETINE AS A SWITCH THERAPY IN PATIENTS WITH MAJOR DEPRESSIVE DISORDER

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Abstract: Background: Guidelines in many countries suggest switching antidepressant therapy if clinically meaningful improvement has not been observed after the initial treatment or if the treatment is not well tolerated. While switching to a different class is generally recommended, the treatment paradigm for switching is not adequately specified due to lack of systematic and specific evidence on key aspects driving the decision to switch treatment (comparative efficacy and tolerability).

Objective: To review the characteristics of vortioxetine (including efficacy and tolerability) regarding its relevance for patients with major depressive disorder (MDD) needing to switch treatment.

Methods: The relative efficacy and tolerability of vortioxetine in MDD patients switching from an SSRI/SNRI was evaluated in a direct comparative study (REVIVE; NCT01488071) versus the approved non-SSRI/SNRI antidepressant agomelatine [1] and in an indirect comparison to sertraline, venlafaxine, bupropion and citalopram from switch studies retrieved in a systematic literature review. The adverse event profile was also evaluated in the pooled dataset of the vortioxetine MDD clinical development program. Vortioxetine's impact on treatment-emergent sexual dysfunction (TESD) was assessed in a comparative study versus escitalopram in stable MDD patients switching due to TESD associated with their current SSRI therapy (NCT01364649 [2]).

Results: Vortioxetine has demonstrated efficacy and tolerability in MDD patients after a switch due to an inadequate response with SSRI or SNRI treatment, with significant benefits over agomelatine on improvement in clinical efficacy measures, work, social and family functioning, quality of life outcomes and withdrawals due to AEs [1]. In the indirect comparison, vortioxetine had statistically significantly higher remission rate than agomelatine and numerically higher remission rates compared to sertraline, venlafaxine, bupropion, and citalopram. Withdrawal rates due to AEs were statistically significantly lower for vortioxetine than for sertraline, venlafaxine, and bupropion and numerically lower for vortioxetine than for citalopram. For effectively treated MDD patients with SSRI-induced TESD, switching to vortioxetine was statistically superior to escitalopram with respect to improved sexual

functioning. Vortioxetine was generally well tolerated and maintained antidepressant efficacy [2].

Conclusions: Vortioxetine may be a clinically relevant alternative for patients needing a therapy switch due to a lack of efficacy or experience of tolerability problems with an SSRI/SNRI. Vortioxetine is well tolerated with significant advantages in TESS over escitalopram, which is an important attribute for patients cycling through multiple therapies. Vortioxetine can be an appropriate therapeutic option to incorporate into clinical practice and treatment guidelines for this patient population.

Learning Objectives:

- Compare the efficacy of vortioxetine (directly and indirectly) to other antidepressants as a switch therapy for patients with major depressive disorder experiencing a lack of efficacy with their current SSRI or SNRI treatment.
- Compare the tolerability of vortioxetine (directly and indirectly) to other antidepressants as a switch therapy for patients with major depressive disorder experiencing tolerability problems with their current SSRI or SNRI treatment (including treatment-emergent sexual dysfunction).

Literature References:

- Montgomery SA, Nielsen RZ, Poulsen LH, Häggström L: A randomised, double-blind study in adults with major depressive disorder with an inadequate response to a single course of selective serotonin reuptake inhibitor or serotonin-noradrenaline reuptake inhibitor treatment switched to vortioxetine or agomelatine. *Hum Psychopharmacol* 2014; 29(5):470-82.
- Jacobsen PL, Mahabeshwarkar AR, Chen Y, Chrones L, Clayton AH: Effect of vortioxetine vs. escitalopram on sexual functioning in adults with well-treated major depressive disorder experiencing SSRI-induced sexual dysfunction. *J Sex Med* 2015; 12(10):2036-48.

Thursday, June 2, 2016

Poster Session II with Lunch

TH1. CORRELATION OF HLD200 DRUG EXPOSURE WITH PERMANENT PRODUCT MEASURE OF PERFORMANCE (PERMP)-CORRECT SCORES IN CHILDREN WITH ADHD

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Abstract: Background: Attention-deficit/hyperactivity disorder (ADHD) is a common childhood disorder that can persist throughout adolescence and adulthood. Several long-acting ADHD stimulant formulations utilize methylphenidate (MPH) in different controlled-release drug-delivery platforms.¹ Despite improvements with drug-delivery systems of MPH, parents report early morning (EM) ADHD symptoms (SX) and related functional

impairments as moderate to severe for a majority of their children (CH) and adolescents (AD) with ADHD.2 HLD200 incorporates MPH into a novel delayed- and controlled-release drug-delivery platform, allowing for nighttime dosing to control EM ADHD SX and SX throughout the following day.

Objective: To examine the safety and tolerability and to evaluate the single-dose pharmacokinetics (PK) of orally administered HLD200 in the evening to CH and AD with ADHD. Secondary pharmacodynamic (PD) exploratory end points were the mean scores on the PERMP-A and PERMP-C (Attempted and Correct).

Methods: This trial was a Phase I/II, single-site, open-label PK study in CH (aged 6-12 y) and AD (aged 13-17 y) diagnosed with ADHD. Subjects received a single oral dose of 54 mg HLD200 (equivalent to approximately 40 mg MPH in vivo) at approximately 9 PM.

Pharmacokinetic samples (4 mL) were collected prior to dosing ($t=0$; 9 PM) and following dosing ($t=4, 6, 8, 9, 10, 11, 12, 13, 14, 15, 16, 18, 20, 22, 24, 36$, and 48 h) to determine plasma MPH concentration. Plasma samples were analyzed by using high performance liquid chromatography with Tandem Mass spectrometry (LC-MS/MS). Pharmacodynamic testing was accomplished using the PERMP math test. Children were baseline-tested at 8 PM.

Subjects were tested the next day at various time points ($t=9, 10, 11, 12, 13, 14, 16, 18, 20, 22, 24$). Means for raw test scores and for change from baseline scores were compared using descriptive analysis. The relationship between HLD200 treatment and math performance was explored using descriptive and linear correlation (Pearson's Product-Moment Correlation) statistical analysis.

Results: Twenty-nine subjects were enrolled including 18 AD and 11 CH. Mean values of body-weight-adjusted PK parameters were similar among CH and AD; mean maximum plasma concentration (C_{max}) [(ng/mL) $\pm$ CV%] was 7.4 ± 30.1 for CH and 8.84 ± 34.5 for AD; area under the concentration-time curve between 0 and infinity (AUC_{0-inf}) [(ng/mL) $\pm$ CV%] was 132.7 ± 27.2 for CH and 134.4 ± 35.7 for AD. Variability in drug exposure between CH and AD appears to be due to weight differences, as weight-corrected values are very similar between the 2 groups. Primary examination of the 11 available PD data sets indicated that there were 4 nonresponders to the treatment who were not included in the PK-PD assessment. The comparison between the mean MPH plasma concentrations and the corresponding mean scores for PERMP-A and PERMP-C for responders ($n=7$) indicates a significant correlation between PERMP scores and MPH plasma concentrations over time. The regression relationship between individual exposure and response ($r^2=0.8$; if $r^2=1$ is a perfect correlation) indicates how well the model fits the data.

Conclusions: Following evening dosing, HLD200 exhibited an approximate 8-hour delayed MPH release profile, as designed, and was well tolerated. When body weight was taken into consideration, there was no clinically significant difference in the MPH drug exposure profile between CH and AD. There was a high correlation between HLD200 exposure and PD data in CH.

Learning Objectives:

- To evaluate the single-dose pharmacokinetics of HLD200, a novel, investigational, oral, delayed- and extended-release stimulant medication, formulated to be dosed in the evening so as to effectively manage ADHD symptoms immediately upon awakening and throughout the day and early evening.
- To describe the pharmacodynamics of HLD200 in terms of PERMP-A and PERMP-C scores, and evaluate its correlation with the HLD200 pharmacokinetic profile.

Literature References:

- Childress AC, Berry SA: Pharmacotherapy of attention-deficit hyperactivity disorder in adolescents. *Drugs* 2012; 72:309-325
- Sallee FR: Early morning functioning in stimulant-treated children and adolescents with attention-deficit/hyperactivity disorder, and its impact on caregivers. *J Child Adolesc Psychopharmacol* 2015; 25:558-565

TH2. ALGORITHM FOR ADULT ATTENTION-DEFICIT/HYPERACTIVITY DISORDER MANAGEMENT FROM THE PSYCHOPHARMACOLOGY ALGORITHM PROJECT AT THE HARVARD SOUTH SHORE PROGRAM

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Abstract: Background: ADHD is a neurodevelopmental disorder with a worldwide rate of approximately 3-10% in school-age children. It often continues to show manifestations in adults, with up to 4% diagnosed adults worldwide. These patients suffer from a multitude of functional impairments with overall negative impacts on their quality of life.

Method: A medication algorithm for adult ADHD was created using systematic literature search to identify relevant studies and key findings. We prioritized treatment considerations based on the following: 1) effectiveness and efficacy 2) Co-morbidity with other psychiatric or medical conditions 3) safety and long-term tolerability.

Results: After an accurate diagnosis of adult ADHD and after accounting for any co-morbidity that may affect the algorithm, we propose initiating treatment with a low dose (5 mg) of methylphenidate (MPH) or amphetamine once daily and titrating the dose every 3 days until effectiveness occurs or until side effects develop, with the usual efficacious dose being 1-1.3 mg/kg for MPH and 0.6-0.9 mg/kg for amphetamines.

In adult ADHD and co-morbid substance use, we recommend deferring ADHD pharmacotherapy until a period of sobriety has been established, after which the first line medication would be atomoxetine at a target dose of 1.2 mg/kg. In patients who develop mania or psychotic symptoms while on stimulants, we recommend discontinuing stimulants and reconsidering your diagnosis. In patients with established bipolar disorder, we recommend stabilizing mood with mood stabilizers followed by a slow and careful addition of low dose stimulants along with close monitoring of symptoms as this patient population remains at a higher risk for developing mania.

Conclusion: This algorithm is supported by the available but limited latest evidence and was created in response to the growing need for a treatment guide to clinicians when choosing medications for Adult ADHD.

Learning Objectives:

- Providing evidence based treatment guide for clinicians treating adult ADHD.
- Highlighting availability of treatment options for adult ADHD with associated co-morbidity including substance use disorder.

Literature References:

- Bolea-Alamanac, B., Nutt, D. J., Adamou, M., Asherson, P., Bazire, S., Coghill, D., . . . Young, S. J. (2014). Evidence-based guidelines for the pharmacological

management of attention deficit hyperactivity disorder: Update on recommendations from the British Association for Psychopharmacology. *Journal of Psychopharmacology*, 28(3), 179-203

- Stern, T. A., Fava, M., Wilens, T. E., & Rosenbaum, J. (2015). *Massachusetts General Hospital Psychopharmacology and Neurotherapeutics* (1st ed.). Elsevier.

TH3. CIRCUIT MODULATION BY STRIATAL CHOLINERGIC INTERNEURONS

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Abstract: Pre-clinical rodent models and human imaging and genetic studies point towards the striatum as a critical brain region sub-serving multiple behaviors relevant to cognitive processes and neuropsychiatric illnesses including obsessive-compulsive disorder, substance-use disorders and schizophrenia. Striatal cholinergic interneurons (ChIs) are the only tonically active cells in the striatum, firing to regulate the efferent spiny projection neurons and afferent dopaminergic mesostriatal neurons. In particular, preliminary data suggest dopamine/ glutamate co-transmission regulate ChIs in ways relevant for the understanding of these behaviors. As psychopharmacologic approaches narrow in on glutamatergic targets for psychiatric illness, understanding this mechanism is critical for the development of novel pharmaceuticals. Our work seeks to understand this mechanism by investigating the activity of ChIs in ex vivo slice preparations as well as in vivo responses of awake behaving animals engaging in learning and memory tasks. Initial studies will include observation of ChI activity using genetically-encoded calcium indicators both in slice and in vivo using Inscopix technology. Based on the results of those observational studies, subsequent assays will employ optogenetic technology to experimentally activate and inhibit ChIs in slice preparations and in awake behaving animals during Pavlovian-Instrumental transfer with and without amphetamine to delineate further ChI function in states of habitual over-responding.

Learning Objectives:

- Understanding the role of dopamine / glutamate cotransmission in regulating striatal cholinergic interneurons.
- Understanding striatal cholinergic interneuron activity in response to amphetamine.

Literature References:

- Chuhma N, Mingote S, Moore H, Rayport S: Dopamine neurons control striatal cholinergic neurons via regionally heterogeneous dopamine and glutamate signaling. *Neuron*. 2014 Feb 19;81(4):901-12. doi: 10.1016/j.neuron.2013.12.027.
- Ferguson SM, Eskenazi D, Ishikawa M, Wanat MJ, Phillips PEM, Dong Y, Roth BL, Neumaier JF: Transient neuronal inhibition reveals opposing roles of indirect and direct pathways in sensitization. *Nat Neurosci*. 2011 Jan;14(1):22-4. doi: 10.1038/nn.2703. Epub 2010 Dec 5.

TH4. FACTORS INFLUENCING GENERALIZED ANXIETY DISORDER (GAD) DIAGNOSIS AND MANAGEMENT: PERSPECTIVES FROM PRACTICING CLINICIANS

*Andrew Goddard¹, Larry Culpepper², Joseph Lieberman³, Katia Zalkind⁴, Purvi Smith*⁴, Anthony Greco⁴, Jani Hegarty⁴, Randi Roberts⁵*

Abstract: Background: Anxiety disorders currently affect approximately 40 million US adults. System, provider and patient barriers may lead to inaccurate misdiagnosis and inadequate treatment. Objective: Characterize factors influencing diagnosis/management of adults with GAD. Method: In January 2016 an electronic survey was distributed to a broad sample of primary care clinicians and psychiatrists. Those who did not treat GAD were ineligible. Participants were asked about prevalence and impact of anxiety; common methods to detect anxiety disorders; and approach to diagnosis/treatment for patients presenting with both anxiety and depression. Participants were also asked about concerns related to misuse, abuse and diversion (MAD) of benzodiazepines and significant issues faced by clinicians when diagnosing and managing GAD. Key Findings: 99 clinicians (78% psychiatrists) who treat patients with anxiety participated. Average prevalence of suspected/known anxiety in their practices was 36.8%(median 30%, SD 21.1). 56% reported having no standardized screening protocol for patients with anxiety symptoms. Most(88%) use patient interview; however, less than one-third use validated screeners, eg, GAD-7(23%), HAM-A(16%) and PHQ-SADS(15%). When asked which symptoms have a greater overall impact on patients with comorbid anxiety and depression, 48% cited anxiety, 33% depression and 19% were unsure. When prescribing medication for a patient with comorbid anxiety and depression, 81% initiate a single treatment, whereas 19% assess for separate diagnoses of depression and/or anxiety and treat each separately. Respondents who differentiate treatment for anxiety and depression are less likely to prescribe an SSRI/SNRI and more likely to prescribe a benzodiazepine as primary treatment compared with those who do not differentiate. 55% indicated that patients receiving an SSRI/SNRI as monotherapy for comorbid anxiety and depression commonly have residual anxiety symptoms 4weeks post-treatment initiation. 68% expressed high levels of concern (4 or 5 on a 5-point scale) related to MAD of benzodiazepines. In all, 104 significant issues facing clinicians when managing anxiety disorders were identified including limitations of current therapies(41%) and MAD(19%). Conclusion: Although adult anxiety disorders are highly prevalent and the impact of anxiety is often greater than that of depression, most clinicians do not use validated screeners for diagnosis. Despite the potential to improve patient outcomes through differential diagnosis and symptom-specific treatment planning, most clinicians do not differentiate treatment approaches for comorbid anxiety and depression symptoms. Most treat comorbid anxiety and depression with an SSRI/SNRI and frequently observe residual anxiety symptoms post-treatment. These findings support development of tailored educational interventions for GAD screening and management, with a focus on treatment planning for comorbid anxiety and depression.

Learning Objectives:

- Describe practice behaviors that complicate the diagnosis of generalized anxiety disorder.
- Discuss real-world practice patterns influencing management and health outcomes for patients with generalized anxiety disorder.

Literature References:

- National Institutes of Health (NIH), US Department of Health and Human Services. Anxiety Disorders. NIH Publication 09-3879. Bethesda, MD: NIH; 2009.
- Locke AB, Kirst N, Shultz CG. Diagnosis and management of generalized anxiety disorder and panic disorder in adults. Am Fam Physician. 2015;91(9):617-624.

TH5. THE ROLE OF CLINICAL OUTCOME ASSESSMENT (COA) DATA IN THE DRUG APPROVAL PROCESS OF PRODUCTS FOR THE TREATMENT OF AUTISM SPECTRUM DISORDER IN THE USA AND EUROPE: A REVIEW OF GUIDANCE DOCUMENTS AND AUTHORIZATIONS OF MEDICINAL PRODUCTS

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Abstract: Objectives. Autism spectrum disorder (ASD) is a group of developmental disorders characterized by disturbance in language, perception and socialization. Autistic children have problems with verbal and nonverbal communication, troubles with social interaction, and present repetitive behaviors or obsessive interests. In the European Union, prevalence rates were estimated at a range between 30 and 63 per 10 000 (all forms of ASDs included). In the USA, the 2010 CDC estimates indicated that 14.7 per 1,000 8 year old were identified with ASD. Prevalence is rising in both areas. There is no cure for ASD. However, behavior and communication approaches, dietary treatments, and medication can be used to relieve some symptoms and behaviors. The objectives of this study were: 1) To review which guidance were published by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) to help industry prepare marketing-authorization applications for medicinal products for ASD treatment; 2) To identify which products were approved specifically for ASD; and 3) To find out about the use of clinical outcome assessments (COAs) in the approval process. COAs measure a patient's symptoms, overall mental state, or the effects of a disease or condition on how the patient functions. There are four types of COA measures: patient-reported outcome (PRO), clinician-reported outcome (ClinRO), observer-reported outcome (ObsRO), and performance outcome (PerfO) measures.

Methods. This research was conducted through a systematic manual review of ASD-specific EMA and FDA regulatory guidelines, product labeling and corresponding assessment reports or medical reviews. The PROLabels database was used for labeling claim identification. Off-label uses were not included.

Results. The search of guidelines revealed that only the EMA has issued a concept paper in 2013 with very few guidance on evaluation endpoints. In addition, a letter of support to the EU-AIMS Consortium was issued recently (09-2015) to encourage the further study and use of the following clinical outcome scales in people with ASD: the Social Responsiveness Scale (2nd Edition), the Children's Social Behaviour Questionnaire, the Repetitive Behaviour Scale-Revised, Autism Spectrum Quotient, and the Short Sensory Profile. The FDA has approved only two products with an indication of autistic disorders, i.e., risperidone and aripiprazole; two atypical antipsychotics for control of behavioural symptomatology. No products with this indication could be found on the EMA website. The main criterion of evaluation was changes in symptoms measured by COAs. Risperidone and aripiprazole used the Aberrant Behavior Checklist (ABC), a measure completed by caregivers (ObsRO), to assess changes in irritability (primary endpoint). Secondary endpoints involved the use of ClinROs: the Clinical Global Impression - Change (CGI-C) scale (risperidone), and the Clinical Global Impression - Improvement (CGI-I) scale (aripiprazole) to measure changes in irritability.

Conclusion. The review revealed major discrepancies between the FDA and the EMA, with no products approved in Europe, while two were approved in the USA (however non-specific to ASD); no guidelines available in the USA, and a concept paper and a letter of support

developed in Europe. COAs (ObsRO and ClinROs) played a major role in the evaluation of medicinal products approved for ASD in the USA. With globalization of research, more harmonization is needed between both agencies.

Learning Objectives:

- To understand the importance of clinical outcome assessments in the evaluation of the treatment benefit of medicinal products to be approved for autism spectrum disorder (ASD).
- To understand the challenges faced by researchers in ASD, e.g., very few regulatory guidance, discrepancies between regulatory agencies in Europe and in the USA, and need for developing ASD-specific medicinal products.

Literature References:

- Simms MD, Jin XM: Autism, Language Disorder, and Social (Pragmatic) Communication Disorder: DSM-V and Differential Diagnoses. *Pediatr Rev* 2015; 36(8):355-62.
- Rossignol DA, Frye RE. The use of medications approved for Alzheimer's disease in autism spectrum disorder: a systematic review. *Front Pediatr* 2014;2:87.

TH6. EFFICACY OF LURASIDONE IN BIPOLAR DEPRESSION: POOLED Results OF TWO ADJUNCTIVE STUDIES WITH LITHIUM OR VALPROATE

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Abstract: Objective: The aim of this pooled analysis was to evaluate the efficacy and safety of lurasidone adjunctive with lithium or valproate for the acute treatment of bipolar depression.

Method: Data were pooled from two adjunctive therapy studies with similar designs: patients meeting DSM-IV-TR criteria for bipolar I depression, with or without rapid cycling, with a Montgomery-Asberg Depression Rating Scale (MADRS) score ≥ 20 and a Young Mania Rating Scale score ≤ 12 , were randomized to 6 weeks of once-daily, double-blind treatment with lurasidone 20-120 mg/d or placebo, in combination with either lithium or valproate. In both Study 1 (N=346) and Study 2 (N=356), patients were treated with lithium or valproate, at therapeutic blood levels, for a minimum of 4 weeks prior to randomization. In Study 1, patients were required to have been treated with therapeutic levels of Li or VPA prior to screening. In study 2, patients could also be treated prospectively with Li for VPA for 4 weeks prior to randomization, as long as they continued to meet inclusion criteria. Changes from baseline in MADRS (primary outcome) and Clinical Global Impression Bipolar Severity of Depression (CGI-BP-S; key secondary assessment) were analyzed using an MMRM analysis. The 16-item Quick Inventory of Depressive Symptomatology, self-rated version (QIDS-SR16) was evaluated using an analysis of covariance (ANCOVA) model.

Results: Mean MADRS scores at baseline were similar (Study 1: 30.7; Study 2: 29.1). For the pooled analysis sample, treatment with lurasidone (vs. placebo) was associated with significant week 6 improvement in the mean MADRS (-14.4 vs. -11.9; $p=0.003$), CGI-BP-S (-1.7 vs. -1.3; $p=0.001$) and QIDS-SR16 scores (-7.4 vs. -5.7; $p\leq 0.001$). Week 6 remission rates (defined as MADRS ≤ 12) were significantly higher for lurasidone (42% vs. 32%;

p=0.004; LOCF-endpoint). The incidence of adverse events resulting in discontinuation was similar (5.8% vs. 4.8%); and treatment-emergent adverse events with an incidence $\geq 5\%$ (and greater than placebo) consisted of the following: nausea (13.9% vs. 10.2%), Parkinsonism (12.8% vs. 8.1%), somnolence (11.4% vs. 5.1%), and akathisia (10.8% vs. 4.8%) in the combined adjunctive lurasidone and placebo groups, respectively. Rates of protocol-defined treatment-emergent mania were also similar (0.8% vs. 1.5%). Minimal changes in weight, lipids, and measures of glycemic control were observed during treatment with lurasidone.

Conclusions: Pooled results from two similarly designed, short-term placebo-controlled studies of patients with bipolar I depression found that treatment with lurasidone adjunctive with lithium or valproate significantly improved depressive symptoms. Short-term treatment with adjunctive lurasidone was associated with low rates of discontinuation due to adverse events, and minimal effect on weight or metabolic parameters.

Clinicaltrials.gov identifier: NCT00868699, NCT00868452

Sponsored by Sunovion Pharmaceuticals Inc.

Learning Objectives:

- After completion of this presentation, the reader will have a better understanding of the effect of the efficacy and tolerability of combined therapy with lurasidone and lithium for the treatment of patients with bipolar depression.
- After completion of this presentation, the reader will have a better understanding of the effect of the efficacy and tolerability of combined therapy with lurasidone and valproate for the treatment of patients with bipolar depression.

Literature References:

- Loebel A, Cucchiaro J, Silva R, et al. Lurasidone monotherapy in the treatment of bipolar I depression: a randomized, double-blind, placebo-controlled study. *Am J Psychiatry* 2014;171:160-8.
- Loebel A, Cucchiaro J, Silva R, et al. Lurasidone as adjunctive therapy with lithium or valproate for the treatment of bipolar I depression: a randomized, double-blind, placebo-controlled study. *Am J Psychiatry* 2014;171:169-77.

TH7. SAFETY AND EFFICACY OF CARIPRAZINE IN FDA-APPROVED DOSE RANGES FOR SCHIZOPHRENIA AND BIPOLAR I DISORDER: A POOLED POST HOC ANALYSIS

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Abstract: Introduction: Cariprazine, a potent dopamine D3/D2 receptor partial agonist, is approved by the FDA for the treatment of schizophrenia (SZ) and manic or mixed episodes associated with bipolar I disorder (BD). Efficacy and tolerability of cariprazine in SZ and BD were demonstrated in randomized, double-blind, placebo-controlled Phase II/III clinical trials. A number of these studies utilized a flexible-dose design and patients received doses outside of the approved dose range. This pooled post hoc analysis evaluated the safety and tolerability of cariprazine using modal daily doses within the FDA-approved 1.5 to 6.0 mg/d dose range.

Methods: Data were pooled for each indication separately. In SZ, four 6-week trials were included (NCT00404573, NCT01104766, NCT01104779, NCT00694707); in BD, three 3-

week trials were included (NCT00488618, NCT01058096, NCT01058668). For safety analyses, patients were grouped into pooled dose groups based on modal daily dose (SZ: placebo [n=584], cariprazine 1.5-3 mg/d [n=539] and cariprazine 4.5-6 mg/d [n=575]; BD: placebo [n=442] and cariprazine 3-6 mg/d [n=263]). Safety parameters included adverse events (AEs), clinical laboratory values, physical examination, and extrapyramidal symptom scales.

Results: Cariprazine demonstrated significant improvement versus placebo in 3 of 4 trials in patients with SZ (primary outcome: Positive and Negative Syndrome Scale [PANSS] total score; all positive studies, $P < .01$) and in all 3 trials in patients with BD (primary outcome: Young Mania Rating Scale total score [YMRS]; all studies, $P < .001$). The rate of discontinuation due to AEs was 12% for placebo and 10% for cariprazine in SZ and 7% for placebo and 11% for cariprazine in BD. The most commonly reported treatment-emergent AE ($\geq 5\%$ and twice placebo) in both indications was akathisia (SZ: placebo, 3.6%; 1.5-3 mg/d, 9.1%; 4.5-6 mg/d, 12.5%; BD: placebo, 4.8%; 3-6 mg/d, 19.8%). Additional TEAEs commonly reported in either SZ or BD trials were extrapyramidal disorder (SZ, 1.5-3 and 4.5-6 mg/d groups), tremor (SZ, 4.5-6 mg/d), restlessness (BD, 3-6 mg/d), and vomiting (BD, 3-6 mg/d). The incidence of serious AEs was similar for cariprazine and placebo. Mean changes from baseline in body weight were small (≤ 1 kg) for all dose groups in both indications. Mean changes in metabolic parameters were similar between treatment groups, with the exception of greater glucose and triglyceride increases in the BD studies (triglycerides: placebo, -4.4 mg/dL; 3-6 mg/d, +8.7 mg/dL; glucose: placebo, 1.7 mg/dL; 3-6 mg/d, 6.6 mg/dL). Mean prolactin levels decreased from baseline in both the placebo and cariprazine groups in both patient populations.

Conclusion: Based on this pooled analysis, cariprazine was generally safe, well-tolerated, and efficacious in the FDA-approved dose ranges in patients with acute exacerbations of schizophrenia and bipolar mania.

Learning Objectives:

- At the conclusion of this session, participants should be able to identify the approved dose ranges for cariprazine for the treatment of schizophrenia and manic or mixed episodes associated with bipolar I disorder.
- At the conclusion of this session, participants should understand the efficacy and safety profiles of cariprazine within the FDA-approved dose ranges for schizophrenia and manic or mixed episodes associated with bipolar I disorder.

Literature References:

- Citrome L: Cariprazine in schizophrenia: clinical efficacy, tolerability, and place in therapy. *Adv Ther* 2013; 30:114-126
- Citrome L: Cariprazine in bipolar disorder: clinical efficacy, tolerability, and place in therapy. *Adv Ther* 2013; 30:102-113

TH8. ACTIGRAPHY BIOMARKER DATA CORRELATE WITH BIPOLAR DISORDER MOOD SYMPTOMS

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Abstract: Background: Proactive identification and prevention of mood episodes in bipolar disorder (BD) patients is of crucial importance, given evidence associating recurrent mood episodes with cumulative neuronal damage, treatment-resistance, and declining functioning over time. Currently, clinicians rely upon psychiatric interview data obtained at in-person visits to assess for emerging mood symptoms, by which time problems may have already progressed to full syndromal hypo/mania or depression. Between-visit continuous physical activity monitoring with wearable actigraphy devices could provide real-time objective data regarding current mood symptoms,(1) enabling proactive/preventive treatment.

Methods: Stanford BD Clinic adult outpatients were initially assessed with the Systematic Treatment Enhancement Program for BD (STEP-BD) Affective Disorders Evaluation and monitored longitudinally with the STEP-BD Clinical Monitoring Form (CMF) while receiving naturalistic, evidence-based treatment. Participants wore a watch-like actigraphy device (ActiGraph Corp., Pensacola, FL) as continuously as possible for at least 3 months. Pearson correlations were used to assess relationships between prior-week daytime and nighttime physical activity (measured with actigraphy) and prior-week CMF-derived mood elevation (SUM-ME) and depressive (SUM-D) symptoms.(2)

Results: 19 BD outpatients had ≥ 1 routine clinical follow-up visit for which actigraphy data were also collected during the 7 prior days, yielding a total of 28 observation points (7 patients had data for >1 visit). Across these observation points, there was a significant positive correlation between mood elevation symptoms (SUM-ME) during the prior 7 days, and mean total daily energy output, measured in terms of Metabolic Equivalents of Task [METs, kcal/(kg*hour)] averaged over the same 7-day time period (Pearson $r=.420$, $p=.026$). There was also a nonsignificant negative correlation between depressive symptoms (SUM-D) experienced over the preceding 7 days, and mean nightly sleep efficiency, measured as total nightly sleep duration/total nightly time in bed, averaged over the same 7-day time period (Pearson $r=-.328$, $p=.102$). In contrast, there was no evidence of a relationship between energy output and depression ($r=.019$, $p=NS$) or between sleep efficiency and mood elevation ($r=-.004$, $p=NS$).

Conclusions: Our preliminary findings suggest increased daily energy expenditure may be a substantive correlate of mood elevation. A potential relationship between decreased sleep efficiency and depression was also observed, although this finding did not reach statistical significance, possibly due to power limitations. Absence of relationships between energy output and depression, and between sleep efficiency and mood elevation, indicate activity/sleep-mood relationships may be mood polarity-specific. Actigraphy monitoring may serve as a biomarker-based preventive strategy for BD, enabling providers to quickly detect and treat emerging mood symptoms.

Learning Objectives:

- Appreciate that actigraphy data in general can correlate with mood state in bipolar disorder patients.
- Understand that total energy expenditure in particular correlates with mood elevation symptoms in bipolar disorder patients.

Literature References:

- Gonzalez R, Tamminga CA, Tohen M, Suppes T. The relationship between affective state and the rhythmicity of activity in bipolar disorder. *J Clin Psychiatry*. 2014;75(4):e317-22.

- Sachs GS, Guille C, McMurich SL. A clinical monitoring form for mood disorders. *Bipolar Disord.* 2002;4(5):323-7.

TH9. POTENTIAL BIOMARKERS OF DEPRESSION AND MANIA: THE ASSOCIATION OF SLEEP, KYNURENINE AND TRYPTOPHAN IN ACUTE BIPOLAR DISORDER

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Abstract: Specific purpose: There is evidence supporting the influence of disrupted sleep patterns, molecules of the kynurenine pathway and inflammatory factors such as neopterin as potential biological markers of bipolar disorder (BD). However, few studies have simultaneously examined the association of sleep, the kynurenine pathway molecules and neopterin in symptomatic patients diagnosed with BD. The present study examined the association of total sleep time (TST), tryptophan, kynurenine and neopterin with clinical symptoms of acutely symptomatic BD to better understand the influence of each on BD.

Content: Bipolar disorder (BD) is a severe psychiatric disorder, with a complex and sometimes heterogeneous range of symptoms. Research shows that BD presents with abnormalities in the kynurenine pathway and immune-inflammatory and sleep dysfunctions (Anderson et al., 2015). Most studies have explored these relationships separately despite the association of stress, inflammation and sleep with one another. Additionally, studies have explored these relationships primarily with BD patients in remission and in uncontrolled settings. In the current study we conduct hypothesis driven as well as exploratory research to determine the relationship between kynurenine, tryptophan, neopterin, and sleep in acutely symptomatic BD patients undergoing inpatient hospitalization and treatment.

Methodology: 21 symptomatic BD patients and 28 healthy controls (HC) were recruited. Total sleep time was objectively measured with an actigraph for one week and blood plasma was collected to measure tryptophan, kynurenine and neopterin levels. Statistical analyses were conducted using independent t tests and linear multiple regression.

Results: Tryptophan was significantly reduced in BD patients. TST and Kynurenine/Tryptophan (Kyn/Try) ratio were significant predictors of depression and mania symptoms in acutely symptomatic BD patients. The inflammation marker, neopterin, was not a predictor of clinical symptoms. Follow up data showed significantly decreased clinical symptoms but no differences in sleep, kynurenine and tryptophan levels.

Importance of the proposed talk: Sleep and kynurenine pathway molecules, specifically, tryptophan and kynurenine/tryptophan, may be biological markers of BD and potential targets for intervention. Targeting these areas for improvement and observing clinically significant changes may lead to more successful treatment and decreased relapse rates.

Future Research: Findings suggest the importance of sleep and the kynurenine pathway as underlying biological markers of BD. Given the growing evidence, future research specifically targeting these markers for intervention is warranted. Current intervention

focuses on overt clinical behavioral symptoms as opposed to underlying biomarkers, which may partially explain increased risks for relapse in BD.

Learning Objectives:

- Identifying sleep, tryptophan and kynurenine/tryptophan ratio as potential biomarkers for bipolar disorder.
- Role of the above variables in acute symptomatic bipolar disorder patients in controlled hospital settings.

Literature References:

- Anderson G, Jacob A, Bellivier F, Geoffroy P. Bipolar Disorder: The Role of the Kynurenine and Melatonergic Pathways. Current pharmaceutical design. 2015.
- Geoffroy P, Scott J, Boudebessé C, Lajnef M, Henry C, Leboyer M, Bellivier F, Etain B. Sleep in patients with remitted bipolar disorders: a meta-analysis of actigraphy studies. Acta Psychiatrica Scandinavica. 2015;131:89-99.

TH10. OPEN BOARD

**TH11. THE SUICIDE IDEATION AND BEHAVIOR ASSESSMENT TOOL:
VALIDATION OF A NOVEL MEASURE OF SUICIDAL IDEATION AND
BEHAVIOR AND PERCEIVED RISK OF SUICIDE**

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¹Janssen, ²Janssen Research & Development, LLC, ³Janssen Scientific Affairs, LLC, ⁴N/A

Abstract: Introduction: Suicide is one of the most preventable types of death. Clinicians who want to monitor suicidal ideation, behavior, and risk require a tool that captures these components both comprehensively and efficiently. Ideally, the tool should also allow assessment of change as the result of potential interventions. The Suicide Ideation and Behavior Assessment Tool (SIBAT) is such a tool. It captures suicidal ideation and behaviors based on patient input, clinical global impressions of suicide risk, and optimal management based on clinician input. Information on the content, validation, and acceptability of the SIBAT will be provided.

Methods: The SIBAT Consortium, a group of clinical trial and academic experts in scale development, suicidology, and clinical management of suicidal patients, met regularly over 30 months. Together, they developed a modular instrument that is based on clinician consensus, a review of suicide literature, and the ISST-Plus. During revisions of provisional versions of the SIBAT, modules were added and item wordings refined. A draft version agreed upon by the SIBAT Consortium was reviewed in a stepwise fashion by multiple potential users. Among these, persons with a history of suicidal ideation evaluated items from the patient-reported modules of the SIBAT in terms of semantic clarity, relevance of questions, and adequacy of response choices. This feedback was incorporated and approved by the SIBAT Consortium. Additional feedback will be provided by 10 adolescents and 10 clinicians not involved with the development of the SIBAT. Their reviews and modifications of selected SIBAT items based on these cognitive interviews will be presented.

Results: The iterative SIBAT-development process, which has included both expert clinician and patient input, has created an instrument that has high face validity for the assessment of suicidal ideation, behavior, and risk. This instrument will be able to capture patient and

clinician estimates of short-term and long-term risk and will be sensitive to changes in these estimates.

Conclusions: As presently developed, the SIBAT supports the comprehensive assessment of suicidal ideation, behavior, and risk based on direct input from patients and their rating clinicians. An ongoing validation program is evaluating the reliability, validity, and psychometric structure of the SIBAT.

Importance of the proposed talk: Results from this validation program support the SIBAT's use as an instrument that efficiently documents a comprehensive clinical assessment of both imminent and long-term suicide risk in a broad range of patients. Results support the usefulness of the SIBAT as an efficient vehicle by which researchers and clinicians can collect suicide-risk information.

Learning Objectives:

- To educate participants on the current tools and assessment instruments for suicidal ideation and behavior and the associated limitations of these tools.
- To educate participants on a new instrument being developed to address the unmet needs of current tools that assess suicidal ideation and behavior.

Literature References:

- Lindenmayer JP, Czobor P, Alphs L, Anand R, Islam Z, Pestreich L. The InterSePT Scale for Suicidal Thinking (ISST): a new assessment instrument for suicidal patients with schizophrenia. *Schizophr Res.* 2001;49(suppl 1-2):5.
- Sheehan DV, Alphs LD, Mao L, Li Q, May RS, Bruer EH, Mccullumsmith CB, Gray CR, Li X, Williamson DJ. Comparative validation of the S-STS, the ISST-Plus, and the C-SSRS for assessing the Suicidal Thinking and Behavior FDA 2012 Suicidality Categories. *Innov Clin Neurosci.* 2014;11(9-10):32-46.

TH12. ADDRESSING DATA QUALITY CHALLENGES IN RARE DISEASE CLINICAL TRIALS

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Abstract: Background: An estimated 350 million people worldwide suffer from rare diseases, yet only 400 of the estimated 7000 rare diseases have a Food and Drug Administration (FDA) approved treatment. Challenges to conducting clinical trials in rare diseases may be impeding the development of effective treatment. Some of these challenges include inconsistent data collection processes, use of smaller sample sizes, lack of standardized endpoints, employing trial naïve sites, and lack of formal scale training programs for site staff. Well-established approaches to endpoint selection and site training in these trials may ameliorate some of these challenges and improve drug development for these underserved conditions. In this study we aim to examine a sample of rare disease trials to identify the types of outcome measures used in an effort to identify ways to improve data collection and quality in rare diseases trials.

Methods: A systematic review of 197 clinical trials (clinicaltrials.gov) was conducted using the following search criteria (Key Words: rare disease disorders, Phase: 2, 3 and 4, Funder Type: Industry). Study demographics including condition, age group, and enrollment and outcome measures were analyzed. The outcome measures were assessed to determine the frequency with which clinician administered and patient-reported outcome measures were

used in these trials. In addition, anonymized case studies were examined to illustrate the challenges posed by the use of outcome measures within rare disease clinical trials, and propose practical strategies to address them.

Results: The review of the rare disease clinical trials and case studies reveals that the types of outcome measures which typically comprise site/rater training programs in larger trials involving more common indications are frequently included as primary or secondary outcome measures in these trials. In addition to survival rates, objective clinical endpoints, pharmacokinetics, and biomarkers, more subjective endpoints including clinician scales/assessments, semi-structured/unstructured interviews, questionnaires, and self-report/PRO measures were used up to 43% of the time. These measures are known to be vulnerable to data variability caused by rater error and inconsistency. Data gathering consistency and rater accuracy are known to improve with formal rater training programs as deployed in more conventional study indications.

Conclusion: Although rare disease clinical trials are utilizing clinician-assessed or patient-reported outcome measures, well-established, standardized assessments for these conditions are often lacking, resulting in use of novel instruments or adaptations of existing measures developed for other populations. Clinical assessments in rare disease clinical trials are frequently highly specialized, and may lack the extensive validation found in the scales used in more common trials. The selection and proper use of outcome measures by a single expert relies heavily upon the expert's own individual experience and expertise - experience that may not be reflected across all study sites. The absence of a formal training program for key endpoints likely increases the likelihood of inconsistency in data collection across study centers. Clinical trials in rare disease populations could benefit from consultation with experts in psychometric validation, clinical trials, and formal scale training to improve accuracy of data collection.

Learning Objectives:

- Understand the frequency that clinical outcome assessments are being used in rare disease clinical trials.
- To identify the need for enhanced rater training programs in rare disease clinical trials.

Literature References:

- RARE Diseases: Facts and Statistics. (2012). Retrieved January 20, 2016, from <https://s.globalgenes.org/rare-diseases-facts-statistics/>
- About | EveryLife Foundation for Rare Diseases. (n.d.). Retrieved January 23, 2016, from <http://everylifefoundation.org/about-us/>

TH13. MARIJUANA EFFECT ON DIFFERENTIATING AN OPIOID FROM PLACEBO DURING THE DISCRIMINATION PHASE OF A HUMAN ABUSE POTENTIAL STUDY

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Abstract: Purpose: Human abuse potential (HAP) studies are conducted to determine the potential abuse of a drug with rewarding properties. Subject selection is an important step in the process to insure subjects have the ability to detect liking with the drug under

investigation. Many subjects recruited for opioid HAP studies use marijuana. The impact of THC on pharmacodynamic assessments in drug discrimination is typically considered insignificant but is not well characterized or understood. Subjects with recreational drug experience are recruited and then required to demonstrate they can discriminate between active test opioid and placebo. A positive drug screen serves as a routine exclusion for study participation to eliminate potential bias or risk of pharmacodynamic carryover. However, THC is usually exempt in the scientific literature from this exclusion in part to improve recruitment and retention of subjects. This study was conducted to assess whether subjects positive for THC would be able to discriminate an opioid from placebo during the discrimination phase.

Methodology: In 64 subjects in a single HAP study, investigators examined the potential influence of THC, including quantitative levels where applicable, on ability to discriminate between 20 mg of intranasal oxycodone and placebo.

Results: Of 64 subjects, 31 (48%) were positive for THC prior to drug discrimination. Ten subjects did not complete drug discrimination and were excluded from analysis due to emesis (5), withdrawn consent (3), and inability to complete study meal (2). Of 10 excluded subjects, 60% were positive for THC. The remaining 54 patients completed drug discrimination: 39 passed and were randomized to treatment; 15 did not successfully discriminate. Positive urine drug screen rate for THC was 48.7% for discriminators vs. 40% for non-discriminators ($p=0.5650$) with corresponding mean urine carboxy-THC concentrations of 705 vs. 417 ng/mL, respectively ($p=0.2797$).

Conclusion: Successful opioid discriminators were associated with a higher positive THC drug screen rate and mean carboxy-THC urine concentrations when compared to non-discriminators but differences were not statistically significant. The objective measurements of THC do not correlate with subjects' ability to discriminate between active drug and placebo in this intranasal opioid HAL study. The presences of THC did not affect whether an individual passed or failed the discrimination phase. This means that it may not be necessary to exclude recent users of marijuana from opioid HAP studies. Further research is necessary to fully elucidate the influence of THC in HAP studies.

Learning Objectives:

- Recent marijuana use does not seem to affect subject's ability to differentiate between placebo and oxycodone 20mg.
- As we review qualifications for inclusion/exclusion criteria in Human Abuse Potential studies, marijuana it seems does not have a statistically significant impact on drug discrimination and therefore should probably not be exclusionary.

Literature References:

- Webster LR, Kopecky EA, Smith MD, Fleming AB: A Randomized, Double-Blind, Double-Dummy Study to Evaluate the Intranasal Human Abuse Potential and Pharmacokinetics of a Novel Extended-Release Abuse-Deterrent Formulation of Oxycodone. *Pain Medicine* December 2015; pii: pnv020
- Summers P, Alemu B, Quidgley-Nevares A: History of drug use predicts opioid treatment agreement violation. *J Opioid Manag.* 2015 Nov-Dec;11(6):501-6. doi: 10.5055/jom.2015.0303

TH14. ITI-007 DOSE SELECTION ACROSS PSYCHIATRIC AND NEUROLOGICAL THERAPEUTIC INDICATIONS

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Abstract: Background: ITI-007 is a first-in-class investigational new drug and through synergistic actions via serotonergic, dopaminergic, and glutamatergic pathways represents a novel approach for the treatment of psychiatric and neurological disorders. At low doses ITI-007 is predominantly a serotonin 5-HT_{2A} receptor antagonist. As the dose is increased, ITI-007 engages dopamine D₂ receptors as a pre-synaptic partial agonist and post-synaptic antagonist with functional mesolimbic/mesocortical selectivity, increases phosphorylation of mesolimbic GluN2B subunits of N-methyl-D-aspartate (NMDA) channels consistent with a cascade of events downstream of dopamine D₁ receptor activation, and inhibits serotonin reuptake. Together, this unique pharmacological profile predicts enhancement of sleep and reduction of agitation and aggression at lower doses and antipsychotic and antidepressant efficacy at higher doses, all with a highly favorable side effect profile.

Methods: ITI-007 has been evaluated in randomized, double-blind, placebo-controlled clinical trials across a wide range of doses. Low doses of ITI-007 were evaluated in patients with primary insomnia, healthy geriatric volunteers and elderly patients with dementia. Higher doses of ITI-007 have been studied in patients with schizophrenia and are currently being evaluated in patients with bipolar depression.

Results: In a Phase 2 trial in patients with primary insomnia, ITI-007 (1 – 10 mg) demonstrated a dose-related increase in deep slow wave sleep, decrease in wake after sleep onset, and increase in total sleep time with no next-day hang-over effects. In patients with dementia, ITI-007 (9 mg) was safe, well-tolerated, and improved measures of cognition. In a Phase 2 schizophrenia trial, ITI-007 at 60 mg demonstrated a statistically significant reduction from baseline on the Positive and Negative Syndrome Scale (PANSS) total score compared to placebo after 4 weeks. In a Phase 3 schizophrenia trial, 60 mg ITI-007 again demonstrated a statistically significant reduction from baseline on the PANSS total score compared to placebo after 4 weeks. Administered orally once daily, ITI-007 is safe and well tolerated across a broad range of doses (1 mg to 140 mg).

Discussion: ITI-007 is an investigational new drug with unique pharmacology that suggests different therapeutic utility across a wide range of doses. Clinical studies are planned to evaluate ITI-007 in the low dose range for the treatment of behavioral disturbances in dementia. Higher doses of ITI-007 are being evaluated in a Phase 3 program for the treatment of schizophrenia and for the treatment of bipolar depression. Additional studies are planned to evaluate ITI-007 for the treatment of major depressive disorder and other neuropsychiatric and neurological disorders.

Learning Objectives:

- Present how unique pharmacology of ITI-007 has potential utility in psychiatric and neurological indications.
- Present the rational for ITI-007 dose selection across different therapeutic indication.

Literature References:

- Peng Li, et al (2014) Discovery of a Tetracyclic Quinoxaline Derivative as a Potent and Orally Active Multifunctional Drug Candidate for the Treatment of Neuropsychiatric and Neurological Disorders. J Medicinal Chemistry (57) 2670-2682

- Gretchen L. Snyder, et al (2014) Functional Profile of a Novel Modulator of Serotonin, Dopamine, and Glutamate Neurotransmission. Psychopharmacology Published online 2014 Aug 15.

TH15. METHODOLOGICAL CONSIDERATIONS IN THE ASSESSMENT OF ABUSE POTENTIAL IN PHASE 1-3 CLINICAL TRIALS OF CNS DRUGS

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Abstract: Introduction (Aims): The FDA’s 2010 Draft Guidance entitled “Assessment of Abuse Potential of Drugs” provides guidance to industry on the types of data that need to be submitted in an NDA in order for FDA to make scheduling and labeling decisions related to abuse potential. This guidance is applicable “if the drug affects the CNS, is chemically or pharmacologically similar to other drugs with known abuse potential, or produces psychoactive effects such as sedation, euphoria, and mood changes.” One of the categories of data requested under this guidance includes “Clinical Trial Data Relative to Abuse and Dependence Potential”. This poster discusses the methodological implications of this guidance on the design and execution of Phase II and Phase III clinical studies. It also discusses the application of the eight factors (“8F”) that are determinative of potential scheduling of a drug under the Controlled Substances Act (CSA), as described in the 2010 Draft Guidance, for identifying potential data gaps and guiding the designs of clinical studies. Methods: The 8F analysis approach is summarized and the method of its application for data gap identification is explained. The data requirements and potential clinical studies outlined in the 2010 draft Guidance on abuse potential were mapped to the typical data sources available during the routine conduct of phase 1-3 clinical trials. Potential gaps were identified where historically some NDAs have struggled to provide the FDA with adequate data to characterize the abuse potential of new molecular entities. A list of strategies related to clinical trial methodology was then developed to address these potential gaps, serving as a ‘best practice’ to help proactively manage the assessment of abuse potential in Phase 1-3 clinical trials.

Results: Based on the 2010 guidance, studies of CNS drugs could include strategies to collect and interpret data related to aberrant drug-taking behaviors, adverse events related to abuse potential and physical dependence/withdrawal. Aberrant drug-taking behaviors and signals of abuse potential may include misuse, overdose, drug diversion/drug accountability, discrepancies in clinical supplies of the study drug, noncompliance, protocol violations, individuals lost to follow-up, and signs of withdrawal upon termination or inadvertent abstinence of the drug. In the assessment of adverse events related to abuse potential, it is important to include as much information as possible in verbatim reports to be able to describe the event (e.g., so that terms such as “high” can be distinguished as being euphoria versus nausea/dizziness), and “withdrawal” versus side-effects of the drug, return of symptoms or other factors. Whereas not all studies will be able to assess all of these measures (i.e., the measurement of physical dependence and withdrawal would not be meaningful in a single-dose pharmacokinetic study), it is important that sponsors plan for the capture, analysis, and interpretation of data that have enough precision to meaningfully inform the abuse potential assessment of new CNS active drugs.

Conclusions: The systematic evaluation of potential gap in studies and data by appropriate analysis of the 8F of the CSA, and inclusion of a proactive and rigorous strategy for the collection and interpretation of clinical trial data related to the assessment of abuse potential can save development time and effort by providing the FDA with key data needed to make decisions regarding scheduling and labeling. In fact, properly collected data from clinical trials combined with preclinical data demonstrating negligible abuse potential may enable the sponsor to avoid conducting a human abuse potential study in recreational drug abusers. In contrast, a less-than-rigorous approach could lead to a requirement of additional studies, or more rigorous scheduling of the drug.

Learning Objectives:

- To understand the importance of clinical trials of safety and efficacy in determining the abuse potential of a new drug.
- To understand how clinical trials can best be designed to capture information to support the abuse potential assessment section of New Drug Applications for all CNS drugs that are, as stated by FDA (2010), “chemically or pharmacologically similar to other drugs with known abuse potential”.

Literature References:

- Food and Drug Administration. Assessment of Abuse Potential of Drugs. Silver Spring, Maryland, Food and Drug Administration, 2010. Available at <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm198650.pdf>, accessed 12/7/2015.
- Brady KT, Lydiard RB, Brady JV. Assessing abuse liability in clinical trials. *Drug Alcohol Depend.* 2003 Jun 5;70(3 Suppl):S87-95.

TH16. AN EVALUATION OF URINE DRUG MONITORING IN THE TREATMENT OF PATIENTS WITH SERIOUS MENTAL ILLNESS

*Mancia Ko^{*1}, Patricia Woster¹, Thomas Smith¹*

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Abstract: Purpose: To assess potential nonadherence among patients prescribed antipsychotic agents and identify the use of illicit substances and/or nonprescribed medications in these patients.

Methods: Urine samples that were submitted to the laboratory from patients prescribed antipsychotic medications were analyzed for the presence of antipsychotics, illicit substances (marijuana metabolite [THC] and/or cocaine metabolite [benzoylecgonine]), and select nonprescribed opioid or benzodiazepine medications that were unknown to the prescribing physician. Samples were classified as positive for the antipsychotic if either parent drug and/or metabolite(s) were confirmed and negative if neither were detected. Antipsychotic medications were tested using liquid chromatography/tandem mass spectrometry. Other drugs were tested using mass spectrometry confirmation following a presumptive screening result.

Results: A total of 22,951 samples were analyzed. The average age was 42.3 years, women provided 51.6% of samples, and the primary payor was Medicaid or Medicare (72.3% of samples). Overall, 24.8% of samples tested negative for an antipsychotic drug prescribed to the patient and 6.5% tested positive for a nonprescribed antipsychotic. Rates of nonadherence varied by antipsychotic medication and were greatest for haloperidol (37.0%) and lowest for

clozapine (4.4%) and paliperidone (7.2%). Nonprescribed opioids/benzodiazepines and/or illicit drugs were significantly more likely to be found in samples from patients who tested negative versus positive for a prescribed antipsychotic medication (41.3% vs 32.8%; odds ratio, 1.44; 95% confidence interval, 1.35-1.54).

Conclusions: Urine drug monitoring may be of value both for monitoring adherence to antipsychotic therapy and for detecting signals of potential substance abuse.

Sponsored by Ingenuity Health, a service of Ameritox Ltd.

Learning Objectives:

- Evaluate urine drug monitoring as a tool in assessing non adherence in patients prescribed antipsychotic medications.
- Assess the prevalence of illicit substances and/or nonprescribed medications in this population.

Literature References:

- Emsley R, Chiliza B, Asmal L, et al. The nature of relapse in schizophrenia. *BMC Psychiatry*. 2013;13:50
- Higashi K, Medic G, Littlewood KJ, et al. Medication adherence in schizophrenia: factors influencing adherence and consequences of nonadherence, a systematic literature review. *Ther Adv Psychopharmacol*. 2013;3(4):200-218

TH17. BRAIN-DERIVED NEUROTROPHIC FACTOR (BDNF) VAL66MET POLYMORPHISM INDUCES MEMORY DEFICITS IN ELDERLY

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Abstract: Memory impairments are important contributors to lower quality of life experienced by elderly populations. It is recognized that in aging processes, individual differences could be attributed, at least in part, to genetic factors. Brain-Derived Neurotrophic Factor (BDNF) Val66Met polymorphism, for example, has been suggested as a viable candidate for understanding the age-related decline. There are evidences indicating that BDNF Val66Met polymorphism and is associated with memory impairments in different clinical and non-clinical population. However, the linking between the polymorphism and the cognitive aging seem to remain unclear. This study was designed to investigate BDNF Val66Met polymorphism and memory performance in elderly adults. Eighty-seven elderly were recruited and the Logical Memory (LM) task was used to assess the immediate (IVR) and delayed verbal recall (DVR) and retention rate. Multivariate general linear models (GLM) were used to test the influence of the BDNF Val66Met polymorphism on the IVR, DVR and retention memory scores. Gender, age, years of education, MMSE, CTQ and GDS score were included as covariates of interest. The BDNF Met allele carriers showed lower DVR scores

[Val/Val x Met allele (mean): 13.87 ± 7.46 x 8.26 ± 7.25 ; $F(1, 85) = 8.710$, $P = 0.004$] and retention rates [Val/Val x Met allele (mean): 71.53 ± 31.20 x 52.06 ± 26.84 ; $F(1, 85) = 5.934$, $P = 0.017$]. Our results revealed that BDNF Val66Met genotype variation affects DVR and retention memory processes, but not influenced the IVR performance. These results support previous findings in both young and elderly individuals for the role of BDNF

Val66Met polymorphism as a vulnerability factor associated with cognitive impairment. In addition, previous findings have been found smaller hippocampal volumes, altered hippocampal patterns and reduced hippocampal neuronal integrity when compared to Val/Val genotype.

Learning Objectives:

- BDNF Val66Met polymorphism are related to cognitive aging decline processes in elderly populations.
- Memory impairments have an important role in the global quality of life perceived by elderly populations.

Literature References:

- Kambeitz JP, Bhattacharyya S, Kambeitz-Ilankovic LM, Valli I, Collier DA, McGuire P (2012) Effect of BDNF val(66)met polymorphism on declarative memory and its neural substrate: a meta-analysis. *Neuroscience and biobehavioral reviews* 36:2165-2177.
- Kennedy KM, Reese ED, Horn MM, Sizemore AN, Unni AK, Meerbrey ME, Kalich AG, Rodrigue KM (2015) BDNF val66met polymorphism affects aging of multiple types of memory. *Brain Res* 1612:104-117.

TH18. MIN-117 – A PROMISING NEW ANTIDEPRESSANT WITH A NOVEL MECHANISM OF ACTION PROFILE

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¹PPRS, ²Minerva

Abstract: Background. Selective serotonin reuptake inhibitors and other antidepressants are thought to require several weeks to achieve their full antidepressant effect. Accelerating this effect is a major medical need. MIN-117 is an investigational antidepressant belonging to a new chemical class, the benzofuran derivatives. MIN-117 is characterized by its affinity for 5-HT_{1A} receptors and 5-hydroxytryptamine transporters (5-HTT). In addition, MIN-117 has high affinity for adrenergic α (α)₁ and 5-HT_{2A} and acts as an antagonist to each receptor. MIN-117 is also active as a dopamine transporter (DAT) inhibitor. Furthermore, MIN-117 has moderate affinity for 5-HT_{2C} and is active as a norepinephrine transporter (NET) inhibitor. Preclinical work suggests that MIN-117 might address some of the major unmet medical needs and shortcomings of existing therapies, including delayed onset of mood improvement, cognitive impairment, and sexual dysfunction. Methods. This was a double-blind, placebo- and positive-controlled (escitalopram), single-center study. The primary objective was to assess the safety and tolerability of MIN-117 after repeated administration in healthy male volunteers (1, 3 and 7.5 mg given once daily) compared to placebo. Secondary and exploratory objectives assessed the pharmacokinetic profile and the pharmacodynamic effects of MIN-117 on sleep parameters, mood, and cognition as compared to placebo and escitalopram following repeated administration for 14 days. Results. In total, 50 subjects were randomized. Overall, MIN-117 was well-tolerated. No SAE was reported. The treatment-emergent adverse event profile was similar in terms of nature and frequency in MIN-117 and placebo groups. Results on the SSRI withdrawal scale indicated that there were no more self-perceived adverse events with MIN-117 than with placebo or escitalopram.

MIN-117, as compared to escitalopram, did not lower rapid eye movement (REM) propensity but increase the REM density (number of eye movements during the REM phases) unlike escitalopram. There were indications that the single and repeated administration of 1 mg of MIN-117 increased slow wave sleep (SWS). These results on SWS were reinforced by the improvement in subjective sleep quality assessed by Leeds Sleep Evaluation Questionnaire. Escitalopram but not MIN-117, increased sedation measured at both day 1 and day 14 with the Pentobarbital Chlorpromazine Alcohol Group subscale of the Addiction Research Center Inventory. Finally, no treatment effect was observed on mood (Profile of Mood Scale) or on emotion (Emotional Visual Analogue Scale ratings). 1 2016 ASCP Annual Meeting Discussion. Results indicate that the three doses of MIN-117 were well tolerated in this sample of young healthy male volunteers. The pharmacokinetic analyses indicate that MIN-117 is rapidly absorbed and that steady state is reached after 10 days of administration. The half-life of MIN-117 is compatible with a once-a-day administration. The effects of MIN-117 on REM sleep parameters suggest that the drug, at these doses, did not functionally affect the human 5-HT transporter, at least in terms of REM sleep generating mechanisms. Based on SWS results and subjective sleep measurements, there were some indications that 1 mg dosage could have sleep maintenance properties. Finally, there was some evidence, characterized by a REM density increase, that MIN-117 could promote dopaminergic transmission based on its DA uptake inhibition.

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TH21. LURASIDONE FOR MAJOR DEPRESSIVE DISORDER WITH MIXED FEATURES: EFFECT OF IRRITABILITY

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Abstract: Objective: Major depressive disorder with mixed features has recently been recognized as a diagnostic subtype in DSM-5. Mixed features may be associated with important clinical differences including increased severity and suicide risk, poor long term prognosis, and differential treatment response. In patients with unipolar major depression in the NIMH Collaborative Depression study, irritability/anger was found to be a clinical marker for this more severe, chronic, and disabling form of major depressive disorder (MDD) [1]. Judd et al defined the criterion for irritability/anger as a severity rating ≥ 2 (mild) on the irritability/anger item on the Schedule for Affective Disorders and Schizophrenia interview. The aim of this post-hoc analysis of a 6-week trial of lurasidone in patients with a diagnosis of MDD with mixed features, we examine the prevalence of irritability, and its impact on treatment response.

Methods: Patients meeting DSM-IV-TR criteria for unipolar MDD, with a Montgomery-Asberg Depression Rating Scale (MADRS) total score ≥ 26 , who presented with 2 or 3 protocol-defined manic symptoms, were randomized to 6 weeks of double-blind treatment with either lurasidone 20-60 mg/d (N=109) or placebo (N=100). To evaluate the efficacy of lurasidone in patients presenting with irritability at study baseline, we defined irritability as a score ≥ 2 on both the Young Mania Rating Scale (YMRS) irritability item (#5) and the

disruptive-aggressive item (#9). Baseline to week-6 changes in MADRS total score (primary) and Clinical Global Impression, Severity Scale (CGI-S; key secondary), and YMRS items 5 & 9 were analyzed using a mixed model for repeated measures analysis for subgroups with and without irritability.

Results: Irritability was present at baseline in 20.7% of patients and was not associated with difference in total MADRS score (MADRS total score, 34.1 with vs 33.1 without irritability) or CGI-S (4.6 with vs 4.5 without irritability). Treatment with lurasidone was associated with significant week 6 change vs. placebo in MADRS total score for both the irritability group (-22.63 vs. -9.47; $P<0.0001$; effect size [ES], 1.41) and the non-irritability group (-19.91 vs. -13.80; $P<0.0001$; ES, 0.66). Lurasidone was also associated with improvement on the CGI-S scale for both the irritability group (-2.01 vs. -0.70; $P=0.0002$; ES, 1.22), and the non-irritability group (-1.78 vs. -1.31; $P=0.0067$; ES, 0.45). In the irritability group, treatment with lurasidone was associated with significant week 6 change vs. placebo in both the YMRS irritability item (-1.38 vs. -0.70; $P=0.0012$; ES, 1.04), and the disruptive-aggressive item (-0.99 vs. -0.32; $P=0.0002$; ES, 1.19).

Conclusions: In this post-hoc analysis of a randomized, placebo-controlled, 6-week trial, treatment with lurasidone significantly improved depressive symptoms in patients with MDD with mixed features regardless of irritability, but had a larger effect in the irritability group. Symptoms of irritability also showed significant improvement. Therefore, in major depressive disorder with mixed features, lurasidone treatment was effective for both depression and irritability.

Clinicaltrials.gov: NCT01421134

Sponsored by Sunovion Pharmaceuticals Inc.

Learning Objectives:

- After completion of this presentation, the reader will have a better understanding of the frequency and characteristics of irritability in the clinical presentation of MDD with mixed features.
- After completion of this presentation, the reader will have a better understanding of the effect of lurasidone on depressive symptoms and symptoms of irritability in patients with MDD with mixed features who present with high levels of irritability.

Literature References:

- Judd LL, Schettler PJ, Coryell W, et al. Overt irritability/anger in unipolar major depressive episodes: past and current characteristics and implications for long-term course. *JAMA Psychiatry*. 2013;70:1171-80.
- Suppes T, Silva R, Cucchiaro J, et al. Lurasidone for the Treatment of Major Depressive Disorder With Mixed Features: A Randomized, Double-Blind, Placebo-Controlled Study. *Am J Psychiatry*. 2015 Nov 10 [Epub ahead of print]

TH22. OPEN BOARD

TH23. A FIVE YEAR STUDY OF VAGUS NERVE STIMULATION COMPARED TO TREATMENT AS USUAL IN HISTORICAL ECT RESPONDERS AND NON-RESPONDERS

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Abstract: Introduction: For patients with severe, difficult to treat depression, electroconvulsive therapy (ECT) has long been regarded as the most effective intervention. While it provides relief acutely, the side effect burden can be difficult to tolerate when it is used for maintenance treatment or for depressive recurrences. There is also minimal evidence to guide treatment for patients who fail to respond to ECT. VNS Therapy has demonstrated efficacy and durability for the treatment of patients with treatment resistant depression and may provide a tolerable alternative. We present the five year experience for patients with a history of an adequate course of ECT who participated in a study comparing outcomes between treatment as usual (TAU) and VNS+TAU treatment.

Methods: Four hundred eighty nine patients with treatment resistant unipolar or bipolar depression who had failed at least 4 trials of antidepressant treatment were implanted with a VNS device. They were compared with a similar population of 276 patients who received TAU in a five year study. As part of the data collection, information about each subject's history of ECT exposure, adequacy of treatment, and response was obtained. There were 290 VNS and 109 TAU patients with histories of adequate courses of ECT. We compared the cumulative first time responders over the five year follow-up based on 50% or more score reduction from baseline in Montgomery Asberg Depression Rating Scale (MADRS). Both the VNS+TAU and TAU patients were interviewed by a blinded central rater group.

Results: The dataset included 181 ECT responders and 109 ECT non-responders who received VNS+TAU, and 65 ECT responders and 44 ECT non-responders who received TAU. Across all time points from 3 months to 60 months, patients in the VNS+TAU treatment arm demonstrated a numerically greater likelihood of cumulative response with statistically significant separation starting at 12 months for the ECT responders and at 24 months for the ECT non-responders and continuing through 60 months. For historical ECT responders, at 60 months the percentage of cumulative first time MADRS responders for VNS+TAU is 71.3% vs. 56.9% for TAU ($p=.026$). For historical ECT non-responders, the percentages of cumulative first time MADRS responders are 59.9% for VNS+TAU vs. 34.1% for TAU ($p=.004$), at 60 months.

Conclusions: Patients in the VNS+TAU treatment arm demonstrated superior efficacy for both ECT responders and non-responders compared to the TAU treatment arm over the five year study duration. VNS Therapy merits greater consideration for the long term management of severe and persistent depressive disorders.

Learning Objectives:

- Participants will be able to describe the treatment options available to patients who have depressive episodes who have not responded to ECT.
- Participants will be able to evaluate the risks and benefits of using VNS in a population of patients who have been historically treated with ECT.

Literature References:

- Aaronson ST, Carpenter LL, Conway CR, Reimherr FW, Lisanby SH, Schwartz TL, Moreno FA, Dunner DL, Lessem MD, Thompson PM, Husain M, Vine CJ, Banov MD, Bernstein LP, Lehman RB, Brannon GE, Keepers GA, O'Reardon JP, Rudolph RL, Bunker M: Vagus nerve stimulation therapy randomized to different amounts of electrical charge for treatment-resistant depression: Acute and chronic effects. *Brain Stimul* 2013;6(4):631-40
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treatment-resistant depression: a naturalistic study. *Biol Psychiatry*. 2005 Sep 1;58(5):355-63.

TH24. IMPACT OF VORTIOXETINE ON FUNCTIONAL CAPACITY IN MDD PATIENTS WITH COGNITIVE DYSFUNCTION: A UCSD PERFORMANCE-BASED SKILLS ASSESSMENT (UPSA) POST HOC ANALYSIS

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Abstract: Objective: The primary objective of NCT01564862 was to evaluate the efficacy of flexible-dose vortioxetine (10–20mg) on cognitive functioning in patients with major depressive disorder (MDD) reporting cognitive symptoms. This post hoc analysis evaluated the effects of vortioxetine on functional capacity in these patients.

Methods: MDD patients (aged 18–65yr, MADRS $\geq$ 26) self-reporting cognitive symptoms were enrolled in an 8-week, double-blind, placebo-controlled study [1]. For study validation, duloxetine 60mg was included as an active reference for treatment-related changes in the Montgomery-Åsberg Depression Rating Scale (MADRS). The UCSD Performance-Based Skills Assessment (UPSA) composite score (comprising the full UPSA and UPSA-B in English- and non-English-speaking patients, respectively; possible range, 0–100) was included to evaluate the change in functional capacity from baseline to Week 8 versus placebo. Exploratory analyses of response rates stratified by baseline severity of functional capacity (UPSA $\leq$ 75, $\leq$ 70) were performed according to pre-specified cutoffs for the change from baseline to Week 8 on the UPSA ($\Delta\geq$ 5, $\Delta\geq$ 7, $\Delta\geq$ 10). An exploratory analysis of efficacy at Week 8 (defined as remission from both depressive symptoms [MADRS $\leq$ 10] and functional impairment [UPSA $\geq$ 75]) was also conducted.

Results: A total of 602 patients were randomized to treatment (vortioxetine, n=198; placebo, n=194; duloxetine, n=210), with 529 patients included in the full analysis set (528 of which had UPSA scores at Week 8). Vortioxetine demonstrated a statistically significant improvement in functional capacity versus placebo in all patients (vortioxetine, n=175, Δ +8.0; placebo, n=166, Δ +5.1; p<0.001), as well as in patients with a baseline UPSA $\leq$ 75 (n=62, Δ +14.9; n=73, Δ +9.9; p=0.003) and an UPSA $\leq$ 70 (n=41, Δ +16.7; n=46, Δ +10.8; p=0.010). Duloxetine did not demonstrate a significant improvement in functional capacity versus placebo in all patients (n=187, p=0.637) or stratified by baseline UPSA scores. A significantly higher proportion of vortioxetine patients were classified as responders versus placebo [2] based on change in UPSA of $\geq$ 7 (n=85, 48.6%; n=59, 35.5%; p=0.015) and $\geq$ 10 (n=66, 37.7%; n=46, 27.7%; p=0.049) (observed cases). Duloxetine was not significantly different versus placebo in response rates for any pre-defined cutoff. Vortioxetine and duloxetine both significantly improved depressive symptoms (MADRS) versus placebo (p<0.05; p<0.001, respectively) at Week 8, validating the study. For the composite efficacy analysis (MADRS and UPSA), only vortioxetine was significantly different from placebo (22.3% versus 10.2%; p=0.005) at Week 8.

Conclusion: In addition to benefits on cognitive dysfunction and depressive symptoms, vortioxetine significantly improved functional capacity, as assessed by the change in UPSA

at Week 8. These results emphasize the distinct profile of vortioxetine in MDD patients with cognitive dysfunction, with clinical utility observed in a wide population of patients.

Learning Objectives:

- Evaluate the efficacy of vortioxetine 10–20mg (versus placebo) in relation to functional capacity in patients with major depressive disorder and subjective cognitive dysfunction using the UCSD Performance-Based Skills Assessment (UPSA), including subgroups with higher baseline functional impairment severity.
- Determine the proportion of these patients who classified as UPSA responders at the study endpoint, as well as the proportion of patients who achieved remission from both depressive symptoms and functional impairment at the study endpoint.

Literature References:

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TH25. SAGE-547 (ALLOPREGNANOLONE) AND SAGE-217: INVESTIGATIONAL NEUROACTIVE STEROIDS TARGETING THE GABAA RECEPTORS FOR TREATMENT OF CNS DISORDERS

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Abstract: Background: Neuroactive steroids modulate GABAA receptors and may possess anxiolytic, antidepressant, and anticonvulsant properties. SAGE-547 and SAGE-217 are investigational neuroactive steroids in development for disorders related to GABAA receptor dysfunction. SAGE-547 is a proprietary, stabilized injectable solution of allopregnanolone with potent activity at extrasynaptic GABAA receptors. SAGE-217 is a next-generation positive allosteric modulator of GABAA receptors with high selectivity and potency. Sage is developing a differentiated pipeline of compounds targeting both GABAA and NMDA receptors.

SAGE-547 in Postpartum Depression (PPD): Perinatal hormonal changes may play a role in PPD and abrupt withdrawal of allopregnanolone may precipitate PPD in susceptible women. In an open-label, proof-of-concept study, SAGE-547 was evaluated in women with severe PPD admitted to the UNC Perinatal Psychiatry Inpatient Unit. SAGE-547 was titrated over 12 hours to approximate prenatal allopregnanolone levels, maintained for 36 hours, then weaned over 12 hours. Primary outcome was safety. Change from baseline in the 17-item Hamilton Rating Scale for Depression (HAM-D) total score at Hour 84 was the primary efficacy outcome.

Four women were enrolled and all completed treatment. Baseline mean HAMD total score was 26.5 (SD 4.12) indicating a severe level of depression. Fourteen treatment-emergent adverse events were reported. All were self-limited and resolved once treatment was completed; none was severe or serious. Two patients reported sedation, each requiring dosage adjustment. Laboratory values, vital signs, and ECGs did not change meaningfully during treatment. At Hour 84, mean HAMD total score decreased by 81% to 5.3, a score considered to be normal in nondepressed individuals. The mean change from baseline of -24.8 was significantly different from zero ($P < 0.001$; paired t-test). Mean HAMD total score revealed substantial reductions at the earliest time point measured (4.8 at Hour 12) and remained decreased through the end of infusion (3.3 at Hour 24, 1.8 at Hour 36, 2.3 at Hour 48, and 1.8 at Hour 60). Clinical Global Impression of Improvement scores indicated that all patients reported “much” or “very much” improvement at the earliest post-infusion measurement (Hour 12) and through the Hour 84 assessment. Other efficacy endpoints improved similarly.

Based on the strong efficacy and tolerability data generated by this open-label study, a placebo-controlled trial of SAGE-547 was recently initiated. This phase 2, randomized, multicenter trial is enrolling a maximum of 32 adult female patients with severe PPD at approximately 15 centers in the US (NCT02614547). Change from baseline in HAMD total score at Hour 60 is the primary efficacy endpoint. Pharmacokinetic analysis of SAGE-547 will also be included.

Optimal Treatment of PPD May Require Oral Therapy: SAGE-217 is a novel synthetic neuroactive steroid that demonstrated activity and potency at synaptic and extrasynaptic GABAA receptors in vitro and in a variety of behavioral measures in animal models. The compound is currently in phase 1 clinical development. The increased selectivity and potency demonstrated by SAGE-217 over first generation neuroactive steroids in animal models, along with oral bioavailability and long terminal half-life, suggest this could be a candidate for development to treat PPD, assuming successful completion of phase 1. The phase 1 study underway will determine the maximum tolerated dose and the pharmacokinetic, pharmacodynamic, and tolerability profiles of SAGE-217 in normal volunteers.

TH26. EVALUATION OF THE EFFICACY AND SAFETY OF ALKS 5461 AS ADJUNCTIVE THERAPY IN MDD: Results OF FORWARD-3 AND FORWARD-4 STUDIES

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Abstract: Accumulating evidence from preclinical studies, human PET imaging and other clinical investigations indicate that major depressive disorder (MDD) is associated with dysregulation of the endogenous opioid system. ALKS 5461 is a sublingual tablet consisting of buprenorphine (BUP) a mu-opioid agonist which also blocks kappa-opioid activation, co-formulated with samidorphan (SAM), a potent mu-opioid antagonist. The agonist-antagonist combination binds with high affinity to opioid receptors with low net intrinsic signaling activity. It is intended to treat MDD by supporting opioid tone in brain regions with impaired

endogenous mu- and kappa-opioid activity and decreasing or dampening opioid tone in regions where endogenous tone is excessive or upregulated.

In a prior phase 2 study, ALKS 5461 2mg/2mg (BUP/SAM) demonstrated clinically and statistically significant efficacy vs. placebo as adjunctive therapy in patients with MDD and an inadequate response to SSRI or SNRI therapy. We present here, two phase 3 studies (FORWARD-3 and FORWARD-4) designed to confirm the efficacy and safety observed in phase 2. Both phase 3 studies enrolled subjects with MDD and an inadequate response to standard antidepressant therapy. ALKS 5461 and matching placebo tablets were evaluated as adjunctive therapy; background antidepressants were continued throughout both studies. FORWARD-4 utilized sequential parallel comparison design (SPCD) and compared ALKS 5461 2mg/2mg and ALKS 5461 0.5mg/0.5mg to placebo. FORWARD-3 employed a double-blind placebo lead-in followed by a 6-week treatment period and tested ALKS 5461 2mg/2mg vs. placebo. The primary endpoint for both studies was change from baseline in the Montgomery–Åsberg Depression Rating Scale (MADRS).

FORWARD-4 enrolled 385 subjects. Retention was high with 86% of subjects completing the study. At the primary prespecified time point, ALKS 5461 2mg/2mg demonstrated a reduction in MADRS compared to placebo that trended but did not reach statistical significance. Additional analyses of 1 2016 ASCP Annual Meeting the MADRS endpoint at earlier and later time points as well as analyses incorporating multiple time points yielded statistically significant ($p < 0.05$) and clinically meaningful results. The lower dose, 0.5mg/0.5mg, did not show a significant treatment effect.

FORWARD-3 enrolled 429 subjects into the double blind lead-in phase. As with FORWARD-4, subject retention was favorable with 86% of subjects completing the study. In FORWARD-3 ALKS 5461 2mg/2mg did not show a significant treatment effect vs. placebo. Of note, the level of placebo improvement in FORWARD-3 was substantially higher than that observed either in FORWARD-4 or the phase 2 study, both of which utilized SPCD. In FORWARD-4 the most commonly reported adverse events were nausea, headache and dizziness. In FORWARD-3, they were nausea, headache and fatigue.

Conclusions: Addressing endogenous opioid dysregulation with ALKS 5461 is a promising treatment approach for patients with MDD. FORWARD-4 showed efficacy of ALKS 5461 2mg/2mg reinforcing positive results from a previously reported phase 2 study. The SPCD design was superior to the double blind placebo lead-in design of FORWARD-3 in terms of controlling placebo effect and demonstrating treatment response. Learning from the design and analyses of the FORWARD-3 and FORWARD-4 studies will be applied to future studies.

TH27. PSYCHIATRIST ATTITUDES ABOUT NOVEL AND EMERGING TREATMENTS FOR DEPRESSION: OFF-LABEL KETAMINE

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Abstract: Background: Relatively novel treatments for depression have emerged over the past decade, with varying degrees of adoption in clinical practice. Ketamine, used as an

anesthetic for over 50 years, is one of these emerging treatments, and has attracted widespread attention as a rapidly-acting antidepressant. Use of ketamine for depression is classified as off-label. Despite its scope and significance, research on decision-making about off-label use is sparse. The purpose of this project was to examine psychiatrist attitudes and decision-making processes behind off-label prescribing, using ketamine as a model.

Methods: Study design was correlational, with a single assessment of the cohort. Psychiatrists and psychiatry residents (n=21) were recruited through email lists or newsletters, and completed an online survey. Items tapped general attitudes regarding off-label prescribing and specific attitudes about ketamine. Additional items assessed perceived efficacy of treatments for depression, current or intended ketamine treatment recommendations, and psychiatrist demographic and clinical practice characteristics.

Results: Perceived efficacy of ketamine treatment was positively associated with having peers who often prescribed off-label ($r=+.49$) and with the belief that its risks were outweighed by benefits ($r=+.43$). Risk-benefit beliefs in turn positively predicted current use of ketamine treatment ($r=+.49$) and/or reported intent to recommend this treatment within the next six months ($r=+.53$). Psychiatrists with greater concern and acknowledgement of the addictive potential of ketamine perceived both ketamine ($r=+.76$) and other newer treatments for depression (e.g., TMS, deep brain stimulation, $r=+.74$) to be more effective, and to report their intention to recommend ketamine treatment in the future. Finally, participants who endorsed stronger rule-based clinical decisions (e.g., FDA-approved or recommended treatment guidelines) perceived ketamine to be less effective ($r=-.78$).

Conclusions: Psychiatrist attitudes predicted their recommendations for ketamine treatment. Concern over potential for abuse was associated with greater, rather than lesser endorsement of this treatment. In contrast, those whose clinical decisions were more heavily guided by external guidelines or rules were less likely to view this as an effective treatment.

Learning Objectives:

- Describe psychiatrists' attitudes toward new, developing treatments for depression that have not been universally adopted in clinical settings.
- Identify psychiatrist, patient, and treatment factors that influence adoption of off-label ketamine treatment.

Literature References:

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- Levinstein MR, Samuels BA. Mechanisms underlying the antidepressant response and treatment resistance. *Frontiers beh neurosc.* 2014;8.

TH28. VALIDATION OF PATIENTS FOR A CNS TRIAL OF MAJOR DEPRESSIVE DISORDER

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Abstract: Successful CNS trials require enrollment of patients with valid illness characteristics likely to be responsive to the mechanism of action of the candidate drug in the

study. Despite meeting DSM IV criteria for a specific psychiatric disorder and study eligibility requirements, there are some clinical presentations in which measurable change and meaningful clinical outcomes might not be expected. CTNI's remote interviews were developed to identify valid patients whose clinical presentation would be appropriate for specific CNS trials. The RAPID LFMS study was a double-blind, placebo-controlled trial of low-magnetic field stimulation for treatment of major depressive disorder. Phone interviews were administered by Massachusetts General Hospital psychiatrists to patients meeting inclusion criteria at recruitment sites. 12.8% of subjects meeting site inclusion criteria were excluded for failing the remote interview. Factors contributing to exclusion were lack of depression severity, not meeting MDD criteria via SCID assessment and inadequate antidepressant (AD) treatment in the current depressive episode. This presentation will illustrate the potential utility of this tool and suggests that remote interviews may be useful for identifying valid patients for CNS trials.

Learning Objectives:

- Learn about the structure and purpose of independent remote interviews in CNS trials.
- Learn about the utility of independent remote interviews for identifying valid patients in CNS trials.

Literature References:

- American Psychiatric Association DSM-IV-TR: Diagnostic and statistical manual of mental disorders, Fourth Edition, Text Revision. Washington, DC, American Psychiatric Association, 2000
- Chandler GM, Iosifescu DV, Pollack MH, Targum SD, and Fava M. Validation of the Massachusetts General Hospital Antidepressant Treatment History Questionnaire (ATRQ). *CNS Neurosci Ther* 2010. 16(5):322-5.

TH29. SUSCEPTIBILITY OF MALE AND FEMALE C57BL/6 MICE TO OXIDATIVE STRESS IN THE HIPPOCAMPUS IN AN LPS MODEL OF DEPRESSION

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Abstract: Background: Two consistent features in the pathophysiology of depressive disorders are inflammation and hippocampal atrophy. One explanation for this phenomenon is neurodegeneration due to excitotoxicity. Excitotoxic insults can increase intracellular zinc levels in neurons, contributing to cell damage and apoptosis in conditions such as seizure and ischemia. However, the factors influencing zinc accumulation and dysregulation in the brain in relation to mood disorders are not understood. We hypothesized that the inflammation found in the brain during depressive states induces a pathological accumulation of zinc in the hippocampus, thus contributing to neuronal death and overall hippocampal atrophy.

Methods: Behavioral tests were performed on group housed (4 per cage) male (N=16) and female (N=16) C57BL/6 mice, between 9-12 weeks old. 24 hours before behavioral testing, males and females were injected (IP) with either lipopolysaccharide (LPS, 0.83 mg/kg) or saline vehicle (0.9% NaCl). Behavior was performed 24-28 hours after injection in the dark under red light. The Open Field Test (OFT) was performed to examine general locomotor activity, total distance traveled, and anxiety-like behaviors. The Forced Swim Test (FST) was performed to measure immobility time (IT), a metric of depressive-like behavior. Tissue was harvested after behavior, 28-32 hours after injection. Brain tissue was either flash frozen in

isopentane over dry ice, and subsequently used for immunofluorescence, or preserved in RNAlater for protein and transcript quantification. Right and left hippocampi were preserved for protein and mRNA analysis, respectively. All samples were stored at -80 °C.

Results: Depressive-like behavior was evident in the FST 24 hours after LPS. We found a significant main effect of LPS, $F(1, 28) = 5.903$, $p = .028$; and sex, $F(1, 28) = 11.55$, $p = .002$. Labile zinc pools in the hippocampus were analyzed by TSQ (50 μ M) staining, and two-factor analysis revealed a significant reduction of TSQ fluorescence in the CA3 region in females given LPS compared to females given saline ($p < .01$). Staining for a marker of oxidative DNA damage, 8-OHdG, revealed a significant interaction between sex and LPS, $F(1, 10) = 4.984$, $p = .049$. Tukey's post hoc analysis revealed a significant increase in 8-OHdG staining in the CA3 region in males compared to females given LPS ($p < .01$).

Discussion: We are reporting a significant difference in behavior between males and females in the LPS model of depressive-like behavior. On average females have a higher immobility time than males, indicating an increased level of depression. Interestingly, males experienced increased levels of oxidative stress in the CA3 region compared to females after LPS. This may indicate that males are more susceptible to neuronal damage from oxidative stress. We found that females have diminished labile zinc pools in the CA3 region after LPS. Future work will aim to understand more fully the role of zinc and inflammation in depressive-states, and the gender differences that may exist. In this way, we may chart a better course for treatment of this complex and heterogeneous disorder.

Learning Objectives:

- Determine the effect of LPS on zinc homeostasis in the hippocampus by measuring zinc transporter expression and quantifying labile zinc in the regions of interest.
- Measure oxidative stress levels in the hippocampi of males and females in a mouse model of depression.

Literature References:

- Berk M, Kapczinski F, Andreazza AC, Dean OM, Giorlando F, Maes M, Yücel M, Gama CS, Dodd S, Dean B, Magalhães PV, Amminger P, McGorry P, Malhi GS. Pathways underlying neuroprogression in bipolar disorder: focus on inflammation, oxidative stress and neurotrophic factors. *Neurosci Biobehav Rev.* 2011;35:804-817.
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TH30. DIRECT AND INDIRECT EFFECTS OF LEVOMILNACIPRAN ER ON FUNCTIONAL IMPAIRMENTS IN MDD PATIENTS WITH COGNITIVE DIFFICULTIES: POST HOC PATH ANALYSES

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Abstract: Background: Patients with major depressive disorder (MDD) often have cognitive difficulties that can adversely affect psychosocial functioning. In clinical trials, treatment with levomilnacipran extended-release (LVM-ER) significantly reduced functional impairment relative to placebo in adults with MDD (Sambunaris, *Int Clin Psychopharmacol* 2014; Cutler, *Prim Care Companion CNS Disord* 2015). Using data from a Phase 3 trial (NCT01034462) that included the Cognitive Drug Research (CDR) computerized battery of tests as an efficacy measure, path analyses were conducted post hoc to explore the direct and indirect effects of LVM-ER on functional outcomes in patients with cognitive impairments. Methods: Path models were constructed using regression analyses of data from LVM-ER-treated patients. All models included LVM-ER as the fixed effect and change from baseline in Sheehan Disability Scale (SDS) total score as the functional impairment outcome. Analyses were conducted in the intent-to-treat (ITT) population and in subgroups with cognitive impairment that were defined using baseline median CDR scores for Power of Attention (POA, score ≥ 1303) and Continuity of Attention (COA, score < 92). The first set of path analyses included changes from baseline in Montgomery-Åsberg Depression Rating Scale (MADRS) total score and POA score as mediating factors. The second set included MADRS total and COA score changes as mediating factors.

Results: In the first set of analyses, direct effects of LVM-ER on SDS total score were as follows: ITT, 3.4%; POA ≥ 1303 , 19.2%; COA < 92 , 0.3%. The indirect effects of LVM-ER on SDS total score were more strongly mediated through changes in MADRS total score (ITT, 24.9%; POA ≥ 1303 , 25.5%; COA < 92 , 10.3%) than POA score (ITT, 2.5%; POA ≥ 1303 , 0.3%; COA < 92 , 6.9%). In the second set of analyses, direct effects of LVM-ER on SDS total score were as follows: ITT, 30.7%; POA ≥ 1303 , 21.8%; COA < 92 , 0.3%. Again, the indirect effects of LVM-ER on SDS total score were more strongly mediated through improvements in MADRS total score (ITT, 32.4%; POA ≥ 1303 , 46.7%; COA < 92 , 7.7%) than COA score (ITT, 0.2%; POA ≥ 1303 , 0.3%; COA < 92 , 4.4%).

Conclusions: Path analyses of data from a Phase 3 trial showed LVM-ER to have some direct effects on functional impairment in adults with MDD, particularly in those with a reduced ability to temporarily focus attention (POA ≥ 1303 subgroup). The indirect effects of LVM-ER on SDS total score through MADRS total score was much larger than the indirect effects through POA or COA scores. These results may have been due to the SDS and MADRS being based on patient reports, whereas the POA and COA were objective measures of attention. Future research using more objective measures of disability (eg, performance-based measures) is warranted to evaluate the relationship between CDR score changes and improvements in patient functioning.

Learning Objectives:

- To promote awareness about the potential impact of cognitive deficits on functional ability in adults with major depressive disorder.
- To identify the extent to which improvements in functional impairment may be attributable to the direct treatment effects of levomilnacipran ER, in addition to the indirect effects of treatment through improvements in cognition.

Literature References:

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TH31. EFFECTS OF ADJUNCTIVE BREXPIRAZOLE ON CHRONOBIOLOGIC PARAMETERS IN PATIENTS WITH MAJOR DEPRESSIVE DISORDER AND SLEEP DISTURBANCES

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Abstract: Background: Sleep disturbances are frequent problems in patients with major depressive disorder (MDD). Circadian rhythm disturbances and changes in melatonin and cortisol chronobiological patterns can be observed in patients with depression and may contribute to sleep symptomatology. A 2009 pilot study suggested that the increased phase angle between melatonin and cortisol in major depression could serve as a potential biomarker for MDD.¹ Brexpiprazole is a serotonin-dopamine activity modulator that is a partial agonist at serotonin 5-HT_{1A} and dopamine D₂ receptors, and antagonist at serotonin 5-HT_{2A} and noradrenaline alpha_{1B/2C} receptors, all with similar potency.² The objective of this analysis was to evaluate the effects of adjunctive treatment with brexpiprazole on chronobiologic parameters of sleep in patients with MDD and inadequate response to antidepressant treatment (ADT) (NCT01942733).

Methods: Patients with MDD and inadequate response to antidepressant therapy (ADT) continued treatment with their current ADT for a period of 2-weeks. Patients who still had an inadequate response and experienced sleep disturbances, received 8-week open-label treatment with their current ADT and adjunctive brexpiprazole (1 to 3 mg/day).

Results: At week 8, total scores on the Biological Rhythm Interview of Assessment in Neuropsychiatry (BRIAN), used to assess disturbances in circadian rhythms, demonstrated a mean decrease (improvement) of 17 points from a baseline of 52 points (N=41). Sleep-related chronobiological patterns were evaluated for a total of 9 patients who were treated with ADT and adjunctive brexpiprazole. In a subgroup of 9 patients, time to melatonin onset (DLMO), peak cortisol (PC) levels and the phase angle between them was calculated at baseline and at week 8. At week 8, the phase angle had decreased from 653 minutes (SD 106) to 545 minutes (SD 155).

Conclusion: Adjunctive treatment with brexpiprazole may represent a strategy for the treatment of sleep disturbances in patients with MDD and inadequate response to ADT. As circadian rhythm disturbances and changes in chronobiological hormone levels are found in patients with MDD and may contribute to associated sleep problems, the normalization of hormonal levels and circadian rhythms found with adjunctive treatment with brexpiprazole may contribute to overall improvements in sleep and symptoms of depression.

Learning Objectives:

- Understand the role of circadian rhythms in sleep disturbances.
- Learn the potential impact of Brexpiprazole on circadian rhythms and their impact on sleep in patients with major depressive disorder.

Literature References:

- Buckley TM, Schatzberg AF. A pilot study of the phase angle between cortisol and melatonin in major depression—A potential biomarker? *Journal of psychiatric research*. 2010 Jan 31;44(2):69-74.
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TH32. TREATMENT PATTERNS, HEALTHCARE RESOURCE UTILIZATION, AND COSTS FOLLOWING FIRST-LINE ANTIDEPRESSANT TREATMENT IN MDD: A RETROSPECTIVE US CLAIMS DATABASE ANALYSIS

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Abstract: Purpose: Major depressive disorder (MDD) is a debilitating condition characterized by high lifetime and yearly prevalence [1]. Although the goal of pharmacotherapy in MDD is resolution of depressive symptoms, the rate of remission within first-line pharmacotherapy is suboptimal [2]. Additionally, the benefit of one treatment strategy over another has not been rigorously examined in inadequate responders in the real-world setting. The goal of this study was to evaluate long-term treatment patterns and economic burden associated with common treatment strategies in routine clinical practice based on a claims database analysis in the USA.

Methods: The Truven Health Analytics MarketScan (1Q2003-1Q2014) database was used. Adults with ≥ 2 MDD-related claims (ICD-9 codes: 296.2x, 296.3x) within a 6-month period, who initiated first-line antidepressant monotherapy, and had continuous enrollment for ≥ 12 months prior to and ≥ 24 months following the index date (i.e., the first documented prescription fill date for an antidepressant) were identified. From this, six cohorts (“persistence”; “dose escalation/switch”; “single switch”; “multiple switches”; “discontinuation”; and “add-on”) were selected a priori based on common treatment strategies in routine clinical practice. Each cohort was evaluated through the 4th line of treatment, and each line was characterized by an adequate course of treatment (≥ 42 days). Patient characteristics at baseline are described, as are healthcare resource utilization (HCRU) and costs during follow-up.

Results: 34,885 patients were included in the total study population. Mean age was 41.7 (± 15.2) years and 60.8% of patients were female. Mean number of days between the first observed MDD-related claim and the index date was 65.4 (± 226.1). Mean duration of follow-up was 4.1 (± 1.9) years. During follow-up, the dose escalation/switch cohort (n=253) had the highest median number of all-cause and mental-health related medical visits per patient per year (PPPY) (16.43 and 6.78 visits PPPY, respectively), while the discontinuation cohort (n=2,417) had the lowest (all cause: 10.66 visits PPPY; mental-health related: 2.02 visits PPPY). The dose escalation/switch cohort also incurred the highest median mental-health related medical costs (\$793 USD PPPY); the lowest median mental-health related medical costs occurred in the discontinuation cohort (\$274 USD PPPY). In contrast, median all-cause total healthcare costs were highest in the multiple switches cohort (n=15) (\$7,104 USD PPPY) and lowest in the discontinuation cohort (\$4,107 USD PPPY).

Conclusion: Results from this study among inadequate responders with MDD show that the greatest overall mental-health related burden occurred in the dose escalation/switch cohort, a recommended treatment strategy in routine clinical practice, and the lowest overall burden occurred in the discontinuation cohort.

Learning Objectives:

- To understand the economic burden among inadequate responders in MDD.
- To compare healthcare resource utilization and costs across common treatment strategies in the US.

Literature References:

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TH33. THE DIGIT SYMBOL SUBSTITUTION TEST (DSST): PSYCHOMETRIC PROPERTIES AND CLINICAL UTILITY IN MAJOR DEPRESSIVE DISORDER

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Abstract: Overview: The Digit Symbol Substitution Test (DSST) is an example of a pencil and paper “coding” test. This paradigm requires the patient to draw or write the matching symbols or numbers into consecutive boxes, each positioned under the number or symbol with which it is paired (as shown on a coding key that remains visible). The DSST is among the most extensively used and validated cognitive measures in neuropsychology and as a Wechsler IQ scale subtest, it has remained largely unchanged since the earliest uses of that scale over 75 years ago. It has high discriminative validity for a range of brain diseases and conditions (including traumatic brain injury, alcoholism, schizophrenia, and major depressive disorder), is sensitive to change, and is widely used in clinical pharmacology experiments and clinical practice. Performance on the DSST correlates with extensive neuropsychological test batteries in clinical populations.

DSST Construct: The DSST is highly polyfactorial in the sense that good test performance requires intact functioning on a broad range of attributes. Among these are speed, attention, visuoperceptual/visuomotor functions (i.e., manual dexterity) as well as “associative learning” (i.e., if pairings are rapidly learned following the first few trials of the test, then performance speed improves because the patient will not need to check the accuracy of each pairing). Conscious engagement of a learning strategy to improve performance speed calls upon the executive functions of planning and strategizing, with working memory required to retain the task rules and for the continual updating of required digit-symbol pairs.

DSST Performance in Patients with MDD: Studies have shown neuropsychological performance is impaired in patients with major depressive disorder (MDD), even from the first episode. A meta-analysis of 1904 patients (mean age 50.5±17.6 years) from 22 studies yielded an impairment on the DSST with a mean standardized effect size relative to healthy controls of 0.55 (P<0.001; confidence interval, 0.34–0.75), in line with the standardized effect sizes found on other measures examined [1]. Similar findings were reported in elderly

depressed patients, where DSST performance is worse in late versus early onset of depression ($P < 0.04$) (Nebes et al. J Psychiatr Res 2003). In MDD patients (aged 18–59 years) studied 6 months after discharge from hospital for an MDD episode, the DSST was strongly associated with the level of functioning achieved in work, school, and home, yielding an odds ratio of 19.95 (scaled to standard deviation units) [2]; this means that a difference of one standard deviation on the DSST was associated with a nearly 20-fold increase in odds of obtaining a 1-point better rating on the 7-point global scale of the Multidimensional Scale of Independent Functioning, an index of real-life functioning in the community.

Conclusions: The DSST is a valid and sensitive measure of cognitive functioning across many domains, including cognitive functions shown to be impaired in patients with MDD. The DSST is a valid indicator of change in cognitive functioning, and performance on the DSST correlates with real-world functional outcomes (e.g., the ability to accomplish everyday tasks) and recovery from functional disability. Importantly, the DSST has been demonstrated to be sensitive to change in cognitive functioning in patients with MDD and may offer an effective means to detect clinically relevant treatment effects.

Learning Objectives:

- To understand the psychometric properties of the Digit Symbol Substitution Test (DSST) for evaluating changes in cognitive functioning in patients with major depressive disorder.
- To appreciate the clinical utility of the DSST for determining changes in cognitive functioning in patients with major depressive disorder.

Literature References:

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TH34. INTO THE ISLAND OF ADDICTION: INSIGHTS INTO THE MECHANISMS OF ACTION OF REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION

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Abstract: Background: Scientific evidence from animal and human imaging studies have demonstrated that addictive disorders (ADs) are brain disorders, which complex clinical manifestations arise, at least in part, as a consequence of altered activity in neural circuits subserving reward/motivation, affective and cognitive functions. Within this framework, neuromodulation interventions, such as transcranial magnetic stimulation (TMS), may not only allow to probe affected brain circuits in ADs, but also seems to have unique therapeutic applications to directly target and remodel these circuits. An ability of TMS to reduce drug craving and consumption in subjects with ADs has been suggested by an increasing number of studies. Nevertheless, the precise mechanisms of action of TMS are still unknown. In particular, it appears crucial to demonstrate whether TMS effects on drug-seeking and taking derives from restored activity in circuits that underlie decision-making or inhibitory control. This could be accomplished by including, among study outcomes, also measures of behaviors

usually impaired in ADs. To test our hypothesis we performed a double-blind, sham-controlled pilot study using repetitive TMS over the right insular cortex, an area playing a crucial role in interoception, craving and self-awareness.

Methods: In a randomized crossover order, eleven healthy volunteers (9F, 2M) underwent 2 sessions (sham; real) of 1 Hz rTMS at an intensity of 120% of individual motor threshold, over the right insular cortex using a novel H-coil. Before, immediately after, and 1h after rTMS, subjects performed 2 tasks that have previously been shown in fMRI experiments to activate insular cortex: 1) forced-choice risk-taking task, where subjects had to choose between a safe and risky option and behavior was measured as the percent of safe choices made; and 2) blink suppression task, where subjects were instructed to resist blinking as much as possible for 5 minutes, while indicating their urge to blink using an interactive visual analog scale. Blink rate was measured by EOG.

Results: Risk taking behavior was differentially affected by rTMS, with real TMS resulting in an elevation of % safe choices that was sustained at the 1-hr timepoint, compared with sham TMS ($p < .05$). Real TMS also increased blink rate, with an associated decrease in urge to blink. The negative correlation between blink rate and self-reported urge to blink ($r = -.26$, $p < .01$) may indicate that participants' awareness of their blinking behavior was increased, while no correlation between blink rate and urge to blink, and no effects on blink rate were observed in the sham condition.

Discussion: Our preliminary results shed some light into some of the possible mechanisms by which rTMS may exert its effects in subjects with ADs. By targeting the insular cortex we observed a decrease in risk-taking behavior, accompanied by an increased interoception and awareness of the ongoing behavior (blinking) that translated in concordance between subjects' self-report and the actual behavior. Moreover, our data supports the investigation of the insula as a target for rTMS interventions in ADs. Further studies in patients with ADs will be necessary to confirm our results.

Learning Objectives:

- To present findings from a pilot study evaluating the effects of rTMS over the insular cortex.
- To discuss which measures and outcomes may be valuable in improving our understanding of the mechanisms of action of TMS in addictive disorders.

Literature References:

- Pierce RC, Vassoler FM: Deep brain stimulation for the treatment of addiction: basic and clinical studies and potential mechanisms of action. *Psychopharmacology (Berl)* 2013; 229(3):487-91
- Gorelick DA, Zangen A, George MS: Transcranial magnetic stimulation in the treatment of substance addiction. *Ann N Y Acad Sci.* 2014 ;1327:79-93.

TH35. CASE STUDY OF MAGNESIUM IN THE TREATMENT OF IMPULSE ATTACK SUICIDALITY DISORDER

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Abstract: Background: This case study reports on the effect of high magnesium oxide coupled with reduced dietary calcium intake (+Mg-Ca) in the treatment of Impulse Attack Suicidality Disorder.

Methods: Using several sensitive assessment instruments (S-STS, S-STS CMCM, T-CASA, SPTS) for suicidality phenomena and suicidality event tracking, the authors tracked the effect on suicidality of magnesium oxide in doses up to 1000 mg/day in 4 divided doses daily, coupled with a reduced dietary intake of calcium below 300 mg / day (<30% of Recommended Daily Intake). The T-CASA was rated daily, and the S-STS, the S-STS CMCM, and the SPTS rated weekly over a 166-week (3.2 year) period and covering 43,690 separate suicidality events. The subject had a 25-year history of daily suicidality that did not responded to any prior treatment including 11 antidepressants, atypical antipsychotics, anticonvulsant mood stabilizers, and lithium dose.

Results: The +Mg-Ca completely eliminated the subject's suicidality. After 6 months free of suicidality the subject stopped the magnesium, while maintaining the low calcium intake. Within 48 hours she had a full relapse of all her prior suicidality and suicidal impulse attacks. This worsened over the ensuing week. On restarting the magnesium the suicidality decreased over the following 8 days after which she remained suicidality free for the ensuing 7 months.

Conclusion: The data from this case study suggests that high dose magnesium oxide coupled with reduced dietary calcium intake merits further investigation for the treatment of Impulse Attack Suicidality Disorder in large double blind, placebo-controlled studies.

Learning Objectives:

Following this presentation, participants will be better able to:

- Understand how a +Mg-Ca (high magnesium oxide low calcium intake) regimen was used to treat a case of chronic Impulse Attack Suicidality Disorder (IASD).
- Identify the symptom response profile in one subject with Impulse Attack Suicidality Disorder (IASD) in response to this +Mg-Ca (high magnesium oxide low calcium intake) regimen.

Literature References:

- Giddens, JM and Sheehan, DV. Study of Magnesium in the Treatment of Impulse Attack Suicidality Disorder. In: Sheehan, DV and Giddens, JM. 2015. Suicidality: A Roadmap for Assessment and Treatment. p. 249-267. Available from: <http://www.HarmResearch.org>
- Sheehan, DV and Giddens, JM. Impulse Attack Suicidality Disorder. In: Sheehan, DV and Giddens, JM. 2015. Suicidality: A Roadmap for Assessment and Treatment. p. 127-155. Available from: <http://www.HarmResearch.org>

TH36. EXTENDED-RELEASE MOLINDONE FOR IMPULSIVE AGGRESSION: PHASE 2 DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL IN CHILDREN WITH ADHD RECEIVING OPTIMIZED STIMULANT MONOTHERAPY AND BEHAVIORAL THERAPY

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Abstract: Background: Impulsive aggression -- an angry, immediate, and maladaptive retaliatory reaction arising out of frustration, annoyance, or hostility to real or perceived provocations -- amplifies the potential for poor outcomes of ADHD, with serious clinical and public health consequences. Approximately 25% of pre-adolescents with Combined ADHD subtype exhibit clinically significant aggression despite optimized stimulant monotherapy with/without behavioral therapy. Although antipsychotics are often used as adjunctive aggression-targeted therapy, no medication is specifically FDA-approved for such use in children with ADHD. Molindone is a medium-potency D2/D5-receptor antagonist with +30-yr clinical history as an immediate-release (IR) formulation to treat schizophrenia. In a Phase 2A study, IR molindone improved disruptive/aggressive behaviors in children with ADHD and serious conduct problems. Extended-release molindone (SPN-810, Supernus Pharmaceuticals, Inc.) is designed to deliver more constant plasma drug concentrations with longer dosing intervals vs. IR molindone in order to improve tolerability and adherence. Presentation will report results of a Phase 2B study of SPN-810 in children with ADHD and impulsive aggression. Methods: Multicenter, randomized, double-blind, placebo-controlled, dose-ranging study in children 6-12 yrs old with confirmed ADHD diagnosis, primarily impulsive aggression per Vitiello Aggression Scale, and >20 R-MOAS score (Retrospective-Modified Overt Aggression Scale) after 3-wk open-label baseline with optimized stimulant and behavioral therapy. Patients randomized to placebo or SPN-810 based on weight. Dose I, II, III targets: 12, 24, 36 mg/day if <30 kg; 18, 36, 54 mg/day if ≥30 kg. Primary efficacy endpoint: percent change from baseline R-MOAS at end of double-blind treatment. Results: In Intent-to-Treat population, Doses I (n=27) and II (n=30) were significantly superior (p<0.05) to Placebo (n=30) in change from Baseline R-MOAS scores, with Dose II (24 or 36 mg/day) producing maximum observed treatment effect; mean score changes in Placebo and Dose III (n=31) groups were similar. Dose I and II effect size: 0.60. Remission rates (R-MOAS score ≤10) were significantly higher (p<0.05) with Dose I (52%) and Dose II (40%) vs. Placebo (20%). Most common adverse events (AEs) were headache (SPN-810 combined doses, 10%; Placebo, 13%); sedation (SPN-810, 9%; Placebo, 7%); increased appetite (SPN-810, 8%; Placebo, 3%). Seven patients discontinued due to AEs: Placebo, n=1 (aggression); Dose I, n=1 (involuntary muscle contractions, jaw pain); Dose II, n=2 (dyskinesia and/or dystonia); Dose III, n=3 (headache, n=1; suicidal ideation, n=1; torticollis and blurred vision, n=1). The few EPS-associated AEs (Placebo, n=1; Dose I, n=1; Dose II, n=2) resolved with SPN-810 discontinuation. Conclusion: Addition of SPN-810 to optimized ADHD therapy significantly reduced persistent impulsive aggressive behavior in children with ADHD. SPN-810 was associated with a low incidence of AEs and no unexpected life-threatening or dose-limiting safety issues. Preliminary data suggest that SPN-810 may be better tolerated than similar total daily dosages of IR molindone. A Phase 3 study has been initiated to further evaluate SPN-810 in children with ADHD and persistent impulsive aggression.

Learning Objectives:

- Summarize the clinical rationale for developing an extended-release formulation of molindone (SPN-810) to manage persistent impulsive aggression in children with ADHD.
- Discuss results of a Phase 2B dose-ranging study that informed the design of a recently initiated Phase 3 study.

Literature References:

- Jensen PS, Youngstrom EA, Steiner H, Findling RL, Meyer RE, Malone RP, Carlson GA, Cocco EF, Aman MG, Blair J, Dougherty D, Ferris C, Flynn L, Green E, Hoagwood K, Hutchinson J, Laughren T, Leve LD, Novins DK, Vitiello B: Consensus report on impulsive aggression as a symptom across diagnostic categories

in child psychiatry: Implications for medication studies. *J Am Acad Child Adolesc Psychiatry* 2007; 46:309-322

- Stocks JD, Taneja BK, Baroldi P, Findling RL: A phase 2a randomized, parallel group, dose-ranging study of molindone in children with attention-deficit/hyperactivity disorder and persistent, serious conduct problems. *J Child Adolesc Psychopharmacology* 2012;22:102-111

TH37. TEACHING THE TEACHERS OF CLINICAL PSYCHOPHARMACOLOGY

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Abstract: This poster focuses on psychopharmacology teachers and their teaching. Based on the authors' experience teaching and the literature, we make broadly based pedagogic suggestions on how to deliver evidence-based and neurobiologically informed prescribing information to clinicians at all levels of experience. Teaching essential psychopharmacology knowledge and practice must be up-to-date, accurate, and consistent with the reality of an individual patient's life experience and beliefs. Educators must teach that nonpsychopharmacological factors in a patient's life may be as relevant to the treatment setting as the actual pharmacological basis of psychotropic drug therapeutics.

Learning Objectives:

- At the conclusion of this presentation, participants will be aware of issues in teaching psychopharmacology.
- At the conclusion of this presentation, participants will be aware of new techniques in teaching psychopharmacology.

Literature References:

- Salzman C, Glick ID. Teaching the Teachers of Clinical Psychopharmacology. *Acad Psychiatry*. 2015; 39:475-481.
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TH38. ASSESSMENT OF AMPHETAMINE WITHDRAWAL SYMPTOMS OF LISDEXAMFETAMINE DIMESYLATE TREATMENT FOR ADULTS WITH BINGE EATING DISORDER

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Abstract: Introduction: In adults with protocol-defined moderate to severe binge eating disorder (BED), lisdexamfetamine dimesylate (LDX) reduced binge eating days per week in 2 randomized, double-blind, placebo (PBO)–controlled, 12-week studies. Maintenance of efficacy was demonstrated in a 9-month study that included a 3-month LDX open-label phase and a 6-month, double-blind, PBO-controlled, randomized-withdrawal phase. Here, amphetamine withdrawal symptoms, assessed with the Amphetamine Cessation Symptom Assessment (ACSA), are described after the last LDX dose in the aforementioned studies.

Objective: To describe ACSA scores after the last LDX dose in adults who completed 1 of 3 LDX clinical studies of BED.

Methods: All 3 studies enrolled adults with protocol-defined moderate to severe BED. Two short-term studies used identical randomized, double-blind, PBO-controlled designs with participants randomized (1:1) to PBO or dose-optimized LDX (50 or 70 mg). The long-term maintenance study used a double-blind, PBO-controlled, randomized-withdrawal design with participants categorized as LDX responders (≤ 1 binge eating day/wk for 28 consecutive days and Clinical Global Impression-Severity scores ≤ 2 [borderline ill or less]) after 12 weeks of open-label LDX (50 or 70 mg) being randomized (1:1) to continued dose-optimized LDX or PBO for 26 weeks. The ACSA, a self-report assessment validated in treatment-seeking amphetamine abusers that contains 16 items rated on 5-point scales (0=not at all to 4=extremely; total score range: 0–64), assessed withdrawal symptoms in each study. Mean $\pm$ SD and median ACSA scores are presented in study completers; data from the 12-week efficacy studies were pooled for assessment.

Results: In the 12-week efficacy studies, on the day of last dose at week 12/early termination (ET), aggregate ACSA total scores were 7.0 ± 7.60 (median, 5.0) with PBO (n=275) and 4.9 ± 6.41 (median, 3.0) with LDX (n=271). Aggregate ACSA total score increased to 7.0 ± 7.62 (median, 4.5) on day 2 post the last LDX dose (n=230) and decreased to 5.5 ± 7.50 (median, 3.0) on day 7 post the last LDX dose (n=221). Over the 7 days following the last PBO dose, aggregate ACSA total scores remained lower than on the day of last dose (4.8 ± 6.82 [median, 2.0] on day 7 post the last dose [n=234]). In the maintenance of efficacy study, on the day of last dose at week 38/ET aggregate ACSA total scores were 4.8 ± 6.67 (median, 2.0) with PBO (n=44) and 4.7 ± 7.78 (median, 2.0) with LDX (n=85). Aggregate ACSA total score increased to 6.1 ± 7.63 (median, 3.5) on day 2 post the last LDX dose (n=78) and to 5.1 ± 7.02 (median, 3.0) on day 1 post the last PBO dose (n=40). Aggregate ACSA total score decreased to 5.2 ± 7.93 (median, 2.0) and 3.9 ± 5.75 (median, 1.0), respectively, on day 7 post the last LDX (n=71) and PBO dose (n=37).

Conclusion: Abrupt LDX termination was not associated with amphetamine withdrawal symptoms as measured by ACSA at the durations of exposure and doses used in these studies.

Learning Objectives:

- To understand the characteristics of stimulant withdrawal and the use of the Amphetamine Cessation Symptom Assessment (ACSA).
- To understand that after 12 to 38 weeks of lisdexamfetamine dimesylate (LDX) exposure, abrupt cessation of LDX was not associated with amphetamine withdrawal symptoms as measured by ACSA.

Literature References:

- McElroy SL, Hudson J, Ferreira-Cornwell MC, Radewonuk J, Whitaker T, Gasior M: Lisdexamfetamine dimesylate for adults with moderate to severe binge eating disorder: Results of two pivotal phase 3 randomized controlled trials. *Neuropsychopharmacology* 2015 (doi: 10.1038/npp.2015.275)
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TH39. CAREGIVER BURDEN IN SCHIZOPHRENIA: POOLED ANALYSIS OF THE INVOLVEMENT EVALUATION QUESTIONNAIRE DATA FOR PALIPERIDONE PALMITATE 3-MONTH FORMULATION

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Abstract: Background: Schizophrenia-related caregiver burden is often under-recognized and associated with significant psychological and physical stress and increased indirect costs on the caregiver. The pooled analysis of 2 double-blind, randomized, multicenter, phase 3 studies (NCT01529515 and NCT01515423) evaluated the predictors of improvement or worsening of schizophrenia-related caregiver burden following paliperidone palmitate (including 1-month and 3-month formulations) treatment.

Methods: Caregivers (family members/friends who had ≥ 1 hour of contact per week with the patients treated with PP 1-month) were offered to complete the involvement evaluation questionnaire (IEQ; 46 items; each item score: 0-4; total score: sum of all items in module 2 [0-124]).

Results: Total, 1497 caregivers (mean [SD] age: 51.5 [13.02] years) were included: 49.3% were parents and >50% of caregivers spent >32 hours/week in caregiving. Caregivers had significant improvement in IEQ sum scores from baseline to end-of-study (n=756; mean [SD] baseline score: 28.3 [15.34] points; mean [SD] improvement: 8.9 [14.73] points); most improvements seen in worrying (2.6 points) and urging (3.7 points) domains. There was significant relationship between improvement in IEQ sum scores and relapse status ($p < 0.001$), and patient age ($p < 0.05$); age of diagnosis, long-acting injectable (LAI) use at baseline, number and duration of prior psychiatric hospitalizations (<24 months) had no significant effect on improvement. Caregiver burden improvement was significant in patients on prior oral antipsychotics post switching to LAI with less leisure days being impacted and less hours spent in caregiving ($p < 0.001$).

Conclusions: Caregiver burden in family members of patients treated for schizophrenia is considerable. Switching from an oral antipsychotic to an LAI can provide a meaningful and significant improvement in caregiver burden.

Learning Objectives:

At the conclusion of the session, the participant should be able to:

- Recognize the caregiver burden in patients with schizophrenia.
- Recognize the extent of improvements in caregiver burden in patients treated for schizophrenia.
- Identify the benefits of reducing caregiver burden within schizophrenia and psychiatry clinics in order to both reduce psychiatric symptom severity and better coordinate mental health care.

Literature References:

- Berwaerts, J., Liu, Y., Gopal, S., Nuamah, I., Xu, H., Savitz, A., Coppola, D., Schotte, A., Remmerie, B., Maruta, N., Hough, D. W. (2015). Efficacy and Safety of the 3-Month Formulation of Paliperidone Palmitate vs Placebo for Relapse Prevention of Schizophrenia: A Randomized Clinical Trial. *JAMA Psychiatry*.
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month formulation for patients with schizophrenia: A randomized, multicenter, double-blind, noninferiority study, accepted for publications at Int J Neuropsychopharmacol.

TH40. A CASE SERIES ON THE EFFECTIVENESS OF LURASIDONE IN PATIENTS WITH STUTTERING

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Abstract: Introduction: Stuttering is a prevalent condition, affecting approximately 3 million people in the United States alone (1) . Thus, there have been multiple pharmacological therapies pursued in the treatment of stuttering. The Dopamine Hypothesis of Stuttering can be considered when approaching treatment strategies. This hypothesis explains that stuttering may possibly result from abnormally increased cerebral dopamine activity (2) . Dopamine levels are crucial to maintaining the basal ganglia circuits, which helps with timing cues in initiating speech (3) . Thus, many atypical antipsychotics are used off-label in the treatment of stuttering, lurasidone is a potent well-tolerated D2 receptor antagonist that can also be considered in the treatment of stuttering (4) . This is a case series of 8 patients, ranging from age 13 to 50 years old, comparing the severity of their stuttering before and after starting off-label use of lurasidone.

Methods: This is a non-randomized, open label study of the use of lurasidone. Patients rated the severity of their stuttering based on the Subjective Screening of Stuttering scale (5) and answered a standardized questionnaire regarding their demographic information and experience with lurasidone and other previous medications trials for stuttering.

Results: Patients showed improvement while on lurasidone. Patients reported lessened severity while on lurasidone, according to the Subjective Screening of Stuttering scale. Most patients felt improvement at 120 mg. Patients reported improvement in quality of life and better than previous trials of asenapine and aripiprazole.

Conclusion: This open label study of the off-label use of lurasidone in patients with stuttering showed lessened severity in symptoms, as evidenced by patients' responses on the Subjective Screening of Severity scale. The limitations lie in the the study being open label and the small sample size. However, this is an important first step in considering lurasidone in the treatment of stuttering and more research is needed to truly measure outcome and effectiveness on a large scale.

Learning Objectives:

- Explain the pathways leading to stuttering.
- Explore novel off-label use of lurasidone to treat stuttering.

Literature References:

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TH41. PSYCHIATRIC STABILITY MAINTAINED IN TARDIVE DYSKINESIA SUBJECTS TREATED WITH VALBENZAZINE (NBI-98854)

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Abstract: Introduction: Tardive dyskinesia (TD) is a persistent movement disorder induced by chronic antipsychotic exposure, for which there are currently no FDA-approved treatments. Valbenazine (VBZ; NBI-98854) is a novel, highly selective vesicular monoamine transporter 2 (VMAT2) inhibitor under investigation for use in TD that exhibited favorable safety in earlier studies. KINECT 2 (NCT01733121) was a dose-escalating trial evaluating safety and efficacy of VBZ for TD, demonstrating significant and clinically meaningful improvement vs placebo. The present analysis evaluated the psychiatric status of subjects across the trial.

Methods: KINECT 2 was a prospective, randomized, double-blind, 6-week, placebo-controlled trial in subjects with schizophrenia, mood disorder or gastrointestinal disorder with moderate or severe TD. VBZ or placebo (1:1) were administered once daily. All subjects randomized to VBZ received 25 mg through Week 2, then the dose was titrated to 50 mg or maintained at 25 mg; at Week 4 the dose was titrated to 75 mg, maintained or reduced to the previous dose. After Week 6, subjects completed a 2-week follow-up. The primary endpoint (previously reported) was Week 6 change from baseline (CFB) in Abnormal Involuntary Movement Scale (AIMS) score vs placebo. AIMS videos were scored by two blinded central raters. Safety assessments were analyzed descriptively and included the following psychiatric scales: the Positive and Negative Syndrome Scale (PANSS), Young Mania Rating Scale (YMRS), Montgomery-Asberg Depression Rating Scale (MADRS), Calgary Depression Scale for Schizophrenia (CDSS), and the Columbia Suicide Severity Rating Scale (C-SSRS).

Results: 102 subjects were randomized; 76% of VBZ subjects reached the maximum dose of 75 mg. The Safety population was 51 (VBZ) and 49 (placebo) subjects. Antipsychotics, antidepressants, and anxiolytics were the most common concomitant medications, taken by ≥40% of subjects in each group. Week 6 CFB in AIMS score (primary endpoint) was significantly greater for VBZ vs placebo ($P=0.0005$). Psychiatric status measured by psychiatric rating scales remained stable or improved from baseline to Week 6 for both groups, as shown by CFB in: PANSS scores for positive symptoms VBZ -0.6 vs placebo -1.0, negative symptoms VBZ 0.5 vs placebo -0.9, and general psychopathology VBZ -0.5 vs placebo -0.7, MADRS VBZ -1.5 vs placebo -0.2, CDSS VBZ -0.9 vs placebo -0.7, and YMRS VBZ -1.1 vs placebo -0.3. The percentage of subjects with suicidal ideation/behavior as measured by the C-SSRS for VBZ vs placebo was 5.9% vs 2.0% (screening) and 5.9% vs 0% (Weeks 2-8).

Conclusion: There was no apparent increase in psychopathology, depression or suicidality with VBZ, and psychiatric status remained stable or improved in subjects with underlying schizophrenia, schizoaffective disorder, depression or bipolar disorder. Together with favorable efficacy findings, these results indicate that VBZ may be a promising therapy for TD.

Learning Objectives:

- To familiarize participants with the clinical data for valbenazine, which has been designated as breakthrough investigational drug by the US FDA for the treatment of tardive dyskinesia.
- To communicate additional safety results from a Phase 2 study (KINECT 2), which indicate stable psychiatric status in subjects with tardive dyskinesia who were treated with once-daily valbenazine.

Literature References:

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TH42. KINECT 3: A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED PHASE 3 TRIAL OF VALBENAZINE (NBI-98854) FOR TARDIVE DYSKINESIA

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Abstract: Introduction: Tardive dyskinesia (TD) is a persistent and often disabling movement disorder resulting from chronic antipsychotic exposure. There are currently no treatments FDA-approved for TD. Valbenazine (VBZ), a novel and highly selective vesicular monoamine transporter 2 (VMAT2) inhibitor, is designated an FDA breakthrough investigational therapy. VBZ demonstrated favorable efficacy and safety profiles in Phase 1 and 2 studies. The efficacy, safety and tolerability of VBZ for TD were evaluated in a Phase 3 trial (KINECT 3; NCT02274558).

Methods: KINECT 3 was a double-blind, parallel-group, 6-week, placebo-controlled trial in subjects with moderate or severe antipsychotic-induced TD and underlying schizophrenia, schizoaffective disorder, or mood disorder. Subjects were randomized (1:1:1) to once-daily treatment with placebo, VBZ 40 mg, or VBZ 80 mg. The primary outcome was an intent-to-treat (ITT) analysis of change from baseline, at Week 6, on the Abnormal Involuntary Movement Scale (AIMS) score, assessed by blinded central video raters, for VBZ 80 mg vs placebo. Safety assessments included adverse event (AE) rates, laboratory, ECG, and psychiatric assessments, including the Positive and Negative Syndrome Scale (PANSS), Young Mania Rating Scale (YMRS), Montgomery-Asberg Depression Rating Scale (MADRS), Calgary Depression Scale for Schizophrenia (CDSS), and the Columbia Suicide Severity Rating Scale (C-SSRS).

Results: Sixty-four sites randomized 234 subjects. Sixty-six percent of subjects had schizophrenia or schizoaffective disorder, and 86% were receiving concomitant antipsychotic medications (16% typical, 77% atypical). The mean baseline AIMS score (SD) was 10.1 (4.0). VBZ 80 mg resulted in a significant improvement in AIMS score vs placebo (LS Mean change from baseline -3.2 vs -0.1; $P<0.0001$). The AIMS score was also reduced in the VBZ 40 mg group vs placebo (LS Mean change from baseline -1.9 vs -0.1; $P=0.0021$; full description of supportive analyses to be presented). AE rates were similar among all groups and were consistent with prior studies. The most commonly reported AE was somnolence: VBZ 80 mg, 5%; VBZ 40 mg, 4%; placebo, 4%. Three percent of subjects discontinued due to treatment-emergent AEs: VBZ 80 mg, 4%; VBZ 40 mg, 3%; placebo, 3%. Across multiple scales (PANSS, YMRS, MADRS, CDSS, C-SSRS), results were generally similar between VBZ and placebo, and psychiatric status remained stable.

Conclusion: Once-daily administration of VBZ was associated with a significant improvement in TD. Both doses of VBZ were generally well tolerated in subjects with underlying schizophrenia, schizoaffective disorder or mood disorder (eg, bipolar disorder, major depressive disorder), even when taken with a wide range of concomitant medications, including antipsychotic agents. Psychiatric scales indicated no apparent increased risk in psychiatric symptoms, depression or suicidality with VBZ during the trial. VBZ may be a promising therapy for TD.

Learning Objectives:

- To familiarize participants with the clinical data for valbenazine, which has been designated a breakthrough investigational drug by the US FDA for the treatment of tardive dyskinesia.
- To provide participants with top-line efficacy and safety results from KINECT 3, a placebo-controlled Phase 3 trial of once-daily valbenazine (80 mg and 40 mg) that included 234 subjects with tardive dyskinesia.

Literature References:

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- Müller T. Valbenazine granted breakthrough drug status for treating tardive dyskinesia. *Expert Opin Investig Drugs* 2015;24:737-742.

TH43. MOODNETWORK.ORG: A SEMINAL ONLINE STUDY

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Abstract: Introduction: Mood disorders are highly prevalent with one in five adults having a lifetime diagnosis of bipolar disorder or depression. Despite this prevalence, stigma

surrounding seeking treatments for mood disorders presents itself as a barrier to treatment. MoodNetwork will bring together 50,000 individuals with mood disorders to provide patient reported outcomes and participate in the research process. MoodNetwork engages patients in all stages of research – from prioritizing research questions, to governance and oversight of the network and studies, to dissemination of results with the ultimate goal of enhancing participants' empowerment and agency through unprecedented collaboration with research and clinical communities. By bringing together a large, diverse group of individuals with mood disorders to provide patient reported outcomes and prioritize research topics, MoodNetwork has the potential to change the face of clinical research. In launching its portal and recruiting participants, the MoodNetwork team has been working closely with clinicians to address questions of importance for the treatment of mood disorders.

Methods: MoodNetwork, based at Massachusetts General Hospital, is working in collaboration with clinicians and patient advocacy groups to recruit a wide variety of individuals with mood disorders to develop a website that promotes inclusion and equality. Patient stakeholders and representatives include individuals from the International Bipolar Foundation, Depression and Bipolar Support Alliance, Anxiety and Depression Association of America, National Organization for People of Color Against Suicide, and National Alliance on Mental Illness. These stakeholder and advocacy group members developed the website, web-based surveys, and recruitment materials to invite individuals with mood disorders to join this community.

Results: As of 1/26/16, MoodNetwork has enrolled 2,217 participants. Of these participants, 96% report experiencing depression and 80.4% endorse past episodes of mania or hypomania. The mean participant age is 43.9 (SD=35.9; range 18-81). Of the sample, 77.4% of participants are female, 18.1% are male, 0.4% report ambiguous gender, and 2.6% are other or unknown. The three most important research topics voted on by participants are reducing stigma (11.5%), alleviating symptoms (11.2%) and new medications (10.3%).

Discussion: MoodNetwork has consistently enrolled 5-15 people daily. This enrollment trajectory can be attributed to the efforts of the MoodNetwork team which is a collaboration of clinicians, researchers, patients, caregivers, members, and advocacy group partners. MoodNetwork is focusing on generating research opportunities and recruiting a representative sample of individuals with mood disorders by targeting men, ethnic and racial minorities, and individuals with unipolar depression. In order to aid in this effort, MoodNetwork has partnered with clinicians and researchers to recruit a diverse, representative sample.

Learning Objectives:

- To highlight the patient-centered approach of MoodNetwork that is based upon a collaboration among clinicians, researchers, patients, caregivers, and advocacy group partners.
- To discover the characteristics of current participants on MoodNetwork, the factors contributing to the study's enrollment trajectory, and how MoodNetwork is an important tool for clinicians.

Literature References:

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TH44. RESULTS FROM AN EXPERT CONSENSUS SURVEY: PATIENT-RELATED FACTORS IN THE USE OF DIGITAL HEALTH TOOLS IN PATIENTS WITH SERIOUS MENTAL ILLNESS

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Abstract: Background: Development of digital health tools (DHT) for patients with serious mental illness (SMI), including schizophrenia, bipolar disorder, and major depressive disorder, requires consideration of patient characteristics and other factors associated with successful use.

Objective: To assess expert opinion on factors affecting use of DHT by patients with SMI.

Methods: A panel of leading experts who met criteria for participation by having contributed to literature on development and evaluation of DHT in psychiatric disorders, completed a 2-part survey containing 19 questions and rated predefined responses on a 9-point Likert scale. In responding, the experts were asked to consider the tool(s) and technology with which they had most experience. Consensus was determined using Chi-square test of score distributions across 3 ranges (1–3, 4–6, 7–9). Categorical ratings of first-, second-, or third-line were designated based on the lowest category in which the confidence interval of the mean ratings fell, with a boundary of >6.5 for first-line. We describe results from 4 questions on patient characteristics relevant to use of DHT (n=40 respondents).

Results: Among patient characteristics likely to affect the ability to successfully engage with and use DHT, greatest consensus was reached for interest in using state-of-the-art technology, whereas, a serious level of disorganization in the patient's life was rated third-line (likely to make it very difficult to use). Among disease-related factors, good occupational functioning was the only option rated first-line in promoting DHT use, whereas, greater severity of cognitive impairment was expected to make it difficult to use DHT. In terms of patient experience and appraisal, those who perceived DHT as beneficial were considered most likely to use it, whereas those with limited insight into their disorder would be unlikely to use it. Improved functioning and reduced symptomology were rated first-line as potential benefits to motivate a patient to use DHT. Experts did not agree on the potential of DHT to reduce healthcare costs as a motivating factor. The experts considered the following most likely to be barriers or produce unintended consequences for patients: beliefs that the DHT is not well suited to their problems, is a burden to use, and/or intrusive; not understanding how to use DHT and/or becoming frustrated with the technology; and/or concerns about privacy. Among activities in which health care professionals could be involved to enable patients to successfully engage with DHT, a high rate of consensus (average rating 8.4; SD 0.9) was reached on the need to provide patients with initial training on using the system.

Conclusions: The experts identified patient characteristics, benefits, and resources that would support the use of DHT by patients with SMI. These results may be used as guidance for facilitating use of DHT in clinical practice.

Supported by Otsuka Pharmaceutical Development & Commercialization, Inc.

Learning Objectives:

- To understand expert opinion regarding factors promoting successful engagement with and use of a digital health tool by patients with serious mental illness.
- To understand expert opinion regarding barriers that may interfere with successful use of a digital health tool by patients with serious mental illness.

Literature References:

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- Rotondi AJ, Eack SM, Hanusa BH, Spring MB, Haas GL: Critical design elements of e-health applications for users with severe mental illness: singular focus, simple architecture, prominent contents, explicit navigation, and inclusive hyperlinks. *Schizophr Bull* 2015; 41(2):440-448

TH45. A TREATMENT REFINEMENT STUDY TO OPTIMIZE THE HABIT FORMATION PROGRAM FOR IMPROVING ADHERENCE TO ORAL MEDICATIONS IN SCHIZOPHRENIA AND SCHIZOAFFECTIVE DISORDER

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Abstract: Background: Medication adherence is a notable problem for patients diagnosed with schizophrenia. A number of psychosocial adherence programs exist to address this problem, yet many require in-person assistance and are typically resource intensive.

Objective: Drawing on a diverse body of empirical literature, a psychosocial treatment program was designed to help patients turn medication-taking into a habit. This program leverages a call-center with an associated technology interaction portal, text messaging and a “habit kit” that is mailed to patients. This adherence program was tested in a pilot study with the following goals: (1) Gain insight on the ease of implementation, the feasibility of implementation, and the preliminary data on the effectiveness of the program, and (2) Determine modifications for improvement of the program to aid medication adherence habit formation. This poster describes findings from this pilot study.

Methods: A single site enrolled 17 patients diagnosed with schizophrenia or schizoaffective disorder who were currently prescribed antipsychotic medication and reported suboptimal medication adherence, yet indicated a willingness to take medicine to treat their schizophrenia or schizoaffective disorder. This study comprised two phases: a screening period (Days -3 to -1) and a treatment refinement period (Days 1 to 24). During the treatment refinement period, patients were sent their “habit kit”, participated in six separate phone calls

with call center agents and if they opted-in, received periodic text messages. Pilot study data was collected using a variety of methods including in-home patient observation, interviews, call center audio recording analyses to evaluate usability and fidelity, engagement metrics regarding call center contact and text messaging as well as traditional clinical screening and psychometric measures. Clinical academic as well as qualitative user-centered design researchers were involved in data collection and all patient contact occurred in the patient homes.

Results: Seventeen patients were enrolled and 16 (94.1%) completed the study. The mean age (SD) was 49.6 (6.2) years and a majority of the enrolled outpatients were male (58.8%). Overall, the Habit Program was successfully implemented over the study period as evidenced by corroborative data on medication adherence (pill counts, self-reported adherence), medication-taking automaticity (Self-Report Habit Index) and information from in-home observations and interviews suggesting the formation of a habit (habit plan, location of containers). Other measures including call center audio recording analyses (for the evaluation of usability and fidelity), call center and text messaging engagement/feasibility metrics and patient reported satisfaction gave insight into the success of program implementation and helped identify areas for potential refinement.

Conclusions: This study supports the feasibility of the habit program as a new intervention to assist with medication taking for patients diagnosed with schizophrenia or schizoaffective disorder. Information from this pilot can be used to inform refinement for the Helpful Habit Program in an attempt to maximize the potential for this program to positively impact clinical outcomes.

Learning Objectives:

- To assess ease of implementation, the feasibility of implementation, and the preliminary data on the effectiveness of a newly developed medication adherence program for adult patients with schizophrenia.
- To gain understanding of the necessary modifications for improvement of the program to aid medication adherence habit formation.

Literature References:

- Lally P, Gardner B. Promoting habit formation. *Health Psychology Review*, 2013;7:sup1, 137-158.
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TH46. RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PHASE 3 STUDY OF ENCENICLINE AS PRO-COGNITIVE TREATMENT IN PATIENTS WITH SCHIZOPHRENIA

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Abstract: Background: Patients with schizophrenia suffer from cognitive impairments [1], which significantly affect quality of life, even when positive and negative symptoms are optimally treated. Encenicline is a selective $\alpha 7$ nicotinic receptor agonist. Phase 2 studies were positive, leading to two follow-up Phase 3 studies [2]. The primary objective of this

Phase 3 study was to assess the efficacy and safety of once-daily encenicline tablets as a pro-cognitive treatment versus placebo in stable patients with schizophrenia.

Methods: NCT01716975 was a randomized, double-blind, placebo-controlled, parallel-dosing, 26-week, Phase 3 study to evaluate the efficacy and safety of once-daily encenicline tablets (0.9 and 1.8 mg) versus placebo. Eligible male and female subjects aged 18–50 years with a diagnosis of schizophrenia of at least 3 years' duration were assigned to treatment in a 1:1:1 ratio, after successful completion of a 14-day single-blind placebo run-in period. The co-primary efficacy endpoints were cognitive function, as measured by the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB) Neurocognitive Composite Score, and patient function, as measured by the interview-based Schizophrenia Cognition Rating Scale (SCoRS). Both tests were administered during the screening visit (Day -14, which preceded the placebo run-in period), and on Days 1 (pre-dose), 28, 56, 84, and 182. The Day 1 MCCB and SCoRS scores represent the baseline for each of the efficacy evaluations. Safety and tolerability were determined by clinical and laboratory assessments.

Results: 1147 subjects were screened and 766 subjects were randomized; 46.2% of subjects were enrolled from sites located in the United States. The effects of encenicline versus placebo on cognition (as measured by the MCCB Neurocognitive Composite Score) and function (as measured by SCoRS), as well as safety and tolerability results, will be presented.

Discussion: The results of this Phase 3 trial may support the efficacy and favorable safety and tolerability of encenicline for the treatment of cognitive impairment in schizophrenia.

Together with a second Phase 3 study using the identical study design, this is the largest database of pro-cognitive schizophrenia treatment to date.

Learning Objectives:

- To review the efficacy, determined by improved cognition and patient function, of two doses of once-daily encenicline as a pro-cognitive treatment when added to chronic, stable atypical antipsychotic therapy in subjects with schizophrenia in the NCT01716975 study.
- To understand the safety and tolerability of encenicline as a pro-cognitive treatment when added to chronic, stable atypical antipsychotic therapy in subjects with schizophrenia.

Literature References:

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TH47. CARIPRAZINE FOR NEGATIVE SYMPTOMS OF SCHIZOPHRENIA: A POOLED POST HOC ANALYSIS OF 2 RANDOMIZED, DOUBLE-BLIND, PLACEBO- AND ACTIVE-CONTROLLED TRIALS

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Abstract: Background: Schizophrenia is a complex neuropsychiatric syndrome characterized by positive symptoms, negative symptoms, and cognitive impairment. Antipsychotics have efficacy on positive symptoms, but the treatment of negative symptoms remains a clinical challenge. Cariprazine, a potent dopamine D2/D3 receptor partial agonist with preferential binding to D3 receptors, is approved for the treatment of schizophrenia. A pooled post hoc analysis of 2 randomized controlled Phase II/III cariprazine trials (NCT00694707, NCT01104766) was conducted to investigate the effects of cariprazine on negative symptoms of schizophrenia in a subset of patients with schizophrenia and predominant negative symptoms.

Methods: Two 6-week, international, randomized, fixed-dose, double-blind, placebo- and active-controlled studies in adults with acute exacerbation of schizophrenia were pooled (RGH-MD-16 [n=732]: cariprazine 1.5, 3, or 4.5 mg/d, or risperidone 4 mg/d; RGH-MD-04 [n=617]: cariprazine 3 or 6 mg/d, or aripiprazole 10 mg/d). The primary efficacy measure in both studies was change from baseline to Week 6 in Positive and Negative Syndrome Scale (PANSS) total score. Cariprazine doses of 1.5-3.0 and 4.5-6.0 mg/d were pooled for post hoc analyses. Patients with predominant negative symptoms were identified based on a model defining 8 states of schizophrenia (Lenert et al, Schizophr Res; 2004). Criteria for the patient subset being investigated (PANSS factor score for negative symptoms ≥ 24 , PANSS factor score for positive symptoms ≤ 19 , and PANSS factor score for cognitive impairment ≥ 27) indicated severe negative symptoms, mild/moderate positive symptoms, and severe cognitive dysfunction. Mean change from baseline in PANSS factor scores for negative symptoms (items N1-N4, N6, G7, G16) was analyzed using a mixed-effects model for repeated measures ($\alpha=0.05$, 2-sided, without adjustments for multiple comparisons); effects sizes (ES) were calculated.

Results: In the pooled subset of patients with predominant negative symptoms (n=285/1349), mean (SD) baseline PANSS factor scores for negative symptoms were 27.5 (2.9) for placebo (n=67), 27.8 (3.4) for cariprazine 1.5-3 mg/d (n=85), 27.5 (3.0) for cariprazine 4.5-6 mg/day (n=64), 27.6 (3.7) for risperidone 4 mg/d (n=34), and 28.2 (3.2) for aripiprazole 10 mg/d (n=35). The least squares mean difference (LSMD [95% CI]) in change from baseline to Week 6 on the PANSS factor score for negative symptoms was statistically significant versus placebo for cariprazine 1.5-3 mg/d (-2.5 [-4.2, -0.8], $P=.0038$; ES=0.54), cariprazine 4.5-6 mg/d (-3.7 [-5.5, -1.9], $P<.0001$; ES=0.79), and risperidone (-2.5 [-4.7, -0.3], $P=.0258$; ES=0.54); the LSMD for aripiprazole versus placebo was not statistically significant (-1.0 [-3.1, 1.2], $P=.3661$; ES=0.21). Significant effect versus placebo was observed by Week 2 for cariprazine 1.5-3 and 4.5-6 mg/d and by Week 3 for risperidone.

Conclusions: Statistically significant improvement was observed for cariprazine versus placebo on the PANSS factor score for negative symptoms; differences versus placebo were significant for risperidone, but not for aripiprazole. This analysis suggests that cariprazine may have an effect on negative symptoms in patients with predominantly negative symptoms of schizophrenia. Prospectively designed trials are warranted.

Learning Objectives:

- At the conclusion of this session, participants should be able to discuss predominant negative symptoms associated with schizophrenia.
- At the conclusion of this session, participants should know that a positive efficacy signal was demonstrated when cariprazine was compared with placebo in a post hoc

analysis of 2 short-term clinical trials in a subgroup of patients with predominant negative symptoms of schizophrenia.

Literature References:

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TH48. UNDERSTANDING FACTORS IMPACTING ON CGI-S VS. CGI-I DISCREPANCIES: AN EXPLORATORY ANALYSIS

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Abstract: Introduction: We have previously reported CGI discrepancies to occur at approximately 5.5% of applicable study visits (Daniel, Kott; 2015). Errors in rating the Clinical Global Impression Scale (CGI), especially discrepancies between the CGI-I and change from baseline in the CGI-S may seriously impair signal detection and connote broader data quality issues. For example, CGI discrepancies may be in individual cases stem from poor protocol understanding, (un)intentional baseline score inflation or other forms of data manipulation.

In the current analysis we aimed to identify what factors impact the presence of CGI discrepancies. Specifically, we examined the differences in the distribution of CGI discrepancies with regard to 1) study type, 2) region, 3) presence of rater change compared to baseline, 4) time from baseline to current assessment, 5) baseline and 6) visit severity and 7) PANSS total score vs. CGI-S score discrepancy at screening and/or baseline.

Methods: We have analyzed blinded data coming from 11 industry sponsored double blind clinical trials in schizophrenia. In the first step we used univariate logistic models to estimate the association between discrepancies between the CGI-I and change from baseline in the CGI-S and each of the predictor variables. In the second step we have created a multivariate logistic regression model from all predictor variables from the univariate analysis with a p value < 0.25.

Results: In the combined dataset from 16 schizophrenia trials, 34,402 visits containing information on all predictor variables were used to fit our models. Overall, there were 1,556 (4.5%) CGI discrepancies in the dataset. Both univariate and multivariate models indicate significant association of the CGI discrepancies with the tested predictor variables.

Specifically, significantly increased odds of recording a CGI discrepancy were associated with the following factors: 1) studies conducted in acutely ill subjects, 2) ratings coming from Western Europe and Asia, 3) increasing time difference between baseline and current visit, 4) different rater assessing the CGI compared to baseline, 5) presence of baseline discrepancy between PANSS and CGI-S scores, and 6) with increasing baseline severity.

Discussion: The most common type of CGI discrepancy was referencing the CGI-I to prior visit rather than to baseline. This may explain the increased odds of CGI discrepancies in acute studies, in more symptomatic subjects at baseline, and at visits with greater time difference between baseline and current visit. Inadequate knowledge of subject's baseline condition may explain the association with rater change. The pre-randomization discrepancies between PANSS and CGI-S scores then likely represent a general misunderstanding of CGI mechanics and thus increase the odds of CGI discrepancies. Currently we do not have a plausible explanation for the regional differences in CGI discrepancies. While cultural effects could be blamed, one would expect those to play a major role in PANSS and CGI discrepancies rather than within the CGI scale itself. Further research is thus needed. CGI discrepancies are responsive to remediation and can be significantly minimized by the use intelligent eCOAs with immediate detection and feedback features.

Learning Objectives:

- Attendees will become familiar with the amount of CGI discrepancies in schizophrenia clinical trials.
- Attendees will become familiar with factors impacting the presence of CGI discrepancies.

Literature References:

- Daniel, D. G., Kott, A.. (2015). Regional Distribution of Scoring Errors in Rating the Clinical Global Impression Scale in Global Schizophrenia Clinical Trials. Poster presented at the 2015 Annual Meeting of the American Society of Clinical Psychopharmacology (ASCP), 22-25 June 2015, Miami, Florida.
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TH49. SWITCHING PATIENTS WITH ACUTE SCHIZOPHRENIA TO BREXPIRAZOLE: POST-HOC ANALYSIS OF A DOUBLE-BLIND RANDOMIZED MAINTENANCE TREATMENT STUDY

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Abstract: Background: The management of schizophrenia requires effective and tolerable treatments to improve outcomes and reduce the risk of relapse. Brexpiprazole is a serotonin-dopamine activity modulator that is a partial agonist at 5-HT_{1A} and dopamine D₂ receptors, and an antagonist at 5-HT_{2A} and noradrenaline alpha_{1B/2C} receptors, all at similar potencies. The efficacy and safety of brexpiprazole for the treatment of adults experiencing schizophrenia was demonstrated in two 6-week, and one maintenance treatment, phase 3 trials.

The short-term pivotal brexpiprazole studies included a wash-out period for the removal of prior antipsychotics and therefore were not designed to investigate therapeutic switching strategies in acutely ill patients. Here we report the rate of adverse events in a group of

patients who were cross-titrated from a previous antipsychotic to brexpiprazole during the conversion phase of the maintenance treatment trial [NCT01668797].

Methods: Patients experiencing an acute exacerbation (PANSS total score >80) of schizophrenia were cross titrated from current antipsychotic treatment(s) to brexpiprazole as part of the study protocol before entering a 12–36-week single-blind stabilization phase. On Day 1 of the cross-titration phase, patients were initiated on brexpiprazole 1 mg/day in addition to their other oral antipsychotic treatment(s). Brexpiprazole was increased in 1 mg increments at scheduled visits to a maximum of 4 mg/day, while other oral antipsychotic treatment(s) were gradually reduced. The cross-titration period for each patient was at the discretion of the investigator as long as it was within the protocol-specified duration of a minimum of 1 week and a maximum of 4 weeks. In order to enter the stabilization phase, subjects must have been able to tolerate a minimum dose of brexpiprazole 1 mg/day.

Results: A total of 406 patients, with a mean (SD) PANSS total score of 91.1 (8.7), entered the cross-titration phase with 404 patients receiving at least 1 dose of brexpiprazole. A total of 8 patients (2.0%) discontinued the cross titration phase due to adverse events, with 346/387 (89%) patients – excluding 19 patients withdrawn due to study termination following a positive interim analysis – being successfully cross-titrated. Duration of cross titration was 4 weeks in 212/406 (52.2%) patients, 3 weeks in 54 (13.3%) patients, 2 weeks in 42 (10.3%) patients, and 1 week in 17 (4.2%) patients. The remaining 79 (19.5%) patients had a cross-titration period of >4 weeks. Over the first 4 weeks of exposure to brexpiprazole (including the cross titration and initial stabilization phases), rates of treatment emergent adverse events were similar to that observed in the 6-week pivotal studies. The average final dose of brexpiprazole after 4 weeks of treatment was 3.2 mg/day.

Conclusion: When given guidance that a 1–4-week cross-titration from previous antipsychotics should be followed prior to patients entering the stabilization phase of a long-term brexpiprazole maintenance study, the majority of investigators chose a cross-titration period of at least 4 weeks. These data provide an evidence base from which clinicians can choose a switching paradigm that best meets their patient’s needs.

Learning Objectives:

- The safety and tolerability profile of brexpiprazole in patients with schizophrenia who were switched from prior medication to brexpiprazole over 1 to 4 weeks as part of a randomized maintenance study.
- Evidence presented here may help clinicians determine the cross-titration period that meets their patient’s needs when switching antipsychotic treatments.

Literature References:

- Correll CU, et al. *Am J Psychiatry*. 2015;172(9):870–880
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TH50. RELATIONSHIP BETWEEN RESPONSE TO ARIPIPRAZOLE ONCE-MONTHLY AND PALIPERIDONE PALMITATE ON WORK READINESS AND FUNCTIONING: A POST-HOC ANALYSIS OF QUALIFY, A HEAD-TO-HEAD STUDY IN SCHIZOPHRENIA

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Abstract: Background: QUALIFY compared the effectiveness of aripiprazole once-monthly 400 mg (AOM 400) to paliperidone palmitate once-monthly (PP) in patients with schizophrenia. Capacity to work, an additional functional endpoint relevant to patients' quality of life, was assessed with the Readiness for Work Questionnaire (WoRQ) [1]. These post-hoc analyses investigated the relationship of different measures of patient functioning with AOM 400 and PP treatment.

Methods: QUALIFY was a 28-week, randomized, open-label, head-to-head study (NCT01795547) of 2 atypical long-acting injectable anti-psychotics (LAIs), AOM 400 and PP (flexible dosing per label, 78-234 mg/month as paliperidone palmitate) in patients with schizophrenia age 18-60 years. The primary endpoint was change from baseline to week 28 on the Heinrichs-Carpenter Quality-of-Life Scale (QLS) total score [2]. QLS comprises 21 items in 4 domains: interpersonal relations (8 items), instrumental role (4 items), intrapsychic foundations (7 items), and common objects and activities (2 items), rated by a blinded clinician; QLS total score changes ≥ 5.3 points are considered clinically relevant [3]. Work readiness (Yes/No) was rated at baseline and week 28 by a non-blinded clinician. The primary analysis used a mixed model for repeated measures (MMRM). Post-hoc analyses used logistic regression to compare relative odds of work readiness after AOM 400 and PP treatment adjusting for baseline work readiness status. Irrespective of treatment, patients were categorized based on work readiness at baseline and week 28 (No to Yes, Yes to Yes, or No at week 28), and changes from baseline to week 28 in QLS total, domain, and items scores were compared with MMRM.

Results: QLS total score showed superior improvement with AOM 400 (n=136) vs PP (n=132; least squares mean [LSM] treatment difference: 4.67, 95%CI: [0.32;9.02], p=0.036). At week 28, 29/110 (26.4%) AOM 400 patients changed from No to Yes in work readiness vs 12/98 (12.2%) with PP; odds of being rated ready for work were higher for AOM 400 vs PP (adjusted odds ratio: 2.67, 95%CI: [1.39; 5.14], p=0.003). Patients (independent of treatment) in the No to Yes group (n=41) had a LSM change ($\pm$ SE) on QLS total score of 14.3 $\pm$ 2.2 points, significantly greater than the No at week 28 group (n=118; LSM change: 2.7 $\pm$ 1.4; LSM difference: 11.6 $\pm$ 2.6, 95%CI: [6.5;16.7], p<0.0001). QLS total scores also improved in the Yes to Yes group (n=49) compared with the No at week 28 group (LSM differences: 7.9 $\pm$ 2.7, 95%CI: [2.5; 13.2], p=0.0045). QLS instrumental role domain scores were significantly improved in the No to Yes group vs the No at week 28 group (p<0.0001), with LSM improvements of ~1 point on each item in the No to Yes group.

Conclusion: These results show a strong association between shifts in work readiness and improvements on QLS, particularly in QLS categories related to work functioning, and highlight consistency between different scales assessed by independent raters (one blinded and one not blinded to treatment). The association between QLS and WoRQ was independent of treatment, but significantly greater improvements in both scales were seen with AOM 400 vs PP. The strong association between functional improvements in health-related quality of life and work readiness suggest that increasing patients' capacity to work is a realistic goal in schizophrenia treatment.

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Learning Objectives:

- To understand the relationship between the Heinrichs-Carpenter Quality of Life scale and the Work Readiness Questionnaire in the treatment of schizophrenia.
- To understand the improvements in quality of life and readiness to work as measured by the Heinrichs-Carpenter Quality of Life scale and the Work Readiness Questionnaire in patients receiving aripiprazole once-monthly in the QUALIFY study.

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TH51. LONG-TERM SAFETY AND DURABILITY OF EFFECT OF ARIPIPRAZOLE LAUROXIL IN A ONE-YEAR SCHIZOPHRENIA EXTENSION STUDY

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Abstract: Introduction: Aripiprazole lauroxil (AL; ARISTADA™, Alkermes, Inc.), a long-acting injectable (LAI) antipsychotic, is approved for the treatment of schizophrenia. We report on efficacy and safety outcomes from a 1-year long-term AL extension study.

Methods: Enrolled subjects (n=478, safety population): de novo subjects with chronic stable schizophrenia who could benefit from switching to a LAI and, rollover subjects who had completed a double-blind, 12-week, placebo-controlled study. De novo subjects received monthly injections of AL 882 mg, and rollover (placebo or AL) subjects received monthly injection with either AL 441 mg or AL 882 mg, depending on their assigned treatment in the preceding placebo-controlled study. Subjects who were first assigned to active AL also received daily oral aripiprazole (15 mg) for 3 weeks. The key primary and secondary objectives were to characterize the safety, and to evaluate the durability of therapeutic effect of AL in subjects with stable schizophrenia.

Results: Of 478 (de novo [n=242]) enrolled subjects, 462 had evaluable post-baseline data. At baseline, the mean (SD) age was 39 (12) years, 58% were male, 64% were white, and the mean (SD) Positive and Negative Syndrome total Score (PANSS) was 61 (14). High proportions of subjects received ≥ 9 (76%) or ≥ 13 injections (69%) of AL. Of the 110 and 368 patients enrolled in the 441 mg and 882 mg AL study arms, respectively, 32% of patients discontinued in each study arm. Drug-related adverse events were reported in 29 (26%) and 112 (30%) of subjects in the 441 and 882 mg AL arms. Treatment-emergent adverse events

observed in $\geq 5\%$ of subjects were insomnia (8%), and increased weight (5%). Serious drug-related adverse events were reported only in the 882 mg arm [3 subjects ($<1\%$)]. Overall incidence of Parkinsonism and akathisia were 7% and 5%, respectively. The majority of patients (77%) gained ≤ 5 kg over 16 months, and at any post-baseline visit, 88 subjects (18%) had a weight increase of $\geq 7\%$. Overall response ($\geq 30\%$ decrease in PANSS from baseline to Day 365 or, CGI-I of 2 or 1) was achieved by 51% of subjects at endpoint. Overall, the mean (SD) change from baseline in PANSS at study endpoint was -8 (10) and in CGI-S was -0.4 (0.7). The mean (SD) reduction in PANSS the placebo to either the 441 mg or 882 mg AL subject group was -19 (15) or -12 (12), respectively.

Conclusion: AL treatment for ≥ 1 year demonstrated continued safety and additional therapeutic effect. Safety extension studies may have the limitation of selecting for treatment responders, but about half of our study subjects were treated de novo. The low drop out/high retention of this study supports the high overall safety and tolerability of AL for patients with schizophrenia. Further, the low proportion with weight gain supports the beneficial metabolic profile of the treatment with AL LAI. This study supports continued reduction in symptoms with maintenance AL with over half of completers meeting response criteria.

Learning Objectives:

- Awareness of the long-term safety and treatment effect of aripiprazole lauroxil, a recently-approved long-acting injectable antipsychotic for the treatment of schizophrenia.
- Awareness of results from an aripiprazole lauroxil extension study that support a beneficial metabolic profile and showed high subject retention.

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TH52. A MULTICENTER, 8-WEEK STUDY TO ASSESS USABILITY OF A DIGITAL HEALTH FEEDBACK SYSTEM IN ADULTS WITH SCHIZOPHRENIA TREATED WITH ORAL ARIPIPRAZOLE

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Abstract: Background: Detection of nonadherence to oral antipsychotics is notoriously difficult and prone to error. A Digital Health Feedback System (DHFS) offers a new opportunity to objectively measure and report a patient's medication ingestion. The DHFS consists of a medication-embedded ingestible sensor, wearable sensor, and mobile- and cloud-based software applications that enable the secure collection and sharing of objective medication adherence information with healthcare professionals (HCP).

Objective: To evaluate the usability of a DHFS in adults with schizophrenia stabilized on oral aripiprazole by assessing their ability to independently replace, pair, and use a wearable

sensor in an 8-week period while taking prescribed doses of oral aripiprazole tablets with embedded ingestible sensors.

Methods: This study consisted of two cohorts in a phase 2a open-label study testing the DHFS. Six US sites enrolled outpatients with schizophrenia taking oral aripiprazole monotherapy for maintenance treatment. The study comprised 3 phases: an initial screening phase, a training phase of 3 weekly site visits to ensure subjects learn how to operate the system, and a 5-week independent phase. Patients and HCP independently rated the usability of the DHFS. (NCT02219009)

Results: Sixty-seven outpatients were enrolled and 49 (73.1%) completed the study. The mean age (SD) was 46.6 (9.7) years, and a majority of the enrolled outpatients were male (74.6%) with a median Clinical Global Impressions – Severity (CGI-S) scale score of mildly ill (73.3%). Overall, based on HCP rating, 32 of 66 (48.5%) subjects were able to pair and apply a patch independently or with minimal assistance at baseline. With respect to subject performance across time, the percent of subjects requiring only minimal assistance improved to 82.7% (43 of 52) by Week 8. Based on subject report, 81.1% were somewhat satisfied, satisfied, or extremely satisfied with the DHFS at week 8.

Conclusions: These results show that a high proportion of both HCPs and subjects diagnosed with schizophrenia were able to use a new DHFS with relative ease. The data supports the potential utility of the DHFS in clinical practice.

Disclosure: Supported by Otsuka Pharmaceutical Development & Commercialization, Inc.

Learning Objectives:

- To assess the usability of a newly developed digital health feedback system (DHFS) in adult patients with schizophrenia.
- To gain understanding of this digital tool that offers the potential to objectively assess medication adherence.

Literature References:

- Sajatovic M, Velligan DI, Weiden PJ, Valenstein MA, Ogedegbe G. Measurement of psychiatric treatment adherence. *J Psychosom Res.* 2010;69(6):591-599.
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TH53. EFFICACY AND SAFETY OF INTRAMUSCULAR ZIPRASIDONE IN CHINESE SCHIZOPHRENIA PATIENTS WITH AGITATION: A RANDOMIZED, BLIND, ACTIVE PARALLEL-CONTROLLED, MULTICENTER CLINICAL TRIAL

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Abstract: Purpose: The aim of this study is to compare efficacy and safety of Intramuscular Ziprasidone in the treatment of Chinese Schizophrenia patients with Agitation with Intramuscular Haloperidol by evaluating the parameters at the end of study (72 hours after first dosing) from baseline.

Methods: Patients

This study was conducted in 5 sites in China, in accordance with the Declaration of Helsinki and the State Food and Drug Administration (SFDA) guideline for good clinical practice. The study protocol was approved by the relevant local ethic committees, and all patients or his/her legal representatives were required to provide written informed consent before entering the study.

Eligible patients were inpatients, who are required to stay at hospital during the study, within 18-65 years old, with a DSM-IV criteria for schizophrenia or schizophreniform psychosis, agitated with a minimum total score of ≥ 15 on the 5-item of Positive and Negative Syndrome Scale Excited Component (PANSS-EC) and at least one individual item score of ≥ 5 or two item score of ≥ 4 using the 1-7 scoring system and score of ≤ 3 on Agitation Calmness Evaluation Scale (ACES).

Study Design: All eligible schizophrenia patients were randomized to 3 days of blind treatment with Intramuscular Ziprasidone (10mg Bid on 1st day, 10mg or 20mg on 2nd and 3rd day) or Intramuscular Haloperidol (5mg Bid on 1st day, 5mg or 10mg on 2nd and 3rd day).

Assessments: The primary efficacy assessment was the PANSS-EC total score change at the end of study (72 hours after first dosing) from baseline. The ratings were conducted by the same person at each visit, whenever possible. Additional efficacy parameters were the Clinical global impression scale (CGI), ACES, PANSS and Brief Psychiatric Rating Scale (BPRS).

Safety and tolerability were evaluated on the basis of adverse events, Rating Scale for Extrapyramidal Side Effects (RSESE), Barnes Akathisia (Rating) Scale (BAS), Electrocardiograms (ECGs), vital signs, and laboratory tests.

Statistical Analysis: According to intention-to-treat (ITT) population, efficacy analyses were conducted on the Full Analysis Set (FAS), which included all randomized patients who took at least 1 dose of blind study medication and who had at least 1 valid post-baseline assessment of the PANSS-EC total score. Efficacy analyses also were conducted on the Per-Protocol Set (PPS), which included all patients who completed 6 dosing of treatment.

The primary efficacy endpoint was defined as the change from baseline to 72 hours in the PANSS-EC total score, using the principle of last observation carried forward (LOCF). The primary analysis was based on a general linear model for analysis of covariance (ANCOVA) with factors for treatment and center, and with baseline PANSS-EC total score as a covariate. The non-inferiority test of Intramuscular Ziprasidone versus Intramuscular Haloperidol was performed at a 5% level of significance using 2 points of the estimated differences on PANSS-EC total score between Intramuscular Ziprasidone and Intramuscular Haloperidol. Response was defined as a $\geq 50\%$ decrease in the PANSS-EC.

Safety analyses were conducted on the Safety Set (SS), which included all randomized patients who took at least 1 dose of blind study medication.

Results: A total of 240 patients entered the blind period (120 patients were randomized to Intramuscular Ziprasidone and 120 to Intramuscular Haloperidol; table1). The FAS and SS is the same as 240. A total of 232 patients completed the study. The incidence of withdrawals was low: 1.67% (1 patient withdrew due to compliance issue and 1 patient withdrew due to adverse events) in the Intramuscular Ziprasidone group and 5.00% (1 patient withdrew

informed consent and 5 patients withdrew due to adverse events) in the Intramuscular Haloperidol group (table 1). Besides, none of patients in 2 groups had serious protocol violation. The PPS population thus comprised 118 patients in the Intramuscular Ziprasidone group and 114 patients in the Intramuscular Haloperidol group. There were no clinically relevant differences at baseline between the two treatment groups on the basis of demography or disease severity. Neither differences was found at dose-increased percentage on 2nd and 3rd day between 2 groups (15.3% vs 15.3%).

Table 1. Disposition, demographics, and mean baseline scores

	Intramuscular Ziprasidone		Intramuscular Haloperidol	
Disposition	Patients randomized (FAS/SS)		120	120
	Patients completed	118 114		
PPS	118	114		
	Patients withdrawn from study		2	6
	Due to adverse events		1	5
	Due to compliance issue/Lost to follow up			1
	Withdraw informed consent		1	
Demographics	Male	63 (52.50%)	72 (60.00%)	
	Female	57 (47.50%)	48 (40.00%)	
	Age in years, mean $\pm$ SD		31.1 $\pm$ 10.3	32.3 $\pm$ 11.1
Baseline Scores	PANSS-EC total score, mean $\pm$ SD		21.4 $\pm$ 3.4	21.3 $\pm$ 3.4

Comparable efficacies of Intramuscular Ziprasidone and Intramuscular Haloperidol were achieved with respect to mean change from baseline in PANSS-EC total score at 72 hours (LOCF). The mean PANSS-EC total score decreased substantially over time for patients in both treatment groups (table 2). However, there was no significant difference between 2 groups.

Table 2. Mean change from baseline in PANSS-EC total scores

Time	Group	N	Change	Compare to baseline			Compare between 2 groups	
			t	P	F	P		
2 hours	Ziprasidone	120	- 4.7 $\pm$ 5.1		10.09	0.0001	0.7529	0.3864
	Haloperidol	120	- 4.2 $\pm$ 4.8		9.40	0.0001		
6 hours	Ziprasidone	120	- 6.5 $\pm$ 5.1		14.00	0.0001	0.9476	0.3313
	Haloperidol	120	- 5.9 $\pm$ 4.8		13.36	0.0001		
24 hours	Ziprasidone	120	-7.4 $\pm$ 4.2		19.36	0.0001	0.9293	0.3360
	Haloperidol	120	-8.0 $\pm$ 4.9		17.94	0.0001		
48 hours	Ziprasidone	120	-9.2 $\pm$ 3.6		20.07	0.0001	1.3712	0.2428
	Haloperidol	120	-9.7 $\pm$ 4.5		20.83	0.0001		
72 hours	Ziprasidone	120	-9.8 $\pm$ 4.8		22.41	0.0001	2.091	0.1495
	Haloperidol	120	-10.4 $\pm$ 5.0		22.99	0.0001		

There were approximately equal numbers of patients in both treatment groups who were responders (66.7% vs 73.3%) at 72 hours.

It was showed that difference value of PANSS-EC between 2 groups (0.64) was in the range of 10% mean change from baseline of Intramuscular Haloperidol group (1.04), which meant the efficacy of Intramuscular Ziprasidone was not inferior to that of Intramuscular Haloperidol.

A total of 40.8% of patients in the Intramuscular Ziprasidone group and 55.8% of the patients in the Intramuscular Haloperidol group reported AEs during the clinical trial with significant difference ($P=0.0201$). Similarly, there were 28.3% patients in study group experienced adverse reactions and 46.7% in controlled group ($P=0.0034$). Especially, there were distinct difference in incidence of EPS (15.8% vs 43.3%, $P<0.001$) and difference of abnormal liver function (2.5% vs 8.3%) between 2 groups. However, there were no apparent trends within or between treatment groups with respect to other laboratory values, ECG, or vital signs.

Discussion: The randomized, blind study comparing Intramuscular Ziprasidone to Intramuscular Haloperidol in the treatment of Chinese Schizophrenia patients with Agitation showed clear treatment-related improvements in PANSS-EC scores in both treatment groups during this clinical trial. On the basis of the primary efficacy endpoint, the efficacy of Intramuscular Ziprasidone was similar to Intramuscular Haloperidol. And this study also supported the opinion that Intramuscular Ziprasidone had the similar responder profile as typical antipsychotics.

On the basis of safety data analysis, it has been suggested that Intramuscular Ziprasidone was associated with less EPS and abnormal liver function. The reason of no significant difference in other adverse reactions could be found between two groups in study might be in relative small sample.

In conclusions, this study showed Intramuscular Ziprasidone was an effective safe antipsychotic for Chinese adult Schizophrenia patients with Agitation.

Learning Objectives:

- To learn the efficacy of Ziprasidone IM in Chinese Schizophrenia patients with Agitation.
- To learn the safety advantages of Ziprasidone IM in Chinese Schizophrenia patients with Agitation.

Literature References:

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TH54. EFFECT OF BREXPIRAZOLE AND ARIPIRAZOLE ON WEIGHT: AN ANALYSIS OF LONG-TERM TRIALS IN SCHIZOPHRENIA

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Abstract: Background: Brexpiprazole is a serotonin-dopamine activity modulator that acts as a partial agonist at 5-HT_{1A} and dopamine D₂ receptors, and as an antagonist at 5-HT_{2A} and noradrenaline α _{1B/2C} receptors, all at similar potencies. Brexpiprazole was approved in 2015 by the FDA for use as an adjunctive therapy to antidepressants (ADT) for the treatment of major depressive disorder (MDD) and for treatment of schizophrenia. Compared with aripiprazole, brexpiprazole is more potent at 5-HT_{1A} receptors and displays less intrinsic activity at D₂ receptors. Here we evaluate the long-term effect of brexpiprazole and aripiprazole, respectively, on weight in patients with schizophrenia, based on a comparison between pooled data from two open-label, 52 week extension studies with brexpiprazole (NCT01649557; NCT01397786) and pooled data from two double-blind, 52 week, haloperidol-controlled studies with aripiprazole ([1]; data on file).

Methods: The studies with brexpiprazole were flexible dose, open-label, 52-week (Study 1: [NCT01649557]: 1 to 6mg/day and Study 2: [NCT01397786]: 1 to 4mg/day) studies with brexpiprazole. Study 1 enrolled patients who had completed a phase II study (NCT00905307) while study 2 enrolled de novo patients as well as patients who had completed one of the two pivotal phase III studies in acute schizophrenia (NCT01396421 [2] or NCT01393613 [3]). As study 2 is still ongoing, the brexpiprazole data presented are based on a data-cut from 15-May-2015. The aripiprazole studies [3] were fixed-dose (30 mg/day), double-blind, 52 week, haloperidol-controlled studies, prospectively designed for pooled data evaluation, enrolling patients with schizophrenia, having an acute relapse.

Results: In the brexpiprazole studies, 1059 patients were enrolled (28 from study 1 and 1031 from study 2, of which 224 were de novo patients); 34.0% of patients (360/1059) completed 52 weeks of treatment. Mean brexpiprazole dose was 3.1 mg/day. The mean change in weight (observed cases) from baseline to week 26 was 1.5 kg (n=485) and 2.2 kg at week 52 (n=357). A total of 18.2% (191/1051) of patients on brexpiprazole had a weight increase that was $\geq 7\%$ in body weight at any time during the studies. In the aripiprazole studies, 1290 patients were randomly assigned to (2:1), and subsequently received double-blind treatment with either aripiprazole, n=859 or haloperidol, n=431. A total of 43% of patients (367/859) completed 52 weeks of treatment with aripiprazole. The mean dose of aripiprazole was 29 mg/day. The mean change in weight (observed cases) from baseline to week 26 was 1.9 kg (n=396) and 2.7 kg at week 52 (n=326). A total of 19.7% (166/842) of patients on aripiprazole had a weight increase that was $\geq 7\%$ in body weight based on LOCF analysis.

Conclusion: A comparable moderate weight increase was observed after treatment with either brexpiprazole or aripiprazole.

Learning Objectives:

- To understand the long term effects of brexpiprazole on weight in patients with schizophrenia.
- To understand the long term effects of aripiprazole on weight in patients with schizophrenia.

Literature References:

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TH55. ARIPIPRAZOLE LAUROXIL PHARMACOKINETICS: APPLICATION OF MODELING AND SIMULATION FOR DOSING CONSIDERATIONS OF A

LONG-ACTING INJECTABLE ANTIPSYCHOTIC IN PERSONS WITH SCHIZOPHRENIA

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Abstract: Introduction: Aripiprazole lauroxil (AL) is a prodrug of aripiprazole, formulated as an extended-release suspension for intramuscular injection and recently approved for the treatment of schizophrenia. Following intramuscular injection, aripiprazole lauroxil is converted by enzyme-mediated hydrolysis to N-hydroxymethyl aripiprazole, which is then hydrolyzed to aripiprazole. Aripiprazole is subsequently metabolized by CYP3A4 and CYP2D6.

Methods: A population pharmacokinetic (PopPK) model of AL developed using data collected from 616 subjects with schizophrenia was used to evaluate the impact of missed doses, and re-initiation of treatment with monthly AL administration of 441, 662 or 882 mg. The PopPK model was also used to assess an additional dose regimen, 882 mg administered every 6 weeks. Separately, a physiologically-based pharmacokinetic (PBPK) model was constructed to evaluate the effect of drug-drug interaction and the effect of metabolic enzyme polymorphisms on aripiprazole exposure.

Results: The extended PK profile of AL results in sustained therapeutic coverage following a missed AL dose. Therefore, no oral aripiprazole supplementation is required when the time from the last injection is ≤ 6 weeks for 441 mg, or ≤ 8 weeks for 662 mg and 882 mg. The basis of these recommendations are consistent with a repeated dose PK study, where aripiprazole concentrations were observed to persist in plasma, and decline minimally within 8 weeks, following discontinuation of the fourth monthly AL dose. Based on simulations using the PopPK model, a dosing interval of every 6 weeks for the 882 mg dose resulted in aripiprazole concentrations within the therapeutic window established for 441 and 882 mg every 4 weeks. Evaluation of the impact of strong CYP2D6 or CYP3A4 inhibitors, or CYP3A4 inducers on the PK of aripiprazole using the PBPK model showed moderate changes in the systemic exposure of aripiprazole, irrespective of CYP2D6 genotype, and that AL dose adjustments are warranted when the CYP450 modulator is co-administered for >2 weeks.

Conclusion: AL demonstrates PK characteristics that may minimize the potential impact of poor adherence to treatment when a dose is missed. The availability of 3 dose strengths and 2 dosing intervals yields aripiprazole concentrations that span the oral aripiprazole dose range, and allows for individual patient dose adjustment for drug-drug interactions or metabolic status, thus providing flexibility in treating patients with schizophrenia.

Learning Objectives:

- Pharmacokinetics of a long-acting injectable antipsychotic
- Impact of long-acting injectable pharmacokinetic characteristics on patient care

Literature References:

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TH56. HANDWRITING KINEMATICS IN THE ASSESSMENT OF PHARMACOTHERAPEUTIC OUTCOMES IN PSYCHIATRIC POPULATIONS

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Abstract: Clinicians face significant challenges when balancing the therapeutic and counter-therapeutic effects of pharmacotherapies available to manage patients with psychosis. Goals of the research community have focused on methods to detect subtle changes in the neuromotor system attributable to these medicines while monitoring side effects and predicting the success of the outcomes in patients treated with antipsychotics. For over 50 years, handwriting has been considered an ideal candidate for such a monitoring system because of its sensitivity to extrapyramidal side effects (EPS). Following the extensive work since the early 1970s there was very little research activity on handwriting as a biomarker of antipsychotic toxicity. With the advent of automated systems that rapidly quantify kinematic features during handwriting known to reflect parkinsonism and other movement disorders, there has been a resurgence in research in handwriting as a behavioral biomarker of motor side effects associated with pharmacotherapy in psychiatric populations¹. Support for handwriting kinematics as a biomarker of dopaminergic tone comes from two key studies from Europe. Using PET imaging researchers identified a strong linear relationship between D2 receptor occupancy and reduction in handwriting height and width. In the second study investigators reported a relationship between substantia nigra hyperechogenicity and dysfluent handwriting movements as measured by velocity and acceleration inversions. This paper presents an overview of the psychometric properties including reliability, sensitivity, specificity, as well as dose response of handwriting kinematics in the quantitative evaluation of antipsychotic pharmacotherapy, particularly drug-induced parkinsonism and tardive dyskinesia (TD) from over 200 patients and controls. Data from our research on handwriting movements in schizophrenia patients will be presented to support handwriting kinematics as an adjunct to conventional observer-based EPS severity ratings².

Procedures used to evaluate parkinsonism exhibit high repeatability with Cronbach's α coefficients ranging from 0.76 to 0.95. Similarly, those for TD had Cronbach's α coefficients ranging from 0.84 to 0.92 for healthy subjects and 0.67 to 0.92 for stable psychosis patients. Our research identified a strong relationship between daily dose of risperidone and handwriting dysfluency ($r=0.78$; $p<0.0001$). Specifically, reduced vertical stroke size, decreased peak vertical velocity, and increased average normalized jerk accounted for 83% of the variability in daily risperidone dose.

Handwriting movement analyses are naturalistic, require minimal training and analytic decisions, and can be performed in any clinical setting in less than 10 minutes. Importantly, the procedure can be standardized for use in multiple sites with no known site-related variability.

Learning Objectives:

- Attendees will learn how automated measurements of handwriting kinematics can provide quantitative data on the nature and severity of extrapyramidal side effects such as drug-induced parkinsonism and tardive dyskinesia.
- Attendees will gain an understanding of the relationships between impaired handwriting movements and antipsychotic potency and dose across in psychiatric populations.

Literature References:

- Caligiuri MP and Mohammed LA. The Neuroscience of Handwriting. CRC Press, Boca Raton, FL., 2012
- Caligiuri MP, Teulings HL, Dean CE, Niculescu AB 3rd, Lohr JB. Handwriting movement kinematics for quantifying extrapyramidal side effects in patients treated with atypical antipsychotics. *Psychiatry Res* 2010 177:77-83

TH57. EFFECTS OF ARIPIPRAZOLE ONCE-MONTHLY AND PALIPERIDONE PALMITATE IN PATIENTS WITH SCHIZOPHRENIA AND CONCOMITANT SUBSTANCE USE: A POST-HOC ANALYSIS OF QUALIFY, A HEAD-TO-HEAD STUDY

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Abstract: Background: The QUALIFY study compared effectiveness of the dopamine D2 receptor partial agonist aripiprazole once-monthly 400 mg (AOM 400) with the D2 antagonist paliperidone palmitate once-monthly (PP) in patients with schizophrenia [1]. Substance abuse is common in patients with schizophrenia, and patients with concomitant substance abuse are harder to treat and usually excluded from controlled clinical studies. Patients with substance use disorder were excluded from QUALIFY only if this was judged to compromise compliance with study procedures. These post-hoc analyses investigated effects of AOM 400 and PP treatment in the subgroup of patients with a positive urine drug screen during the study.

Methods: QUALIFY was a 28-week, randomized, open-label, head-to-head study (NCT01795547) of 2 atypical long-acting injectable antipsychotics (LAIs), AOM 400 and PP (flexible dosing per label, 78-234 mg/month as paliperidone palmitate) in patients with schizophrenia. Included patients were ages 18-60 years needing a change from current oral antipsychotic treatment and, in the judgment of the investigator, would benefit from LAI treatment. Urine screens for drugs of abuse including, but not limited to, opiates, cocaine, and cannabinoids were conducted at screening, baseline, and completion/withdrawal visits; patients with a positive urine drug screen were excluded if further study compliance was judged to be compromised. The primary endpoint of QUALIFY was change from baseline to week 28 on the Heinrichs-Carpenter Quality-of-Life Scale (QLS) total score (rater-blinded scale); higher QLS scores indicate improvement in functioning and total score change ≥ 5.3 points was considered clinically relevant [2]. Secondary endpoints included change from baseline on the Clinical Global Impression–Severity (CGI-S) scale; Work Readiness

Questionnaire (WoRQ) total score assessed changes in patients' functional capacity. A mixed model for repeated measures was used to analyze changes from baseline to week 28 on QLS total, CGI-S, and WoRQ total scores.

Results: In the full analysis set (FAS), least square mean (LSM) changes from baseline to week 28 in QLS total score were 7.5 ± 1.5 (AOM 400, $n=136$) and 2.8 ± 1.6 (PP, $n=132$); treatment difference [95% CI] was 4.7 [$0.3; 9.0$] ($p=0.036$). Patients with a positive urine drug screen at any time during the study included 26/136 (19.1%) in the AOM 400 and 29/132 (22.0%) in the PP groups. In the positive drug screen subgroups, LSM changes from baseline to week 28 on QLS total score were 6.4 ± 5.9 (AOM 400) and -4.7 ± 5.4 (PP); LSM treatment difference was 11.1 [$-5.2; 27.4$] ($p=0.174$). LSM differences in change from baseline to week 28 were numerically better with AOM 400 vs PP for CGI-S (-0.1 [$-0.5; 0.3$] ($p=0.657$) and WoRQ total scores (-1.4 [$-3.3; 0.4$], $p=0.126$).

Conclusion: Patients with a positive urine drug screen receiving AOM 400 showed numerical improvements in QLS total score similar to the total treatment group. Patients with a positive screen receiving PP showed worsening in the QLS total score. The results suggest that the treatment effectiveness of AOM 400 on health-related quality of life and functioning is not compromised by concomitant recreational drug use. Further investigation is warranted into potential benefits of dopamine partial agonists in patients with schizophrenia using recreational drugs.

Supported by H. Lundbeck A/S and Otsuka Pharmaceutical Development & Commercialization, Inc.

Learning Objectives:

- To understand the effectiveness of aripiprazole once-monthly and paliperidone palmitate in patients who had a positive urine drug screen during QUALIFY.
- To understand the safety and tolerability of aripiprazole once-monthly and paliperidone palmitate in patients who had a positive urine drug screen during QUALIFY.

Literature References:

- Naber D, Hansen K, Forray C, Baker RA, Sapin C, Beillat M, Peters-Strickland T, Nylander AG, Hertel P, Andersen HS, Eramo A, Loze JY, Potkin SG: Qualify: a randomized head-to-head study of aripiprazole once-monthly and paliperidone palmitate in the treatment of schizophrenia. *Schizophr Res* 2015;168(1-2):498-504
- Falissard B, Sapin C, Loze JY, Landsberg W, Hansen K: Defining the minimal clinically important difference (MCID) of the Heinrichs-carpenter quality of life scale (QLS). *Int J Methods Psychiatr Res* 2015. DOI: 10.1002/mpr

TH58. LONG-TERM EFFECTIVENESS OF ARIPIPRAZOLE ONCE-MONTHLY IS MAINTAINED IN THE QUALIFY EXTENSION STUDY

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Abstract: Background: The QUALIFY (QUALity of LIfe with AbiliFY Maintena®) study is the first to directly compare two different atypical long-acting injectable antipsychotics with health-related quality of life and functioning as primary outcome in patients with schizophrenia. The primary analysis showed superior improvements with the dopamine D2 partial agonist aripiprazole once-monthly 400 mg (AOM 400) vs the dopamine D2 antagonist paliperidone palmitate once-monthly (PP) on the Heinrichs-Carpenter Quality-of-Life scale (QLS) total score (Naber et al. 2015, NCT01795547). This extension assessed long-term tolerability and effectiveness of AOM 400 treatment in patients who completed the QUALIFY study.

Methods: This was an open-label, flexible-dose, 28-week extension study (NCT01959035) in patients with schizophrenia who received AOM 400 treatment and completed the lead-in QUALIFY study (n=100). Patients received 6 monthly injections of AOM 400 in the extension, with safety and effectiveness data collected at each visit. The 24-week treatment extension allows, when aggregated to the data from the lead-in study, for nearly one year of safety and effectiveness data for AOM 400 in the maintenance treatment of schizophrenia. Effectiveness data comprised QLS total and Clinical Global Impression – Severity of Illness (CGI-S) scores with changes from baseline assessed using a mixed model for repeated measures, in the extension study alone and in the lead-in and extension studies combined.

Results: Of the 88 enrolled and treated patients, 77 (88%) completed the study. The treatment-emergent adverse events (TEAEs) with highest incidence during the extension study were weight increased (6/88, 6%), toothache (3/88, 3%), and headache (3/88, 3%). Three patients (3%) had serious adverse events of alcoholism, dysphoria, and gastroesophageal reflux disease (1 patient each). Effectiveness assessed during the extension study was maintained with AOM 400 treatment, with continued minor improvements from baseline: least squares mean (LSM) changes [95% confidence interval] from baseline of the extension to week 24 were 2.32 [-1.21; 5.85] in QLS total score and -0.10 [-0.26; 0.06] in CGI-S score. The aggregated LSM changes from baseline of the lead-in study were 11.54 [7.45; 15.64] for QLS total score and -0.98 [-1.18; -0.79] for CGI-S score.

Conclusions: Continued long-term treatment with AOM 400 was safe and well tolerated in patients rolling over from the lead-in QUALIFY study. In terms of effectiveness, the completion rate in the extension study was close to 90% with robust and clinically meaningful improvements on health related quality of life and functioning being maintained. These results further support the clinical benefits of AOM 400 for long-term treatment in patients with schizophrenia.

Supported by H. Lundbeck A/S and Otsuka Pharmaceutical Development & Commercialization, Inc.

Learning Objectives:

- To describe the long-term tolerability of aripiprazole once-monthly in patients with schizophrenia who enrolled in the open-label extension study after completing QUALIFY.
- To understand the long-term effectiveness of aripiprazole once-monthly in patients with schizophrenia who enrolled in the open-label extension study after completing QUALIFY.

Literature References:

- Naber D, Hansen K, Forray C, Baker RA, Sapin C, Beillat M, Peters-Strickland T, Nylander AG, Hertel P, Andersen HS, Eramo A, Loze JY, Potkin SG. Qualify: a

randomized head-to-head study of aripiprazole once-monthly and paliperidone palmitate in the treatment of schizophrenia. *Schizophr Res.* 2015;168:498-504

- Heinrichs DW, Hanlon TE, Carpenter WT, Jr. The Quality of Life Scale: an instrument for rating the schizophrenic deficit syndrome. *Schizophr Bull.* 1984;10:388-398

TH59. ANTIPSYCHOTIC AUGMENTATION VS MONOTHERAPY IN SCHIZOPHRENIA: SYSTEMATIC REVIEW, META-ANALYSIS AND METAREGRESSION ANALYSIS

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Abstract: Background: Antipsychotic polypharmacy in schizophrenia is much debated since it is common and costly with unclear evidence for its efficacy and safety (1; 2).

Methods: Systematic literature search of PubMed/PsycInfo/CJN/

WangFan/CBM without language restrictions from database inception until 05/25/2015 for randomized trials comparing augmentation with a second antipsychotic vs antipsychotic monotherapy in adults with schizophrenia. Co-primary outcomes were symptom reduction and study-defined response Random effects meta-analysis was conducted in all, double-blind/high-quality and open-label/low-quality studies.

Findings: Meta-analyzing 31 studies (n=2,073, duration=12.5±5.5 weeks), antipsychotic augmentation was superior to monotherapy regarding overall symptom reduction (studies=16, n=694, standardized mean difference (SMD)=-0.53, 95% confidence interval (CI)=-0.87 to -0.19, p=0.002). However, superiority was only apparent in open-label/low-quality studies (studies=7, n=316, SMD=-0.83, 95%CI=-1.16 to -0.50, p<0.001), but not in double-blind/high-quality studies (studies=9, n=378, SMD=-0.30, 95%CI=-0.78-0.19, p=0.226). Study-defined response did not differ between antipsychotic augmentation and monotherapy (studies=14, n=938, risk ratio (RR)=1.0, 95%CI=0.99-1.42, p=0.990), with superiority again only in open-label/low-quality studies (studies=4, n=245, p=0.016), but not in double-blind/high-quality studies (studies=10, n=693, p=0.328). Findings were replicated in augmentation studies of clozapine and non-clozapine antipsychotics. Furthermore, no between-group differences emerged regarding all-cause and specific-cause discontinuation, global impression, positive, general and depressive symptoms. However, negative symptoms improved more with augmentation treatment (studies=18, n=931, SMD=-0.38, 95%CI=-0.63 to -0.13, p<0.003), but only in studies with aripiprazole augmentation of a D2-antagonist (studies=8, n=532, SMD=-0.41, 95%CI=-0.79 to -0.13, p=0.036), not with D2-antagonist augmentation (SMD=-0.36, 95%CI=-0.72 to 0.01, p=0.55). Few adverse effect differences emerged, except that D2-antagonist augmentation was associated with less insomnia (p=0.028), but more prolactin elevation with risperidone augmentation (p=0.015), while

aripiprazole augmentation of a D2-antagonist was associated with reduced prolactin levels ($p < 0.001$) and body weight ($p = 0.030$).

Interpretation: The common practice of antipsychotic augmentation in schizophrenia lacks double-blind/high-quality evidence for efficacy, except for negative symptom reduction with aripiprazole augmentation. D2-antagonist augmentation increases prolactin levels, whereas aripiprazole augmentation reduces prolactin levels and body weight.

Learning Objectives:

At the end of the presentation, the audience should be able to:

- Comprehensively evaluate the comparative efficacy and safety of antipsychotic augmentations strategies versus monotherapy.
- Appreciate the impact of study design and quality on efficacy and tolerability outcomes (relevant biases).

Literature References:

- Correll CU, Rummel-Kluge C, Corves C, Kane JM, Leucht S: Antipsychotic Combinations vs Monotherapy in Schizophrenia: A Meta-analysis of Randomized Controlled Trials. *Schizophr. Bull.* 2009; 35:443–457
- Gallego JA, Bonetti J, Zhang J, Kane JM, Correll CU: Prevalence and correlates of antipsychotic polypharmacy: a systematic review and meta-regression of global and regional trends from the 1970s to 2009. *Schizophr. Res.* 2012; 138:18–28

TH60. A PHASE 2, EFFICACY, SAFETY, AND TOLERABILITY STUDY OF ALKS 3831 IN SCHIZOPHRENIA WITH ALCOHOL USE DISORDER

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¹*Alkermes, Inc.*

Abstract: Background: Alcohol use disorder (AUD) occurs commonly in the schizophrenia population and worsens the course of schizophrenia. There is currently no approved treatment specifically for schizophrenia with AUD. ALKS 3831 is composed of the established antipsychotic drug olanzapine, and, samidorphan. ALKS 3831 is being developed for the treatment of schizophrenia. It is intended to have utility in treatment of schizophrenia with AUD and for addressing olanzapine-induced weight gain. The objectives of the current study are to evaluate the efficacy, safety and tolerability of ALKS 3831 compared with olanzapine in subjects with schizophrenia and AUD.

Methods: This is an ongoing phase 2, randomized, active comparator-controlled, multi-center, multi-national study. There is an initial 4-week open-label olanzapine treatment period followed by a 2-week open-label ALKS 3831 period. The double-blind treatment period then begins for up to 15 months' duration where subjects (planned N = 270) will be randomized 1:1 to receive either daily flexible dose olanzapine or ALKS 3831 (olanzapine + 10 mg samidorphan). Inclusion criteria include men and women, 18-65 years of age (inclusive), a DSM-IV-TR diagnosis of schizophrenia, a DSM-5 diagnosis of AUD, meeting pre-specified symptom severity criteria including a recent (within 6 months) exacerbation of schizophrenia symptoms and have experienced at least 10 drinking days in the 30 days prior to screening (as measured by the Timeline Follow-Back [TLFB] method), with at least two of these drinking days meeting criteria for a heavy drinking day (4 drinks in a day for women and 5 drinks in a day for men). The primary efficacy measure will be an event of disease exacerbation

symptoms based on the occurrence of pre-specified events indicative of exacerbation of disease symptoms (confirmed by an independent adjudication committee [IAC]). Other efficacy measures include Positive and Negative Syndrome Score (PANSS), Clinical Global Impression-Improvement and –Severity (CGI-I, CGI-S), TLFB assessment of alcohol drinking, and Visual Analog Scale (VAS) for perception of desire for alcohol. Safety assessments will include parameters for suicide, vitals, weight and movement disorders. Other analyses may include pharmacokinetic and pharmacodynamic parameters. As of November 9, 2015 preliminary data include the following baseline demographics: Subjects enrolled n=205 (United States [n = 161], Bulgaria [n = 41], Poland [n = 3]), 80% male, age (mean $\pm$ SD) = 46 $\pm$ 10 years, White 38%, Black or African American 58%, weight (mean $\pm$ SD) 87 $\pm$ 19 kg, PANSS total score (mean $\pm$ SD): 70 $\pm$ 9. Average drinks/day: 4.6; 13.6 heavy drinking days over the previous 30 days. Frequency of events in the six months prior to screening included: hospitalization (35%), aggression/intentional injury (12%), change in medication (37%) and ER visit (25%). Randomized to ALKS 3831 or olanzapine, n = 127. The demographics will be updated when the study is complete.

Learning Objectives:

- Awareness of a new treatment being developed for schizophrenia (ALKS 3831).
- Awareness of preliminary results from an ALKS 3831 clinical study enrolling subjects diagnosed with schizophrenia and alcohol use disorder.

Literature References:

- Owen MJ, Sawa A, and Mortensen PB. (2016). Schizophrenia. *Lancet*. [http://dx.doi.org/10.1016/S0140-6736\(15\)01121-6](http://dx.doi.org/10.1016/S0140-6736(15)01121-6). [Accessed 21 January 2016].
- Silverman B. et al. (2015, September). A Phase 2, Randomized, Olanzapine-Controlled Study of the Safety, Tolerability, and Efficacy of ALKS 3831 in Adults With Schizophrenia. Poster presented at the Annual U.S. Psych. Mental Health Congress, San Diego, CA.

TH61. EVALUATION OF PALIPERIDONE PALMITATE LONG-ACTING INJECTABLE THERAPY BY DURATION OF ILLNESS IN PATIENTS WITH SCHIZOPHRENIA

*Maju Mathews^{*1}, Brianne Browne², Ibrahim Turkoz¹, Branislav Mancevski³*

¹Janssen Research & Development, LLC, ²Janssen Pharmaceuticals, ³Janssen Scientific Affairs, LLC

Abstract: Introduction: Guidelines specify long-acting injectable (LAI) antipsychotic use earlier in schizophrenia because it may delay functional deterioration. Paliperidone palmitate (PP) LAI therapy in patients with schizophrenia was evaluated by duration of illness. Methods: Post hoc analysis of a randomized, double-blind (DB), parallel-group, multicenter, noninferiority study (NCT01515423). Subjects with schizophrenia were treated with PP once-monthly (PP1M) in a 17-week open-label (OL) phase. Upon meeting clinical stabilization criteria, they were randomized 1:1 to PP1M or PP once-every-3-months (PP3M) in a 48-week relapse-prevention phase. Subjects were evaluated based on duration of illness (≤ 5 , 6-10, and > 10 years since diagnosis); PP1M and PP3M results were combined. Positive and Negative Syndrome Scale (PANSS) and Personal and Social Performance (PSP) scale scores and functional remission rates (PSP > 70 from week 13 [OL] and during DB phase for ≥ 6 months) were analyzed. No adjustment was made for multiplicity.

Results: 532, 337, and 558 subjects diagnosed with schizophrenia ≤ 5 , 6-10, and >10 years ago, respectively, entered OL phase. Of these, 379 (71.2%), 235 (69.7%), and 380 (68.1%) met clinical stabilization criteria and entered DB phase. Significant differences were observed in the ≤ 5 and 6-10 groups versus the >10 group from DB baseline to DB endpoint for PANSS and PSP total scores ($P < 0.03$ for all). More patients achieved functional remission in the ≤ 5 (26.4%) and 6-10 (30.2%) groups versus the >10 group (18.6%).

Conclusion: Improvements were observed with PP LAIs in all subgroups, with greater improvements among patients earlier in the illness (< 5 or 5-10 years) compared to those with more chronic illness (>10 years).

Support: Janssen Scientific Affairs, LLC

Learning Objectives:

At the conclusion of the session, the participant should be able to:

- Recognize the effect of longer duration of illness in patients with schizophrenia.
- Recognize the extent of improvements in patients with longer duration of illness treated for schizophrenia.

Literature References:

- Berwaerts, J., Liu, Y., Gopal, S., Nuamah, I., Xu, H., Savitz, A., Coppola, D., Schotte, A., Remmerie, B., Maruta, N., Hough, D. W. (2015). Efficacy and Safety of the 3-Month Formulation of Paliperidone Palmitate vs Placebo for Relapse Prevention of Schizophrenia: A Randomized Clinical Trial. *JAMA Psychiatry*
- Savitz, A., Xu, H., Gopal, S., Nuamah, I., Ravenstijn, P., Janik, A., Schotte, A., Hough, D., Fleischhacker, W.W. (2016) Efficacy and safety of paliperidone palmitate 3-month formulation for patients with schizophrenia: A randomized, multicenter, double-blind, noninferiority study. Accepted for publications at *Int J Neuropsychopharmacol*.

TH62. THE NATIONAL PREGNANCY REGISTRY FOR ATYPICAL ANTIPSYCHOTICS: EFFECTS OF FETAL EXPOSURE ON RISK FOR MAJOR MALFORMATIONS

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Abstract: Background: Despite the widespread use of atypical antipsychotics in women of childbearing potential, reproductive safety data across these medicines is 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: Eligible enrollees include pregnant women between 18 and 45 years of age. 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. Three phone interviews are conducted: 1) baseline, proximate to the time of enrollment, 2) 7 months gestation, and 3) 3 months postpartum. Obstetric, labor and delivery, and pediatric medical records are obtained. Following receipt of medical records, relevant information is abstracted regarding primary and secondary outcomes including obstetrical, maternal, and neonatal outcomes. Potential major malformations are identified and relevant records are sent to a dysmorphologist blinded to drug exposure for adjudication.

Results: As of December 2015, 433 women in the exposed group and 195 women in the comparison group were enrolled (N=628). The overall drop-out and loss to follow-up rate of subjects was 12%. The proportion of study subjects for whom medical records were obtained was 86%. A total of 351 women completed the study and were eligible for inclusion in the current analysis. Of 240 live births with first trimester exposure to atypical antipsychotics, three (N=3) major malformations were confirmed. Of the 111 control group live births, one (N=1) major malformation was confirmed. The absolute risk of major malformations was 1.3% for infants exposed to an atypical during the first trimester and 0.9% for unexposed infants. The odds ratio for major malformations was 1.39 (0.14, 13.54) comparing exposed to unexposed infants, not reaching statistical significance.

Conclusion: This preliminary analysis indicates a modest level of risk that may be reassuring for both clinicians and women trying to make risk/benefit treatment decisions about using atypical antipsychotics during pregnancy. The importance of registries which systematically gather data regarding the reproductive safety of psychiatric medications is also underscored by recent FDA guidance

(<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm>).

Learning Objectives:

- To address critical elements of the current state-of-knowledge regarding risks of fetal exposure to atypical antipsychotics used to treat psychiatric disorders during pregnancy.
- To provide a conceptual framework for understanding the state of the science regarding relative risks of both treated and untreated psychiatric disorder during pregnancy.

Literature References:

- Cohen LS, Viguera AC, McInerney KA, et al: Reproductive Safety of Second-Generation Antipsychotics: Current Data From the Massachusetts General Hospital National Pregnancy Registry for Atypical Antipsychotics. *Am J Psychiatry* 2015; 0(0):appi.ajp.2015.15040506.
- Cohen LS, Viguera AC, McInerney KA, et al: Establishment of the National Pregnancy Registry for Atypical Antipsychotics. *J Clin Psychiatry* 2015; 76:986–989.

TH63. RELATIONSHIP BETWEEN DEPRESSION AND PREGNANCY IN RURAL GUATEMALA: A PILOT STUDY

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Abstract: Introduction: 80% of the world's population lives in developing nations (DN). Females make up about half of this population. The female gender in DN is associated with higher rates of psychiatric disorders, especially when they have less education and low social class. A combination of factors leads to higher rates of pregnancies in the DN. We wanted to see if there was a relationship between depression and pregnancies in a rural population in a DN.

Method: Our study was conducted at a rural health clinic catering to female patients. Patients who came to the clinic over a span of 3 days were asked if they were interested and willing to participate in a study. 23 (n) patients agreed to participate and were asked a list of questions which included the number of times they have been pregnant, number of lost pregnancies and the number of living children. These patients were also screened by a health care provider by utilizing HAM D.

Results: Our cohort (n=23) completed a questioner and a HAM D. We were unable to finish HAM D on one patient per her request. After removing her information from our data set Pearson's r correlations were computed between the HAM-D (M = 12.41, SD = 4.29), number of current live children (M = 3.77, SD = 1.60), and the number of lost pregnancies (M = .39, SD = .78). We found that having more living children was associated with less reported depression ($r(20) = -.50$; $p = .02$), whereas number of lost pregnancies was not significant ($r(20) = -.17$; $p = \text{ns}$). The average age of our cohort was 39.8 years.

Discussion: Previous studies have shown that access to health care in the DN is limited. Access to mental health is even scarce. Studies also suggest that females living in DN are associated with higher rate of pregnancies and mental health issues. Studies also suggest that post partum depression in DN is associated with an increased risk of physical problems in the newborn children. We wanted to explore the relationship between depression and pregnancy. In our cohort we found that having more living children was associated with less reported depression ($r(20) = -.50$; $p = .02$). Rationale behind this relationship could be cultural, social, economic or a combination of all. Though our cohort was small (n=22) this is an important finding as it is contrary to previous reports and perception in the developed counties.

Learning Objectives:

- Examine the relationship between depression and pregnancy for a rural population in a developing nation.
- Contribute to literature on women's health developing nations.

Literature References:

- Patel, V. (2007). Mental health in low-and middle-income countries. *British Medical Bulletin*.
- Saxena, S., Thornicroft, G., Knapp, M., & Whiteford, H. (2007). Resources for mental health: scarcity, inequity, and inefficiency. *The lancet*, 370(9590), 878-889.