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FROM
PREVENTION to RECOVERY

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Poster Session I

T1. THE ANTIDEPRESSANT ACTIVITY OF BASIMGLURANT, A NOVEL MGLU5-NAM; A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY IN THE ADJUNCTIVE TREATMENT OF MDD

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Abstract Background: Therapies targeting the glutamatergic system are known to be efficacious in the treatment of mood disorders. Antagonism of the post-synaptic mGlu5 receptor is a novel approach to indirectly modulate glutamatergic (NMDA) function and has shown efficacy in a number of preclinical behavioral models of depression. Basimglurant is a potent and selective negative allosteric modulator of the mGlu5 receptor which has been comprehensively profiled in Ph1 and Ph2a trials. The main objectives of this Ph2b trial were to evaluate the safety and efficacy of basimglurant modified release (MR) vs. placebo, as adjunctive therapy to ongoing antidepressant treatment in patients with major depressive disorder (MDD) who showed inadequate response to at least one but no more than three treatment failures within the current episode.

Methods: In this 9-week study (6-week double-blind treatment, 3-week post-treatment follow-up), adult patients with DSM-IV-TR diagnosis of MDD were randomized to basimglurant 0.5 mg/d, 1.5 mg/d, or placebo (adjunctive to ongoing SSRI or SNRI). The primary endpoint was the mean change from baseline in the Montgomery-Åsberg Depression Rating Scale Sigma total score (MADRS), as rated by the clinician at week 6. Concomitantly, patient-rated MADRS scores were also collected and analyzed. Secondary endpoints included change in the Quick Inventory of Depressive Symptomatology (QIDS-SR16), MADRS response ($\geq$ 50% reduction in score from baseline), MADRS remission (score of $\leq$ 10), and Clinician and Patient Global Impression scales (CGI-I, PGI-I and CGI-S). Exploratory endpoints included change in the Quality of Life Enjoyment and Satisfaction Questionnaire Short Form (Q-LES-Q-SF) and the Sheehan Disability Scale (SDS). Due to the exploratory nature of this study, one-sided p values were estimated with no adjustment for multiplicity. Completers (observed cases) ANCOVA and ITT MMRM statistical analysis were performed.

Results: 333 male and female patients were randomized in to the study. The primary endpoint for the study (clinician-rated MADRS) was not met ($p=0.127$ ITT MMRM analysis); a trend for improvement was observed for basimglurant 1.5 mg vs. placebo ($p=0.061$ completers ANCOVA analysis) while statistical significance was reached utilizing the patient-rated MADRS ($p<0.025$ in both analyses). Regarding the secondary endpoints basimglurant 1.5 mg showed significant improvements vs. placebo in QIDS mean change from baseline ($p=0.004$ in both analyses), CGI-I mean score ($p<0.039$ in both analyses), PGI-I mean score ($p<0.029$ in both analyses). Significant improvements were also seen with in the patient-rated MADRS remission rate ($p<0.024$ both analyses), and to a lesser degree in the patient-rated MADRS response ($p<0.1$ both analyses). Lastly, significant improvements were observed in the Q-LES-Q-SF ($p=0.011$) and the SDS items 2-3 ($p=0.047$) (ITT MMRM). Basimglurant dosed at 0.5 mg showed no benefit over placebo in any of these measures. Withdrawal rates due to adverse events were 5.4%, 7.2% and 4.5% for basimglurant 0.5 mg, 1.5 mg, and placebo, respectively.

The most common adverse event was dizziness (4%, 23%, and 6%), mostly transient and of mild intensity. Mania (spontaneously resolved) lead to withdrawal of 2 patients from the study in the 1.5 mg arm.

Discussion: Adjunctive 1.5 mg/d basimglurant showed a consistent antidepressant effect across primary and secondary endpoints. Greater effects were seen in patient-rated endpoints such as the patient-rated MADRS and the QIDS, which statistically separated from placebo at several time-points including week 6, while clinician-rated MADRS only separated at earlier time-points but not at day 42. Basimglurant 0.5 mg/d was not effective compared to placebo. Study results should be considered in the context of the observed high placebo response in this trial (47% on the clinician-rated MADRS). Placebo response rates ☐ 40% have been reported as a threshold that impedes observing statistical separation for active arms in adjunctive MDD treatment trials, minimizing the possibility of detecting true antidepressant effects. In this trial, nevertheless, basimglurant 1.5mg response rates were still consistently superior to placebo. Furthermore, basimglurant was overall safe and well tolerated in combination with SSRI/SNRI with mild transient dizziness as the most common emergent adverse event. These results warrant further investigation of basimglurant in the treatment of MDD both in the adjunctive as well as monotherapy settings.

T2. DASOTRALINE: A NOVEL DRUG CANDIDATE FOR THE TREATMENT OF ADHD

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Abstract Several classes of drugs have demonstrated efficacy in the treatment of ADHD, including short- and long-acting stimulant and non-stimulant medications. However, there continues to be a need for additional treatment options that may offer a more differentiated clinical profile than current agents. Dasotraline [(1R,4S)-4-(3,4-Dichlorophenyl)-1,2,3,4-tetrahydronaphthalen-1-amine], currently in development for adult and pediatric ADHD, is a potent inhibitor of human DA transporters (DAT; dopamine uptake IC50 3 nM) and NE transporters (NET; norepinephrine uptake IC50 4 nM), and a weaker inhibitor of human serotonin transporters (SERT; serotonin uptake IC50 15 nM; data-on-file, 2014). In humans, dasotraline has a tmax of 10-12 hours, a terminal elimination half-life (t½) of 47-77 hours, and achieves steady state plasma concentration by 2 weeks of daily dosing. A clinical trial has been completed in adults meeting DSM-IV-TR criteria for ADHD who were randomized, without titration, to 4 weeks of double-blind, once-daily treatment with fixed doses of dasotraline 4 mg/d (N=114), 8 mg/d (N=107), or placebo (N=110). On the ADHD Rating Scale, Version IV (ADHD RS-IV) total score, significant LS mean improvement was observed at Week 4 for dasotraline 8 mg/d versus placebo (-13.9 vs -9.7; P=0.019), with trend level significance for 4 mg/d (-12.4; P=0.076). LS mean improvement in a modified CGI-S scale was significantly greater at Week 4 for dasotraline 8 mg/d versus placebo (-1.1 vs -0.7; P=0.013), and for 4 mg/d (-1.1 vs -0.7; P=0.021). The most frequent adverse events reported were insomnia, decreased appetite, nausea, and dry mouth. The pharmacokinetic and pharmacodynamic characteristics of dasotraline suggest that it may have a favorable therapeutic profile for the treatment of ADHD, offering once-per-day dosing that provides sustained inhibition of DA and NE reuptake throughout the 24 hour dosing interval, with possible low risk of abuse potential due to its delayed tmax. The results of this first clinical trial provide preliminary evidence indicating that once-daily dosing with dasotraline, a long-acting, dual monoamine reuptake inhibitor, may be a safe and efficacious treatment for adult ADHD.

Learning objectives:

1. Participants will learn about the efficacy and tolerability of dasotraline in adult patients diagnosed with ADHD

2. Participants will learn about the pharmacokinetic profile of a dasotraline, a new drug candidate for the treatment of ADHD

T3. OPEN BOARD

T4. NON-INVASIVE NEUROMODULATION WITH TRIGEMINAL NERVE STIMULATION IN MAJOR DEPRESSIVE DISORDER AND OTHER CNS DISORDERS

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Abstract Background: Modulation of brain activity via external Trigeminal Nerve Stimulation (eTNS) is an emerging therapy for CNS disorders, with an excellent safety profile and significant improvements in seizures, mood, cognition, and anxiety reported in preliminary open studies. Mechanistically, PET imaging findings showed acute, robust changes in cerebral perfusion in limbic and frontal regions. In a recently-completed dose ranging project, eTNS was examined under double-blind conditions in major depressive disorder (MDD) as an adjunct to pharmacotherapy.

Methods: Forty-three adults with MDD (age 23-65, avg 43.0 (11.5 sd), ATHF 1-10) completed at least six weeks of the trial (primary endpoint). Subjects stimulated the trigeminal nerve for 8 hours each night at home using custom patch electrodes placed on the forehead. Clinical outcomes were assessed with scales including the Beck Depression Inventory (BDI), Inventory of Depressive Symptomology (IDS-SR) and Hamilton Depression Rating Scale (HDRS17). Medications remained constant throughout.

Results: Symptom severity improved significantly for subjects receiving active stimulation (e.g., paired 2-tail t-test BDI 24.6 (8.5 sd) baseline vs 14.2 (7.3) week 6, $p<0.00001$). Subjects receiving active stimulation had significantly greater symptom improvement than subjects randomized to the control condition (e.g., BDI -41.7% vs -10.9% t=-2.61 2-tail p=0.013).

Conclusions: Significantly greater symptom reductions were achieved in the 6 weeks of acute eTNS treatment than in our control condition. These findings replicate open trial results, extend them under double-blind controlled conditions, and justify further development. Symptom improvement did not differ across stimulation frequencies ('doses'), suggesting that low doses of stimulation may lead to meaningful symptom improvement in MDD, and that the cumulative integration of stimulation events may be an important determinant of clinical effects. Trigeminal Nerve Stimulation is a unique form of neuromodulation because can be delivered at home using a non-invasive system, or may be deliverable with an implantable system that is under development. This novel approach to brain stimulation may have use as an adjunct to pharmacotherapy once efficacy and tolerability are confirmed with additional studies.

T5. BREMELANOTIDE FOR HYPOACTIVE SEXUAL DESIRE DISORDER: ANALYSES FROM A PHASE 2B DOSE-RANGING STUDY

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Abstract Introduction: Bremelanotide (BMT) is a novel heptapeptide melanocortin-receptor-4 agonist. This study examined its subcutaneous self-administration by premenopausal patients with hypoactive sexual desire disorder (HSDD), female sexual arousal disorder (FSAD), or both, and included exploratory analyses specifically in subjects with HSDD.

Methods: Premenopausal women with HSDD and/or FSAD underwent a no-treatment diagnosis-confirmation month, followed by 4 weeks of single-blind, at-home placebo self-dosing (baseline). Subjects were then randomized to double-blind placebo or BMT 0.75, 1.25, or 1.75 mg self-administered for 12 weeks. Outcomes included changes from baseline to end of study in the number of satisfying sexual events (SSEs), Female Sexual Function Index (FSFI) scores, and Female Sexual Distress Scale-Desire/Arousal/Orgasm (FSDS-DAO) scores.

Results: Of 327 at-home study-drug users, 281 either had mixed HSDD/FSAD with a primary diagnosis of HSDD (n=206) or had solely HSDD (n=75). Among all 281 women, mean SSE change (per 4 weeks) was +0.2 for placebo, versus +0.8 for 0.75 mg, +0.7 for 1.25 mg, and +0.7 for 1.75 mg. Mean FSFI change was +1.55 versus +1.45, +3.11, and +4.24 for total score, and +0.37 versus +0.33, +0.58, and +0.97 respectively for desire subscore. Mean FSDS-DAO change was −6.6 versus −8.0, −9.6, and −12.7 for total score and −0.6 versus −0.5, −0.7, and −1.0 for Question 13 ("bothered by low desire"). On all outcomes, BMT benefit was statistically significant ($p < 0.05$, Van Elteren test) with the 1.75 mg dose.

Conclusions: In premenopausal HSDD, subcutaneous BMT yielded improvements across all key HSDD measures, with robust dose-dependence attaining statistical significance at the 1.75 mg dose.

Funding: Palatin Technologies, Inc.

T6. ALKS 3831: A NOVEL DRUG CANDIDATE FOR THE TREATMENT OF SCHIZOPHRENIA

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Abstract The biology of the strong association between many atypical antipsychotics and adverse weight gain and metabolic dysfunction has not been fully elucidated. The same could be said for the high rate of co-occurrence between schizophrenia and substance abuse. As a consequence, complexities of these associations present significant obstacles in the treatment and management of many patients with schizophrenia by limiting patient adherence and adversely impacting treatment outcomes.[1,2] However, the role of the opioid system, specifically mu antagonism, for the treatment of substance abuse has been well established.[3] As such, an antipsychotic designed to address these complexities through appropriate engagement of the opioid system and reward circuitry would present a substantive advancement in the treatment of schizophrenia.

Olanzapine (OLZ) is regarded as one of the most effective treatments for schizophrenia, but concerns with weight gain and adverse metabolic effects prevent its use as part of a first line treatment paradigm, which is of particular importance for the treatment of early psychotic episodes.[1]

Samidorphan (SAM), a novel opioid modulator, acts as an antagonist at mu opioid receptors. Nonclinical studies suggested that SAM may be useful in mitigating or preventing OLZ-induced weight gain. Using a standard rodent model, it was demonstrated that co-administration of SAM mitigated OLZ-induced weight gain, whereas naltrexone did not.[4] In a subsequent study using non-human primates to investigate OLZ-induced changes in weight

gain and metabolic effects, SAM attenuated OLZ-induced weight gain and fat accretion following 28-days of repeat daily dosing.5

Additionally, by virtue of its pharmacology, SAM may present additional benefits to patients with schizophrenia who have comorbid substance use disorder. Nonclinical studies have demonstrated that SAM, at doses that result in exposure similar to therapeutically relevant doses in humans, blocked mu-opioid agonist effects and reduced ethanol self-administration in rodents. In an early clinical study, it was found that SAM significantly reduced the event rate of heavy drinking compared to placebo in non-schizophrenic subjects.

ALKS 3831, a novel drug candidate, is a fixed-dose combination of OLZ and SAM currently under development for the treatment of schizophrenia. This formulation is intended to confer a more favorable safety profile compared to OLZ alone. To investigate the safety and effect on weight of ALKS 3831 in comparison to OLZ, a Phase I study in healthy, normal weight (BMI 18-25) male volunteers was conducted. This was a double-blind, parallel group design with daily dosing for 21 days. Subjects were randomized (n=106) to OLZ, ALKS 3831, SAM or placebo in a 2:2:1:1 ratio. Efficacy was determined by the mean change from baseline to last treatment period assessment in body weight (kg) for OLZ vs. ALKS 3831. After 21 days of daily dosing, the mean±SD change in body weight for OLZ and ALKS 3831 was +3.4±1.8 and +2.5±1.4, respectively. The weight gain observed in the ALKS 3831 group was significantly less than that of the OLZ group (p=0.014). Overall safety and tolerability of ALKS 3831 was similar to OLZ alone.

In a subsequent Phase 2 OLZ-controlled dose-ranging study, the safety, tolerability, and efficacy of ALKS 3831 was evaluated in adults with stable schizophrenia. Subjects were randomized in a 1:1:1:1 ratio to receive daily OLZ + placebo or 3 different ALKS 3831 treatment options (OLZ + 5, 10, or 20 mg SAM) in a double-blind paradigm following a 1-wk OLZ lead-in period. The primary efficacy endpoint was change in Positive and Negative Syndrome Scale (PANSS) total score from baseline to Week 12 to test equivalence of antipsychotic efficacy of the 3 pooled ALKS 3831 groups vs. OLZ. The analysis was performed for the full analysis set (FAS1) that included all randomized subjects who received ≥1 dose of study drug and had ≥1 post-baseline PANSS assessment. The pre-specified secondary endpoint, percent change in weight from baseline to Week 12 was evaluated in FAS1 (n=300) and the subset of subjects with observed weight gain during the 1-wk OLZ lead in period (FAS2, n=195). Safety and tolerability of ALKS 3831 relative to OLZ was also assessed. The change from baseline in PANSS total score with ALKS 3831 was equivalent to OLZ (LS mean difference±SE: 0.6±0.9; 95% CI: -1.2, 2.5). At Week 12, treatment with ALKS 3831 demonstrated a 37% lower mean weight gain vs. OLZ alone in FAS1 (p=0.006) and a 51% lower mean weight gain vs. OLZ in FAS2 (p<0.001). The risk of weight gain of ≥10% of baseline weight with OLZ was 2.7 times that of ALKS 3831 (95% CI: 1.1, 6.7; p=0.023) in FAS1 and 4.1 times that of ALKS 3831 (95% CI: 1.4, 12.3; p=0.008) in FAS2. The most common adverse events (≥5%) in the pooled ALKS 3831 subjects relative to OLZ subjects were somnolence, sedation, and dizziness. In this study, ALKS 3831 demonstrated efficacy equivalent to OLZ over the course of the 12-wk treatment. ALKS 3831 was associated with a clinically meaningful and statistically significant lower weight gain compared to OLZ alone. ALKS 3831 was well-tolerated with a safety profile similar to OLZ, with the exception of lower weight gain.

Evidence to date suggests that ALKS 3831 may represent a new advancement in the treatment of schizophrenia through maintaining benefits of the highly effective antipsychotic OLZ with an enhanced safety profile that addresses weight and metabolic liabilities. The potential utility of ALKS 3831 to treat patients with schizophrenia and co-occurring alcohol use disorder is the focus of an ongoing Phase 2 study.

References:

1.   Lieberman J, et al. N Eng J Med. 2005;353:1209-23.
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3.   De Hert M, et al. World Psychiatry. 2011;10:52–77.
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T7.   A   DOUBLE-BLIND,   PLACEBO-CONTROLLED   STUDY   OF   THE ANTIDEPRESSANT EFFECTS OF THE MGLU2 NEGATIVE ALLOSTERIC MODULATOR RG1578 IN PATIENTS WITH INADEQUATE RESPONSE TO ANTIDEPRESSANT THERAPY

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Abstract   Background: Abnormalities in glutamate transmission have been implicated in major depressive disorder (MDD). In particular, normal glutamate transmission may be disrupted via excessive autoinhibition through metabotrobic glutamate receptors type 2 (mGlu2). mGlu2 antagonists should correct this abnormal state and offer a therapeutic approach. We evaluated the antidepressant effects of the mGlu2 negative allosteric modulator RG1578 in patients with an inadequate response to SSRIs or SNRIs.

Methods: 310 patients with MDD and an inadequate response (inclusion criterion for severity of illness: MADRS $\geq$ 25, CGI $\geq$4) to up to two antidepressant trials were randomized to double-blind treatment and with placebo (N=86), 5 mg (N=89), 15 mg (N=88) or 30 mg (N=47) of RG1578 as an adjunct to ongoing treatment with an SSRI or SNRI. Patients completed 6 weeks treatment without major protocol violations The primary endpoint (MADRS) was assessed by fully blinded centralized raters. Secondary endpoints included the IDS-SR30, CPFQ, SDS and the CANTAB battery.

Results: At baseline the mean MADRS total score was 31 ($\square$6 [SD]) and the CGI-S 4.4 ($\square$0.7). At the end of treatment the decreases in the MADRS total score did not differ significantly between any active treatment arm and placebo (placebo: -11.8 $\square$11.2; 5 mg: – 12.8$\square$11.2; 15 mg: -11.8$\square$11.2; 30 mg: -13.2$\square$11.2). Response and remission rates did not differ significantly between treatment arms. Similar results were observed for all secondary outcome measures.

Discussion: Adjunctive treatment with RG1578 was not associated with significant antidepressant effects in patients with MDD and inadequate response to antidepressants.

T8.   METADOXINE   EXTENDED   RELEASE   (MDX):   A   NOVEL   DRUG CANDIDATE FOR THE TREATMENT OF ADHD & FRAGILE X SYNDROME

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Abstract Metadoxine (pyridoxol L-2-pyrrolidone-5-carboxylate) is an ion-pair salt of pyridoxine (vitamin B6) and 2-pyrrolidone-5-carboxylate (PCA, also known as L-PGA). Metadoxine modulates GABAergic activity, and does not increase levels of brain neurotransmitters such as dopamine, norepinephrine and serotonin. In animal studies, Metadoxine has shown no signs of abuse or addiction potential. Metadoxine Extended Release (MDX) is a novel, immediate release and sustained release formulation in a bi-layer tablet.

Placebo-controlled studies of MDX in adults with ADHD produce a consistent signal of efficacy, and analysis of secondary endpoints and sub-scales suggest an impact on attention and cognitive function. No treatment-emergent serious adverse events or any meaningful differences in adverse events profile between the drug and placebo groups have been observed so far. A phase III 10-week, randomized, multicenter, placebo-controlled, double-blind, parallel group, study of MDX once daily in adults with ADHD was recently launched. The design of the study will be discussed.

Findings to date also suggest that MDX could improve attention and cognition in Fragile X Syndrome (FXS), a rare neuro-genetic disease and the most common inherited form of autism. Furthermore, pre-clinical studies in an animal model of Fragile X Syndrome demonstrated improvements in behavioral outcomes with metadoxine treatment.

A phase II 6-week, randomized, multicenter, placebo-controlled, double-blind, parallel group, study of MDX once daily in adults and adolescents with FXS was recently completed. Subjects had molecular confirmation of FXS (greater than or equal to 200 CGG repeats) and were between 14 and 55 years. The study was conducted at 12 sites in the US and 1 site in Israel. Results of this study will be presented.

Preclinical and clinical evidence demonstrates that MDX has a unique mechanism of action and consistent procognitive effects. Results from ongoing and recently completed studies in ADHD and FXS may provide important information about a novel and highly differentiated nonstimulant drug candidate.

Learning Objectives:
1. Participants will learn about a new drug candidate, Metadoxine Extended Release (MDX), as a novel potential treatment for ADHD and Fragile X Syndrome
2. Participants will learn about the pharmacological profile of Metadoxine Extended Release (MDX), a monoamine-independent GABA modulator.

Prior publications / presentations:
1. Rubin J, et al. Metadoxine in ADHD and fragile X syndrome: a novel mechanism of action. Poster 1364 presented at: Society of Biological Psychiatry 69th Annual Scientific Meeting; May 10, 2014; New York, NY.
2. Manor I et al. A randomized, double-blind, placebo-controlled, multicenter study evaluating the efficacy, safety, and tolerability of extended-release metadoxine in adults with attention-deficit/hyperactivity disorder. J Clin Psychiatry. 2012; 73(12):1517-1523.
3. Manor I et al. Attention Benefits after a single dose of Metadoxine Extended Release in Adults with Predominantly Inattentive ADHD. Postgrad Med 2014; 126(5): 1-10.
4. Adler L et al. Randomized Controlled Trials of Metadoxine Extended Release in Adults with Attention-Deficit/Hyperactivity Disorder. Symposium presented at AACAP 61st Annual Meeting; October 22, 2014; San Diego, CA.

T9. A SINGLE INTRAVENOUS DOSE OF THE NMDA RECEPTOR GLYCINE SITE MODULATOR NRX-1074 DOSE DEPENDENTLY REDUCED DEPRESSION SCORES WITHIN 24 HOURS IN SUBJECTS WITH MAJOR DEPRESSIVE DISORDER (MDD)

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Abstract Background: NRX-1074 (threonyl-prolyl-2R-(2-benzyl)-prolyl-threonine amide) has the same tetrapeptide sequence as rapastinel (GLYX-13) except that the second Pro is benzylated. NRX-1074 is more potent in vitro, in animal models of antidepressant-like activity, NRX-1074 is more potent than GLYX-13 (100-fold) and orally active, and NRX-1074 does not exhibit a U-shaped dose-response like GLYX-13.

Methods: This randomized, double blind, placebo controlled study enrolled 142 subjects with MDD at 12 United States study sites. Subjects who were taking another antidepressant agent were required to discontinue all antidepressants for at least two weeks prior to receiving NRX-1074. Subjects received a single IV dose of placebo (N=52) or NRX-1074, 1 mg (23), 5 mg (54), or 10 mg (20), as monotherapy in order to determine the dose at which antidepressant activity is observed in order to provide pharmacokinetic-pharmacodynamic correlation to provide dose level guidance for oral administration. HDRS-17 and CGI-S scores, psychotomimetic effects (BPRS+), dissociative effects (CADSS) and other adverse events were monitored for 14 days.

Results: Demographics and baseline HDRS-17 (25.2-26.9) and CGI-S (4.4-4.6) scores were not significantly among treatment groups. NRX-1074 demonstrated a dose dependent antidepressant effect within 24 hours. In response to 10 mg, HDRS-17 declined 5.4 points compared to placebo (p=0.004) with an effect size of 0.7. CGI-S declined 0.9 points compared to placebo (p=0.0005). NRX-1074 did not induce significant changes in dissociative (CADSS) or psychotomimetic (BPRS+) scores. Adverse events were mostly mild to moderate with similar incidence to placebo and no discernible dose response.

Conclusions: A single IV dose of NRX-1074 induced a rapid and significant antidepressant effect with clear dose-response without dissociative or psychotomimetic side effects. NRX-1074 is undergoing repeat dose clinical trials using IV and oral dosing.

T10. A RANDOMIZED PLACEBO-CONTROLLED ADJUNCTIVE TRIAL OF RILUZOLE IN TREATMENT-RESISTANT MAJOR DEPRESSIVE DISORDER

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Abstract Background: Preclinical studies have shown that riluzole, a FDA-approved drug for amyotrophic lateral sclerosis, modulates glutamate release and clearance, and has potent neuroprotective properties. Riluzole has shown antidepressant-like effects in rodent models used to screen for antidepressant activity. In addition, several small open-label clinical studies have suggested that riluzole has antidepressant and anxiolytic properties, even in patients resistant to conventional monoaminergic medications. The aim of this NIMH-sponsored collaborative study was to examine the antidepressant efficacy and safety of riluzole, by conducting the first double-blind, placebo-controlled trial of this agent in adults with major depressive disorder (MDD) who were inadequately responsive to antidepressant medication.

Methods: Patients were enrolled at three academic medical centers (Baylor College of Medicine, Massachusetts General Hospital, Yale University School of Medicine), with oversight by a NIMH Data Safety and Monitoring Board. Patients were between the ages of 18-65, met DSM-IV criteria for MDD, and had at least a moderate level of depressive severity, indexed by an Inventory of Depressive Symptomatology-Self Rated (IDS-SR) score of >20 and a Montgomery Asberg Depression Rating Scale (MADRS) score of 18 or higher. Exclusion criteria included patients with serious suicide risk, unstable medical illness, substance use disorders within the last 6 months, lifetime histories of bipolar disorder or

psychotic disorders, and those who had failed to respond to 3 or more adequate antidepressant trials during the current major depressive episode. Patients meeting initial eligibility criteria were assigned to one of 2 groups (A or B), depending on whether they were receiving concurrent antidepressant treatment at Screening. MDD patients not taking an antidepressant (Group A) were given an 8-week prospective trial of open-label sertraline (flexibly dosed to 150 mg/day). Following the 8 week sertraline treatment period, Group A patients were eligible for a subsequent randomized, placebo-controlled double-blind phase if they continued to meet depressive severity thresholds and had < 50% decrease in the IDS-SR total score. Group B participants were individuals receiving an adequate dose of a SSRI, SNRI, or bupropion for at least 8 weeks, and were taking a stable dose for at least 4 weeks prior to randomization.

A sequential parallel comparison design was used for the 56 day double-blind, randomized adjunctive, placebo-controlled trial, which comprised two phases of approximately 28 days each. Patients were randomized to adjunctive treatment with either riluzole (50 mg BID) or placebo, with a 2:3:3 ratio for random assignment to the treatment sequences drug/drug, placebo/placebo, and placebo/drug, respectively. Clinical assessments were performed by trained raters every 7 days during the double-blind treatment period, followed by a 7 day taper period. The primary outcome was the change in the MADRS from baseline to the end of the double-blind treatment period. Secondary outcomes include the response rate, defined as at least a 50% improvement in MADRS compared to baseline. Safety and tolerability was assessed with the Systematic Assessment for Treatment Emergent Events (SAFTEE-SI).

Results: Enrollment occurred between June 2011 and December 2014, with the final study visit completed in February 2015. Across the three sites, 104 patients were randomized, and 85 patients completed the 8 week double-blind placebo phase. The database lock is scheduled for April 2015. The results of primary and key secondary analyses, including safety and tolerability information, will be presented.

Discussion: The implications of this study on research and clinical practice will be discussed. As riluzole is now available as a generic medication, a positive trial would support its broader use for difficult-to-treat depression and spur further investigations into mechanisms of action. NCT01204918 Efficacy and Tolerability of Riluzole in Treatment Resistant Depression

T11. A DOUBLE-BLIND, DOUBLY-RANDOMIZED, PLACEBO-CONTROLLED STUDY OF INTRANASAL ESKETAMINE IN AN ADAPTIVE TREATMENT PROTOCOL TO ASSESS SAFETY AND EFFICACY IN TREATMENT-RESISTANT DEPRESSION

Jaskaran Singh, Janssen Pharmaceutical Companies of JNJ

Abstract Background: Esketamine and ketamine have been shown to produce rapid antidepressant action in patients with treatment-resistant depression (TRD). The aim of the current study was to assess the efficacy, safety and dose response of intranasal esketamine in patients with TRD.
Methods: This was a 2-Panel, doubly-randomized, double-blind, placebo-controlled, multicenter study. Panel A was conducted in the United States and Belgium and Panel B is currently ongoing in Japan. In both panels, each subject participated in up to 4 phases: a screening phase of up to 4 weeks, a double-blind treatment phase which included two 1-week periods (Periods 1 and 2), a 9-week optional open-label treatment phase and an 8-week posttreatment follow-up phase. Only Panel A double blind phase data are available, and will be presented at this time. The primary efficacy endpoint was the change from baseline to Day 8 in each period in the Montgomery-Asberg Depression Rating Scale (MADRS) total score combined. Safety and secondary efficacy endpoints were also assessed.

Results: A total of 67 subjects with TRD were randomly assigned in a 3:1:1:1 ratio to one of four treatment groups: placebo (n=33), esketamine 28 mg (n=11), esketamine 56 mg (n=11), or esketamine 84 mg (n=12) in Period 1. In Period 2, 28 placebo subjects who were eligible for re-randomization at the end of Period 1 were randomly assigned to placebo (n=6), esketamine 28 mg (n=8), esketamine 56 mg (n=9), or esketamine 84 mg (n=5) in a 1:1:1:1 ratio. Subjects were eligible for re-randomization if the patient-rated 16 item Quick Inventory of Depressive Symptomatology (QIDS-SR16) total score was ≥11 at the end of Period 1. The analysis of Period 1 and Period 2, combined using the weighted combination test, showed that the mean change in MADRS total score in all three esketamine groups was statistically superior to that obtained under placebo, based on a one-sided 0.05 significance level ($p=0.021$, $p=0.001$ and $p<0.001$ for esketamine 28 mg, 56 mg and 84 mg respectively). The mean differences (SE) from placebo (after one week of treatment) were -4.2(2.09) for esketamine 28 mg, -6.3(2.07) for esketamine 56 mg, and -9.0(2.13) for esketamine 84 mg. The magnitude of effect size in Period 1 increases from a low Cohen's D effect size in the 28 mg dose group (0.43) to a high Cohen's D effect size for the 56 (0.92) and 84 mg (1.19) dose groups.

The most common TEAEs during the double-blind phase (≥10% of subjects in any group) were: dizziness, dissociation, headache, dysgeusia, nasal discomfort, nausea, hypoaesthesia oral, dissociative symptoms, tunnel vision, oropharyngeal pain, throat irritation, blurred vision, hypersomnia, feeling abnormal, insomnia, hypertension, vertigo, polyuria and sedation. No death was reported. Transient elevation in blood pressure and heart rate was also observed on dosing days. The perceptual changes and dissociative symptoms measured by the Clinician administered Dissociative Symptom Scale (CADSS), suggest onset of these symptoms occurred shortly after the start of intranasal dosing and resolved by 2 hours postdose, and with repeated dosing these symptoms reduced significantly.

Conclusions: Intranasal esketamine administered in doses of 28, 56 and 84 mg across the study period showed statistically and clinically significant improvement of depressive symptoms in subjects with TRD, as demonstrated by the mean changes in the MADRS total score for the combined analysis of both periods. The doses evaluated were well tolerated and adverse events were similar to what has been observed previously with IV ketamine and eskatamine.

T12. DISCOVERY AND DEVELOPMENT OF EMB-001 FOR THE TREATMENT OF SUBSTANCE USE DISORDERS

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Abstract Background: EMB-001 is a combination of two FDA-approved drugs: metyrapone, a cortisol synthesis inhibitor, and oxazepam, a benzodiazepine. Metyrapone is approved for one day only as a test; oxazepam is approved for various anxiety disorders. We hypothesized that a combination of drugs working by different stress-related mechanisms may be useful for the treatment of substance use disorders, at doses that minimize the safety/tolerability risks of each individual drug.

Methods: We summarize a range of preclinical and clinical data supporting the potential utility of EMB-001 for the treatment of substance use disorders including a pilot human study in cocaine dependent subjects, including measures of cocaine use and craving. New safety data from a Phase 1 study will be available in time for the meeting.

Results: Metyrapone and oxazepam together reduce cocaine self-administration in rats at doses where each is ineffective alone (Goeders, 2008). A formal dose-finding study in rats confirmed

the effective doses in EMB-001 are lower than the effective doses of each drug alone. EMB-001 also reduces nicotine self-administration in rats (Goeders, 2012), and attenuates cocaine and methamphetamine cue reactivity in rats (Keller, 2013).

In five trials (O'Dwyer 1995; Murphy 1998; Eriksson, 2001; Jahn, 2004; Rogoz 2004) metyrapone was generally safe and well-tolerated at 500-4000 mg/day for 2-8 weeks. A human study of EMB-001 in cocaine dependence (Kablinger, 2012) showed a significant reduction in cocaine use and EMB-001 was generally well-tolerated.

Conclusions: Preclinical data demonstrate that EMB-001 is effective in several animal models of drug addiction. A pilot human study suggested efficacy in cocaine dependent subjects, with reduced cocaine use at endpoint. New data from a Phase 1 combined single/multiple ascending dose GCP-compliant study to assess safety will be presented, along with plans for Phase 2 efficacy studies in cocaine use disorder and tobacco use disorder.

No pharmaceutical treatments are currently available for cocaine use disorder, and treatments for tobacco use disorder are only effective approximately 25% of the time. This pharmacological intervention has potential to treat methamphetamine use disorder as well, for which no FDA-approved treatments exist.

T13. PH94B NASAL SPRAY AS A PRN TREATMENT FOR SOCIAL ANXIETY DISORDER: A PHASE 3 PILOT TRIAL

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Abstract Social Anxiety Disorder (SAD) is a prevalent anxiety disorder that is often chronic and disabling. Several medications have been approved for this condition, but they require sustained treatment, are of limited help for many affected individuals, and often have troubling side effects. Cognitive behavior therapy (CBT) is also helpful but many individuals do not participate or fully benefit.
Given the predictable occurrence of the performance and social encounters many individuals with SAD dread and avoid, an effective rapidly acting treatment for the symptoms of SAD that could be used just before such events could be highly useful. PH94B is a synthetic neurosteroid developed by Pherin Pharmaceuticals that is delivered intranasally in low microgram doses and acts via nasal chemosensory receptors to rapidly affect brain structures such as hypothalamus, amygdala, prefrontal cortex and hippocampus. We have previously presented data to show that PH94B rapidly and transiently relieved symptoms of generalized anxiety disorder (GAD). PH94B was also shown in a Phase 2 double blind placebo controlled trial to be significantly more effective than placebo in reducing public speaking and social interaction anxiety during clinic challenges of individuals with SAD. The next logical step was to ascertain whether PH94B would be reduce public speaking and social interaction anxiety and avoidance in people with SAD using the medication as needed in their daily lives. Given that prior clinical studies of PH94B involved only women, we also wanted to evaluate the effectiveness of PH94B in both sexes. Women were given the same dosage as used in our study, while men were given twice the dose.

The study reported here was a Phase 3 pilot/feasibility trial to test a methodology for comparing PH94B and placebo used on a PRN basis by individuals meeting DSM 5 criteria for SAD. Subjects meeting study inclusion and exclusion criteria carried a diary for 2 weeks during which they recorded any anxiety producing social or performance events, and rated the severity of their anxiety on the 0-100 SUDS scale. Those who met predetermined criteria for event frequency and severity were then randomized to 2 weeks of PH94B or placebo, used on a PRN

basis up to 4 times per day. Subjects were instructed how to self-administer PH94B or placebo intranasally 15 minutes before entering a feared situation, and how to record both their anticipatory anxiety prior to the event and their peak anxiety during the event in their paper diaries. After 2 weeks, subjects were crossed over to the opposite treatment for an additional 2 weeks. During the trial subjects were seen weekly for ratings on the Liebowitz Social Anxiety Scale (LSAS) and CGI, and they also completed a patient global rating (PGI) and received new weekly diary forms and fresh bottles of medication.

The predetermined primary outcome measure was a within subjects comparison of mean peak SUDs for all events recorded during the 2 weeks on PH94B versus mean peak SUDS on placebo. Secondary outcome measures included total LSAS, PGI, CGI-S, CGI-I, HAMD-17 and HAM-A at the end of each treatment phase. When carry over effects between the two phases of treatment were observed, between groups comparisons were conducted using data from the first 2 weeks of treatment.

Thirty one subjects were evaluated for the study, 23 were randomized to treatment, and 22 had sufficient exposure to both treatments to be included in efficacy assessments. The mean age of the 22 subjects was 40.2 years, the average age of onset of SAD was 10.3 years, there were 11 male and 11 female subjects, and their mean baseline LSAS total score was 98, indicating severe SAD symptoms.

The mean SUDS peak score for all patients receiving placebo was 58.4 vs 51.1 for PH94B, a difference of 7.3 points, which was statistically significant (paired t 3.09, p=.006) with an effect size of .658 (Cohen's D) in favor of PH94B. Drug superiority over placebo on peak SUDS was similar for males and females. There was a small carry over effect on this variable, such that PH94B followed by placebo showed a smaller difference in favor of drug than did placebo followed by PH94B. However, the carryover effect was not sufficient to nullify the overall significant difference between drug and placebo.

On several secondary endpoints such as the LSAS and the PGI, the carry over effect of placebo being more effective following PH94B than when given as a first treatment, resulted in no overall difference between drug and placebo. However, when only the first 2 weeks of treatment were compared in between subjects analyses, PH94B showed significant superiority to placebo on the LSAS and PGI. CGI-I, Ham D and Ham A differences were not significant between treatments.

Adverse effects were mild, and did not show drug placebo differences.

Overall, despite the small study size, PH94B showed superiority to placebo in the whole sample on the primary outcome measure, and on several important secondary measures using between subjects comparisons of the first 2 week data. In addition, male and female subjects seemed to both benefit from PH94B. The findings are important for several reasons. For one, if larger follow-up Phase 3 trials confirm our findings, PH94B could represent the first systematically studied PRN treatment for social anxiety disorder that could be used either as monotherapy, or if effective on further testing, as an adjunctive treatment. Secondly, if PH94B's effectiveness is confirmed, it would further validate the nasal chemosensory system as a novel pathway for administering medication.

T14.   SKELETAL EFFECTS OF PSYCHOSTIMULANTS IN YOUTH

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Abstract   Background: Psychostimulants have been associated with reduced bone mass and increased bone fragility. Here, we evaluated the skeletal effects of chronic psychostimulant treatment in children and adolescents.

Methods: Medically healthy 5 to 17 year-old males from four different clinic-based studies were combined for this analysis. Most (95%) had received risperidone for six months or more. Treatment history was extracted from medical and pharmacy records. Anthropometric and bone measurements, using dual-energy x-ray absorptiometry (DXA) and peripheral quantitative computed tomography (pQCT), were obtained at each research visit. Multivariable linear regression analysis models examined whether skeletal outcomes differed among three groups of patients who had taken psychostimulants continuously, intermittently, or minimally to not at all. The first group (MPH-Cont) included boys who never discontinued psychostimulants (n=64) as well as those who may have discontinued them at some point but had taken them continuously for two years prior to undergoing the bone scan (n=28). The second group (MPH-Intermit, n=63) consisted of boys who had taken psychostimulants intermittently, including during the two years prior to the bone scan. Finally, the third group (No-MPH) included participants who never received psychostimulants (n=26) as well as those who had received them but not for at least two years prior to undergoing the bone scan (n=14). The period of two years was set, somewhat arbitrarily, given that psychostimulant holidays allow the rapid recovery of longitudinal growth delays.

Results: The sample consisted of 194 males with a mean age of 11.7±2.8 years at study entry. The majority had an externalizing disorder. Among the MPH-Cont group, participants had taken psychostimulants for 5.3±0.2 years by study entry while the MPH-Intermit group had taken them for 3.4±0.2 years. There was no significant difference across the three treatment groups in skeletal outcomes at the radius, lumbar spine, or whole body.

One hundred forty-four boys had valid follow-up skeletal data 1.4±0.7 years after study entry. Again, the skeletal outcomes were not different among those who remained on psychostimulants between the two visits, started psychostimulants anew, or had not taken psychostimulants.

Conclusions: Following chronic treatment, psychostimulants did not appear to significantly affect bone mass accrual in children and adolescents. There was a small, but statistically not significant, negative impact on longitudinal growth.

Learning Objectives
1. To review the value of using DXA vs. pQCT to measure bone mass in a psychiatric population.
2. To discuss the skeletal effects of extended use of psychostimulants in youths.

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T15. A COMPARISON OF PARENT AND TEACHER SENSITIVITY TO SIDE EFFECTS OF MEDICATIONS FOR ADHD

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Abstract When titrating medication for children with attention-deficit hyperactivity disorder (ADHD), physicians monitor both effectiveness and associated side effects. The most common side effects of stimulant medications include insomnia, decreased appetite, irritability, abdominal pain and headaches. It is critical to monitor side effects since up to 50% of children taking stimulant medication experience side effects and 3.6% had side effects severe enough to warrant stopping medication (1).

Since side effects can prompt changes in treatment or justify ending treatment, it is important they be measured reliably. Generally, they are measured with parent and teacher ratings of side effects. Naturally, these rating are quite subjective. Parents and teachers see the child in different settings and times in their medication schedule. Thus, having ratings from both may show the physician a more complete side effect profile. Given that parents and teachers only agree moderately on ratings of ADHD symptomatology, it is important to investigate whether they agree on side effects ratings and/or whether one rater is more sensitive than the other to detecting specific side effects. Investigating this question may provide physicians insights into the need for and interpretation of parent and teacher side effects ratings.

We utilized data collected from a double-blind placebo controlled trial of the stimulant methylphenidate (MPH) for 94 school-aged children with ADHD (2). Over 4 weeks, children were one week each of high dose MPH, medium dose MPH, low dose MPH, and placebo in a random order, counterbalanced across patients. Parents and teachers completed weekly ratings of 13 side effects on the Pittsburgh Side Effects Scale.

The percentages of children experiencing side effects were compared at each MPH dosage to the percentage experiencing side effects on placebo. A ranking of "often" or "very often" indicated that the side effect was present. Comparisons were computed separately for teachers and parents, yielding results that demonstrated whether parents or teachers were sensitive to individual side effects at specific dosages.

According to parent report, a significantly higher percentage of children experienced "headaches" (at low and high dosages), "stomachaches" (at medium and high), "trouble sleeping" (at high) and "worried/anxious" (at low and high) compared to placebo. Conversely, teachers only reported a significantly higher percentage of children experiencing "sadness and crying" (at high dosage) compared to placebo.

These results argue for the continued use of both parent and teacher ratings for monitoring side effects. Parents generally reported more side effects than teachers and were especially sensitive to physical side effects, as well as anxiety. This input is critical, as physical side effects are most common and there are clear strategies for managing these effects that parents can implement. In contrast, teachers were most sensitive to side effects related to mood. Monitoring of mood is important since mood worsening may signal the need for a medication change and can alert the physician to screen for risks related to suicidality. The difference in sensitivity could be due to a multitude of potential reasons, including parents giving their child more one-on-one attention or children's tendency to complain more at home. Teacher's increased propensity to note "sadness and crying" could be due to additional challenges or frustrations children face at school.

Learning Objectives
1. To educate providers on the relative sensitivity of parents and teachers to stimulant medication side effects
2. To educate providers on the value of collecting both parent and teacher ratings of side effects for stimulant medications

Literature References

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T16. THE MANAGEMENT OF ATTENTION DEFICIT HYPERACTIVITY DISORDER AND CONCURRENT SUBSTANCE USE

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Abstract Attention Deficit Hyperactivity Disorder (ADHD) is a chronic, persisting neuropsychiatric disorder that affects children and adults in varying degrees (1, 2). The disorder is characterized by inattention, hyperactivity and impulsivity. Previously thought to be a disorder of childhood, it has been found that symptoms may persist in 65 % of cases to adulthood. (Barkley 2006). The prevalence rate of current adult ADHD is estimated to be 4.4% (Kessler et al., 2006). Untreated ADHD may have significant negative impact on an individual's academic, occupational and social functioning. Adults with untreated ADHD have been found to have higher divorce rates, a greater number of car accidents and hold lower position jobs when compared to individuals whose ADHD symptoms were treated. Importantly, adults with ADHD have an approximately two to three fold higher lifetime risk of developing a substance use disorder (SUD) compared to adults without ADHD (Biederman et al., 1993). In various populations of patients with SUD who present for treatment, the prevalence of ADHD was 10–30% (Wilens et al. 1994). Biederman and colleagues found that individuals with ADHD and comorbid substance use disorder (SUD) will have an earlier onset of substance use and exhibit a more severe and more resistant pattern of substance use. Therefore it is important that in treating substance use, the co-morbid presence of ADHD should be addressed. Effective medications for ADHD include the stimulants, alpha-agonists, noradrenergic agents and catecholaminergic antidepressants. The first line treatment for adults with ADHD is central stimulants (). However, adults with a history of substance use are treated with nonstimulants as the first line fueled by a number of factors regarding concerns of the abuse potential of stimulants, diversion and safety. To date, atomoxetine is the only FDA approved nonstimulant for the treatment of ADHD. Additionally, Individuals who abuse substances comprise the great majority of adults who present for clinical care later – an even greater diagnostic challenge for clinicians.
Although ADHD is overrepresented in individuals seeking SUD treatment, ADHD frequently goes unrecognized primarily because its' detection is not integrated into routine diagnostic protocols (Levin 2012). Three commonly used instruments are the Wender Utah Rating Scale (WURS), which screens for ADHD using the Utah criteria; the Conners Adult ADHD Rating Scale (CAARS), in the self-report short version18; and the Adult ADHD Self-Report Scale-Version 1.1 (ASRS-V1.1). Levin et all concluded in their 2012 study that clinicians treating substance users can be confident that incorporating any or all of these instruments into the preliminary diagnostic process will increase their capacity to detect ADHD and, with proper DSM-based interview- guided diagnosis and ADHD management, improve quality of life in affected individuals, including the course of their SUD treatment.

The question remains how to best improve not only the ADHD Symptoms but also the substance use disorder when treating adults with ADHD and SUD. In order to answer this question, we attempted to examine the current pharmacological/psychotherapy treatment strategies in the management of adults with ADHD and co-morbid SUD. We hypothesized that if the substance use disorder is treated specifically and concurrently in an adequate time frame there will be an improvement in both disorders. Our outcome measures were improvement of ADHD symptoms and substance use behaviors.

Methods: We searched PubMed, the Cochrane database, PsychInfo and the EMBASE database for relevant publications. We developed and followed a standard protocol, using the following search keywords: ''Attention Deficit Hyperactivity Disorder'' "ADHD" AND ''pharmacotherapy'' or ''stimulants'' or ''antidepressant'' or ''atomoxetine'' or ''modafinil'' or Bupropion or ''psychotherapy'' or ''cognitive behavioral therapy'' AND "substance use disorder" or "substance abuse" or "substance dependence" or "drug use" or "addiction". The above databases were searched up to May 2014. No limit for date was set. We manually searched reference lists of pertinent reviews and trials for relevant citations and retrieved those as well. The matches were restricted to publication type, and only original English language publications were retrieved.

Results: This search resulted a total of 940 records from our search of Pubmed, EMBASE, PsychInfo and Cochrane databases. We obtained 265 records from Pubmed; 245 records from EMBASE; 216 from PsychInfo; 123 records from OVID and 91 from the Cochrane database. We screened 647 records after removing 283 duplicates

Discussion: In our study we found that ADHD symptoms improved when treated with pharmacotherapy regardless of the specific medication (stimulant or nonstimulant) used, which is in keeping with the current literature. We also found that improvement in the substance use disorder was not significant. However, it appeared that when specific substance use treatment was included such as relapse prevention and cognitive behavioral therapy specific for substance use, there was a trend toward more significant improvements in substance use. This was also true for the retention rate – when specific substance use treatment was included in the treatment approach, the study retention rate was higher. With all the limitations considered, what can be garnered from this study is that when there is concurrent substance use specific treatment and ADHD specific treatment (pharmacotherapy or psychotherapy), treatment outcomes will be better for both.

Conclusion: We concluded that not all adults diagnosed with ADHD and SUD require medication treatment for ADHD. Factors necessitating treatment for ADHD should be based on the severity of symptoms in multiple settings. Also clear treatment goals should be outlined at the start of treatment which should include specific goals.

Learning Objectives
1. Examine the efficacy and adverse effects of nonstimulant medications on ADHD and SUD symptoms.
2. Examine the role of non-pharmacological therapies for comorbid ADHD and SUD.

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T17. OPEN BOARD

T18. PHARMACOKINETICS OF NOVEL METHYLPHENIDATE EXTENDED-RELEASE ORAL DISINTEGRATING TABLETS FOR ADHD

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Abstract Objective: Methylphenidate (MPH) is a first-line treatment for ADHD (1). Due to the short half-life of MPH and the challenges associated with multiple daily doses, several long-acting MPH formulations have been developed. However, difficulty swallowing the available solid oral dosage forms of MPH may be a barrier to treatment (2). Two formulations of methylphenidate extended-release oral disintegrating tablets (MPH XR-ODT) have been developed as potential alternatives for patients who cannot or will not swallow tablets or capsules. This study compared the bioavailability and absorption of these 2 formulations with a reference medication, MPH HCl extended-release (XR) capsules, under fasting conditions. Pharmacokinetic (PK) data from the formulation that was progressed through clinical development are presented.

Methods: This was a randomized, single-dose, open-label, 3-period, 3-treatment crossover study. Following a $\geq$10-h fast, 42 healthy adult volunteers aged 20 to 70 years received a 60-mg dose or dose equivalent of reference medication and each of 2 formulations of MPH XR-ODT (2 x 30 mg) in a randomized sequence with a 7-day washout period separating each dosing period. Blood samples for assessment of PK parameters were collected at specified times from predose to 36 hours postdose. Plasma samples were analyzed for d-MPH and l-MPH and the following PK parameters were determined: maximum plasma concentration (Cmax), time to maximum concentration (Tmax), elimination rate constant (λz), terminal half-life (T1/2), and areas under the concentration-time curve from time zero to the time of the last quantifiable concentration (AUClast) and from time-zero extrapolated to infinity (AUCinf). Secondary pharmacokinetic endpoints included partial AUCs (eg, AUC0-5 and AUC5-tlast). Bioequivalence between MPH XR-ODT and MPH HCL XR capsules was established if the 90% confidence intervals (CI) for ln(Cmax), ln(AUClast), and ln(AUCinf) geometric means ratios (MPH-XR-ODT/reference) were within 80% to 125%. Safety was also assessed.

Results: Of the 42 volunteers who enrolled (mean [SD] age 35.2 [14.56] years, 57.1% male, 73.8% white); 39 completed the study. PK parameters were generally comparable between the MPH XR-ODT formulation and the reference capsule. The 90% CI was within 80% to 125% limits for total MPH (d-MPH + l-MPH) ln(AUC0-tmax) (90% CI:94.67, 108.56). The 90% CIs for total MPH ln(AUClast) were within accepted limits as well (90% CI:100.39, 107.55), with similar results for ln(AUCinf). The 90% CIs for total MPH ln(Cmax) were not within the accepted limits (90% CI: 117.98, 131.46). Of the 42 subjects, 20 (47.6%) reported a total of 57 treatment-emergent adverse events (TEAEs). The most commonly reported TEAEs were nausea (8 reports) and anxiety (6 reports), which were similar across treatments.

Conclusions: Overall systemic exposure to MPH after administration of MPH XR-ODT was similar to that of the reference product. However, the 25% increase in Cmax suggests that an efficacy study should be conducted to assess endpoints including onset and duration, as the higher Cmax for MPH XR-ODT might confer additional efficacy. MPH XR-ODT exhibits similar absorption kinetics to a marketed XR capsule formulation of MPH and may represent a patient-friendly therapy for patients with ADHD.

Learning Objectives
1. Discuss the clinical utility of an extended-release (XR) oral disintegrating methylphenidate (MPH) formulation for patients with attention-deficit/hyperactivity disorder.

2. Describe the similarities in rates of absorption and bioavailability of different formulations of novel MPH XR oral disintegrating tablets compared with the reference product, MPH HCl XR capsules.

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T19. BRAIN SURGERY IN SMOKE (COCA PASTE) COCAINE ADDICTED-PATIENTS: REVIEW OF LONG TERM RESULTS

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Abstract   Aims: The use of brain surgery in the form of trepanation to relieve headaches and the evil spirits was used for the ancient Peruvians in the Andean regions (> 3000 years B.C.), and we have been applying with modern variants since the early 1980s in our region in addicted-patients that smoke cocaine as coca paste and were considered unrecoverable and refractory to several standard treatments. Is the first use of brain surgery in cocaine dependence. Material and Methods: Between 1981 and 1983 our team performed bilateral anterior cingulotomy (BAC) in 33 coca paste addicted-patients. Coca paste is smoke in commercial cigarettes (CPC). Typical CPC contains avg 152 mg of coca paste (avg 95 mg of cocaine) plus 298 mg of tobacco (avg 2 mg of nicotine). Typically addict (mean 20 CPC a day, sd 8 to 50) smoke avg of 1900 mg of cocaine, plus sufficient nicotine (mean 10 mg, range 1.2 mg to 40 mg) to produce and sustain nicotine dependence even if they do not otherwise use tobacco products. Reviewing our schedule and long-term results (> 10 years) the BAC offered at least 50% of positive results (significant statistically results p<0.001 compared with control group). No neurological, psychological nor legal sequels were observed in recovered, nor in relapse patients. Patients of control group (11 patients that fit the criteria for BAC inclusion but no accepted be operated) did not maintain significant abstinence. Monitoring was done at the beginning with urine tests and family reports. Over one year, subsequent controls were obtained from self-reports, family, school, work, police and legal information.

Conclusions: FDA no approved treatment for cocaine addiction. Brain surgery as bilateral anterior cingulotomy tracking over long periods showed positive results compared with control group, and warrants further research.

Learning Objectives

1. Because the smoking cocaine as coca paste has proved to be very refractory to treatments should be treat as double addiction cocaine-nicotine as we postulated.
2. Brain surgery showed a recovery of 50% of unrecoverable patients. We believe that BAC with simultaneous anti-tobacco treatment could increase the number of positive results.

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T20. OPIOID RECEPTOR ANTAGONIST ODELEPRAN DOES NOT CAUSE ADDICTION IN WISTAR RATS

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Abstract   Educational Objectives: antagonists of opioid receptors are widely and safely used for the relief of symptoms of alcohol and drug abuse. However, they can provoke risk of self administration and further drug dependence. Studying of addictive properties of such substances is an extremely important part of the pre-clinical testing.

Purpose: the investigation of the drug addiction properties of the opioid receptor antagonist Odelepran in a free choice model, and Odelpran deprivation effect in Wistar rats. Odelepran is a new pan opioid receptor antagonist for the treatment of alcohol dependence. Odelepran demonstrates high in vitro binding affinity (Ki) and antagonist potency (Kb) at all 3 classic human opioid receptors (mu, kappa, and delta).

Methods: the research was performed on 7 week-old Wistar male rats (SPF, n=24). Animals were kept one rat per cage under conditions approved by ethics committee. In the first part of the study rats were offered the free choice between the Odelepran at doses 10 or 50 mg/kg and water for two weeks. In the second part, Odelepran was provided with saccharin, which was used to mask the taste of substance making it more palatable. The concentration of Odelepran was increased either from 1 to 5 mg/kg or from 10 to 50 mg/kg in saccharin. At the same time the saccharin concentration was weekly reduced from 0,2% to 0%. The highest doses of Odelpran (5 or 50 mg/kg) were given to the animals without saccharin for the last 14 days (Eastwood EC, 2014). One week before the end of the experiment the rats were deprived from Odelepran for one day and their behaviour was assessed the same day in the Open field test using Noldus Ethovision XT.

Results: The Wistar rats did not choose Odelepran solution at doses 10 to 50 mg/kg over water. Addition of saccharin to the Odelepran solution did not cause Odelepran preference. Deprivation of Odelepran did not cause such symptoms as anxiety, hyperactivity, or exploratory and locomotor activity changes in Open field test, which are the signs of the withdrawal syndrome.

Conclusions: Our data indicate that the voluntary intake of Odelepran at doses 10 and 50 mg/kg does not induce addiction to this drug. Also, Odelepran deprivation didn't induce the withdrawal syndrome in Wistar rats.

T21. EXPLORING RELATIONSHIPS BETWEEN MEDICAL MARIJUANA LAWS AND CANNABINOID RELATED TREATMENT ADMISSIONS USING THE TREATMENT EPISODE DATA SET FOR ADMISSIONS (TEDS-A)

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Abstract   Background: The perception of cannabinoids (CB) in terms of use prevalence and harmfulness has fluctuated in recent years. Questions regarding the impact of CB-related laws on the perceived harmfulness, use, and actual negative consequences have been posed before. For example, previous studies have investigated associations between medical marijuana laws (MMLs) and CB use prevalence rates with mixed results. Furthermore, research is lacking regarding potential relationships between state MMLs, CB use, and adverse consequences. The current study objective was to explore relationships between documented increases in

percentages of CB treatment admissions and approval of MMLs over a 20-year time period Furthermore, because CB use among adolescents may be associated with greater deleterious effects than in adults, we performed a subgroup analysis among adolescents (12 to 17 years of age). The original a priori study hypothesis was that states with MMLs would demonstrate increases in CB-related behaviors and adverse consequences following initiation of an MML (e.g., possibly related to lower perceived harmfulness) and this relationship would also exist specifically among adolescents.

Methods: This study was approved by the relevant university Institutional Review Board. Data was gathered from the nationally-recognized Treatment Episode Data Set for Admissions (TEDS-A) over a 20-year time period from 1992 to 2012 among individuals 12 years of age and older. The TEDS-A variable of marijuana/hashish (including THC and other Cannabis sativa preparations) as the primary substance of abuse was the outcome variable of interest. We compared percentages of CB admissions from total substance use admissions both pre- and post-MML in each state, in addition to a comparison between states with and without MMLs. Trends were inspected to determine if relationships existed between MMLs and CB-related treatment admissions. Adolescents were examined separately, using the identical outcome variable of interest among states with and without MMLs.

Results: Overall, we identified increases over time in the percentage of cases with CB (i.e., "marijuana/hashish") as the primary substance leading to treatment, according to TEDS-A. These increases were present both prior to and following initiation of MMLs in most circumstances. Following initiation of MMLs, no clear changes in patterns of CB admissions were identified compared to pre-MML increases. We found no temporal relationship between passing of MMLs and decreases or increases in percentage CB treatment admissions. Geographical patterns in MMLs were evident, but had no apparent effect on CB treatment admissions (i.e, with CB as the primary substance leading to admission). Notably, over the 20-year time period for which TEDS-A data was available, we observed a very large increase in the percentage of CB treatment admissions (from total substance use admissions) in the age group 12-17 years of age. Specifically, the percentage of admissions with CB as the primary substance of use increased from approximately 25% of treatment admissions (1992) to approximately 75% (2012). However, this increase was consistent across all states regardless of MML status.

Conclusions: We believe the rise in the percentage of CB treatment admissions over the 20-year period assessed is most likely due to a multi-factorial cause, requiring more research to explore the roots of this public health issue. The largest increases seen in percentage CB treatment admissions occurred among adolescents, who should be the focus of intervention, prevention, and treatment efforts. Lastly, multiple limitations exist when utilizing TEDS-A for secondary data analyses to address our study objective, and these limitations need to be considered during future research efforts.

Learning Objectives
1. Describe the relationships that exist between state medical marijuana laws and cannabinoid treatment admissions as assessed using the Treatment Episode Data Set for Admissions (TEDS-A).
2. Recognize the large increases in percentage of cannabinoid treatment admissions from total substance use treatment admissions that occurred from 1992 to 2012, specifically among adolescents 12 to 17 years of age.

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T22. A DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED, FLEXIBLE-DOSE STUDY OF VILAZODONE IN PATIENTS WITH GENERALIZED ANXIETY DISORDER

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Abstract Introduction: Generalized anxiety disorder (GAD) is characterized by pervasive worries that cause psychiatric symptoms, physical symptoms, and functional impairment. Poor remission and high relapse rates support the need for additional treatment options for the 6.8 million adults in the US with GAD. Vilazodone is a selective serotonin reuptake inhibitor (SSRI) and 5-HT1A receptor partial agonist approved for the treatment of major depressive disorder (MDD) in adults. The objective of this study was to evaluate the safety and efficacy of flexibly dosed vilazodone in the treatment of GAD.

Methods: This was a multicenter, randomized (1:1), double-blind, parallel-group, flexible-dose study comparing vilazodone 20-40 mg/d and placebo in patients (age, 18-70 years) with GAD (NCT01844115 ClinicalTrials.gov). Primary and secondary efficacy outcomes were total score change from baseline to Week 8 on the Hamilton Rating Scale for Anxiety (HAMA) and Sheehan Disability Scale (SDS), respectively, analyzed using a mixed-effects model for repeated measures (MMRM) on the modified intent-to-treat (m-ITT) population. Safety assessments included adverse events (AEs), laboratory and vital sign measures, and the Changes in Sexual Functioning Questionnaire (CSFQ).

Results: There were 404 patients (vilazodone=202; placebo=202) in the safety population and 400 patients (vilazodone=200; placebo =200) in the m-ITT population; 81% of placebo patients and 71% of vilazodone patients completed the study. The LSMD (95% CI) versus placebo for total score change from baseline to Week 8 was statistically significant in favor of vilazodone on the HAMA (-2.20 [3.72, -0.68]; P=.0048) and SDS (-1.89 [-3.52, -0.26]; P=.0236). Statistically significant Week 8 differences for vilazodone versus placebo were also seen on each SDS domain score (Work/School: P=.0423; Social Life: P=.0012; Family Life: P=.0036), the HAMA Psychic (P=.0024) and Somatic (P=.0250) Anxiety subscales, and HAMA Anxious Mood (P=.0038) and Tension (P=.0042) items. Treatment-emergent AEs (TEAEs) were reported by 64% of placebo- and 79% of vilazodone-treated patients; the majority of TEAEs in both groups were considered to be mild or moderate in severity. TEAEs that were reported in ≥5% of vilazodone patients and at least twice the rate of placebo were nausea, diarrhea, dizziness, fatigue, ejaculation delayed, and erectile dysfunction. Serious AEs (SAEs) were reported in 3 vilazodone patients; none were considered treatment related or resulted in study discontinuation. Mean changes in laboratory values, vital signs, and CSFQ scores were low and similar between groups; no patient had a QTcB or QTcF interval increase >500 msec.

Conclusion: Statistically significant reductions in HAMA and SDS total scores were seen in favor of vilazodone over placebo suggesting improvement in anxiety symptoms and functional impairment for vilazodone patients in this study. Vilazodone was generally well tolerated in patients with GAD; no new safety concerns were identified.

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

1. Evaluate the safety and efficacy of flexibly dosed vilazodone in the treatment of generalized anxiety disorder.
2. Evaluate the effects of vilazodone on functional impairment in patients with generalized anxiety disorder.

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T23. EVALUATION OF TRYPTOPHAN, KYNURENINE AND SEROTONIN PLASMATIC LEVELS IN A LARGE POPULATION OF AGGRESSIVE PRISONERS

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Abstract Aggressive behavior is a major concern in social and criminal justice settings and also in mental health. Up to date, the complex neurobiological and genetic mechanisms as well as psychosocial factors at the basis of aggressive behavior have not yet been univocally elucidated by basic and clinical research. Serotonin (5-HT) is a neurotransmitter that has been associated to the pathophysiology of aggression and is also one of the targets of anti-aggressive medications. 5-HT is synthesized from the essential amino acid tryptophan (Trp) that, along the kynurenine (Kyn) pathway, is also metabolized to other neuroactive compounds such as quinolinic and kynurenic acids. The conversion of Trp to Kyn is catalyzed by the enzymes tryptophan 2,3-dioxygenase (TDO) and indoleamine 2,3-dioxygenase (IDO). Until now, studies on 5-HT and aggression have been conducted in limited number of aggressive patients. Moreover, it is still unknown at which level the tryptophan via serotonin and kynurenine metabolic pathways are impaired in aggression.

In this study, we collected a unique databank of 360 male prisoners from a federal penitentiary in Quebec, Canada, in which we evaluated biological correlates of aggressive behavior related to the 5-HT system including serum levels of Trp, 5-hydroxytryptophan (5-HTP), 5-HT, Kyn, and several psychosocial factors linked to aggressive behavior such as Axis-I and -II disorders (SCID I and II), global assessment of functioning (GAF), intelligent quotient (IQ), levels of impulsivity, and adult attention-deficit/hyperactivity disorder (ADHD) indices. The presence/absence of aggressive behavior against others and/or themselves was evaluated on the basis of two aggression/violence rating scales: the MacArthur Community Violence Instrument and the Lethality of Suicide Attempt Rating Scale.

We found that aggressive prisoners exhibited lower serum levels of Trp (mean $\pm$ S.E.M.: 11.70 ± 0.16 vs. 11.87 ± 0.23 µg/mL; P=0.021) and Kyn (445.90 ± 9.24 vs. 488.75 ± 14.42 ng/mL; P=0.015) but higher serum levels of 5-HT (173.69 ± 9.55 vs. 135.05 ± 10.56 ng/mL; P=0.047).

Regarding psychosocial factors, they showed higher levels of impulsivity and ADHD indices, lower IQ and GAF score, higher prevalence of mood disorders, drug abuse/dependence, and borderline, conduct and antisocial behaviors. Interestingly, the ratio Kyn/Trp, an indirect measure of TDO and IDO enzyme activities, was positively correlated to the number of severe aggressive acts (r=0.617, P<0.001). After adjusting for confounding factors, logistic regression analysis indicated that the ratio 5-HT/Trp, antisocial behavior, and GAF score were significant predictors of aggressive behavior. Finally, we asked whether these factors can be considered a prognostic index for aggression and we found that the area under the ROC curve for the model resulting by the combination of these three predictors of aggressive behavior was 0.851 (95% CI 0.806-0.895).

These findings indicate that in aggressive individuals there is an increase of circulating 5-HT and a reduction of peripheral Trp which leads to a reduced availability of the amino acid in the brain for the synthesis of 5-HT. Moreover, in agreement with the heterogeneous construct of aggression, we found that only a combination of psychosocial and biological markers, namely a high 5-HT/Trp ratio in the serum, the presence of an antisocial personality disorder, and a low GAF Axis-V score, is a marker of aggressive behavior. Up to date, medications used to treat aggressive patients are still prescribed as ''off-label use'', and thus, several lines of research are trying to discover and validate novel targets for anti-aggressive drug development. According to our data, the conversion of Trp into 5-HT and Kyn in the periphery may be a novel potential target for therapeutic intervention in individuals with aggressive behavior.

Learning Objectives
1. Aggression is a complex phenomenon associated with genetic, neurobiological, and psychosocial factors. Given this heterogeneous construct of aggression, only a combination of psychosocial and biological markers may help predicting the behaviour.
2. Aggressive behaviour is associated to impairments of the peripheral serotonin pathway which lead to 1) an hyperserotonemia and 2) a decrease of peripheral tryptophan levels and thus to a reduced availability of the amino acid for the synthesis of serotonin in the brain. The conversion of Trp into 5-HT and Kyn in the periphery may thus be a novel potential target for anti-aggressive drug development.

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T24. HEALTHY BRAIN ACTIVATION TO ATTENTIONAL AND EMOTIONAL STIMULI OVER EIGHT WEEKS: PRELIMINARY DATA FOR STAGING MOOD DISORDERS TREATMENT USING FMRI

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Abstract Background: Yamasaki et al., (2002) used functional MRI (fMRI) to demonstrate a dissociation between attentional and emotional brain functions on a visual oddball task in healthy adults. Responses to attentional targets were segregated from responses to distractors with emotional salience. Presently, we attempted to replicate and extend this work by investigating a larger number of brain regions-of-interest (ROIs) at three study visits over eight weeks. It is hoped that this work will form the basis for a cognitive/emotional fMRI probe of

pharmacological targets in mood disorders. Methods: Forty-one healthy participants were recruited for this study. Participants received an fMRI scan during a "baseline" visit and follow-up scans one and eight weeks later. All participants were scanned at the University of Cincinnati Center for Imaging Research using a 4.0 Tesla Varian Unity INOVA Whole Body MRI/MRS system. During the fMRI scan participants performed a Continuous Performance Task with Emotional and Neutral Distracter (CPT-END; Strakowski et al., 2011). This is a visual oddball paradigm with the addition of emotional and neutral pictures taken from the International Affective Picture System (IAPS). Participants were asked to press "2" every time they saw a circle (i.e., the target) and press "1" for all other stimuli (i.e., emotional and neutral distractors). This task has been shown to activate neural networks involved in both attentional control and emotional processing. An exploratory whole-brain analysis was followed by an ROI-based analysis for which average MR signal values were converted to percent signal change scores. Results: Voxel-wise analysis revealed a pattern of differential activation between attentional targets and emotional distractors. The former primarily activated the superior frontal gyrus while the later activated the inferior frontal gyrus. The ROI analysis provided a fine-grained context for the voxel-wise results. Emotional and neutral distractors elicited more activation than did target stimuli in the amygdala and prefrontal lobe ROIs. For inferior frontal gyrus in particular, the heightened activation did not differ by distractor type at baseline, however, emotional distractors elicited significantly greater activated at weeks 1 and 8 in both hemispheres. By contrast, target stimuli elicited more activation than did emotional and neutral distractors in dorsal anterior cingulate cortex and posterior insular cortex ROIs. Targets elicited more caudate activation at baseline but not week 8 relative to both distractor types while emotional distractors elicited more thalamic activation at week 8 but not baseline relative to neutral distractors and targets. Conclusions: Taken together, these findings partially replicate those of Yamasaki et al., (2002) and extend them for use as an fMRI probe of attentional and emotional processing over an 8-week period. They demonstrate a dissociation between inferior frontal gyrus/amygdala and dorsal anterior cingulate/posterior insula for processing emotional and attentional stimuli, respectively. Additionally, these results extend previous findings by suggesting that subcortical structures such as the caudate and thalamus are differentially activated over time by the CPT-END, which is an important consideration in neural outcomes research. These findings will form the basis for further work characterizing the neurofunctional signature of mood disordered patients over time.

Learning Objectives
1. Be able to identify brain targets for regulating attention and emotion over eight weeks in healthy individuals.
2. Understand how the work of Yamasaki et al. (2002) can be extended to characterize short-term neurofunctional treatment outcomes for mood disorders.

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T25. META-ANALYSIS OF CYTOKINE ALTERATIONS IN CHRONICALLY ILL PSYCHIATRIC PATIENTS: COMPARISONS BETWEEN SCHIZOPHRENIA, BIPOLAR DISORDER, AND DEPRESSION

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Abstract Background: Schizophrenia, major depressive disorder (MDD), and bipolar disorder have all been associated with immune system dysfunction, including aberrant blood cytokine levels, in both acute and chronic phases of the illness. However, the pattern of cytokine alterations across disorders has not been compared. We performed a meta-analysis comparing and contrasting blood cytokine levels in chronically ill patients with schizophrenia, MDD, and euthymic bipolar disorder.

Methods: We identified articles by searching Pub Med, PsycInfo, and ISI, and the reference lists of identified studies.

Results: 36 studies met the inclusion criteria, including 10 studies of schizophrenia, 12 studies of major depressive disorder, and 14 studies of euthymic bipolar disorder. Levels of sIL-2R were increased in all three disorders ($p < 0.01$ for all). IL-6 levels were significantly increased in patients with chronic schizophrenia and MDD compared to controls ($p < 0.01$ for both). Each individual disorder also had significant elevations in multiple inflammatory cytokines as compared to healthy controls.

Discussion: Overall, we found a significant increase in the cytokine receptor sIL-2R, a marker of T-cell activation, in all three disorders as well as the pro-inflammatory cytokine IL-6 in chronic schizophrenia and MDD. These findings suggest a role for persistent immune activation that is thought to be common to these disorders. Though these findings are limited by a small number of studies, they have important implications for our understanding of the pathophysiology and treatment of persistent symptoms in major psychiatric disorders.

Learning Objectives
1. Taken together, our findings suggest a broad pattern of immune activation across euthymic bipolar disorder, chronic major depressive disorder, and chronic schizophrenia.
2. There are critical limitations to interpreting the data in this meta-analysis, highlighting the need to identify a common set of inflammatory markers that must carefully be studied in order to understand the role of the cytokines in chronic psychiatric disorders and inform novel treatment decisions that may only be relevant to a subset of patients.

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T26. AN 8-WEEK, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF CARIPRAZINE MONOTHERAPY FOR THE TREATMENT OF BIPOLAR I DEPRESSION

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Abstract Introduction: The majority of time spent unwell for a patient with bipolar disorder is accounted for by depressive symptoms, which are the most enduring, prevalent, and disabling symptoms of the disorder. Cariprazine, a potent dopamine D3 and D2 receptor partial

agonist with preferential binding to D3 receptors, is in late-stage clinical development for the treatment of schizophrenia and bipolar mania. The objective of this study was to evaluate the efficacy, safety, and tolerability of cariprazine, an atypical antipsychotic candidate, in patients with bipolar depression.

Methods: This was an 8-week multinational, multicenter, randomized, double-blind, placebo-controlled, parallel-group, fixed-dose study in adult patients (age, 18-65 years) with bipolar I disorder (NCT01396447 ClinicalTrials.gov) and a current major depressive episode; the primary efficacy endpoint was Week 6. Patients were randomized (1:1:1:1) to placebo or cariprazine 0.75 mg/d, 1.5 mg/d, or 3.0 mg/d. The primary and secondary efficacy outcomes were change from baseline to Week 6 on the Montgomery-Åsberg Depression Rating Scale (MADRS) and Clinical Global Impressions-Severity (CGI-S), respectively, analyzed using a mixed-effects model for repeated measures (MMRM) on the intent-to-treat (ITT) population; P values were adjusted for multiple comparisons. Cohen's d effect size estimates were calculated for the primary analysis and MADRS single items were evaluated in post hoc analyses.

Results: The ITT population comprised 571 patients (placebo=141, cariprazine: 0.75 mg/d=140, 1.5 mg/d=145, 3.0 mg/d=145); 73% of patients completed the study (placebo=72%, cariprazine: 0.75 mg/d=73%, 1.5 mg/d=80%, 3.0 mg/d=64%). Cariprazine 1.5 mg/d versus placebo showed significantly greater improvement on MADRS total score change from baseline to Week 6; the least squares mean difference (95% confidence interval) (LSMD [95% CI]) was -4.0 [-6.3, -1.6] (adjusted for multiple comparisons P=.0030). Cariprazine 3.0 mg/d showed greater MADRS score reduction than placebo (-2.5 [-4.9, -0.1], unadjusted P=.0374), but the difference was not significant when adjusted for multiple comparisons (adjusted P=.1122). Cariprazine 0.75 mg/d was similar to placebo. Effect sizes for the cariprazine 0.75-, 1.5-, and 3.0-mg/d groups after 6 weeks of treatment were 0.20, 0.42, and 0.26, respectively. A similar pattern of significance versus placebo was observed on the CGI-S (1.5 mg/d=-0.4 [-0.6, -0.1], adjusted P=.0132; 3.0 mg/d=-0.3 [-0.5, -0.0], unadjusted P=.0489; adjusted P=.1122). In post hoc analyses, statistically significant improvement for cariprazine 1.5 mg/d versus placebo was seen on 6 of 10 MADRS single items (P<.05 each). Adverse events (AEs) that occurred at an incidence ≥10% in any cariprazine group were akathisia, and insomnia. Serious AEs were reported in 5 placebo patients and 5 cariprazine patients (0.75 mg/d=1, 1.5 mg/d=2, and 3.0 mg/d=2).

Conclusions: Cariprazine 1.5 mg/d demonstrated consistent efficacy versus placebo across outcomes and was generally well tolerated, suggesting potential efficacy for the treatment of bipolar depression.

Learning Objectives At the conclusion of this session, participants should be able to:
1. Evaluate the efficacy and tolerability of cariprazine in a study of patients with bipolar depression.
2. Evaluate the efficacy of cariprazine across the range of symptoms associated with bipolar depression in this study.

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T27. THE PREVENTIVE EFFECT OF MINOCYCLINE IN GBR 12909-INDUCED MANIC-LIKE BEHAVIOR

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Abstract   Introduction: Mania is the cardinal feature of Bipolar Disorder (BD) and it has been associated to some behavioral aspects, such motoric hyperactivity, increased exploratory activity, lower anxiety and increased risk-taking behavior. Previous studies suggest that the selective dopamine transporter (DAT) inhibition may be an useful animal model of BD mania. Growing body of evidences suggests that oxidative stress, inflammation, changes in glutamatergic pathways and neurotrophins, interacting with classical neurotransmitters systems, play important roles in many psychiatric illnesses, including bipolar disorder. These novel insights into pathophysiology allow new treatment targets to be explored. In this context, minocycline (MINO) is a tetracycline antibiotic that can modulate glutamate-induced excitotoxicity, and has antioxidant, anti-inflammatory and neuroprotective effects 1. Given that these mechanisms overlap with the newly understood pathways involved in BD pathophysiology, minocycline has potential as alternative therapeutic agent for this disorder. Aims: To investigate the preventive effect of minocycline in manic-like behavior induced by administration of compound GBR 12909, a selective inhibitor of dopamine re-uptake. Methods: Male Swiss mice (25 to 30g) were used. The animals were submitted to preventive treatment protocol for 14 days. During the first 7 days of treatment, the animals received intraperitoneally MINO (25mg / kg or 50mg / kg), lithium (47,5mg / kg) or saline. From 8th to 14th day, with an interval of 30 minutes between administrations, the animals began to also receive the compound GBR 12909 (10 mg / kg). On the 14th day, two hours after the last administration, the animals were submitted to behavioral tests, open field test and predator odor test 2, using as evaluation parameters: the frequency of contact with the source of predator odor and the total time (in seconds) in close contact with the source of the predator odor. Results: In the open field test, the animals pretreated with saline and that received GBR (GBR group) showed a significant increase in both the horizontal activity (number of crossings) and the vertical activity (number of rearings) compared to animals not submitted to this model (SAL group) (p <0.05). Pretreatment with MINO at both doses significantly reduced these parameters compared to the GBR group (p <0.05) and similar to lithium (Li + GBR group). In predator odor test, the GBR group showed a significant increase in both the frequency of contacts with predator odor source and the total time in contact with this object compared to the SAL group (p <0.05). The pre-treatment with the higher dose of MINO (50mg / kg) was able to reduce the both parameters regarding the GBR group (p <0.05).Conclusion: Our results indicate that minocycline has the potential preventive effect of GBR 12909-induced manic-like behavior (hyperlocomotion, increased exploration activity and increased risk-taking behavior). Therefore, it is possible to suggest that minocycline is a promising tool for the alternative treatment for bipolar disorder, but more studies are needed to confirm this potential of this drug.

Learning Objectives

To investigate the preventive effect of minocycline in manic-like behavior induced by administration of compound GBR 12909, a selective inhibitor of dopamine re-uptake.

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T28. SUBJECTIVE AND OBJECTIVE SLEEP IN SYMPTOMATIC BIPOLAR DISORDER SUBJECTS

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Abstract Aim: Sleep disturbances are common in patients with bipolar disorder (BD) and can trigger mood episodes1,2. The aims of this study are: 1) to explore differences between subjective sleep report and objective sleep parameters as measured by actigraphy in BD and controls, 2) to explore the correlation between subjective and objective sleep variables in the BD and HC, and 3) To identify the proportion of subjects in BD and HC group who accurately estimate their sleep latency, TST and sleep efficiency.

Methods: Thirty BD subjects in episode and thirty one healthy controls (HC) were recruited. Diagnosis was established using Mini International Neuropsychiatric Interview. We evaluated subjective sleep measures with the Pittsburgh Sleep Quality Index (PSQI), a clinically-relevant measure of sleep quality, and objective sleep measures by actigraphy for duration of one week. Actigraphic sleep variables were computed with ActiLife, v. 6.4.5. Absolute discrepancy variables were calculated by subtracting objective sleep latency, duration, and efficacy on actigraphy from respective subjective variables on the PSQI.

Results: BD and the HC groups were comparable for age, sex, marital status. The BD group had a mean YMRS score of 12.47 ± 10.7 and a mean HAM D 17 score of 23.83 ± 10.08. Subjects in the BD group significantly differed from HC on all PSQI variables including sleep latency, duration, disturbance, day time dysfunction, sleep efficiency, sleep quality, need medications to sleep and PSQI total scores ($p < 0.05$). On the actigraphy measures, BD subjects significantly differed from the HC only for the mean number of awakenings, with more number of awakenings in the controls (17.7 ± 7.38) than in BD group (11.02 ± 6.12) ($p=0.001$). On the absolute discrepancy variables, the BD group differed significantly from the controls for sleep latency (BD=64.87 ± 59.9, HC=11.5 ± 12.66, $p<0.001$), Total Sleep Time (TST) (BD=2.6 ± 1.24, HC=0.9 ± 0.82, $p<0.001$) and sleep efficiency (BD=29.38 ± 29.31, HC=11.07 ± 6.35, $p=0.006$). TST as measured by PSQI did not correlate with the TST measured by actigraphy for the BD group ($r=0.08$, $p=0.7$), but significantly correlated for the control group ($r=0.42$, $p=0.02$). Sleep latency was inaccurately estimated by more than 30 min in 2/30 (7%) HC and 14/24 (58%) BD subjects (Chi-square=17, $p<0.001$). Sleep efficiency was inaccurately estimated by 10% in 3/30 (10%) HC and 12/24 (50%) BD subjects (chi=10.6, $p=0.001$). TST was inaccurately estimated by more than one hour in 12/30 (40%) HC and 20/24 (83%) BD subjects (Chi=10.3, $p=0.001$).

Conclusion: Subjective sleep perception of total sleep time, sleep latency and sleep efficiency may be inaccurate in symptomatic BD subjects. Mood state may affect perception of sleep and the impact of mood state on subjective-objective differences of sleep parameters needs to be further explored. Objective measures of sleep like actigraphy may be essential to accurately measure sleep in BD subjects. Behavioral interventions directed to address sleep misperception may be helpful in BD subjects.

Learning Objectives
1. Subjective sleep perception is inaccurate in Bipolar disorder subjects,

2. Objective measures of sleep may be essential to accurately measure sleep in bipolar subjects.
3. Behavioral methods to address sleep misperception may be helpful in bipolar subjects

Literature References

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2. Ng TH, Chung KF, Ho FYY, Yeung WF, Yung KP, Lam TH. Sleep–wake disturbance in interepisode bipolar disorder and high-risk individuals: A systematic review and meta-analysis. Sleep medicine reviews. 2014.

T29. SYMPTOMATIC AND FUNCTIONAL RECOVERY IN LURASIDONE-TREATED PATIENTS WITH BIPOLAR DEPRESSION

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Abstract   Aims: The objective of this post-hoc analysis was to evaluate symptomatic and functional remission and recovery in patients with bipolar depression treated with lurasidone. Methods: Outpatients meeting DSM-IV-TR criteria for bipolar I depression, with or without rapid cycling, were randomized to 6 weeks of once-daily, double-blind treatment with lurasidone 20-60 mg (LUR20-60), lurasidone 80-120 mg (LUR80-120) or placebo (PBO). A total of 318 subjects enrolled in a subsequent 6-month, open-label extension study. Subjects initially treated with placebo were started at extension baseline with flexible once-daily doses of lurasidone 40-160 mg/d (PBO-LUR; N=107). Recovery was defined as meeting criteria for both sustained symptomatic remission (Montgomery-Asberg Depression Rating Scale [MADRS] total score $\leq$ 12) and sustained functional remission (Sheehan Disability Scale [SDS] mean score $\leq$ 3 and all SDS domain scores $\leq$ 3 representing no more than mild impairment) for at least 3 months in the 6-month continuation study.

Results: At end of the 6-week, randomized, acute phase, a significantly higher proportion of lurasidone-treated subjects met criteria for both symptomatic remission (MADRS total score $<$ 12) and functional remission (mean SDS total score $<$ 3 and all SDS domain scores $<$ 3 for mildly impairment) (33%,N=273 pooling the LUR20-60 and LUR80-120 groups) compared to the placebo group (15%, N=143,p<0.05, NNT = 6). In the 6-month continuation study, the proportion of lurasidone-treated subjects achieving recovery was 61% (85/140) and 45% (31/69), in subjects who continued lurasidone treatment (LUR-LUR) and who switched from placebo to lurasidone (PBO-to-LUR), respectively. Multivariate logistic modeling revealed that statistically significant predictors of recovery included: lower baseline global clinical severity (CGI-BP OVERALL), non-white race, and taking lurasidone (rather than placebo) during the acute phase.

Conclusions: These findings, derived from a 6-week acute and 6-month continuation study period, suggest lurasidone was associated with substantial rate of recovery from bipolar depression (combined symptomatic and functional remission for at least 3 months) in patients treated for up to 6 months in an open-label, continuation study after an initial acute treatment phase. Predictors of recovery from bipolar depression were identified.

Learning Objectives

1. To gain understanding of recovery outcome (combined symptomatic and functional remission for an extended period of time) in bipolar depression patients treated with lurasidone.
2. To learn about predictors of recovery in bipolar depression.

Literature References

1. Loebel A, Cucchiaro J, Silva R, Kroger H, Hsu J, Sarma K, Sachs G. Lurasidone monotherapy in the treatment of bipolar I depression: a randomized, double-blind, placebo-controlled study. Am J Psychiatry. 2014;171:160-168.
2. Tohen M, Frank E, Bowden CL, Colom F, Ghaemi SN, Yahtam LN et al. for the International Society for Bipolar Disorders (ISBD) Task Force. The International Society for Bipolar Disorder (ISBD) Task Force Report on the nomenclature of course and outcome in bipolar disorders. Bipolar Disord 2009; 11: 453-473.

T30. EFFICACY AND SAFETY OF ASENAPINE 5 MG BID AND 10 MG BID IN ADULTS WITH A MANIC OR MIXED EPISODE ASSOCIATED WITH BIPOLAR I DISORDER

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Abstract Background: Sublingual asenapine (ASN) is an approved antipsychotic with demonstrated efficacy in the treatment of manic and mixed episodes associated with bipolar I disorder as well as schizophrenia.1 In ASN pivotal trials, patients (pts) had the option to flexibly titrate from 10 mg twice daily (bid) to 5 mg bid if clinically indicated. However, <10% of pts had their dose reduced to 5 mg bid. This study aimed to further characterize, by a fixed-dose design, the efficacy and safety of ASN 5 mg bid and 10 mg bid vs placebo (PBO) in adults currently in an acute manic or mixed episode associated with bipolar I disorder.

Methods: This was a phase IIIb, multicenter, international, double-blind, fixed-dose, parallel-group, 3-week, PBO-controlled trial in adults with a current manic (DSM-IV 296.4x) or mixed (DSM-IV 296.6x) episode. Pts were randomized 1:1:1 to PBO, ASN 5 mg bid, or ASN 10 mg bid. The primary efficacy outcome was the difference between ASN and PBO in the change in Young-Mania Rating Scale (YMRS) total score from baseline to day 21. Secondary efficacy outcomes included the difference between ASN and PBO in the change from baseline to day 21 in the Clinical Global Impression Scale for use in Bipolar Illness–Severity subscale (CSGI-BP-S), response (ie > 50% improvement in total YMRS score), Positive and Negative Symptom Scale (PANSS) score, and Montgomery–Åsberg Depression Rating Scale (MADRS) score.

Results: 367 pts were randomized and 264 completed the study, with similar numbers completing across the 3 groups. The mean age was 43.8 years. The least-squares (LS) mean change from baseline at day 21 in YMRS total score was –10.9, –14.4, and –14.9 for PBO, ASN 5 mg bid, and ASN 10 mg bid, respectively; significant differences were observed between both doses of ASN and PBO. Both doses of ASN were superior to PBO in improving CGI-BP-S overall scores. Both the PANSS and MADRS total score results support these findings, with significant differences observed between ASN and PBO for both scales at day 21. There was no significant difference between ASN and PBO in YMRS response rates at day 21. Oral hypoesthesia, sedation, akathisia, somnolence, and headache were the most commonly reported adverse events.

Conclusion: This is the first study to demonstrate that ASN administered 5 mg bid has similar efficacy as the currently approved 10 mg bid dose. Both doses of ASN were shown to be efficacious in the treatment of manic and mixed episodes associated with bipolar I disorder.

Learning Objectives
1. To understand the safety and efficacy of fixed-dose ASN 5 mg bid compared with ASN 10 mg bid in treating manic and mixed episodes associated with bipolar I disorder in adults.
2. To understand the tolerability profile of ASN 5 mg bid and ASN 10 mg bid.

Literature References
1. Asenapine Prescribing Information, available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/022117s011lbl.pdf. Accessed February 13, 2015.

T31. RESILIENCE IN HIGH-RISK OFFSPRING OF MOTHERS WITH BIPOLAR DISORDER: A LONGITUDINAL INVESTIGATION

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Abstract Aims: There is growing evidence that approximately 50% of high-risk offspring of parents with bipolar disorder (OBD) develop moderate to severe forms of psychopathology during childhood and adolescence, including bipolar spectrum disorders. Despite exposure to multiple risk factors, however, the remaining 50% of OBD follow normative and resilient developmental trajectories and do not experience psychopathology. Currently, very limited knowledge exists on resilience in this population and mechanisms contributing to adaptive development remain unknown. The present study, an investigation of high-risk offspring and their mothers with BD from pregnancy until 24 months of age, aims to address this gap in the literature. The study findings have the potential to: 1) aid in delineating mechanisms contributing to adaptive trajectories, 2) serve as a translational platform for prevention and early intervention initiatives, and 3) guide the development of targeted early interventions for an appropriate subgroup of children at the youngest possible age.

Methods: A repeated-measures design was used to assess mothers during a pregnancy screening visit and mother-child dyads at 5-7 days, 3, 6, 12, 18, and 24 months postpartum. Clinician-rated, maternal, and child measures were completed at each study visit. Mother-child interactions reflective of social-emotional development and resilience (i.e., Face-to-Face Still-Face paradigm) were conducted. Pre-and post-interaction saliva was collected to assay for oxytocin.

Results: 16 women with BD (mean age=32.5; SD=3.9; range=25-39; BD I=10; BD II=6) were enrolled in the study during pregnancy. The recruitment and data collection are ongoing. To date, 15 infants were born into the study (male=10; female=5) and the following study visits were competed: screening visit (n=16), 5-7 days (n=12), 3 months (n=13), 6 months (n=14), 12 months (n=12), 18 months (n=9), and 24 months (n=6).

Conclusions: This longitudinal investigation is the first study to enroll mothers with BD during pregnancy and to follow a cohort of OBD during the earliest stages of development. The emerging data has the potential to: 1) facilitate answers to research questions focused on the trajectory of social-emotional development, mother-child interaction, and resilience and risk factors in infants and toddlers of mothers with BD, and 2) inform the development of novel evidence-based prevention and early intervention approaches grounded in resilience models.

Learning Objectives

1. To inform researchers and clinicians about the rationale and importance of investigating resilience in high-risk offspring of parents with bipolar disorder.
2. To inform researchers and clinicians about an ongoing longitudinal investigation of infants and toddlers of mothers with bipolar disorder and the potential of this research to contribute to the development of novel prevention and early intervention approaches.

Literature References

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T32. LONG-TERM USE OF LURASIDONE IN PATIENTS WITH BIPOLAR DISORDER: SAFETY AND EFFECTIVENESS OVER 2 YEARS OF TREATMENT

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Abstract Introduction: Bipolar disorder is a chronic, recurrent illness typically requiring maintenance therapy. Lurasidone is an atypical antipsychotic that has been approved by the FDA for the treatment of schizophrenia; and for the treatment of bipolar depression, both as monotherapy, and as adjunctive therapy with lithium or valproate. The aim of the current study was to evaluate the safety and effectiveness of lurasidone over 2 years of treatment in patients with bipolar disorder who initially presented with a major depressive episode.

Methods: Patients with bipolar I depression were enrolled in one of three 6-week, double-blind, placebo-controlled trials (monotherapy with lurasidone, 1 study;1 adjunctive therapy with lurasidone and lithium or valproate, 2 studies);2,3 followed by a 6-month open-label extension study of lurasidone in flexible daily doses of 20-120 mg. Six month study completers were then treated, open-label, for an additional 18 months with flexible, once-daily doses of lurasidone in the range of 20-80 mg. Concomitant therapy with mood stabilizers and antidepressant medications was permitted during both the 6-month extension study, and the current 18 month study. The Clinical Global Impression–Severity (CGI-S) scale was included as a measure of treatment efficacy.

Results: A total of 941/1199 patients (78.5%) completed the 6 week acute treatment studies (lurasidone, 77.4%; placebo, 80.0%), of whom 817 entered the 6-month extension study, with 559/817 (68.4%) completing the study. A total of 122 patients entered the 18-month continuation study (52.5% male; mean age, 41.3 years; 76.2% receiving adjunctive therapy with lithium or valproate). Overall, 19.7% of patients discontinued during 18 months of treatment, including 6.6% due to adverse events and 1.6% due to lack of efficacy. An additional 58 patients (47.5%) were ongoing at the time the study was terminated by the sponsor. Among patients who entered the 18-month continuation study, the mean CGI-S score at baseline of the acute study was 4.3, and improved to 2.8 at baseline of the 6-month extension study, and was 2.1 at baseline of the 18-month continuation study. At 18-month endpoint, the mean CGI-S score was 1.7 (observed case [OC] analysis; LOCF, 1.9). Median change in weight, from acute baseline to 18-month continuation endpoint was +0.10 kg (OC, n=55); median change in cholesterol was -3.0 mg/dL, and median change in triglycerides was +26.0 mg/dL (OC, n=54 for both).

Conclusions: Up to 2 years of treatment with lurasidone was safe and well-tolerated in this bipolar depression population, with minimal effects on weight and metabolic parameters. Efficacy was maintained during extended treatment with lurasidone.

ClinicalTrials.gov identifier: NCT01485640.

Learning Objectives
1. After completion of this presentation, the reader will have a better understanding of the safety and tolerability of long-term treatment with lurasidone in patients with bipolar depression.
2. After completion of this presentation, the reader will have a better understanding of the effectiveness of long-term treatment with lurasidone for managing patients with bipolar depression.

Literature References
1. Loebel A 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.
2. Loebel A 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.

T33. LURASIDONE PHARMACOKINETICS AND SAFETY PROFILE IN PEDIATRIC PATIENTS WITH PSYCHIATRIC DISORDERS

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Abstract Objectives: To characterize the pharmacokinetic (PK), safety, and tolerability profile of lurasidone in a pediatric population (6-17 years old) and to identify a tolerated dose range for subsequent clinical studies.

Methods: This open-label, multicenter, single and multiple ascending-dose study enrolled patients aged 6 to 17 years diagnosed with attention deficit hyperactivity disorder with aggressive behavior, bipolar disorder, schizophrenia, Tourette syndrome, or autism spectrum disorder. Patients from 4 age groups (6-9, 10-12, 13-15, and 16-17 years) were assigned to 1 of 5 lurasidone sequential dosing level cohorts (20, 40, 80, 120, and then 160 mg/d). If a dose level was tolerated, the next cohort was initiated. In the single-dose phase, blood samples for PK analysis were collected predose and for a 48-hour period postdose. After a 2-day washout period, patients entered the multiple-dose phase and received once-daily lurasidone for 7 to 9 days; blood samples for PK analysis were collected before and during a 24-hour period after the final dose. Lurasidone PK parameters, including maximum serum concentration (Cmax) and area under the concentration-time curve (AUC), were calculated. For comparison, corresponding adult PK parameters were derived from a population PK model.

Results: A total of 105 patients (64.8% male) enrolled in the study; 85.7% completed all planned lurasidone doses. Adverse events (8.6%) leading to study discontinuation were vomiting (n=3), somnolence (n=2), akathisia (n=1), parkinsonism (n=1), blurred vision (n=1), and dystonia (n=1). The observed lurasidone pediatric PK exposures (Cmax and AUC0-24) across 20 to 160 mg/d generally were similar to exposures at steady state from the adult PK model. The most common adverse events (AEs) were somnolence (41.9%), sedation (18.1%), nausea (17.1%), and vomiting (15.2%); incidence of AEs was generally dose-dependent across

the 20- to 160-mg/d dose range. All 6- to 9-year-old patients experienced somnolence at 120 mg/d, so a 160 mg/d cohort was not enrolled in this age group. Two serious AEs (parkinsonism, dystonia) were reported, both at 80 mg/d.

Conclusions: The PK and AE profiles of lurasidone in this heterogeneous pediatric population generally were consistent with those observed in adult patients. Based on the results of this study, lurasidone is being evaluated in pediatric clinical studies in the dose range of 20 to 80 mg/d.

ClinicalTrials.gov identifier: NCT01620060.

Sponsored by Sunovion Pharmaceuticals Inc.

Learning Objectives
1. Assess consistency of pharmacokinetic profile of lurasidone in a heterogeneous pediatric population with those observed in adult patients following single and multiple doses of lurasidone 20 to 160 mg/d
2. Identify a tolerated dose range of lurasidone for subsequent pediatric clinical studies

Literature References
1. Findling RL. Atypical antipsychotic treatment of disruptive behavior disorders in children and adolescents. J Clin Psychiatry. 2008; 69 Suppl 4:9–14.
2. Olfson M, Blanco C, Liu SM, Wang S, Correll CU. National trends in the office-based treatment of children, adolescents, and adults with antipsychotics. Arch Gen Psychiatry. 2012; 69(12):1247–1256.

T34. IMPEDIMENTS TO CLINICAL TRIAL ELIGIBILITY FOR PHARMACOLOGIC INTERVENTIONS IN AUTISM

Lindsay DeVane[1], Charles Jane[2], Ruth K. Abramson[3], John Williams[4], Laura A. Carpenter[2], Mark E Geesey[2], Catharine Bradley[2], Sarah Ravan[3], M. Frampton Gwynette[2], Marcus Kruesi[2], Eve Spratt[2], H.H. Wright[3]

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Abstract Background: The FDA approved pharmacologic treatments of autism spectrum disorder (ASD) consist of two drugs, risperidone and aripiprazole, originally developed as antipsychotics for adults but approved in ages 6-17 years for irritability. Each drug has supportive evidence of efficacy and safety from multi-site, randomized clinical trials using placebo controls. The major outcome variable has been an improvement in the irritability scale of the Aberrant Behavior Checklist. With successful treatment, a reduction in raw scores over 8 weeks is expected to be 40 to 50%. Adverse events (AEs) with both drugs have been similar to data collected from adults. AEs that frequently influence drug selection and dosage are weight gain and sedation. Anecdotal evidence supports the practice of switching from one drug to the other when outcomes are inadequate. Empirical dosing is practiced with few guidelines based on objective measures to minimize a broad variability in dosage titration schedules.

Objectives: In the Biomarkers in Autism of Aripiprazole and Risperidone Treatment (BAART) study (clinical trials.gov NCT01333072) we designed a randomized prospective clinical trial of these two pharmacologic interventions to test genetic polymorphisms and other potential biomarkers as predictors of efficacy and AEs. Based on epidemiologic data of the prevalence of ASD in South Carolina (SC), we set a target enrollment of 180 subjects over a 4 year period utilizing 4 clinical sites across SC.

Methods: The protocol is double-blind with a placebo lead-in followed by titration based on response with weekly evaluations for 10 weeks. Blood is collected for DNA analysis of genetic polymorphisms of genes related to drug disposition and molecular targets. Steady-state drug concentrations are measured prior to an elective 3-month blinded extension phase. Recruitment efforts have been extensive and included IRB-approved mailings to over 2000 families of patients seen at a university clinic over 2 years with a ASD diagnosis; to 2,425 families who receive state benefits for disabilities; all pediatricians and ABA therapists in the tri-county Charleston area, greater Greenville area, and Columbia.

Results: Between October, 2011 and February, 2015, 399 children had been screened at 4 study sites in South Carolina, 83 were enrolled, and 57 completed the 10-week trial. The trial design adheres closely to FDA approved prescribing guidelines for age (6 to 17 years) and dosage titration of both drugs. Despite substantial recruitment efforts, enrollment has been difficult. Screening logs, hospital diagnostic codes, clinic records, and anecdotal evidence from community practitioners and public support groups all indicate widespread utilization of drug therapy before age 6 in ASD patients. For example, of the 399 subjects screened, 60 (15%) had recent or current exposure to one of the study drugs.

Conclusion: The limited number of FDA-approved pharmacologic treatments for ASD serves as an impediment for obtaining evidence-based differentiation between risperidone and aripiprazole. Early treatment of many children below age 6 undermines a desirable eligibility requirement of minimal or no previous drug exposure, a trial design considered important to reduce confounding variables. The trial is expected to be completed in 2015.

Learning Objectives
1. Be able to discuss clinical trial design features to evaluate biomarkers
2. State reasons for difficulty in recruitment in clinical trials of autism

Literature References
1. Aman M, SIngh NN, Stewart AW, et al: Psychometric characteristics of the Aberrant Behavior Checklist. Am J Mental Deficiency 1985; 89:492-502.
2. McCracken J, McGough J, et al: Risperidone in children with autism and serious behavioral problems. N Eng J Med 2002; 347:314-321.

T35. LOW VITAMIN D LEVEL INTERACTS WITH PERIPHERAL BODY FAT TO PREDICT HEPATIC FAT CONTENT IN ANTIPSYCHOTIC TREATED AND NON-TREATED YOUTH

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Abstract Background: Antipsychotic drug therapy enhances cardiometabolic risk by increasing adiposity, and possibly other pathways. Vitamin D levels have been observed to be low in the context of antipsychotic treatment, (1) thus supplementation has been proposed as a potential target for reducing metabolic side effects and weight gain during antipsychotic treatment. Low Vitamin D level (< 30 ng/ml) has been associated with inflammation and cardiovascular disease risk, and is known to play a role in the development of complex disease processes like atherosclerosis, type 2 diabetes and hepatic steatosis. In animal models, the development of non-alcoholic steatohepatitis can be accelerated by the combination of vitamin D deficiency and a high fat diet, and is corrected by the administration of 1,25(OH)2 Vitamin D3. (2,3) We aimed to evaluate the moderating effect of Vitamin D on the relationships between whole body adiposity and both intra-hepatic triglyceride content (IHTG) and carotid intima media thickness (CIMT) in children with and without antipsychotic drug treatment.

Method: Participants were 44 youth: 25 antipsychotic-treated and 19 not receiving antipsychotics who were frequency-matched on age, gender and body mass index. Dual-energy X-ray absorptiometry percent body fat (DEXA %fat), IHTG and CIMT were measured. Standard plasma and anthropomorphic measures of metabolic risk were obtained to characterize participants. ANCOVA tested for main and interaction effects of DEXA %fat and case-control status on IHTG and CIMT. Vitamin D was added as a continuous covariate to test for main effects and interactions with DEXA % fat and group status.

Results: DEXA %fat predicted IHTG ($R2 = 0.3$), and this relationship was unaffected by antipsychotic treatment status. Vitamin D modified the effect of DEXA % fat on IHTG, with low levels of Vitamin D associated with larger effects of DEXA % fat on IHTG. There was no observed relationship between DEXA % fat and CIMT ($R2 = 0.003$). The relationship between DEXA % fat and IHTG content appeared to be moderated by Vitamin D level in the pooled group ($F[1,42] = 6.83$, $p = 0.013$); this relationship appeared to be primarily driven by low Vitamin D level ($F[1,20] = 11.67$, $p = 0.003$). We were unable to detect any main or interactive effects of predictor variables in relationship to CIMT

Conclusion: The results provide evidence regarding the adverse effect of increasing adiposity and low Vitamin D levels on liver fat content in both antipsychotic treated and non-treated youth. This study supports the use of biomarkers to directly measure and accurately quantify adiposity and liver fat content, both measures of cardiometabolic risk. While preliminary, the results of the current study support clinical proposals to monitor adiposity and Vitamin D level in youth in order to mitigate future risk of cardiometabolic disease in children with and without antipsychotic drug treatment.

Learning Objectives
1. Learn potential mechanisms for developing hepatic steatosis during antipsychotic treatment
2. Understand how Vitamin D impacts developing hepatic steatosis in antipsychotic treated individuals

Literature References
1. Kong M, Zhu L, Bai L, et al. Vitamin D deficiency promotes nonalcoholic steatohepatitis through impaired enterohepatic circulation in animal model. Am J Physiol Gastrointest Liver Physiol. 2014;307(9):G883-893.
2. Yin Y, Yu ZW, Xia M, Luo XQ, Lu XF, Ling WH. Vitamin D attenuates high fat diet-induced hepatic steatosis in rats by modulating lipid metabolism. European Journal of Clinical Investigation. 2012;42(11):1189-1196.
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T36. THE SUICIDE IDEATION AND BEHAVIOR ASSESSMENT TOOL (SIBAT): DEVELOPMENT OF A NOVEL MEASURE OF SUICIDAL IDEATION/BEHAVIOR AND PERCEIVED RISK OF SUICIDE

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Abstract Purpose: To describe the development of the Suicide Ideation and Behavior Assessment Tool (SIBAT) and present preliminary information on its content.

Content: Suicide is one of the leading causes of preventable death. Clinicians wanting to monitor suicidal ideation, behavior, and risk require a tool that includes all of these components. Ideally, it should allow assessment of change as the result of intervention. The SIBAT is based on an established measure of suicidal ideation and behavior: the InterSePT Scale for Suicidal Thinking–Plus (ISST-Plus). Items from the ISST-Plus have been reorganized into 10 modules that allow for efficient, comprehensive data collection. The SIBAT is divided into patient-self-report and clinician-rated sections. Its modular structure allows for customization, and the administration of specific modules can be adjusted to meet clinicians' needs. Thus, responses less susceptible to change (eg, demographics, medical history) are segregated into modules distinct from responses more likely to fluctuate (eg, current suicidal ideation).

Methodology: The SIBAT Consortium, a group of clinical trial and academic experts in scale development, suicidology, and clinical management of suicidal patients, met regularly over 18 months and developed a modular instrument based on clinician consensus, a review of suicide literature, and the ISST-Plus. During revisions of the provisional version of the SIBAT scale, modules were added and item wordings refined. A draft version agreed upon by the SIBAT Consortium was reviewed by 14 patients from a psychiatric clinical research setting and by 686 members of Patients Like Me, an online patient community who self-identified as being at risk for suicide. All participants 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. A validation study is planned to examine reliability and validity of a computerized version of the instrument. This study will also include exploratory factor analyses and item response theory analyses. Modifications of selected SIBAT items based on these cognitive interviews will be presented.

Implications: The SIBAT facilitates comprehensive assessment of suicidal ideation, behavior, and clinician assessment of risk by combining a flexible modular structure and comprehensive patient-reported assessments. Its patient-reported modules provide a broad, standardized background of information that is efficiently collected on a computer. This provides a robust basis for clinical judgments of imminent and long-term suicide risk. The validation of this instrument, which incorporates extensive cognitive reviews from diverse sources, will support its broad application across patient populations.

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

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STS, the ISST-Plus, and the C-SSRS for assessing the Suicidal Thinking and Behavior FDA 2012 Suicidality Categories. Innov. Clin. Neurosci. 11 (9-10), 32-46.

T37. US AND EASTERN AND CENTRAL EUROPEAN RATER PERFORMANCE ADMINISTERING THE MINI INTERNATIONAL NEUROPSYCHIATRIC INTERVIEW (MINI): ARE THERE IMPLICATIONS FOR TRAINING AND SPONSOR GLOBAL SITE SELECTION?

Elan Cohen[1], Rolana Avrumson[1], Bethanne Friedmann[1], Kim Baldwin[1], Melissa Carbo[1], Natalie Glaug[1], Andrew Komorowsky[1], Sean Meighan[1], John Perrett[1], Colleen Rock[1], Michael Murphy[1]

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Abstract Background: Sponsors increasingly rely on data from clinical trial sites in Central and Eastern Europe (CEE; Ghosh, 2013; GSK Report, 2014). FDA inspections demonstrate compliance with good clinical practice in these regions over other regions (US Department of Health and Human Services, 2010). However, research investigating differences between US and CEE rater quality for industry sponsored, interventional studies in psychiatric disorders has been limited. In schizophrenia, Daniel and Kott (2013) found mixed results regarding lower quality interviews in the United States but raters were not different in their application of scale anchor points and other instructions as compared to European counterparts. Williams et al. (2012) illustrated how depression and schizophrenia studies conducted outside of the US may fail to detect signal, with implications for global rater credentialing, training, and surveillance. The current study adds to the literature by examining overall errors and specific errors made by US versus CEE raters in administration of a diagnostic tool typically used in clinical trials. Method: The Mini International Neuropsychiatric Interview (MINI V.6; Sheehan et al., 1998) was used to assess US and CEE (5 countries) raters' administration and scoring performance in an industry sponsored interventional outpatient study in schizophrenia. Only raters with an advanced doctoral degree and ≥ 2 years' indication experience were selected to obtain standardized training on scale administration and scoring at an Investigators' Meeting or through a web portal. Feedback regarding performance followed each screening visit by expert clinicians. Results: The MINI was administered by 29 US and 57 CEE raters to 139 and 286 subjects, respectively. Statistically significant differences were observed for US vs. CEE raters on the following (US vs CEE): experience administering the MINI (data were categorical and a Wilcoxon non-parametric analysis was performed; 75% v 50% had ≥ 5 years MINI administration experience; p=0.003), working within schizophrenia research (12.9 v 8.4 yrs.; p=0.002), working with schizophrenia clinical settings (19.1 v 14.1 yrs.; p=0.006), MINI administration duration (28.0 v 38.3 mins; p=0.007), and coding errors (0.53 v 0.87; p =0.04). US and CEE raters did not significantly differ on total MINI errors (1.8 v 2.4; p=0.11) or on specific errors of missing notes (0.45 v 0.57; p=0.10), recording errors (0.20 v 0.28; p=0.51), and administration errors (0.67 v 0.65; p=0.91). Conclusion: Results indicate that despite US raters having more experience administering the MINI, more experience in the assessment of schizophrenic patients, and shorter MINI administration time, the total errors in administration and scoring were comparable between groups. Differences noted in MINI experience and administration duration were not considered clinically impactful, even when statistically significant. For example, although the average US and CEE MINI duration of administration differed (28 v 38 min), both are within the range for diagnosing psychotic disorders (22 min [$\pm$ 7.7 SD] min; Amorim et al., 1998). Overall, data do not support different training foci by region for the MINI or exclusion of sites based upon a priori assumptions regarding data integrity. Other implications for global training, site selection, and recommendations for future research will be discussed in the poster.

Literature References
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2. Department of Health & Human Services USA. Challenges to FDA's ability to monitor and inspect foreign clinical trials. June 2010.

T38. DRUG-INDUCED NEUROCOGNITIVE CHANGES ON CHOICE REACTION TIME IN CNS POLYDRUG RECREATIONAL USERS

Talar Hopyan[1], Beatrice Setnik[1]

[1]INC Research

Abstract   Study Purpose: To investigate the neurocognitive effects on a test of psychomotor performance in recreational drug users following the oral administration of sedative-hynoptics (alprazolam, 1.5 mg and 3.0 mg; zolpidem, 15 mg, 30 mg); ethanol (1.0 g/kg); a dissociative anaesthetic (oral ketamine, 100 mg); and a cannabinoid (dronabinol, 40 mg and160 mg).

Method: Neurocognitive performance was measured using the choice reaction time (CRT) task, including data from 4 single-dose, randomized, double-blind, placebo-controlled, crossover studies. Participants were a total of 95 individuals with a history of recreational polydrug use who were experienced with the drug class of interest (ages 18-55 years). CRT is a classic test of psychomotor performance; electronic data for reaction times were captured through validated neurocognitive testing software. Peak effect (Emax) was calculated for CRT reaction time outcomes across different drugs compared to placebo.

Results: Analysis of variance showed Emax values were significantly larger for all doses of alprazolam, zolpidem, and ethanol ($p < 0.0001$) against placebo. No significant differences in Emax for CRT outcomes were observed for ketamine and dronabinol ($p > 0.05$).

Conclusions: Outcomes on CRT vary according to drug class. As expected, impaired reaction times (i.e., significant increase) on the CRT task were associated with administration of CNS depressants (alprazolam, ethanol, and zolpidem). Oral administration of ketamine was not associated with significant decreases in reaction time on the CRT task. Dronabinol drug administration had no effect on psychomotor performance, suggesting that either it does not impair reaction time or users of this drug may have developed palpable tolerance to the acute disruptive cognitive effects. Findings also suggest that performance on CRT is an effective measure for capturing neurocognitive impairment of CNS depressant drugs, which is relevant for evaluating potential impairments on driving as per the new FDA Draft Guidance, Evaluating Drug Effects on the Ability to Operate a Motor Vehicle (Jan 2015).

Learning Objectives
1. To determine if distinct psychomotor response patterns are present for drugs of abuse with different mechanisms of action.
2. To determine whether experience with a particular drug class of choice can influence acute psychomotor responses of drugs of abuse in a different class.

Literature References

1. FDA Draft Guidance for Industry: Evaluating Drug Effects on the Ability to Operate a Motor Vehicle (January 2015). Center for Drug Evaluation and Research (CDER).
2. Ramaekers, JG, Theunissen EL, de Brouwer M, Toennes SW, Moeller MR, and Kauert G. (2011). Tolerance and cross-tolerance to neurocognitive effects of THC and alcohol in heavy cannabis users. Psychopharmacology, 214(2):391-401.

T39. DETERMINING AND ADDRESSING RECRUITMENT CHALLENGES IN AN EFFICACY TRIAL IN BIPOLAR DISORDER, DEPRESSED PHASE

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Abstract   Objective: Based on the work of Hoertel and colleagues, we estimated 1 out 300 individuals in the general population would be eligible for a usual efficacy trial in bipolar disorder (BD) (type 1 and 2) depression based on the point prevalence of individuals with BD in the depressed phase and seeking treatment being O.1 % and 36% of this population meeting the inclusion and exclusion criteria commonly applied in such clinical trials (1). This poster presents how this recruitment challenge was managed while not compromising the study integrity.

Method: This trial initially had a two-by-two design with two active agents and two matched placebos and was conducted at three sites. The study management was performed by the overall principal investigator (PI) aided by consensual input from each site's PI and their team via biweekly meetings. Management included: continuous review and assessment of the recruitment approaches being used, examining which criteria were restricting recruitment and evaluating whether criteria could be adjusted or clarified to facilitate enrolment without compromising the integrity of the study, increasing the duration of study and budget, and performing an interim analysis at the mid-way point and then using an adaptive trial approach to increase the efficient use of subjects and simultaneously decrease the number needed to test the study hypothesis. Multiple recruitment approaches were used. Potential subjects were first screened by phone and then face-to-face.

Results: One patient for every two patients screened face-to-face were excluded, a rate consistent with the Hoertel findings. No recruitment effort was clearly superior to the others. Although the original time allotted for study recruitment was 22 months, the duration was increased to 40 months. Cost per participant nearly doubled from $5,000 /subject to $9,100 /subject. This increase was largely attributable to the increased effort needed for enrollment. The criteria were modified to include BD NOS and to increase the upper age limit from 55 to 65. At the mid-way point of the study, a blinded interim analysis was conducted to determine whether any of the four cells were showing separation. If not, the study would be stopped for futility. Two groups were showing separation in terms of the main outcome measures but not yet achieving statistical significance. A power calculation based on the results of these two groups indicated the number needed to achieve statistical separation could be accrued by reducing the number of groups from 4 to 2 by eliminating the two intermediate groups. A non-blinded individual not involved in the study determined that the two cells chosen would test the a priori hypothesis. Therefore, this adaptive approach was taken.

Conclusion: Ongoing study management can address one of the most common problems encountered in psychiatric clinical trials, namely slower than expected enrollment, without compromising the integrity of the study.

Learning Objectives
1. To learn to become more aware of participant recruitment criteria for clinical trials.
2. To learn how the managers of a clinical trial adapted to account for problems that may arise during a clinical trial.

Literature References
1. Hoertel n, Le Strat Y, Lavaud P, et al; Generalizability of clinical trial results for bipolar disorder to community samples: findings from the National Epidemiologic Survey on Alcohol and Related Conditions. J Clin Psychiatry 2013; 74:265-70.
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T40. DEVELOPMENT AND APPLICATION OF AN ADHERENCE METRIC DERIVED FROM POPULATION PHARMACOKINETICS TO INFORM CLINICAL TRIAL ENRICHMENT

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Abstract Purpose: To construct and evaluate an aggregate metric of relative adherence from sparse plasma sampling using a population pharmacokinetic (POPPK) approach in a clinical population, which may be used to assess possible correlations of subjective clinical response questionnaires with objective expected plasma steady-state concentrations of prescribed medication. While groups have investigated the effect of nonadherence on POPPK estimation (Gibiansky et al., 2014; Soy et al., 2004), there has yet to be an approach designed to quantify a relative measure of adherence to be used for comparison with subjective questionnaire responses.

Methodology: A single visit clinical trial was conducted in 47 patients of bipolar-1 or schizophrenic disposition, who were on stable doses of oral aripiprazole for at least 2 weeks so that a "presumed steady-state" would be valid. During the visit, 4 plasma samples were drawn at one-hour intervals and patients filled out the Modified 8-item Morisky Adherence scale (MMAS8). Preceding study conduct, a POPPK model was built for oral aripiprazole using 24 independent studies and over 440 subjects. An aggregate metric for adherence (ADHMET) was defined as the ratio of observed versus "expected" exposure: ADHMET=AUCobs/AUCexpected=CLexpected/CLobs. The expected clearance (CLexpected) was defined using the expression for the typical value of clearance in the POPPK model accounting for relevant covariates, while the observed clearance (CLobs) was defined by the empirical Bayesian estimates (EBEs) for each individual after applying the previously developed model to the new clinical data. During modeling, all parameters were fixed except for the interindividual variability term on clearance, and the residual error term. Deviation from expected variability of apparent clearance was attributed in part to a deviation from the prescribed dosing regimen and therefore suitable for comparing groups defined by questionnaire responses. Additional simulations were conducted to assess the performance of the ADHMET as an individual diagnostic for classifying a patient as adherent or not. (NCT02050854)

Results: The ADHMET metric was adequate for comparing relative adherence levels across questionnaire response groups. Aggregate MMAS8 scores were not correlated with group

ADHMET values; however, one question was statistically correlated with group ADHMET values with $p<0.05$, and another question was suggestive with $p<0.1$.

Importance: Population pharmacokinetic principles can be applied to reverse-engineer an objective adherence-like metric that may be used to compare relative adherence levels across groups. Applying this metric to correlate clinical questionnaire responses represents a novel "pseudo" pharmacodynamic application of population pharmacokinetics. This approach offers a new way clinicians and scientists may approach patient selection in clinical trials. Additionally, a metric such as ADHMET may be used as stratification of responders versus non-responders, or as a covariate in a hazard function.

Learning Objectives
1. Provide evidence that population pharmacokinetics may be used to reverse-engineer an objective relative adherence metric that may be used to compare groups based on clinical questionnaire responses.
2. Correlate levels of observed versus expected steady-state plasma exposures in patients on stable doses of aripiprazole.

Literature References
1. Gibiansky L, Gibiansky E, Cosson V, Frey N, Stark FS: Methods to detect non-compliance and reduce its impact on population PK parameter estimates. J Pharmacokinet Pharmacodyn 2014; 41:279-289
2. Soy D, Beal SL, Sheiner LB: Population one-compartment pharmacokinetic analysis with missing dosage data. Clin Pharmacol Ther 2004; 76:441-451

T41. GOING DIGITAL IN CLINICAL DEVELOPMENT

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Abstract Background: Clinical trial conduct has changed little over the last two decades. Collecting study data in traditional trials can delay data visibility from weeks to months, resulting in an inability to gain timely insights from the data early on, reduced ability of researchers to mitigate risks during the trial, and impedance of early decision making. Innovative tools and technology are readily available for use in the clinical trial process. Generation, collection, and processing of data are changing dramatically, from eConsent to eSource to digital medicine, with improvements in information technology, accessibility, and bandwith. Combining emerging technologies and digital health solutions can improve the clinical trial process, and provide timely data to authorized end users. Otsuka Pharmaceutical Development and Commercialization is collaborating and partnering with patients, clinical investigators, clinical research organizations, and innovative companies in an effort to integrate insights, operations, and digital medicine into complex CNS clinical trials.

Methods: New technologies in conducting clinical trials include (a) shifting from paper and Electronic Data Capture collection process to eSource to increase transparency and reduce site workload; (b) leveraging eConsent to enhance patient understanding and improve overall consent compliance; (c) implementing eSupply management of clinical supplies to reduce risk, decrease errors, and increase visibility; (d) applying digital medicine solutions (eg, wearables, ingestible sensors, mobile and web-based applications) to access clinical data with appropriate patient consent and provide greater insights into patient behavior for the patient, caregiver, and physician/treatment team; (e) developing novel combinations of cloud computing and storage capabilities to provide adequate and secure data management of multiple types of data streams mentioned in (a) to (d).

Results: A secure, cloud-based, scalable and flexible data processing/analytics platform has been constructed to collect structured, semi-structured, and unstructured data simultaneously. This platform utilizes unique combinations of readily available computing tools to provide information in a readable format that can be accessed by any tool that has Hadoop/Impala interface capability or can be mapped to this interface. Our group is currently utilizing business intelligence tools and analytics engines to interface with the data and is now developing interfaces with traditional drug development statistical packages.

Conclusions: eTools have enabled almost immediate access to data. Cloud-based technologies combined with open source processing applications have enabled near-time access to study data in a single view. Access to clinical data in hours and days rather than in weeks and months now allows for earlier decision-making and troubleshooting by all stakeholders in the trial process. And finally, the ability to provide integrated and streamlined analytics greatly improves the potential for breakthroughs and insights into complex disorders.

Learning Objectives
1. To describe the new technologies (eTools) available for conducting clinical trials being leveraged by Otsuka.
2. To describe the advantages of using eTools compared with the traditional clinical trial process based on current experience and observed benefits.

Literature References
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T42. OPTIMIZATION OF A DIGITAL HEALTH FEEDBACK SYSTEM IN PSYCHIATRY

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Abstract   Introduction: Medication adherence is a significant unmet medical need in psychiatry (Sajatovic et al., 2010) as nonadherence substantially compromises the effectiveness of available psychiatric treatments (Ascher-Svanum et al., 2006). A currently developed digital health feedback system (DHFS) offers new opportunities. This investigational system includes a tablet with an embedded ingestible sensor that sends a signal to a wearable sensor after ingestion. An application on the patient's mobile device receives data transmitted from the wearable sensor and displays healthcare information for the patient and treatment team based on the patient's data (ie, medication ingestion, activity, and rest); this data also includes patient input entered into the application (ie, self-reported rest quality and mood).

Objective: Creation and coordination of an integrative development strategy for a DHFS in psychiatric populations employing novel and agile research principles and incorporating

assessment of a patient's ability to use individual system components, as well as the system as a whole.

Methods/Results: Several successive studies (316-13-204, 316-13-205, and 316-13-206) were planned in concert and required rapid refinement and adaptation to proceed to the next level. Such an approach is necessary to optimize the DHFS. First, to evaluate potential skin irritation, a standard 28-day study (205) was conducted with the wearable sensor. This study was able to exclude skin irritation issues and demonstrated acceptable wear-ability. Second, the mobile application was tested and improved through a prototype refinement study (204) where 35 bipolar patients and 23 major depressive disorder patients as well as 22 caregivers provided quantitative and qualitative usability feedback based on 16-week use of the system. Third, using the 204 study data, end-to-end bench-level integrated system-testing prompted the establishment of a master protocol (206, NCT02091882) with up to 24 sub-studies to investigate various aspects of the system (eg, latency for ingestible sensor) in healthy volunteers and patients. Finally, a method testing human factors has been employed to assess the safe and effective use of the entire system in a psychiatric population.

Conclusions: In order to develop a DHFS in psychiatry, multiple components of the system must be considered simultaneously using various methodologies (ie, safety studies, end-to-end bench-testing, human factors). A patient-centric focus on usability, along with agile evaluation and feedback across studies, provides an optimal strategy for ensuring adequate patient acceptance and successful regulatory meetings.

Learning Objectives
1. To describe functions of a digital health feedback system.
2. To describe the process of development of a digital health feedback system in psychiatry.

Literature References
1. Sajatovic M, Velligan DI, Weiden PJ, Valenstein MA, Ogedegbe G. Measurement of psychiatric treatment adherence: J Psychosom Res 2010; 69:591-599
2. Ascher-Svanum H, Faries DE, Zhu B, Ernst FR, Swartz MS, Swanson JW: Medication adherence and long-term functional outcomes in the treatment of schizophrenia in usual care. J Clin Psychiatry 2006; 67:453-460

T43. OPEN BOARD

T44. SYMPTOM SEVERITY AND THE GENERALIZABILITY OF ANTIDEPRESSANT EFFICACY TRIALS: CHANGES OVER THE PAST 20 YEARS

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Abstract Introduction: In a review of the inclusion/exclusion criteria used in antidepressant efficacy trials (AETs) Zimmerman and colleagues found that the most commonly used inclusion/exclusion criterion was a minimum score on a symptom severity scale. While meeting the diagnostic criteria for MDD already conveys a significant level of symptom severity, AETs further restrict the range of symptom severity by requiring a minimum severity level on measures such as the Hamilton Rating Scale for Depression (HAMD). When we reviewed the literature more than a decade ago our review was limited to 39 AETs published between 1994 and 2000 in 5 journals.

We conducted a comprehensive review of placebo-controlled AETs published over the past 20 years in order to determine whether there has been a change in symptom severity inclusion criterion subsequent to the publications that highlighted the unrepresentativeness of the depressed patients studied in AETs. On the one hand, we speculated that the increased attention given to the lack of generalizability of AETs would result in a broadening of the inclusion/exclusion criteria for study participation. On the other hand, we considered the possibility that research suggesting that drug-placebo differences are greater for more severely depressed patients might result in studies using higher symptom severity thresholds for inclusion.

Methods: To ascertain the sample of studies of AETs we reviewed the tables of contents of 49 journals from January, 1995 through December, 2014. We also examined the reference lists of meta-analyses of AETs, and the studies identified from our literature review. Two of the authors independently reviewed each article and completed a form listing the psychiatric inclusion and exclusion criteria used in the study. The reviewers met, compared the results of their data abstraction, and resolved discrepancies. We compared the inclusion/exclusion criteria of studies published during the past 5 years (2010-2014) compar

Learning Objectives
1. At the conclusion of this presentation the participant should become familiar with the changes in the symptoms severity inclusion criterion used in placebo-controlled studies of antidepressant medication over the past 20 years.
2. At the conclusion of this presentation the participant should become familiar with the impact of the symptom severity inclusion criterion on the generalizability of antidepressant efficacy studies.

Literature References
1. Zimmerman, M., Mattia, J.I. & Posternak, M.A. Are subjects in pharmacological treatment trials of depression representative of patients in routine clinical practice. American Journal of Psychiatry, 2002, 159, 469-473.
2. Zimmerman, M., Chelminski, I. & Posternak, M.A. Exclusion criteria used in antidepressant efficacy trials: Consistency across studies and representativeness of samples included. Journal of Nervous and Mental Disease, 2004, 192, 87-94.

T45. MODULATING TOLERABILITY OF ACUTE PAINFUL STIMULI WITH TRANSCRANIAL DIRECT CURRENT STIMULATION (TDCS) TARGETING DORSOLATERAL PREFRONTAL CORTEX

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Abstract Background: Pain remains a critical challenge to medicine. Current treatments primarily target nociception, rather than the affective "suffering" component of pain. Dorsolateral prefrontal cortex (DLPFC) has been implicated in these cognitive aspects of pain processing and is a current target of neuromodulation for depression. tDCS can noninvasively modulate the activity of underlying cortex including DLPFC. We therefore hypothesized that anodal (activating) tDCS over left DLPFC should increase tolerability of acute painful stimuli as compared to cathodal (inhibitory) tDCS.

Methods: This pilot study enrolled 40 healthy volunteers. Each participant separately received anodal and cathodal stimulation targeting left DLPFC, in two randomized and counterbalanced sessions. During stimulation, each subject performed the cold pressor (CP) and breath holding tasks.

Results: Preliminary statistical analysis shows no overall main effect of stimulation polarity for either task ($F(1,38) < 1.25$, $p > 0.25$). However, there was a significant main effect of stimulation order (anodal first vs. cathodal first) on mean CP endurance ($F(1,38) = 4.54$, $p = 0.040$), with greater endurance for anodal first trials.

Conclusions: Our results do not suggest that polarity of tDCS targeting left DLPFC differentially modulates tolerability of pain-related distress in healthy volunteers. This contrasts with our previous pilot findings of tDCS targeting left dorsal anterior cingulate cortex showing a trend towards higher mean CP tolerance with cathodal versus anodal stimulation. Future sham-controlled studies targeting both regions in clinical pain populations are needed.

Learning Objectives
1. Differentiate between the sensory and affective components of pain.
2. Neuromodulation may be a means of addressing the inadequately treated affective symptoms, pending further study.

Literature References
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T46. ANTIPSYCHOTIC PRESCRIBING AND PHYSICAL HEALTH MONITORING PRACTICES IN PATIENTS ON A PSYCHIATRIC WARD

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Abstract Background: Individuals suffering from depression, anxiety, bipolar disorder, and psychosis are all at an increased risk of cardiovascular disease. Schizophrenia appears to be an independent risk factor for metabolic syndrome, diabetes, coronary heart disease, hypertension, and emphysema. Those diagnosed with schizophrenia have a two to three fold higher mortality risk and a 20% shorter life expectancy than the general population. Similarly, individuals with bipolar disorder are also more vulnerable to hypertension, dyslipidemia, and type II diabetes mellitus. All of these conditions are leading risk factors for cardiovascular disease, which is the strongest contributing factor to morbidity and mortality among those with bipolar disorder as well.

Atypical antipsychotics have generally become first-line agents in the treatment of psychosis.In the recent years atypical antipsychotics have been increasingly recommended for the treatment of mood and anxiety disorders as well. However, they pose a substantially increased risk of metabolic side effects including weight gain, dyslipidemia, and impaired glucose regulation or type II diabetes mellitus. Thus the use of atypical antipsychotics heightens the risk of metabolic side effects in a population already at elevated risk of cardiovascular disease.

Due to the increased morbidity and mortality from the physical health problems associated with severe mental illness (SMI) and the use of atypical antipsychotics in its treatment, physical

health monitoring is especially important in this patient population. As such, many guidelines have been put forth in order to effectively monitor physical health in patients on antipsychotics as a means of health promotion. Many of the published guidelines including those from the Canadian Psychiatric Association (CPA), the American Psychiatric Association (APA), the National Institute for Health and Clinical Excellence (NICE), and the Royal Australian and New Zealand College of Psychiatrists have come to similar conclusions, indicating that weight, BMI, waist circumference, blood pressure, ECG, fasting glucose, fasting lipids, and prolactin when applicable, should be done on a regular basis, ranging from every three months to yearly.

This study assesses the prevalence of antipsychotic prescribing and physical health monitoring practices in patients receiving antipsychotics on a psychiatric ward.

Method: Retrospective chart review of patients discharged from an acute psychiatry ward between January and March 2012 was conducted and patients prescribed atypical antipsychotics routinely for more than three days were assessed to determine if physical health parameters were measured within a year of admission.

Results: 96 (62%) patients were prescribed atypical antipsychotics out of a total of 187 charts reviewed. Only 22% of patients were prescribed atypical antipsychotics for the diagnosis of a primary psychotic disorder, with an additional 49% prescribed for a mood disorder with and without psychotic features. 29% of patients who were prescribed atypical antipsychotics had other diagnoses including PTSD, adjustment disorder, dementia, delirium, and substance use disorder. 18% of patients received more than one antipsychotic medication. Height and weight were measured in 73%, although none had a BMI calculated or waist circumference measured. After calculating BMI, 24% were in the obese range and 23% were considered overweight. Only 31% and 36% of patients had fasting glucose and lipids measured, respectively. 10% had an abnormal glucose and 63% had at least one abnormal lipid parameter. Only 25% with an abnormal value had action taken to address this. Overall, only 27% had mention of physical health follow-up by the family physician at discharge. In order to improve the physical health monitoring of patients with severe mental illness, medical directives requiring measurement of certain physical health parameters at admission, were agreed and implemented on the ward.

Conclusions: Patients prescribed atypical antipsychotics on the psychiatric ward are inadequately monitored for physical health. There is an urgent need for improvement in this area and for mindful prescribing of atypical antipsychotic medications tailored to individual needs.

The presentation will, in addition discuss the current barriers to effective delivery of physical healthcare in patients with severe mental illness. The current evidence examining the role of various interventions to improve physical healthcare of these patients will be presented, including the presenter's (KV) previous studies in this area. Our experience of initiating medical directives and their implementation on the ward, will be shared.

This presentation will provide the attendees with the tools and strategies that they can implement in their own practice in order to improve the physical health monitoring of their patients.

Learning Objectives
1. Recognize the importance of physical health monitoring in patients prescribed atypical antipsychotic medications.
2. Identify the current barriers and implement effective strategies to improve physical health care of patients with severe mental illness.

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1. De Hert M, Correll CU, Bobes J, et al. Physical illness in patients with severe mental disorders. Prevalence, impact of medications and disparities in health care. World Psychiatry. 2011;10(1):52-77.
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T47. DEXTROMETHORPHAN/QUINIDINE FOR PSEUDOBULBAR AFFECT IN DEMENTIA: CORRELATION OF THE CNS-LS PBA SYMPTOM SCALE WITH PBA EPISODES, GLOBAL, QUALITY OF LIFE, & DEPRESSION MEASURES IN AN OPEN-LABEL TRIAL

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Abstract Background: Pseudobulbar affect (PBA) results from neurologic diseases or brain injuries that damage neuronal pathways regulating emotional expression. PBA is characterized by sudden, uncontrollable laughing/crying episodes that are exaggerated or incongruent with mood or social context; episodes are often disruptive, socially embarrassing, and may be mistaken for depression or other behavioral symptoms. Dextromethorphan/quinidine (DM/Q) received FDA-and EMA-approval as a PBA treatment, based on clinical trials in patients with PBA secondary to ALS or MS. The objective of the PRISM II study was to provide additional evidence of DM/Q safety and effectiveness in patients with PBA secondary to dementia, stroke, or traumatic brain injury. Primary results of the dementia cohort have been reported. The primary outcome in PRISM II was the Center for Neurologic Study-Lability Scale (CNS-LS), a PBA symptom rating scale, scored from 7 (no symptoms) to 35 (maximum), that was validated in persons with ALS or MS but not specifically in persons with dementia. Here we evaluate the association between the CNS-LS, PBA episode counts and other outcomes in the PRISM II dementia cohort.

Methods: Open-label, 12-week, US multicenter trial. Patients with dementia (including MMSE ≥ 10) and PBA (including CNS-LS ≥ 13) received DM/Q 20/10 mg twice daily (once daily in Week 1). Outcomes included CNS-LS change from baseline to Day 90/early termination (primary), PBA episodes/week, quality of life visual analog scale (QOL-VAS), Clinical and Patient/Caregiver Global Impression of Change (CGIC, PGIC), and 9-item Patient Health Questionnaire (PHQ-9; a depression symptom measure). Adverse events were also collected.

Results: 134 patients were enrolled (safety set) and 108 were evaluable for effectiveness; 106 completed. Mean age was 70.7 years. Statistically significant improvement was seen at Day 90 compared to baseline for both mean [SD] CNS-LS score (-7.2 [6.0] P<0.001) and PBA weekly episode count (67.7% reduction P<0.001). CNS-LS score was associated with PBA episode count but not PHQ-9 at baseline (Pearson correlation, 0.42 and 0.16; P<0.001; P<0.09, respectively), suggesting CNS-LS was reflecting PBA symptoms and not depression. CNS-LS improvement was associated with reduced PBA episode count (Pearson correlation 0.33; P<0.001) and also with improved QOL-VAS (0.38; P<0.001), PGI-C (0.46; P<0.001); CGI-C (0.49; P<0.001) and PHQ-9 (0.36; P<0.001) ratings. AEs were reported in 36.6% of patients and were considered treatment–related in 11.9%. The most common AEs were headache (7.5%), urinary tract infection (4.5%), and diarrhea (3.7%). Fourteen patients (10.4%) had serious AEs, none considered treatment-related.

Conclusions: In this first systematic trial to evaluate PBA treatment in persons with dementia, DM/Q demonstrated statistically significant and clinically meaningful improvement in PBA symptoms and good tolerability, consistent with its approved labeling. Improvement in the CNS-LS, the primary outcome, was associated with reduced PBA episode count, and improved QOL-VAS, patient and clinician-assessed global improvement, and reduced depressive symptoms. Correlation of PBA symptom measures with other health outcomes supports the validity of the findings in this open-label trial. The association of CNS-LS with baseline, change, and endpoint PBA episode count supports the utility of this scale as a PBA symptom measure in persons with dementia.

Learning Objectives
1. To provide clinical data describing the utility of DM/Q for treatment of pseudobulbar affect in persons with dementia.
2. To evaluate the association of PBA symptoms measures with global impression, QOL and depressive symptoms measures.

Literature References
1. Pioro EP, Brooks BR, Cummings J et al. Dextromethorphan plus ultra low-dose quinidine reduces pseudobulbar affect. Ann Neurol 2010;68(5):693-702.
2. Smith RA, Berg JE, Pope LE, Callahan JD, Wynn D, Thisted RA. Validation of the CNS emotional lability scale for pseudobulbar affect (pathological laughing and crying) in multiple sclerosis patients. Mult Scler 2004;10(6):679-685.

T48. PHARMACOKINETIC STUDY COMPARING TOPICAL, RECTAL, AND ORAL QUETIAPINE

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Abstract Background: The use of non-commercially compounded topical and rectal medications is increasing. Compounded formulations provide an alternative route of administration when there are barriers to administering medications orally or parenterally. Medications that are commonly incorporated into topical and rectal delivery mediums include non-steroidal anti-inflammatory agents and antiemetics. These formulations have been reported to be utilized in patients with end-stage dementia, delirium, and those at the end of life to treat symptoms associated with conditions such as nausea, pain and agitation. Quetiapine has been used off-label to manage agitated delirium or behavioral and psychological symptoms of dementia. Quetiapine is only commercially available as an oral tablet, creating an administration barrier in patients who are unable to take oral medications. For this reason, quetiapine may be incorporated into a delivery medium which is applied onto the skin or given rectally with the intent of systemic absorption. However, there are no studies to date that have investigated pharmacokinetics of these alternative formulations compared to oral formulation.

Objectives: To investigate serum concentrations of quetiapine in a topical and rectal route compared to equal doses of orally administered quetiapine.

Methods: This study was approved by our institutional review board. Participants were healthy adults with no active medical or psychiatric disorders. Each participant received topical, rectal, and oral quetiapine, each given as a single dose of 25 mg at least 72 hours apart in 3 separate visits. Blood collection for each study visit occurred 10 minutes prior to and 15, 30, 60, 90,

120, 180, 240 and 480 minutes following drug administration for the determination of plasma quetiapine concentrations. In the event serum levels after topical or rectal quetiapine administration were reported as below detectable limits for all blood draws in the first 2 subjects, the dose of 25 mg could be increased to 75 mg for all subsequently enrolled subjects. Differences quetiapine exposure overtime was assessed by comparing area under the curve measurements.

Results: Reported are the preliminary results from 8 completed subjects. The area under the curve (AUC0-∞) for the oral and rectal groups were 7702.5 ng*h/mL and 15,810 ng*h/mL, respectively. The mean AUC difference between oral and rectal (oral minus rectal) was -8107.5 (95% CI -13584.1 to -2630.9, p=0.01). The mean maximum concentration of quetiapine (+ standard deviation) was 44 + 9 ng/mL in the oral group and 62 + 21 ng/mL for the rectal group. The first 2 subjects received 25 mg of topical quetiapine producing no detectable serum levels. The remaining 6 subjects received 75 mg of topical quetiapine. Only one of 8 subjects had detectable serum levels of topical quetiapine at any time period. This subject had detectable levels beginning at 240 minutes (13 ng/mL), persisting until 480 minutes (14 ng/mL).

Conclusion: Quetiapine rectal formulation resulted in drug exposure that was nearly twice that of an equal dose of oral quetiapine. There were no detectable serum concentrations with topical quetiapine in 7 subjects, with low levels detectable after 4 hours that maintained at the eighth hour in one subject. This preliminary data suggests that rectal administration of quetiapine produces exposure to the medication that is nearly 2-fold compared to an equal oral dose. Rectal quetiapine can be considered as an alternative to oral quetiapine when there is a lack of oral or parenteral access. Based on undetectable and delayed serum concentrations, topical administration of quetiapine does not appear to produce meaningful concentrations and would not be beneficial for the treatment of acute symptoms. Additional studies are required to assess serum levels of topical quetiapine administrated over a longer duration of time with repeated administration.

Learning Objectives
1. Compare the extent of systemic absorption between topically, rectally, and orally administered quetiapine.
2. Disucss alternative delivery options for quetiapine.

Literature References
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2. Thyrum PT, Wong YWJ, Yeh C. Singel-dose pharmacokinetics of quetiapine in subjects with renal or hepatic impairment. Prog. Neuro-Psychopharmacol & Biol Psychiat. 2000; 24: 521-533.

T49. RTMS USING A TWO COIL ELECTROMAGNETIC ARRAY: EFFICACY FOR TREATMENT RESISTANT MAJOR DEPRESSIVE DISORDER

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Abstract Background: Repetitive Transcranial Magnetic Stimulation (rTMS) was first cleared by the FDA as a treatment for depression in 2008. Since that time there has been an increasing adoption of this technology as a standard of care for patients with major depressive disorder (MDD) who do not sufficiently benefit from, or have been unable to tolerate antidepressant medication.   A second generation rTMS system by Cervel Neurotech (Redwood City, CA) uses a two-coil array to generate electrical field potentials at multiple brain network locations, both deep and superficial. The positioning of coils in this device is designed to produce both a summation of the fields at relatively deep cortical sites and avoidance of non-targeted areas.

Methods: A randomized, double-blind, sham-controlled, parallel-groups clinical trial was conducted to examine the safety and efficacy of Cervel rTMS as the sole or adjunctive treatment of MDD in adult patients (n=92). Both treatment intolerant and treatment resistant participants (who failed to achieve satisfactory improvement from at least one prior adequate antidepressant medication but not more than three) were enrolled at 6 US sites. Adults meeting eligibility criteria received 20 daily rTMS treatments over 4 weeks. The majority of participants got rTMS as an adjunct to stable (but inadequately effective) pharmacotherapy. Targeted coil centers were positioned over left dorsolateral prefrontal cortex (dlPFC) and posterior dorsomedial prefrontal cortex (pdmPFC) with 10 Hz stimulation (4-second trains, 26 inter-train interval); maximum summated power for both coils was $\leq 120\%$ of resting motor threshold. Durability of effect was measured 1 month after completion of the final treatment . Serial HAMD-24 assessments were administered electronically via algorithm-based computer program, and the primary efficacy endpoint was change in HAMD-24 score from baseline to endpoint (4 weeks).

Results: Data from n=75 patients were included in the per-protocol (PP) sample. Mean HAMD-24 improvement at week 4 for the active treatment group (-15.1±9.6) was significantly greater (p=0.033; Cohen's d=0.5) than for the sham group (-10.4±8.7). Week 4 HAMD-24 response rates were 55.3% for active versus 32.4% for sham (p=.063) , and remission rates were 26.3% versus 18.9% (not significant).

Discussion: Positive results were found in the first controlled clinical trial of rTMS therapy using a new device designed to optimally direct and summate the magnetic energy fields generated by a two-coil array. Despite the modest sample size, results on the primary endpoint support antidepressant efficacy of Cervel rTMS for pharmaco-intolerant or -resistant MDD, with an effect size comparable to those reported for large trials using devices with FDA clearance. Secondary endpoints were generally supportive.

Learning Objectives
1. Differentiate treatment offered by a two coil TMS design vs. currently offered TMS equipment.
2. Discuss the significance of improvement for patients treated with a two coil TMS design vs. sham treatment.

Literature References
1. Dunner DL, Aaronson ST, Sackeim HA, Janicak PG, Carpenter LL, Boyadjis T, Brock DG, Bonneh-Barkay D, Cook IA, Lanocha K, Solvason HB, Demitrack MA. A multisite, naturalistic, observational study of transcranial magnetic stimulation for patients with pharmacoresistant major depressive disorder: durability of benefit over a 1-year follow-up period. J Clin Psychiatry. 2014 Dec;75(12):1394-401
2. Carpenter LL, Janicak PG, Aaronson ST, Boyadjis T, Brock DG, Cook IA, Dunner DL, Lanocha K, Solvason HB, Demitrack MA. Transcranial magnetic stimulation (TMS) for major depression: a multisite, naturalistic, observational study of acute treatment outcomes in clinical practice. Depress Anxiety. 2012 Jul;29(7):587-96

T50. INCREASING SIGNAL OVER NOISE IN MDD CLINICAL TRIALS: RATING IMPROVEMENT AFTER EFFICACY SCALE RATER TRAINING AMONG EXPERIENCED MDD INVESTIGATORS

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Abstract Introduction: Inconsistent use and interpretation of psychiatric rating scales amongst investigators are major contributing factors to bias in efficacy evaluation in clinical trials. This analysis evaluates the effect of pre-study rater training on scoring proficiency and concordance among highly experienced psychiatric clinical trials investigators, using their scores of the same standardized patient interview before and after training at face to face industry-sponsored Investigators' Meetings. Method: A videotaped patient interview of a Montgomery Åsberg Depression Rating Scale (MADRS) [1] was shown online to 307 psychiatric trials investigator-raters from 20 countries prior to attendance at one of 6 live Investigators' Meetings (IMs) for two industry-sponsored MDD trials. Raters were required to view the video and provide scoring of each of the 10 MADRS items as one of many prerequisites to be eligible to rate the MADRS, the primary efficacy measure in the clinical trial. Gold standard scores had been pre-determined by an independent expert panel. At each IM, live training on MADRS administration and scoring conventions was provided, and the raters were then asked to view and re-score the identical patient interview they had scored prior to the training. Following guided discussion designed to build consensus, raters then scored a new MADRS video, the performance on which determined eligibility to rate actual patients in the trial. The occurrence of 6 separate IMs, worldwide, allowed for individual IM as well as cross-IM examination of the pre vs post training effect and the effect on qualification video performance. Results: As required by the industry sponsor, the MADRS raters were highly credentialed and experienced: 88% were psychiatrists and the mean (SD) years' experience with MDD, MDD clinical trials, and the MADRS scale, respectively, was 18 (9), 9 (7), and 11(6). As shown by paired t-tests, the average inter-rater agreement (kappa) [2] was significantly lower pre-training than post-training, $t(306) = 12.9$, $p < .001$, two-tailed. The finding held overall and for 5 of the 6 IMs. SDs on the training video reduced significantly from pre to post scoring conditions [$f(306,306) = 1.73$, $p < 0.001$], yielding an overall 1.4x increase in signal to noise ratio. The findings were significant individually for 4 of the 6 IMs. Post training, using predetermined "gold standard" scores, the proportion of raters who achieved the usual proficiency standard of concordance on at least 80% of MADRS items on the qualification video ranged from 79.5% to 96% across the 6 IMs (mean=91%) compared to 11% to 36% (mean=20%) during the first training video scoring. Conclusions: Rater training improved the inter-rater concordance (kappas) and increased signal to noise ratios among highly credentialed and experienced psychiatric investigators who viewed the identical efficacy scale (MADRS) video prior to and following live training, with 91% subsequently achieving 80% or greater concordance on a separate qualification video, and thus being permitted to rate in the study. Such improvement would be expected to help reduce noise when conducting clinical trials patient ratings. These findings for this widely used primary efficacy measure, among these unusually high-credentialed and experienced clinical trials investigators, strongly suggest the value of study-specific MADRS training for both highly and less experienced MADRS investigators when initiating MDD clinical trials.

Learning Objectives
1. Attendees will become familiar with difficulties in establising interrater concordance in global MDD clinical trials

2. Attendees will become familiar with a means of improving interrater concordance and signal to noise detection in MDD clinical trials

Literature References

1. Montgomery, S.A., Asberg, M., 1979. A new depression scale designed to be sensitive to change. Br J Psychiatry 134,382-9.
2. Cicchetti, D., Bronen, R., Spencer, S., Haut, S., Berg, A., Oliver, P. Tyrer, P., 2006. Rating scales scales of measurement, issues of reliability: resolving some critical issues for clinicians and researchers. J Nerv Ment Dis 194, 557-564.

T51. DEPRESSION AND PAIN PERCEPTION: STUDY ON PAIN PERCEPTION IN SUBJECTS WITH REPORTED HISTORY OF DEPRESSION

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Abstract Background: Many studies have shown that there exist a relationship between depression and chronic pain. However, this relationship is still poorly understood.

Objective: The objective of this study is to determine if any association exists between subjects with history of depression and high pain perception.

Subjects: 2092 pain subjects across 45 clinical research sites in the US. 1030 with history of depression and 1062 controls matched for age, gender and race. History of depression was collected from the ORT (Opioid Risk Tool) questionnaire.

Methods: All 2092 subjects completed a Pain Numeric Rating Scale (NRS) rating their perception of pain on a scale from 0 to 10. Subjects with a Pain NRS score of 0 were excluded from the study and were stratified into Low, moderate and high perception groups. Low pain perception was defined as a score of 1, 2 or 3. Moderate pain perception was defined as a score of 4, 5, or 6. High pain perception was defined as a score of 7, 8, 9 or 10.

Results: A Mann-Whitney test using SPSS V21 found significant difference in pain perception between subjects with a history of depression and the controls (p= 0.001). Further analysis using an ordinal regression found that subjects with reported history of depression are more likely to be associated with high pain perception compared to those with no history of depression (p= 0.001).

Conclusion: This study suggests that depression may play a role in high pain perception. Findings in this study will hopefully illuminate the extra pain burden caused by depression in pain patients and help clinicians in decisions regarding the management of such patients.

Learning Objectives
1. To demonstrate the role of Depression in pain perception.
2. To explain the interrelationship between depression and pain.

Literature References

1. Michael J. Robinson, Sara E. Edwards et al 2009. Depression and pain. Frontiers in Bioscience 14, 5031-5051, June 1, 2009.
2. David Spiegel M.D., Susan Sands Ph.D. and Cheryl Koopman Ph.D. 1994. Pain and depression in patients with cancer. Cancer Volume 74, Issue 9, pages 2570–2578, 1 November 1994.

T52. ADJUNCTIVE BREXPIPRAZOLE (OPC-34712) IN PATIENTS WITH MAJOR DEPRESSIVE DISORDER AND IRRITABILITY: AN EXPLORATORY STUDY

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Abstract Background: Irritability is common in patients with major depressive disorder (MDD) and is associated with greater overall severity and impaired functioning [1]. Brexpiprazole is a rationally designed serotonin-dopamine activity modulator (SDAM) that is a partial agonist at serotonin 5-HT1A and dopamine D2 receptors with similar potency, and an antagonist at 5-HT2A and noradrenaline alpha1B/2C receptors [2]. The efficacy, tolerability and safety of brexpiprazole as adjunctive treatment in patients with MDD were demonstrated in two pivotal studies [3]. The objective of this study was to evaluate adjunctive treatment with brexpiprazole on irritability symptoms in patients with MDD who demonstrated inadequate response to antidepressant (ADT) (NCT01942785).

Methods: Patients with inadequate response to ADT were treated with their current ADT for a period of 2 weeks. Patients who still had an inadequate response, and were irritable (IDS-C30 item 6 $\geq$2), then entered a 6-week open-label treatment with their current ADT at the same dose and adjunctive treatment with brexpiprazole. Brexpiprazole was discontinued at Week 6, and the patients continued with their current ADT up to Week 10. Changes from Baseline to Week 6, and changes between Week 6 and Week 10 of patient-rated and clinician-rated instruments assessing irritability, hostility, impulsivity and anger, as well as depressive symptoms were analyzed.

Results: A total of 54 patients were treated with ADT and adjunctive brexpiprazole. At Week 6, clinically relevant improvements from baseline irritability symptoms were observed in the Kellner Symptom Questionnaire (KSQ) total score (mean: -24.4; CI: -30.3, -18.4; n=50); KSQ anger-hostility subscale score (mean: -7.7; CI: -9.5, -5.9; n=50); the Sheehan Irritability Scale (SIS) total score (mean: -21.1; CI: -26.3, -16.0; n=50) and SIS Item 1 (Irritability) score (mean: -3.5; CI: -4.2, -2.7; n=50), and the Inventory of Depressive Symptomatology (IDS)-C30 Item 6 (Irritability) score (mean: -1.2; CI: -1.5, -1.0; n=50). More patients stopped having anger attacks (15 patients) than patients developing anger attacks during treatment (5 patients), as measured by the Anger Attacks Questionnaire (AAQ). Depressive symptoms also improved at Week 6 as assessed by the MADRS total score (mean: -14.2; CI: -16.7, -11.6; n=50), CGI-S score (mean: -1.4; CI: -1.8, -1.1; n=54), IDS-C30 total score (mean: -17.8; CI: -21.0, -14.6; n=50), and the KSQ depression subscale score (mean: -7.7; CI: -9.6, -5.8; n=50). Irritability symptoms moderately worsened after brexpiprazole treatment discontinuation when assessed at Week 10. Brexpiprazole was well tolerated, with no new safety concerns compared to previous brexpiprazole studies.

Conclusion: Adjunctive treatment with brexpiprazole in MDD patients with an inadequate response to ADT may represent a novel strategy for the treatment of irritability symptoms.

Learning Objectives
1. To understand the effect of adjunctive brexpiprazole on symptoms of irritability in patients with MDD
2. To understand the safety of adjunctive brexpiprazole in patients with MDD and irritability

Literature References

1. Fava M, Hwang I, Rush AJ et al. The importance of irritability as a symptom of major depressive disorder: results from the National Comorbidity Survey Replication. Molecular Psychiatry. 2010;15:856-867.
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3. Thase ME, Youakim JM, Skuban A et al. Efficacy and safety of adjunctive brexpiprazole (OPC-34712) in major depressive disorder: results of two pivotal clinical studies. Neuropsychopharmacology. 2014; 39:S357. Poster T100.

T53. CLINICAL IMPACT OF SWITCHING ANTIDEPRESSANT PHARMACOTHERAPY IN WELL-TREATED MDD DUE TO SSRI-INDUCED SEXUAL DYSFUNCTION: COMPARISON BETWEEN A DIRECT SWITCH TO VORTIOXETINE OR ESCITALOPRAM

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Abstract   Purpose: Patients with major depressive disorder (MDD) often report symptoms of sexual dysfunction despite being well treated for mood symptoms [1]. Patients taking SSRIs are at a greater risk for treatment-emergent sexual dysfunction (TESD), often switching treatment to manage symptoms [2]. This 8-wk, randomized, double-blind, head-to-head comparison (NCT01364649) of vortioxetine and escitalopram examined the severity of TESD in MDD patients taking SSRIs and the clinical impact of switching to vortioxetine or escitalopram.

Methods: Well-treated MDD patients with SSRI-induced TESD were switched to vortioxetine 10mg (n=225) or escitalopram 10mg (n=222) for Wk 1 and escalated to 20mg for Wk 2. Investigators could adjust the dose (10–20mg) at Wks 2, 4, or 6. TESD was assessed at baseline (BL), Wks 2, 4, 6, and 8 using the Changes in Sexual Functioning Questionnaire Short-Form (CSFQ-14). Adverse events (AEs) were assessed at each study visit.

Results: Patients taking citalopram (randomized to vortioxetine, 53.3%; escitalopram, 51.8%), sertraline (30.7%; 34.7%), or paroxetine (16.0%; 13.5%) prior to enrollment had well-treated depression (BL MADRS, 7.9; 8.3) with significant TESD (BL CSFQ-14, 36.5; 36.3) independent of age or current SSRI. All patients were below the threshold (CSFQ-14 men ≤47; women ≤41) for healthy sexual functioning (BL CSFQ-14 men 39.9; 40.7; women 33.5; 33.3). 348 patients completed the study (vortioxetine, n=169/225 [75.1%]; escitalopram, n=179/222 [80.6%]). Vortioxetine-switched patients experienced superior improvement in TESD and sexual functioning compared to escitalopram (Wk 8 CSFQ-14 difference: +2.2, P=0.013; MMRM), and more vortioxetine-switched patients improved from abnormal to normal sexual functioning at Wk 8 (52.1%; 44.2%; P=0.112). Antidepressant efficacy was maintained or slightly improved for both treatments and independent of previous SSRI. The most common AEs (≥5%) for vortioxetine were nausea (25.0%), headache (9.4%), and dizziness (8.0%), and for escitalopram were headache (7.7%), irritability (7.2%), nausea (5.4%), fatigue (5.4%), and anxiety (5.4%). Incidence of AEs was similar across groups when evaluated by previous SSRI; the majority of AEs resolved after 14 d of treatment.

Conclusion: MDD patients experience significant TESD symptoms with current SSRIs, despite being well treated for depression. Patients treated with citalopram, paroxetine, or sertraline were safely and effectively switched to improve the symptoms of TESD. More vortioxetine-treated patients shifted to normal sexual functioning with maintenance of clinical efficacy

compared to escitalopram. Vortioxetine had an AE profile similar to previous trials which was independent of previous SSRI therapy.

Learning Objectives
1. To examine the degree and severity of TESD in MDD patients taking SSRIs
2. To understand the clinical impact of switching patients with SSRI-induced TESD to vortioxetine or escitalopram

Literature References
1. Duenas H, et al. Int J Psychiatry Clin Pract. 2011;15:242-254.
2. Clayton AH, et al. J Clin Psychiatry. 2006;67(Suppl 6):33-37.

T54. PATTERNS OF ANTIDEPRESSANT EFFICACY WITH QUETIAPINE XR AS ADJUNCT TO DIFFERENT ONGOING ANTIDEPRESSANTS; EXPLORATION OF MOA HYPOTHESES

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Abstract Introduction: The rationale for adjunctive antidepressant therapy utilizes potentially complementary hypothesized mechanisms of antidepressant activity. Quetiapine extended release (QXR) is thought to have antidepressant efficacy primarily due to the mechanism of norepinephrine transporter inhibition plus 5-HT1A partial agonism by its active metabolite, norquetiapine. In this regard, patients taking different classes of antidepressant may benefit differentially from adjunctive QXR.

Methods: Two randomized, placebo-controlled trials of similar design studied QXR as adjunct treatment in patients with acute depressive episodes of major depressive disorder (MDD), who demonstrated an inadequate response to an ongoing antidepressant [1,2]. The ongoing adjunct antidepressants were categorized as selective serotonin reuptake inhibitors (SSRIs; sertraline, citalopram, escitalopram, paroxetine, fluoxetine), serotonin-norepinephrine reuptake inhibitors (SNRIs; venlafaxine, duloxetine) or other (bupropion, amitriptyline). Patients used the antidepressant dose for at least 6 weeks before adding QXR 150 or 300 mg once daily in the evening. The primary endpoint of the studies was change in total MADRS score from baseline to Week 6. Results from the QXR treatment arms were pooled in this post hoc descriptive analysis.

Results: 615 patients were randomized to adjunct QXR and 303 patients to placebo. The most frequently used adjunctive antidepressants were escitalopram, sertraline (SSRIs) and venlafaxine (SNRI), with approximately 150 patients per group. The majority of patients were women, ranging from 57-87% across groups. Median age across groups ranged from 42-53 years. Baseline illness mean measures were similar across groups and ranged from: MADRS total score 25.0-30.0; CGI-S 4.3-4.8 (except amitriptyline, 4.6-5.3); HAM-D total score 23.4-27.6; and HAM-A total score 16.8-23.6. Addition of QXR to antidepressant therapy was associated with a greater reduction in MADRS from baseline ranging from -12.5 to -17.5 at 6 weeks compared to placebo for all antidepressants studied, except amitriptyline. Tolerability and safety of QXR were similar across antidepressant groups and consistent with the established safety profile of QXR.

Conclusion: QXR was efficacious as adjunctive therapy in treating MDD regardless of the hypothesized mechanism of action of the ongoing antidepressant (with the exception of amitriptyline), and tolerability of QXR was consistent with the known safety profile.

Learning Objectives

1. At the conclusion of this presentation, the participant should be able to demonstrate knowledge and understanding of the efficacy and safety of quetiapine XR in patients with acute depressive episodes of MDD as adjunct to an ongoing antidepressant
2. At the conclusion of this presentation, the participant should understand that addition of QXR to antidepressant therapy was associated with a greater reduction in MADRS score at 6 weeks compared to placebo for all antidepressants studied, with the exception of amitriptyline

Literature References

1. Bauer M, Pretorius HW, Constant EL, et al. J Clin Psychiatry 2009; 70:540-549.
2. EI-Khalili N, Joyce M, Atkinson S, et al. Int J Neuropsychopharmacol 2010; 13:917-932.

T55. ILOPERIDONE AUGMENTATION OF SSRIS FOR RESIDUAL ANGER AND IRRITABILITY IN PATIENTS WITH PARTIALLY-REMITTED MAJOR DEPRESSIVE DISORDER: A PLACEBO-CONTROLLED CROSSOVER STUDY

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Abstract   Background: Even when patients experience remission with antidepressants, such as SSRIs, many continue to report anger attacks and excessive irritability despite continued treatment. Iloperidone antagonizes 5-HT2a, D2, and alpha-1 receptors. Such actions have been shown to have anti-aggressive effects. Therefore, we examined Iloperidone's safety and efficacy as an antidepressant augmentation agent in outpatients with partially-remitted major depressive disorder (MDD) with residual symptoms of anger and irritability.

Methods: 13 outpatients with partially-remitted MDD (currently treated with SSRIs) received four weeks of iloperidone or placebo, followed by one week of wash-out. Patients were then crossed-over to the other treatment arm for four weeks. Treatment arms were randomized and double-blind; two sites were used for the study. Analyses compared treatment response using the Symptom Questionnaire (SQ) Anger/Hostility Sub-scale as the primary outcome measure. The Hamilton Depression Rating Scale (HDRS) and SQ Anxiety Sub-scale were used as secondary outcome measures for depression and anxiety, respectively.

Results: There was no significant differential effect of iloperidone x weeks on the SQ Anger/Hostility Sub-scale over the course of the study, compared to placebo x weeks, regardless of administration order (p=0.77). Iloperidone showed no significant advantage compared to placebo on HDRS change (p=0.82). Similarly, there was no significant advantage of iloperidone over placebo on the SQ Anxiety Sub-scale (p=0.77). Additionally, there were several significant order effects indicating carry-over effects for both treatment arms.

Conclusions: Iloperidone did not significantly outperform placebo on measures of anger, irritability, anxiety, and depression in patients with partially-remitted MDD and residual anger/irritability.

Learning Objectives
1. Understand that anger and irritability are common residual symptoms in partially-remitted patients with MDD.
2. Describe the mechanistic theory for iloperidone's potential use as a pharmacological agent for residual anger and irritability in partially-remitted patients with MDD.

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T56. ADJUNCTIVE BREXPIPRAZOLE (OPC-34712) IN PATIENTS WITH MAJOR DEPRESSIVE DISORDER AND SLEEP DISTURBANCES: AN EXPLORATORY STUDY

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Abstract   Backgound: Sleep complaints are frequent in patients with MDD [1]. Several lines of evidence show that the 5-HT2A/2C receptor antagonists potently promote slow wave sleep and may improve daytime functioning [2]. Brexpiprazole is a rationally designed serotonin-dopamine activity modulator (SDAM) that is a partial agonist at serotonin 5-HT1A and dopamine D2 receptors with similar potency, and antagonist at 5-HT2A and noradrenaline alpha1B/2C receptors [3]. The objective of this study was to evaluate the effects of adjunctive treatment with brexpiprazole on sleep disturbance parameters in patients with MDD and inadequate response to antidepressant treatment (ADT) (NCT01942733).

Methods: Patients with MDD and inadequate response to 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: A total of 44 patients were treated with ADT and adjunctive brexpiprazole. At week 8, improvements from baseline, as measured by polysomnography (PSG) and the Consensus Sleep Diary for Morning (CSD-M), respectively, were observed in Sleep Efficiency (10.4% and 13.4%), Total Sleep Time (49.0 min and 69.9 min), Sleep Onset Latency (-19.7 min and -37.1 min), and Wake-Time after Sleep Onset (-26.4 min and -43.0 min). The Insomnia Severity Index (ISI) total score also improved (-9.2), as well as sedation measured by the Epworth Sleepiness Scale (ESS) total score (-2.1) and cognition as measured by the Cognitive and Physical Functioning Questionnaire (CPFQ) score (-8.4). Adjunctive treatment with brexpiprazole also improved sleep architecture, as reflected by an increase in the duration of Stage N2 sleep and a reduction in the duration of latency to REM sleep. No new safety concerns were observed compared to previous brexpiprazole studies.

Conclusion: Adjunctive treatment with brexpiprazole may represent a novel strategy for the treatment of sleep disturbances in patients with MDD and inadequate response to ADT.

Learning Objectives
1. To understand the effect of adjunctive brexpiprazole on sleep disturbances in patients with MDD
2. To understand the effect of adjunctive brexpiprazole on day time functioning in patients with MDD and sleep disturbances

Literature References
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T58.   BRAIN METABOLITE ABNORMALITIES IN DEPRESSED ADOLESCENTS

Kailyn Bradley[1], Xiangling Mao[2], Julia Case[1], Amira Hanna[1], Danielle Goldman[1], Dikoma Shungu[2], Vilma Gabbay[1]

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Abstract   Background: Major depressive disorder (MDD) often begins during the critical developmental period of adolescence and can have devastating consequences such as suicide. However, limited research has assessed early neurobiological correlates of MDD prior to the accumulation effects of medication, aging, and chronicity. Evidence in adults suggests that neural mechanisms associated with mitochondrial dysfunction contribute to MDD (1), with alterations in reward circuitry specifically implicated in symptomatology (2). Here, we examined ventricular cerebrospinal fluid lactate, a marker for mitochondrial function, as well as N-acetyl-aspartate (NAA; a marker of white matter integrity and mitochondrial metabolism) and total choline (tCho; involved in membrane peroxidation and turnover) in the striatum due to its role in reward and motivation. We hypothesized medication-free adolescents with MDD would exhibit increased lactate and tCho and decreased NAA compared to healthy controls, and brain metabolite levels would be correlated with anhedonia and fatigue. Methods: Twenty-three adolescents with MDD and 29 healthy controls, ages 12-20, were evaluated with the Kiddie-Schedule for Affective Disorders and Schizophrenia-Present and Lifetime. Anhedonia and fatigue were quantified by summing items on both clinician-rated (Children's Depression Rating Scale Revised) and self-rated (Beck Depression Inventory) scales. Ventricular lactate, as well as NAA and tCho in the bilateral caudate, putamen, and thalamus were measured using proton magnetic resonance spectroscopy. Results: Adolescents with MDD exhibited increased ventricular lactate compared to healthy controls [0.60 (.81) versus 0 (.72); $F(1, 41) = 6.98$, p = .01]. However, there were no group differences in NAA or tCho in the bilateral caudate, putamen, or thalamus. Dimensional analyses in the depressed group showed no relation between lactate levels and symptomatology such as anhedonia [rs(16)= .33, p = .18], fatigue [rs(13) = .39, p = .15], or overall illness severity [rs(16) = .06, p = .83]. Conversely, NAA and tCho in the left putamen were correlated with anhedonia [r(20) = .50, p = .02; r(20) = .47, p = .03 respectively], while NAA in the right caudate was related to fatigue [r(20) = .53, p = .02]. Conclusions: Our finding of increased lactate in depressed adolescents fits similar data across adult psychiatric conditions (1), but the lack of association with symptomatology suggests that this abnormality might reflect a more general central nervous system impairment that is not specific to a particular disorder. Additionally, the relation between tCho in the putamen and anhedonia highlights the possible role of reward circuitry toxicity in the pathogenesis of anhedonic subtypes of adolescent MDD. Conversely, increased NAA in anhedonic adolescents suggests increased striatal white matter integrity, a possible compensatory mechanism due to early reward circuitry dysfunction. These contrasting results demonstrate the complexity of metabolic brain function in the pathogenesis of depression and support the need for further dimensional examination of neurobiological markers early in the course of the illness.

Learning Objectives
1. To understand early neurobiological markers of depression in adolescents.
2. To understand the dimensional relationship between brain metabolites and symptomatology in adolescent depression.

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T59. THE EFFICACY OF VORTIOXETINE ON COGNITIVE DYSFUNCTION IN PATIENTS WITH MAJOR DEPRESSIVE DISORDER (MDD) ACROSS STUDIES

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Abstract Purpose: Vortioxetine was approved in 2013 for the treatment of adults with MDD [1, 2]. This analysis presents data on the efficacy of vortioxetine on cognitive dysfunction in patients with MDD from 2 adult (≤65yr) and 1 elderly (≥65yr) 3-arm, short-term, placebo-controlled studies, two of which included duloxetine as an active reference.

Methods: The Digit Symbol Substitution Test (DSST), an objective measure of global cognitive function that involves multiple cognitive domains, was the primary efficacy endpoint in Study 202 (NCT01564862), a part of the primary composite efficacy endpoint in Study 14122A (NCT01422213), and a secondary efficacy endpoint in Studies 14122A and 12541A (NCT00811252). One study included the University of California San Diego Performance-Based Skills Assessment (UPSA), an objective measure of functional capacity. Two studies included the patient-rated Perceived Deficits Questionnaire (PDQ) to assess the patient's perspective of cognitive function. Across studies, change from baseline to Week 8 (LOCF) was used to compare results and standardized mean differences to placebo were used to evaluate the magnitude of effect on DSST. Path analyses were used to separate how much of the effect on cognition could be considered direct and how much could be considered indirect through relief of depressive symptoms (as measured by the Montgomery-Åsberg Depression Rating Scale).

Results: Patients in 202 (N=602), 14122A (N=602) and 12541A (N=453) were randomized 1:1:1. Vortioxetine (5-20 mg/day) significantly improved performance on the DSST in all 3 studies, with standardized effect sizes vs placebo ranging from 0.25 to 0.48 (202: Δ=0.25, P=0.019; 14122A: Δ=0.48 P<0.001 (both doses); 12541A: Δ=0.27, P=0.023). Duloxetine did not separate from placebo on the DSST in the studies where included (202: Δ=0.18, P=0.099; 12541A: Δ=0.07, P=0.534). Path analysis showed that the effect of vortioxetine on the DSST was driven primarily by a direct effect on cognitive performance, whereas the effect of duloxetine was primarily an indirect effect mediated by the effect on depressive symptoms. In the active reference study that included the UPSA, vortioxetine was superior to placebo (202: Δ=2.94, P<0.001); duloxetine did not separate from placebo (Δ=0.38, P=0.637). On subjective measures of cognitive function, both vortioxetine and duloxetine showed a significant effect on the PDQ; path analysis showed these effects were mainly indirect effects.

Conclusion: Vortioxetine significantly improved depressive symptoms and cognitive dysfunction vs placebo as substantiated by improved functional capacity. In contrast, duloxetine did not separate from placebo on performance-based measures of cognitive function and functionality. Patient's perception, although relevant, is highly influenced by mood and is therefore less distinct.

Learning Objectives
1. To evaluate the efficacy profile of vortioxetine on cognitive dysfunction in patients with MDD.

2. To compare the efficacy profile of vortioxetine with placebo and duloxetine on cognitive dysfunction in patients with MDD.

Literature References

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T60. DEVELOPMENT AND VALIDATION OF THE PSYCHOTIC DEPRESSION ASSESSMENT SCALE (PDAS)

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Abstract Background: Psychotic major depression (PD) is a severe and debilitating condition, which needs intensive treatment and monitoring. Therefore, precise measurement of the severity of PD is crucial. However, until recently there was no rating scale dedicated for the assessment of severity in PD. We therefore developed and validated the Psychotic Depression Assessment Scale (PDAS) through a series of studies based on data from North America and Denmark. Our aim was to establish a rating scale for PD, which would display both clinical validity (the rating scale captures the severity of both depressive and psychotic symptoms in PD and reflects the overall clinical severity of the syndrome), and unidimensionality (the symptoms represented by the items of the rating scale appear in an orderly fashion as the severity of PD increases, such that scoring on higher prevalence items (representing less severe symptoms) precedes scoring on lower prevalence items (representing more severe symptoms)). When these two criteria are met, the individual item scores of the rating scale can be added to a total score, which reflects the overall severity of PD.

Methods: The items included in the PDAS were identified through an item-level analysis of ratings on the 17-item Hamilton Depression Rating Scale (HAM-D17) and the Brief Psychiatric Rating Scale (BPRS) from the 259 patients with PD participating in the Study of Pharmacotherapy of Psychotic Depression (STOP-PD). Subsequently, the validity of the PDAS was tested in an independent Danish sample of 50 patients with PD.

Results: The analysis of the STOP-PD data indicated that a rating scale (the PDAS) consisting of 11 items, namely the 6 items from the melancholia subscale (HAM-D6) of the HAM-D17 (depressed mood, guilt feelings, work and activities, psychomotor retardation, psychic anxiety and somatic symptoms (general)), plus five psychosis items from the BPRS (hallucinatory behavior, unusual thought content (delusions), suspiciousness, emotional withdrawal and blunted affect) was both clinically valid and unidimensional in the measurement of the severity of PD. Furthermore, the PDAS was able to separate the treatment effect of Olanzapine+Sertraline from that of Olanzapine+Placebo in PD (the first combination being superior). The analysis of the Danish data confirmed the clinical validity and the unidimensionality of the PDAS.

Conclusions: We have demonstrated that the PDAS is a valid measure for the severity of PD in two different settings: 1) A North American randomized controlled trial (STOP-PD), where the participants were diagnosed with DSM-IV psychotic depression according to strict research criteria, and 2) A dedicated psychometric validation study taking place in Denmark, where the participants were diagnosed with psychotic depression according to the ICD-10 as part of standard clinical practice at psychiatric hospitals. The PDAS is the only validated measure for the severity of PD and should be considered as an outcome measure in future research studies as well as in clinical practice.

Learning Objectives
1. To become acquainted with the basic psychometric concept of clinical validity and unidimensionality.
2. To learn why the Psychotic Depression Assessment Scale (PDAS) is likely to be superior to other rating scales currently employed in studies of psychotic depression.

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T61. THE BURDEN OF TREATMENT SWITCH IN PATIENTS WITH MAJOR DEPRESSION: A US RETROSPECTIVE CLAIMS DATABASE ANALYSIS

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Abstract Purpose: Major depressive disorder (MDD) is a common, persistent psychiatric disorder with a significant economic burden [1]. The rate of remission with treatment is low [2]; thus, switching antidepressant (AD) medications is common. This study describes US MDD patients who switched to selected ADs to determine rates of further treatment changes (switches/discontinuation) and adherence, and to quantify the healthcare costs following treatment switch.

Methods: Data were extracted from the Truven Health Analytics MarketScan (1Q2001-4Q2012) database, which contains data on ≥25 million US individuals covered by employer-based private healthcare plans annually. Adults with ≥2 MDD diagnoses (ICD-9 codes: 296.2x, 296.3x) who switched from an AD to bupropion, citalopram, desvenlafaxine, duloxetine, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, venlafaxine, or vilazodone were identified. Continuous enrollment for ≥12 months prior to and ≥6 months following the index date (date of first treatment switch occurring on or after 1 January 2012) was required. Patient and treatment characteristics during the 12-month baseline (BL, pre-index) period are described. For the 6-month follow-up period, index AD discontinuation (treatment gap of ≥45 consecutive days), treatment adherence (≥80% of days covered with the index AD), switch rates (from index AD to another AD), and monthly healthcare costs incurred are reported.

Results: 9912 patients were included. Mean age was 45.9 (±14.6) years, and 72.7% of patients were female. A mean of 1.9 (±1.0) ADs were prescribed during the 12-month BL period. Mean length of AD therapy at BL was 230.6 (±108.4) days. The most common comorbidities were

anxiety (40.0%), hypertension (28.7%), sleep-wake disorders (19.1%), and chronic pulmonary disease (13.7%). During the 6-month follow-up, 11.5% of patients switched to a different AD, 41.6% discontinued the index AD, and 26.5% discontinued all ADs. The proportion of adherent patients during the first 3 and 6 months post-index was 68.8% and 52.2%, respectively. Over the 6-month follow-up, patients incurred an average total monthly healthcare cost of $1617 (inflated to 2013 US$; comprising 41% outpatient, 27% inpatient, 22% pharmacy, and 10% other costs).

Conclusion: Switching ADs is common and a notable financial burden is observed among switchers in the US. The rate of treatment discontinuation is high, and the proportion of adherent patients is suboptimal. Future research is needed to determine which AD-switching strategies are associated with the best treatment patterns and lowest healthcare costs.

Learning Objectives
1. To describe US MDD patients who switched to selected antidepressants and determine the rates of further treatment changes and adherence.
2. To quantify the healthcare costs following treatment switches to selected antidepressants.

Literature References
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T62. NEUROINFLAMMATION IS LIKELY ASSOCIATED WITH DEPRESSION AS EVIDENCED BY INCREASED PET RADIOLIGAND BINDING TO TRANSLOCATOR PROTEIN

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Abstract   Background: Inflammation may be a predisposing factor for major depressive disorder (MDD) (1). Translocator protein 18 kDa (TSPO) is a highly expressed protein in glial cells of the brain and, therefore, a potential biomarker of neuroinflammation. TSPO can be accurately quantified using positron emission tomography (PET) and [11C]PBR28, a TSPO tracer developed in our laboratory. Recently, elevated TSPO distribution volumes were identified in the frontal cortex, the anterior cingulate cortex and the insula in a group of 20 unmedicated MDD patients compared to healthy controls (2). The effect of antidepressant medications on neuroinflammation is not well known. The primary aim of this study is to further assess whether TSPO binding is increased in the brain of subjects with MDD. Secondary aims include determining if the medication status of the patient influences neuroinflammatory status and investigating the relationship between CRP levels and TSPO binding.

Methods: Unmedicated MDD (n = 7), medicated MDD (n = 5) and healthy control (n = 9) subjects underwent PET imaging using [11C]PBR28. We measured total distribution volume (V_T, proportional to B_{max}/K_d) using arterial input function and corrected for TSPO genotype. Based on previous post-mortem findings, we chose the subgenual prefrontal cortex and anterior cingulum as regions of interest and compared V_T values obtained in medicated and unmedicated MDD subjects and healthy controls. We also obtained peripheral blood samples and cerebrospinal fluid, for later analysis, to investigate the relationship between peripheral and central inflammatory markers and TSPO binding.

Results: In the anterior cingulum, the VT was 14.9% higher in healthy controls compared to medicated MDD patients (p=0.03) and 27.8% higher in unmedicated patients compared to medicated MDD patients (p=0.01). In the subgenual cortex, there was a trend for a higher VT in unmedicated vs. medicated MDD patients (p=0.05). Although not significant, in both brain regions, the VT was numerically greater in unmedicated MDD patients compared to healthy controls. No significant differences in VT were found in the cerebellum or the whole brain and TSPO binding did not correlate to CRP levels.

Conclusions: These preliminary results, of this on-going study, suggest that brain inflammation in the anterior cingulum and subgenual cortex is associated with major depression and is likely affected by the medication status of the patient. These findings are important because they may help further elucidate pathways involved in the development of MDD as well as identify potential novel treatments and pharmacological targets.

Learning Objectives
1. To gain a better understanding of the role of inflammation in major depression and how this is affected by medication status.
2. To explore the relationship between neuroinflammation, as evaluated by PET imaging, and other peripheral and central markers of inflammation.

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T63. VORTIOXETINE ON OVERALL PATIENT FUNCTIONING IN PATIENTS WITH MAJOR DEPRESSIVE DISORDER

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Abstract Purpose: Patients with major depressive disorder (MDD) experience functional impairment. This impairment is an important outcome to consider beyond the evaluation of common treatment efficacy outcomes like symptom remission. The aim of this analysis was to assess the effect of vortioxetine on overall patient functioning in randomized, placebo-controlled studies of MDD patients. A secondary analysis was performed to evaluate the impact of vortioxetine on functional remission.

Methods: Effects on patient functioning were evaluated in 9 short-term (6/8 weeks) placebo-controlled clinical studies of vortioxetine in adult MDD patients (aged 18-75 years) using the Sheehan Disability Scale (SDS), a patient-rated measure of functional disability in work, social, and family life [1]. A random effects meta-analysis was performed using patient-level data for all therapeutic doses of vortioxetine (5, 10, 15, & 20mg/day), presented as change from baseline vs. placebo. Analyses were conducted using Mixed-Effect Model Repeated Measures (MMRM) and ETRank analysis as a sensitivity analysis.

Results: 2464 patients were randomized to placebo (n=911) or vortioxetine (n=1553) in 9 short-term trials. The meta-analysis (Full Analysis Set, MMRM) showed an improvement for vortioxetine vs. placebo in patient functioning, as measured by change from baseline vs. placebo at study end on SDS (vortioxetine 5mg, n=564, –0.24, P=NS; 10mg, n=445, –1.68,

P≤0.001; 15mg, n=204, –0.91, P=NS; 20mg, n=340, –1.94, P≤0.01), with similar results in patients with substantial baseline functional impairment, defined as SDS total score ≥18 (vortioxetine 5mg, n=364, –0.67, P=NS; 10mg, n=312, –1.93, P≤0.001; 15mg, n=141, –0.84, P=NS; 20mg, n=219, –2.39, P<0.05). Similar results were observed using ETRank analysis. Standardized effect sizes (Cohen's d) for vortioxetine vs. placebo were 5mg, –0.04, P=NS; 10mg, –0.22, P≤0.001; 15mg, –0.14, P=NS; 20mg, –0.27, P≤0.001. Functional remission at study end (defined as SDS ≤6, odds ratio vs. placebo) was observed with vortioxetine 10mg (n=170/573; OR 1.7, P<0.001) and 20mg (n=144/447; OR 1.6, P<0.05), but not with vortioxetine 5mg (n=207/757; OR 1.1, P=NS) or 15mg (n=92/295; OR 1.3, P=NS).

Conclusion: This meta-analysis of patient functioning in adults with MDD, as measured by change from baseline vs. placebo at study endpoint in SDS and achievement of functional remission (SDS ≤6), showed a statistically significant and clinically relevant improvement in favor of vortioxetine vs. placebo at doses of 10mg and 20mg.

Learning Objectives
1. To assess the effect of vortioxetine on overall patient functioning in adults with MDD
2. To evaluate the clinical utility of vortioxetine on functional remission in patients with MDD

Literature References
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T64. PSYCHOSOCIAL RELATIONSHIP STATUS AND QUALITY AS PREDICTORS OF EXERCISE-BASED TREATMENT ADHERENCE AND SUBSTANCE USE OUTCOMES: RESULTS FROM THE STRIDE (CTN-0037) STUDY

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Abstract Social and intimate relationship status and functioning are associated with adherence to health-promoting behaviors (DiMatteo, 2004). Living with another person is generally protective against physical disease or treatment non-adherence, while living alone, being socially isolated, or being lonely have been adversely associated with physical and mental health outcomes (Holt-Lunstad, Smith, & Layton, 2010; Steptoe, Shankar, Demakakos, & Wardle, 2013; Udell et al., 2012). However, limited research has investigated how particular components of psychosocial functioning – general living arrangements and satisfaction with those arrangements – are related to mental health treatment outcomes. We extend prior research by investigating – in a sample of treatment-seeking substance users – several specific aims: (1) analyzing whether the status and quality of one's general living arrangements are associated with adherence to interventions and with reduction in substance use throughout treatment; (2) investigating whether broad social and family discord are related to these outcomes and (3) testing whether gender or living with a problematic substance user moderate these analyses.

Our sample is comprised of 302 individuals meeting substance abuse/dependence criteria from the Stimulant Reduction Intervention using Dosed Exercise Trial (STRIDE; Trivedi et al., 2011). Individuals received 12 weeks of study intervention, which consisted of either three sessions of supervised exercise or health education per week. At baseline, participants also completed self-report questionnaires, including the Addiction Severity Index- Lite. This measure inquired about subjects' usual living arrangements over the past three years (collapsed

for analyses into living with partner, living with another person, or living alone), dichotomous satisfaction with these arrangements, the dichotomous presence/absence of social and family discord (following Denton, Adinoff, Lewis, Walker, & Winhusen, 2013), and dichotomous presence/absence of living with a person who uses non-prescribed drugs or has a current alcohol problem.

Preliminary results indicate that individuals who usually lived with children, parents, family or friends attended a significantly greater percentage of study sessions (76.5%) as compared to individuals who were generally living with a partner (62.5%, p = .004). No differences were found between these groups and those who lived alone. A three-way interaction was also determined between gender, usual living arrangements, and satisfaction with those arrangements (F =3.7, df =2,236, p =.026); however, follow-up pairwise comparisons did not find any significant differences after correcting for multiple comparisons. No significant effects were found analyzing family discord or living with another problematic substance user as a main effect or moderator of treatment outcomes. These results indicate that individuals who live with someone aside from a romantic partner may be more likely to adhere to treatment and suggest additional investigation into the qualities of romantic relationship partners, in order to clarify under what conditions they might promote intervention fidelity.

Learning Objectives
1. Understand how the main effects of usual living arrangements and social/family discord affect treatment outcomes and study adherence in a sample of treatment-seeking adults with substance use disorders.
2. Clarify how gender and social/family discord moderate the relationship between usual living arrangements and treatment outcomes/study adherence in a sample of treatment-seeking adults with substance use disorders.

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T65. EFFECT OF ADJUNCTIVE BREXPIPRAZOLE (OPC-34712) ON DEPRESSIVE SYMPTOMS IN PATIENTS WITH SYMPTOMS OF ANXIOUS DISTRESS: RESULTS FROM POST-HOC ANALYSES

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Abstract Background: High levels of anxiety is prevalent in MDD and associated with greater illness severity, suicidality, impaired functioning and poor response to antidepressants (ADT) [1]. The "with anxious distress" specifier was introduced in the DSM-5 to alert attention to the hazards posed by anxiety symptoms. Brexpiprazole is a rationally designed serotonin-dopamine activity modulator (SDAM) that is a partial agonist at 5-HT1A and dopamine D2 receptors at similar potency, and an antagonist at 5-HT2A and noradrenaline alpha1B/2C receptors [2]. The efficacy, tolerability and safety of brexpiprazole as adjunctive treatment in patients with MDD were demonstrated in two pivotal randomized, double-blind, placebo controlled studies [3]. The objective of this post-hoc analysis was to assess the efficacy of

adjunctive brexpiprazole when added to an ADT in patients with MDD and symptoms of anxious distress as proxies for DSM-5 specifier criteria. The data analyzed herein were obtained from two phase III clinical studies.

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 after this prospective phase were randomized to ADT+brexpiprazole or ADT+placebo for 6 weeks. Both studies included fixed doses (2mg [Study 1: NCT01360645]; 1mg and 3mg [Study 2: NCT01360632]). In these post-hoc analyses, proxies were used to categorize patients as having anxious distress if they had ≥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). The efficacy endpoint was the change in MADRS total score from baseline to week 6 in patients with or without anxious distress. The analyses were conducted using a Mixed Model Repeated Measure (MMRM) approach with pooled placebo groups.

Results: A total of 55% of the patients met the criteria for having anxious distress at baseline. At baseline, the mean MARDS total score was 29.1 for patients with anxious distress and 23.9 for patients without anxious distress. Adjunctive brexpiprazole showed greater improvement than adjunctive placebo in the change from baseline to week 6 in the MADRS total score in patients with anxious distress (least square mean difference to placebo+ADT [n=209]: 1mg+ADT [n=119]: -1.74, p=0.0583; 2mg+ADT [n=103]: -2.95, p=0.023; 3mg+ADT [n=112]: -2.81, p=0.0027) as well as in patients without anxious distress (least square mean differences to placebo+ADT [n=172]: 1mg+ADT [n=92]: -2.37, p=0.0093; 2mg+ADT [n=72]: -1-60, p=0.1101; 3mg+ADT [n=101]: -2.23, p=0.0131). Anxious distress was not associated with an increased incidence of activating adverse events (akathisia, restlessness, agitation, anxiety, and insomnia).

Conclusion: These post hoc analyses suggest that adjunctive brexpiprazole may be efficacious in reducing depressive symptoms and is well tolerated, in patients with MDD and anxious distress.

Learning Objectives
1. To understand the efficacy of adjunctive brexpiprazole in treating depressive symptoms in patients with MDD with anxious distress who demonstrated inadequate response to antidepressants
2. To understand the safety of adjunctive brexpiprazole in patients with MDD with anxious distress

Literature References
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T66. INCIDENCE, ONSET, DURATION AND SEVERITY OF AKATHISIA WITH ADJUNCTIVE BREXPIPRAZOLE (OPC-34712) IN MAJOR DEPRESSIVE DISORDER: ANALYSIS OF TWO PIVOTAL STUDIES

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Abstract Background: Despite demonstrated efficacy in major depressive disorder (MDD), the side-effect profile of atypical antipsychotics may limit their use in clinical practice.

Available atypical antipsychotics are associated with a risk of discontinuation due to adverse events including akathisia [1]. Brexpiprazole shows partial agonism with lower intrinsic activity at the D2 receptor and stronger antagonism at the 5-HT2A receptor than the only currently available D2 partial agonist, aripiprazole, suggesting a relatively lower potential to induce D2-mediated adverse effects, e.g. akathisia [2]. The occurrence of akathisia was evaluated in patients with MDD treated with adjunct brexpiprazole, based on safety data from two pivotal phase III studies. The efficacy and the additional safety endpoints have been reported elsewhere [3].

Methods: Patients with MDD and an inadequate response to 1−3 antidepressant treatments (ADTs) were enrolled and received single-blind ADT for 8 weeks. Patients with inadequate response after this prospective phase were randomized to ADT+brexpiprazole or ADT+placebo for 6 weeks. Both studies included fixed doses (2mg [Study 1: NCT01360645]; 1mg and 3mg [Study 2: NCT01360632]). Patients randomized to brexpiprazole+ADT received 0.5mg for week 1 followed by 1mg for week 2. Patients randomized to 1mg continued on 1mg whereas patients randomized to 2 and 3 mg received their final dose from week 3 onwards. Treatment related adverse events were assessed by investigators at every study visits. The placebo groups from the two studies were pooled in the data presented.

Results: The incidence of akathisia in the brexpiprazole+ADT groups was dose dependent (1mg+ADT: 4.4% [10/226], 2mg+ADT: 7.4% [14/188], 3mg+ADT: 13.5% [31/229]) and higher than that reported in patients treated with placebo+ADT group (pooled placebo+ADT: 1.7% [7/411]). All the events of akathisia were assessed as mild or moderate. The majority of the akathisia events occurred 2 to 4 weeks after treatment initiation. Following this period, there was no difference among doses in the incidence of first onset of akathisia. The median duration of akathisia was similar among the brexpiprazole+ADT doses, ranging from 20 to 22.5 days while the median duration in the placebo+ADT group was 33 days. A total of 6 patients treated with brexpiprazole+ADT withdrew from treatment due to akathisia (0.9%), 5 patients (2.2%) in the 3 mg/day brexpiprazole+ADT group and 1 patient (0.5%) in the 2 mg/day brexpiprazole+ADT group. No patient treated with placebo+ADT withdrew from treatment due to akathisia.

Conclusion: In two pivotal clinical studies in patients with MDD, adjunctive brexpiprazole was associated with low rates of akathisia which appeared to be dose-dependent. The events of akathisia were mild or moderate and <1% of the patients treated with adjunctive brexpiprazole withdrew from treatment due to akathisia.

Learning Objectives
1. To understand the frequency and severity of akathisia induced by brexpiprazole in patients with MDD
2. To understand the onset and duration of akathisia induced by brexpiprazole in patients with MDD

Literature References
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T67. THE FUTURE OF SUBJECT REGISTRIES: INTEGRATION OR REDUNDANCY?

Thomas Shiovitz[1], Mitchell Efros[2], Adnan Shawkat[1], Kerri Weingard[2], Sabrina Schoneberg[1]

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Abstract Purpose: To examine how integrating existing subject registry systems could improve the efficiency and success of CNS clinical trials.

Background, Content: The need for a national clinical trial registry has been recognized for decades. A registry for tracking volunteers in Phase I studies in France and the U.K.is currently in place. In the U.S., local attempts have been made to reduce dual subject enrollment since 2008, and in the last four years, several national registries have become more extensively utilized, especially in CNS and Phase 1 studies.

Recently, pharmaceutical sponsors and investigators have asked whether the major registries can "talk to each other" to reduce redundancy and increase the chances of picking up duplicate subjects.

Methodology: This poster will explore how, technically and pragmatically, such an integration might this occur.

Results: There following options will be critically explored:

1. Each registry remains separate. Sponsors try them individually or two at a time and choose the one that provides the best service for future protocols. Within three years there is a clear preference for the services of one vendor. The other vendors fold their services into the lead registry.

2. Government (or a consortium of pharma) develop and mandate use of a centralized registry for all subjects in all clinical trials (as in ClinicalTrials.Gov), which, after a period of several years, replaces or integrates with the private registries.

3. A single website that allows duplicates to be checked by all three major registries from a single access point for a single fee (as in Equifax, Transunion and Experian).

4. The registries learn to "talk" to each other. This integration would take significant resources but would allow access to all the databases when any of the databases were utilized. Integration between all three systems is technically possible using Application Programming Interfaces (APIs). APIs help disparate software systems to communicate with each other through a secure SSL tunnel. It would require extensive collaboration between the technical teams of all three systems to design the specifications for a standard API and many months to design, test and get the API production ready. In this manner each system could send and receive information from each other about subject enrollments using the call and send parameters defined in the joint specifications.

Conclusion: For the time being, sponsors should continue to use single or redundant registry systems to reduce duplicate enrollment. They are easy enough to use and add only a small amount to the complexity of studies. However, the desire to increase the efficiency and sensitivity of competing subject registries is likely to lead to significant consolidation or integration in the near future.

Importance of poster: Methods of registry integration proposed seek to streamline the clinical trial process while adding sensitivity in detecting professional subjects.

Learning Objectives
1. Participants will be able to describe how accessing a subject registry may reduce the enrollment of duplicate and/or professional subjects.

2. Participants will be able to describe two advantages to the integration of existing subject registries.

Literature References
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2. Efros M, Weingard K: The Impact of Implementing a National Research Subject Database to prevent Dual Enrollment in Early and Late Phase Central Nervous System Trials. Poster Presentation. CNS SUmmit. Nov. 2014

T68. ORAL ATYPICAL ANTIPSYCHOTIC ADHERENCE PATTERNS IN MEDICAID PATIENTS DIAGNOSED WITH SCHIZOPHRENIA

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Abstract Background: Although adherence in the real world varies over time, many researchers measure average adherence over a single fixed time period. For instance, a common measure of adherence—proportion of days covered (PDC)—measures adherence over a 1-year period, often using data from health insurance claims. However, recent research indicates that there is a clinically meaningful increase in risk of psychotic exacerbation after missing as little as 25% of the prescribed oral antipsychotic over a period of 2 consecutive weeks. To better understand the variability in adherence over time, this study uses a group-based trajectory model to measure how patients diagnosed with schizophrenia vary in their adherence to atypical antipsychotics in the months following initiation of therapy. To our knowledge, this is the first application of the trajectory model to patients with serious mental illness.

Methods: Using the Truven Health MarketScan Medicaid Database (2007-2013), we identified patients with a schizophrenia diagnosis initiating oral atypical antipsychotics. We required patients to be continuously enrolled for 12 months after therapy and no atypical antipsychotic prescriptions in the 6 months prior to initiation of therapy. We defined patients as adherent in each month when PDC ≥ 80%. To model patient adherence patterns over time, we estimated a group-based trajectory model, using a third-order polynomial to fit adherence trends and multinomial logistic regression to model a patient's probability of belonging to each adherence trend group. We controlled for patient demographics, comorbidities, substance abuse, and other factors.

Results: The 29,562 patients diagnosed with schizophrenia meeting our inclusion criteria were divided into 6 adherence groups, as this number produced the best model fit based on the Bayesian Information Criterion statistic. Of the 6 groups, one was primarily "adherent," three were primarily "discontinuing," and two exhibited a "stop-start" pattern. In the adherent trajectory group (33% of the sample), average adherence was over 95% in all months. In the three discontinuing groups, PDC fell below 25% after 1 (21%), 3 (9%) or 6 (11%) months of initiating therapy. The two stop-start groups exhibited adherence that declined initially and then increased at 3 (12%) or 6 (15%) months. Further, there were significant differences in the patient characteristics across trajectory groups. Compared to patients in the adherent group, patients displaying a stop-start pattern were more likely to have a history of drug abuse (odds ratio (OR): 2.57, 95% CI 2.26–2.92) or alcohol abuse (OR: 1.74, 95% CI: 1.53–1.98), respectively, have a higher Charlson comorbidity index score (OR: 1.29, 95% CI: 1.13–1.47), and less likely to be between 35 and 54 years of age (OR 0.49, CI 0.43–0.56).

Conclusions: Patients diagnosed with schizophrenia's adherence to antipsychotic therapy exhibits three distinct patterns: adherent, discontinuing and stop-start, but the timing of adherence changes varied within the discontinuation and stop-start groups. Patient groups with stop-start or more gradually declining adherence may benefit from new adherence monitoring technologies such as digital pillboxes or ingestible sensors.

Learning Objectives
1. Gain a better understanding of the variability in adherence over time in a schizophrenic patient population.
2. Gain an understanding of the patient characteristics that influence adherence in this population to identify those who may benefit from better adherence monitoring.

Literature References
1. Weiden PJ, Kozma C, Grogg A, Locklear J: Partial compliance and risk of rehospitalization among California medicaid patients with schizophrenia. Psychiatric Services 2004; 55:886-891
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T69. INVESTIGATION OF ANTIPSYCHOTIC MEDICATION RELATED CARDIOMETABOLIC RISK FACTORS IN PATIENTS WITH PSYCHOTIC VS NON-PSYCHOTIC DISORDERS IN COMPARISON WITH A CONTROL GROUP

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Abstract Purpose: Use of atypical antipsychotic (AAP) medications has been on the rise secondary to increasing on and off label use of these medications in patients with psychiatric illnesses. Use of AAPs has been associated with weight gain and metabolic syndrome. Cardiometabolic risks related to AAPs have been well documented in patients with primary psychotic disorders. However it is unclear if patients with non-psychotic disorders receiving AAPs carry differential risks of cardiometabolic complications.

The objective of the present study is to investigate cardiometabolic risks in patients receiving AAPs for psychotic and non-psychotic indications in comparison with a control group of patients with psychiatric illness not receiving these medications.

Methods: A retrospective, cross-sectional chart review was conducted by randomly selecting records of active patients in the outpatient psychiatry clinic over a 1 year period. Inclusion criteria: Patients 18-79 years of age receiving AAPs for at-least 8 weeks for the Psychotic Disorder (PD) and Non-psychotic Disorder (NPD) indications & patients with psychiatric illness but not receiving any antipsychotic medications as the Control group. Exclusion criteria: Patients with diagnosis of bipolar disorder excluded from the NPD group, patient charts missing data required for study analyses. Patients receiving typical antipsychotic medications were also excluded

The chart review included assessment of body mass index (BMI) (primary outcome), and specific cardiovascular (BP, HR and QTc prolongation) and metabolic parameters (lipid panel, fasting blood glucose of HbA1c) as secondary outcomes. The data on demographic and clinical characteristics was gathered including data on medical, psychiatric comorbidities, smoking status and other lifestyle factors.

Results: A total of 211 charts were reviewed. Out of the total 211 subject records, 71 subjects had PD, 88 subjects had NPD and 72 subjects were in the control group. All three groups had predominantly white, non-Hispanic subjects, higher number of females and higher number of subjects 40 years of age or older. All three groups had similar medical comorbidities. Most frequently prescribed AAPs for the PD group were clozapine, olanzapine, risperidone and aripiprazole. Most frequently prescribed AAPs for the NPD group were olanzapine, risperidone, aripiprazole and quetiapine.

No differences in BMI were seen between all three (PD, NPD and Control) groups. However, the mean BMI for all three groups fell in the obese range. Similarly no differences were noted in the cardiometabolic health parameters, specifically lipid profile, glycemic control and other cardiovascular indices (BP, HR and QTc intervals). However, specific metabolic parameters (triglycerides, LDL) were at the higher end of the normal range.

Limitations: Small sample size and lack of control group without mental illness

Conclusion & Importance: The cardiovascular risk factors did not differ between the patient groups receiving AAPs for psychotic and non-psychotic indications as well as a control group of patients with mental illness not receiving AAPs. However, all three groups showed high cardiovascular risks based on BMI data and data on metabolic parameters. The physical health of all patients receiving psychiatric care need close monitoring and interventions to improve cardiometabolic health.

Learning Objectives
1. To compare body mass index (BMI) of patients with psychotic disorders and non-psychotic disorders receiving atypical antipsychotic medications in comparison with a control group of patients not receiving these medications.
2. To compare specific metabolic and cardiovascular parameters of patients with psychotic disorders and non-psychotic disorders receiving atypical antipsychotic medications in comparison with a control group of patients not receiving these medications.

Literature References
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T70. THE COST OF ADHERENCE MISMEASUREMENT: A CLAIMS-BASED ANALYSIS

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Abstract Background: Physicians often wish to measure how adherence to pharmaceuticals affects disease, disability and downstream medical costs. To answer this question, many researchers calculate metrics such as the proportion of days covered (PDC) or medication possession ratio (MPR) using health insurance claims data. Claims-based measures, however, may overestimate patient adherence when patients do not ingest all doses purchased or may underestimate adherence when patients purchase prescriptions out of pocket. This study

quantifies the effect of these adherence measurement errors on inferences about the benefits of adherence among patients with serious mental illness (SMI).

Methods: We derived a formula that measures the statistical bias that occurs in adherence-utilization studies when adherence measurement is inaccurate. The statistical bias depends on the correlation between true and measured adherence and on amount of real-world variation in adherence across patients. We conducted a literature review to determine these key parameters and computed the resulting statistical bias. We applied this bias-correction methodology to a case study of SMI patients initiating atypical antipsychotic therapies using data from Truven MarketScan Commercial and Medicaid databases (2007-2013). We identified patients with a SMI diagnosis of bipolar disorder, major depressive disorder or schizophrenia who were continuously enrolled for 12 months after initiating an atypical antipsychotic. Adherence was measured using PDC. We calculated naïve and bias-adjusted effects of adherence on inpatient costs controlling for patient demographics, comorbidities, and prior spending.

Results: Among the 231,526 SMI patients who initiated atypical therapy, a ten percentage point increase in PDC lowered annual inpatient costs for all patients by $43 (95% CI: -$66 to -$20) per person and for patients with schizophrenia in particular by $103 (95% CI: -$164 to -$42). After adjusting for bias due to mismeasurement, we found that this same increase in PDC decreased inpatient costs by $239 (95% CI: -$366 to -$111) and $568 (95% CI: -$909 to -$233) per person, respectively. Extrapolating these results to the entire US population of patients with schizophrenia, the effect of a 10% increase in adherence is $0.3 billion using the naïve approach and the $1.5 billion after adjusting for bias.

Conclusions: Studies examining the effect of adherence on cost among SMI patients may underestimate the importance of adherence by a factor of 5 or more due to mismeasured adherence in claims data. Failing to account for adherence measurement inaccuracies underestimated the effect of a ten percentage point improvement in adherence on inpatient cost by $1.2 billion. Improving the accuracy of adherence data – through electronic pillboxes, smart caps, or ingestible sensors – can help provide clearer insight into the full value of improving adherence.

Learning Objectives
1. Gain a better understanding of the need for accurate adherence data.
2. Gain a greater appreciation for how improving adherence would impact the cost of care.

Literature References
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T71. ANTIPSYCHOTIC TREATMENT PATTERNS AMONG COMMERCIALLY-INSURED PATIENTS WITH SCHIZOAFFECTIVE DISORDER

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Abstract Schizoaffective disorder (SCA) is a chronic mental disorder with symptoms of both schizophrenia and major mood disorder. The complexity of SCA makes treatment with antipsychotics (APs) in combination with mood stabilizers and/or antidepressants a common practice to manage SCA. A review of several studies of chronic illnesses, including mental disorders, identified treatment regimen complexity as a determinant of medication adherence.

There is sparse information on the characteristics and treatment patterns of commercially insured patients with SCA. The objectives of this study were to evaluate demographics and clinical characteristics, as well as treatment patterns and AP adherence among commercially insured patients with SCA in the U.S. Adults (≥18 years) with ≥1 inpatient or ≥2 outpatient diagnoses of SCA were identified from the Clinformatics Data Mart database between 1/1/2009 to 12/31/2012. Patients were required to have 12 months of continuous medical/prescription coverage prior to (baseline period) and after (follow-up period) the diagnosis of SCA. Patients were grouped into 2 cohorts based on having incident (i.e. absence of SCA diagnosis in baseline period) or prevalent SCA (i.e. SCA diagnosis in baseline period). Demographics and clinical characteristics were evaluated during the baseline period. During the follow-up period the proportions of patients treated with psychiatric medications were determined, as well as adherence to AP medications, defined by proportion of days covered (PDC). ANOVA and Chi-square tests were used for the comparison of continuous and categorical variables, respectively. Of the study population, 1,961 (mean age: 38.7 years; 51% female) were categorized as having incident SCA and 752 (mean age: 43.9 years; 57% female) as having prevalent SCA. The majority (60%) of the overall study population had a point-of-service health plan type. Patients with incident SCA had a lower mean Charlson Comorbidity Index than patients with prevalent SCA (0.61 versus 0.72, p=0.03), but were diagnosed with significantly more psychiatric conditions. Among the overall study population, APs were used by 75% of patients; the most commonly prescribed oral AP drug during the follow-up period was risperidone (23.9%), followed by quetiapine (21.4%), and aripiprazole (20.4%). Less than 5% of the overall study population was treated with oral or long-acting injectable (LAI) paliperidone, the only AP medications FDA approved for SCA indication. Usage of any LAI APs during the follow-up period among the overall study population was low (<3%). Among the overall study population, the most common treatment regimen consisted of APs and mood stabilizer/antiepileptic (31.7%). Approximately 18% of the overall study population had usage of ≥3 psychiatric medication classes. A total of 38% of the overall study population had PDC ≥80% to APs, with a greater proportion of patients with PDC ≥80% in prevalent versus incident SD (48.5% versus 33.6%, p<0.001). This retrospective study demonstrated that commercially insured patients with SCA were frequently treated with multiple psychiatric medications. Additionally, less than 50% patients were adherent to AP medications. While existing evidence suggests LAI AP treatments may help increase medication adherence and improve patient outcomes; its use remains low in the commercially insured patients with SCA.

Learning Objectives
1. To understand the demographic and clinical characteristics of commercially insured patients with schizoaffective disorder in the U.S.
2. To examine treatment patterns and antipsychotic medication adherence among commercially insured patients with schizoaffective disorder in the U.S.

Literature References
1. Olfson M, Marcus SC, Wan GJ. Treatment patterns for schizoaffective disorder and schizophrenia among Medicaid patients. Psychiatr Serv 2009;60(2):210-16.
2. Ingersoll KS, Cohen J. The impact of medication regimen factors on adherence to chronic treatment: a review of the literature. J Behav Med 2008;31(3):213-24.

T72. DIMENSIONAL TRAITS OF PSYCHOSIS AND ASSOCIATION WITH GLYCINE RECEPTOR POLYMORPHISM: AN EXPLORATORY CANDIDATE-GENE ASSOCIATION STUDY

Anvi Vora[1], Larry Siever[1], Antonia New[1], Erin Hazlett[1], Quiaoping Yuan[2], Zhifeng Zou[2], Colin Hodgkinson[2], David Goldman[2], Panos Roussos[1], Mercedes Rodriguez-Perez[1]

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Abstract Background: There is a known genetic relationship with schizotypal personality disorder and psychosis, yet few studies have investigated polymorphisms that may be relevant in this pathology. This is an exploratory candidate gene study examining the relationship between single nucleotide polymorphisms (SNPs) and dimensional markers of psychosis in subjects with schizotypal personality disorder and controls.

Methods: 137 cases and controls (88 males, 71 females matched for age) were screened using the Schizotypal Personality Questionnaire (SPQ). 1350 SNPs were analyzed using a custom Illumina SNP array chip for association with psychotic symptom ratings. Ancestry markers were used to include subjects with Caucasian heritage. Linear regression was performed using PLINK, for association between psychotic symptoms and candidate SNPs. Logistic regression was used to analyze the association of SNPs between schizotypal personality disorder diagnosis versus controls.

Results: A significant relationship was found between rs11167557 SNP that is positioned within the Glycine receptor (GLRA1), for dimensional traits including odd behavior (p=0.000019), odd speech (p=0.0011), perceptual experiences (p=0.0011), and total SPQ score (p=0.0026) in the risk alleles, and remained significant after bonferroni correction. There was no significance between risk allele in these SNPs and diagnosis of schizotypal personality disorder versus controls.

Conclusions: This study indicates that glycine receptor polymorphisms may have an impact on phenotypic portrayal of dimensional symptoms in psychosis.

Learning Objectives
1. Glycine receptor polymorphism may have relationship with dimensional symptoms of psychosis.
2. This supports the importance of dimensional symptom measurements in clinical research.

Literature References
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T73. THE THERAPEUTIC EFFECT OF 1-METHYL-D-TRYPTOPHAN, INDOLEAMINE 2,3-DIOXYGENASE ENZYME INHIBITOR, ON KETAMINE-INDUCED SCHIZOPHRENIA-LIKE SYMPTOMS IN MICE

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[1]*UFC*

Abstract Schizophrenia is in a chronic mental disorder characterized by positive, negative and cognitive symptoms that affects about 1% of the population above 18 years old. This disease is able to compromise the thought, self-will, perception, affect, and social interaction. Recent studies indicate that an immune response associated with the activation of the enzyme

indoleamine 2,3 dioxygenase (IDO) would be implicated in pathophysiology of schizophrenia. This activation would lead to an imbalance in tryptophan/ kynurenine metabolism with important consequences in the glutamatergic neurotransmission. A useful animal model of schizophrenia involves repeated exposure to ketamine (1). The aim of this study was to investigate the possible therapeutic effect of 1-methyl-d-tryptophan (1-MDT), an IDO enzyme inhibitor, on schizophrenia-like symptoms in ketamine animal model of schizophrenia. Male Swiss mice were used (25-30g). The animals were kept in a controlled temperature (23 ° C) with light / dark cycle of 12 hours (lights on at 07:00) and free access to water and food. In the reversal protocol, different groups of animals received ketamine (20 mg / kg) or saline (vehicle used for the control groups) for 14 days. From the 8th to the 14th day, with 30 minutes between administrations, the animals additionally received 1-MDT (20 or 40mg / kg) or saline. On the 14th day, the animals were subjected to behavioral tests: open field test (for positive symptoms) and y maze test (2) (for cognitive symptoms). In the Open Field test, repeated exposure to ketamine significantly increased the locomotor activity when compared to animals treated with saline (control). On the other hand, the animals that were treated with 1-MDT, at doses 20 and 40 mg, presented a significant decrease in the locomotor activity. In the y maze test, whose the evaluation parameter was the correct sequence of entries in the arms without repetition. A switchover was considered correct when the animal visited a new arm and not return to previously visited arm. The animals were treated with 1-MDT showed a significant improvement ($p < 0.05$) in the working memory when compared to mice that received saline followed ketamine. Our results indicated that 1-MDT presents a possible therapeutic effect on schizophrenia-like symptoms, since it was able to reduce locomotor activity and to improve working memory in mice submitted to ketamine-induced schizophrenia model. However, more studies are needed to better understand the role of inflammation and immunological processes, specially the importance of IDO pathway, in the pathophysiology and treatment of schizophrenia.

Learning Objectives
1. The aim of this study was to investigate the possible therapeutic effect of 1-methyl-d-tryptophan (1-MDT), an IDO enzyme inhibitor, on schizophrenia-like symptoms in ketamine animal model of schizophrenia.

Literature References
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3. Dalli'nga OP, Fett P, Gomes MW et al. Caffeine and Adenosine a(2a) Receptor Antagonists Prevent Beta-Amyloid (25-35)-Induced Cognitive Deficits in Mice. Exp Neurol v.203, p.241-245, 2007.

T74. EFFECTS OF SWITCHING TO ARIPIPRAZOLE ONCE-MONTHLY ON DOMAINS OF THE HEINRICHS–CARPENTER QUALITY OF LIFE SCALE IN PATIENTS WITH SCHIZOPHRENIA

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Abstract Objective: To assess the effects of switching from oral antipsychotics to aripiprazole once-monthly 400 mg (AOM 400), an extended release injectable suspension of aripiprazole, on the Heinrichs–Carpenter Quality of Life in Scale (QLS) in patients with schizophrenia.

Methods: This multicenter, open-label, mirror-image, naturalistic study (NCT01432444)1 compared prospective treatment (6 months) with AOM 400 with retrospective treatment (6 months) with standard-of-care (SOC) oral antipsychotics. Adults with a current diagnosis of schizophrenia (DSM-IV-TR criteria), history of illness >1 year, 6 months of hospitalization data, and a 1-month stable outpatient period were eligible. The primary endpoint was psychiatric hospitalization rate in the prospective period (AOM 400) vs the retrospective period (SOC oral antipsychotic).1 The QLS, a secondary endpoint, is a well validated, clinician-rated scale designed to assess negative symptoms of schizophrenia and their impact on functioning; it is sensitive to change over time.2 The QLS consists of 21 items in 4 domains: Interpersonal Relations (8 items), Intrapsychic Foundations (7 items), Instrumental Role (4 items), and Common Objects and Activities (2 items). Each item is rated on a 7-point scale from 0 (severe impairment) to 6 (normal or unimpaired functioning). Mean changes in QLS total and domain scores from baseline (BL) to week 24 of the prospective treatment phase were analyzed post hoc using observed cases of the efficacy sample. Safety was also assessed.

Results: 433 patients received ≥1 injection of AOM 400 in the prospective treatment phase. Hospitalization rates were significantly lower with AOM 400 (prospective period months 4−6: 2.7%) than in the same patients treated with oral antipsychotics (retrospective period months −4 to −1: 27.1%; P<0.0001). The mean (±SD) QLS total score at BL was 55.8±20.7, indicating a moderate level of functioning. Despite patients being stable at BL, treatment with AOM 400 produced a statistically significant improvement from BL in QLS total score at week 24 (5.8±19.8, P<0.0001 [n=281]). At week 24, significant improvements from BL were also observed in all 4 QLS domains: Interpersonal Relations (2.3±9.4, P=0.0001); Intrapsychic Foundations (1.8±7.3, P<0.0001); Instrumental Role (1.0±5.8, P=0.003); Common Objects and Activities (0.6±2.6, P=0.0001). Insomnia (6.7%; 29/431) and akathisia (6.5%; 28/431) were the most common treatment-emergent adverse events.

Conclusion: In a naturalistic setting, switching from oral antipsychotics to AOM 400 produced statistically significant improvements in patient functioning measured using the QLS total score. Statistically significant improvements were also demonstrated for all specific QLS domains, indicating a broad effect of AOM 400 treatment. AOM 400 is a viable consideration when making choices about schizophrenia treatment.

Learning Objectives
1. To understand the Heinrichs–Carpenter Quality of Life in Schizophrenia scale.
2. To describe the effects of aripiprazole once-monthly on functioning in patients with schizophrenia.

Literature References
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T75. EFFECTS OF ARIPIPRAZOLE ONCE-MONTHLY AS LONG-TERM MAINTENANCE TREATMENT IN PATIENTS WITH SCHIZOPHRENIA

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Abstract Introduction: The primary objective of this open-label, 52-week extension study was to evaluate the long-term safety and tolerability of aripiprazole once-monthly 400 mg (AOM 400), an extended release injectable suspension of aripiprazole, in the maintenance treatment of patients with schizophrenia. Here we report efficacy measures in long-term maintenance of the therapeutic effect.

Methods: This study (NCT00731549) enrolled new patients or patients who participated in 1 of 2 randomized, double-blind, placebo- or active-controlled pivotal studies assessing the efficacy and safety of AOM 400 mg (NCT007057831 and NCT007066542). The study comprised a screening phase, a conversion phase to oral aripiprazole, an oral stabilization phase, and an open-label 52-week maintenance phase where AOM 400 was administered every 4 weeks. Clinical assessments of symptoms, symptom severity, functioning, cognition, and attitude to medication were performed during the long-term AOM 400 treatment phase, and mean changes from baseline were analyzed in the observed cases (OC) of the efficacy sample. Since this study focused on maintenance of stability, no formal statistical testing was conducted for these analyses.

Results: A total of 79.4% (858/1081) of patients completed 52 weeks of AOM 400 treatment, and the primary efficacy analysis showed that 95.0% (1018/1072) of patients who were stable at baseline remained stable at the last visit. The mean change in Positive and Negative Syndrome Scale (PANSS) total score from baseline to last visit was −1.72±10.21 (baseline: 54.5±12.9), indicating stability in clinical symptoms over long-term treatment. Symptom severity, assessed with Clinical Global Impression of Illness Severity (CGI-S), and patient functioning, measured with the Personal and Social Performance Scale (PSP), also showed stability from baseline to last visit (CGI-S, −0.14±0.70 [baseline 2.99±0.85]; PSP, 0.78±8.56 [baseline: 67.8±11.7]). Mean change from baseline to week 52 in total time to complete the cognitive test Trails A was −1.92±18.71 seconds (baseline: 52.8±29.6 seconds), demonstrating stability in cognitive function, and mean change from baseline to week 52 in patient-rated attitude towards the use of antipsychotic medication (Drug Attitude Inventory) indicated a positive subjective response (0.45±6.49; baseline: 20.7±8.5). The adverse event profile was consistent with previous long-term trials.

Conclusions: Long-term treatment with AOM 400 maintained stability in clinical symptoms and social functioning, preserved cognitive function, and sustained a positive attitude towards medication in patients with schizophrenia over a 52-week period.

Learning Objectives
1. To understand the impact of long-term treatment with aripiprazole once-monthly on symptoms and disease severity in patients with schizophrenia.
2. To understand the impact of long-term treatment with aripiprazole once-monthly on social functioning, attitude towards medication, and cognitive function in patients with schizophrenia.

Literature References
1. Kane J, Sanchez R, Perry P, Jin N, Johnson B, Forbes R, et al. Aripiprazole intramuscular depot as maintenance treatment in patients with schizophrenia: a 52-week multicenter, randomized, double-blind, placebo-controlled study. J Clin Psychiatry. 2012;73(5):617-24.
2. Fleischhacker WW, Sanchez R, Perry PP, Jin N, Peters-Strickland T, Johnson BR, et al. Aripiprazole once-monthly for treatment of schizophrenia: double-blind, randomised, non-inferiority study. Br J Psychiatry. 2014;205(2):135-44.

T76. TOLCAPONE'S EFFECT ON NEUROCOGNITION AND NEUROPHYSIOLOGICAL MEASURES IN COMT- GENOTYPED HEALTHY ADULTS

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Abstract Background: Tolcapone, a reversible catechol O-methyl transferase (COMT) enzyme inhibitor has been shown to improve neurocognitive performance and increase prepulse inhibition (PPI) in healthy subjects (HS) carrying the Val/Val genotype of the COMT gene (SNP rs4680). However, the anatomical basis for tolcapone's action and the neurocognitive targets engaged by it are still unclear. Studies will identify the latter by investigating tolcapone's effect on MATRICS Consensus Cognitive Battery (MCCB), and the 5 Choice-Continuous performance test (5C-CPT) with simultaneous electroencephalography (EEG) will help identify the anatomical basis for its actions.

Methods: Carefully screened, COMT-genotyped, medically and psychiatrically healthy males and females aged 18-35 years will receive a single dose of tolcapone (200 mg or placebo p.o.) across 2 test days separated by 1 week in a double-blind, randomized, counterbalanced, crossover design. The main effect of tolcapone will be analyzed using repeated measures ANOVA.

Preliminary results: 15 subjects (Met/Met:Val/Val= 3:12) have completed the study thus far. Overall, tolcapone was well tolerated; it mildly elevated blood pressure and decreased heart rate (effect size (d)=0.5) in a time-dependent manner. Tolcapone significantly increased verbal fluency task performance (F= 6.4, df (1,14), p<0.05), decreased false alarm rate (FlA) on 5C-CPT (F=4.58, df(1,14), p=0.01) and activated frontal electrodes during "non-target trials" (p<0.05) compared to placebo.

Discussion: Our preliminary findings suggest that tolcapone (200 mg) is biologically active, and significantly increases verbal fluency task performance and response inhibition measured by FlA during non-target trials. Tolcapone activated frontal electrodes during non-target trials, consistent with its behavioral effects, suggesting a frontal locus of bioactivity for this drug. Functional brain imaging studies have been initiated to further localize these tolcapone effects.

Learning Objectives
1. The pharmacogenetic approach of investigating cognitive and neurobiological phenomena of tolcapone, a COMT-enzyme inhibitor in healthy subjects (HS) characterized by COMT genotype that is conceptually and biologically related to psychosis will likely minimize the challenges of design and implementation of pro-cognitive drug trials in SZ.
2. Investigating the effect of tolcapone 200 mg single dose on neurophysiological measures eg. Sensorimotor gating and ERPs will inform the neurobiological activity of the given dose and localize tolcapone's activity in the brain.

Literature References
1. Apud JA, Mattay V, Chen J, Kolachana BS, Callicott JH, Rasetti R, Alce G,Iudicello JE, Akbar N, Egan MF, Goldberg TE, Weinberger DR: Tolcapone improves cognition and cortical information processing in normal human subjects. Neuropsychopharmacology 2007; 32(5):1011-20. Epub 2006 Oct 25. PubMed PMID:17063156.

2. Giakoumaki SG, Roussos P, Bitsios P: Improvement of prepulse inhibition and executive function by the COMT inhibitor tolcapone depends on COMT Val158Met polymorphism. Neuropsychopharmacology 2008; 33(13):3058-68.

T77. THE EFFECT OF BREXPIPRAZOLE (OPC-34712) VERSUS ARIPIPRAZOLE IN ADULT PATIENTS WITH ACUTE SCHIZOPHRENIA: RESULTS FROM A MULTICENTER, RANDOMIZED, OPEN-LABEL, FLEXIBLE-DOSE, EXPLORATORY STUDY

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Abstract Background: Adverse effects caused by second-generation antipsychotics may impair the patient's ability to function and interact with others, and diminish their subjective well-being and quality of life [1]. There is a need for a rational approach to the treatment of schizophrenia that optimizes symptom control while minimizing tolerability trade-offs that can affect the patient's ability to remain on treatment and maintain meaningful social interactions. Brexpiprazole is serotonin-dopamine activity modulator (SDAM) that is a partial agonist at 5-HT1A and dopamine D2 receptors at similar potency, and an antagonist at 5-HT2A and noradrenaline alpha1B/2C receptors [2]. Brexpiprazole has a lower intrinsic activity at the D2 receptor than the only currently available D2 partial agonist, aripiprazole, suggesting a lower potential to induce D2 agonist-mediated adverse events such as akathisia, insomnia, restlessness, and nausea [2]. In this open-label study the effects of 6-week treatment with brexpiprazole or aripiprazole in patients with schizophrenia were explored (NCT02054702).

Methods: Patients who would benefit from hospitalization or continued hospitalization for acute relapse of schizophrenia were enrolled and randomized to flexible doses of open-label brexpiprazole 1 to 4 mg/day (3 mg/day target dose) or aripiprazole 10 to 20 mg/day (15 mg/day target dose) (2:1) for 6 weeks. The efficacy endpoint was the change in Positive and Negative Syndrome Scale (PANSS) total score from baseline to Week 6 and additional endpoints were the change in Barratt Impulsiveness Scale (BIS-11) total score from baseline to Week 6.

Results: A total of 97 patients were enrolled and randomized to brexpiprazole (N=64) or aripiprazole (N=33). A reduction in the symptoms of schizophrenia assessed by the PANSS total score were observed from baseline to week 6 in patients treated with brexpiprazole and in patients treated with aripiprazole (LS mean change at week 6: -22.9 and -19.4 for brexpiprazole and aripiprazole, respectively). A divergent signal on impulsivity was observed assessed by the BIS-11 total score though a relatively small change was observed and the sample size was small (mean change at week 6: -2.7 and 0.1 for brexpiprazole and aripiprazole, respectively). Brexpiprazole was well tolerated and the incidence of EPS-related adverse events including akathisia was lower in the patients treated with brexpiprazole (14.1%) compared with the patients treated with aripiprazole (30.3%). No clinically relevant changes in the mean laboratory test values, vital signs, or ECG parameter values were observed.

Conclusion: Clinically relevant improvements in psychopathology were observed in patients with acute schizophrenia treated with brexpiprazole or aripiprazole. Brexpiprazole was well tolerated with a lower incidence of EPS-related adverse events than aripiprazole.

Learning Objectives
1. To understand the efficacy of brexpiprazole in patients with schizophrenia as compared to that of aripiprazole.

2. To understand the safety and tolerability of brexpiprazole in patients with schizophrenia as compared to that of aripiprazole

Literature References
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T78. EFFICACY AND SAFETY FROM A 6-WEEK DOUBLE-BLIND TRIAL OF ASENAPINE 2.5 AND 5 MG BID IN ADULTS WITH AN ACUTE EXACERBATION OF SCHIZOPHRENIA

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Abstract Background: Asenapine (ASN) is an atypical antipsychotic approved for acute and maintenance treatment of adults with schizophrenia as well as manic or mixed episodes associated with bipolar I disorder at doses of 5 mg twice daily (bid) or 10 mg bid.1 In one randomized controlled trial of patients with schizophrenia, the ASN 5 mg bid dose had an improved safety profile over the ASN 10 mg bid dose,2 providing the impetus for evaluating the safety and efficacy of a lower dose of ASN. The aim of this study was to evaluate the efficacy and safety of ASN 2.5 mg bid or 5 mg bid relative to placebo (PBO) in adults with schizophrenia.

Methods: In this 6-week, double-blind, double-dummy, fixed-dose, PBO- and active-controlled, multicenter trial, patients were randomized 2:2:2:1 to PBO, ASN 2.5 mg bid, ASN 5 mg bid, or olanzapine (OLZ) 15 mg once daily (qd). The primary efficacy outcome was the change from baseline in positive and negative symptom scale (PANSS) total score for ASN vs PBO at day 42. Secondary efficacy analyses included evaluation of ASN vs PBO in the Clinical Global Impression Severity of Illness (CGI-S) and rate of PANSS responders. Safety was monitored throughout the trial.

Results: Overall, 360 patients were randomized to treatment; 60 (58.3%), 52 (53.1%), 67 (59.3%), and 35 (76.1%) patients completed in the PBO, ASN 2.5 mg bid, ASN 5 mg bid, and OLZ groups, respectively. Least-squares (LS) mean change from baseline in PANSS total score at day 42 was –16.2 for PBO, –17.4 for ASN 2.5 mg bid (P=0.6043 vs PBO), –21.7 for ASN 5 mg bid (P=0.0178 vs PBO), and –21.6 for OLZ (P=0.0587 vs PBO). No statistically significant difference was observed between ASN or OLZ and PBO for the change in CGI-S from baseline to day 42 or for PANSS responders.

Safety results are similar to previous studies of ASN; rates of serious adverse events were generally low. Among key safety events (insomnia, extrapyramidal symptoms [EPS], somnolence, akathisia, hypoesthesia/dysgeusia combined, and dizziness), insomnia was most common and was reported by 13.9%, 9.3%, 15.0%, and 8.7% of patients treated with PBO, ASN 2.5 mg bid, ASN 5 mg bid, and OLZ, respectively. Oral hypoesthesia/dysgeusia was reported by 5.2% and 7.1% of patients treated with ASN 2.5 mg bid and ASN 5 mg bid, respectively; neither adverse event was reported with olanzapine or placebo. The incidence of other key safety events was similar between treatment groups.

Conclusions: Schizophrenia symptom improvements were observed in patients treated with the established 5 mg ASN dose (P=0.0178 vs PBO) and OLZ (P=0.0587); however, ASN 2.5 mg bid did not separate from PBO. ASN was generally safe and well tolerated.

Learning Objectives
1. To understand the safety and efficacy of ASN 2.5 mg bid compared with ASN 5 mg bid.
2. To understand the efficacy and tolerability profile of ASN relative to PBO and OLZ.

Literature References
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T79. EFFECTS OF ARIPIPRAZOLE ONCE-MONTHLY IN PATIENTS WITH SCHIZOPHRENIA SWITCHED FROM ORAL ANTIPSYCHOTICS

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Abstract Objective: To assess the effects of aripiprazole once-monthly 400 mg (AOM 400), an extended release injectable suspension of aripiprazole, on clinical symptoms and clinical global improvement in patients with schizophrenia.

Methods: This was a multicenter, open-label, mirror-image, naturalistic study (NCT01432444) comparing prospective treatment (6 months) with AOM 400 with retrospective treatment (6 months) with standard-of-care (SOC) oral antipsychotics.1 Adults with a current diagnosis of schizophrenia (DSM-IV-TR criteria), a history of illness >1 year, 6 months of hospitalization data, and a 1-month stable outpatient period were eligible. The prospective treatment period included a conversion phase (Phase A; 4 weeks) where patients were cross-titrated to oral aripiprazole monotherapy and a 24-week, open-label treatment phase (Phase B) where patients received AOM 400. The primary endpoint was the psychiatric hospitalization rate in the prospective vs retrospective period.1 Other endpoints assessed in Phase B included mean change from baseline (BL) in PANSS total and positive and negative subscale scores, mean CGI-I score, and proportion of responders (≥30% decrease from BL in PANSS total score or a score of 1 [very much improved] or 2 [much improved] on the CGI-I scale). Analyses were performed using last observation carried forward. Safety was also assessed.

Results: Hospitalization rates were significantly lower in patients receiving AOM 400 (prospective period months 4–6: 2.7%) vs the same patients previously treated with oral antipsychotics (retrospective period months −4 to −1: 27.1%; P<0.0001). During open-label treatment, mean ± SD PANSS total score improved from 75.0±18.3 at BL to 66.9±17.1, 66.5 ±17.3, and 66.4±17.2 at weeks 4, 12, and 24, respectively (P<0.0001 at all time points). PANSS positive and PANSS negative scores also showed significant improvements from BL at all time points (P<0.0001). Mean ± SD CGI-I scores were 3.0±1.0 at week 4, 2.9±1.1 at week 12, and 2.8±1.2 at week 24, indicating that at all time points investigators rated patients as improved. Despite being stable at BL, 34% of patients responded by week 4 (after 1 injection), and 49% demonstrated a clinical response by the end of the study. The most common (≥5%) treatment-emergent adverse events were insomnia 6.7% (29/431) and akathisia 6.5% (8/431).

Conclusion: In this naturalistic study, switching from oral antipsychotics to AOM 400 produced significant improvement in clinical symptoms, as reflected in PANSS total, positive,

and negative symptom subscale scores, as well as CGI-I scores. Responses were observed in one-third of patients after the first injection. AOM 400 was well tolerated, with rates of treatment-emergent adverse events similar to those previously reported with oral aripiprazole and AOM 400 for the maintenance treatment of schizophrenia.2

This research was supported by H. Lundbeck A/S and Otsuka Pharmaceutical Development & Commercialization, Inc.

Learning Objectives
1. To describe the effects of aripiprazole once-monthly on symptoms in patients with schizophrenia switched from oral antipsychotics in a community setting
2. To describe the safety and tolerability of aripiprazole once-monthly in patients with schizophrenia switched from oral antipsychotics in a community setting

Literature References
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T80. METABOLIC SAFETY MEASURES OF ARIPIPRAZOLE ONCE-MONTHLY IN THE LONG-TERM MAINTENANCE TREATMENT OF SCHIZOPHRENIA

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Abstract Introduction: The primary objective of this open-label, 52-week extension study was to assess the long-term safety and tolerability of aripiprazole once-monthly 400 mg (AOM 400), an extended release injectable suspension of aripiprazole, and maintenance of the therapeutic effect in stable patients with schizophrenia. Here we report metabolic safety parameters relevant to the long-term maintenance treatment of schizophrenia, including weight changes and plasma measures of glucose, triglycerides, cholesterol, and prolactin.

Methods: This study (NCT00731549) enrolled de novo patients (n=143) or patients who participated in one of 2 randomized, double-blind, placebo- or active-controlled pivotal studies assessing the efficacy and safety of AOM 400 (NCT007057831 [n=464] and NCT007066542 [n=474]). The study comprised a screening phase, a conversion phase to oral aripiprazole, an oral stabilization phase, and an open-label 52-week maintenance phase where AOM 400 was administered every 4 weeks. Incidences of adverse events and potentially clinical relevant changes in laboratory values were analyzed using descriptive statistics.

Results: A total of 79.4% (858/1081) of patients entering the maintenance phase completed 52 weeks of treatment with AOM 400, and the primary efficacy analysis showed that 95.0% (1018/1072) of patients who were stable at baseline remained stable at the last visit. During the maintenance phase, modest mean ± SD increases from baseline (82.2±21.4 kg) in weight were observed after 12 weeks (0.2±2.7 kg), 24 weeks (0.6±3.6 kg), and 52 weeks (0.8±4.9 kg) of AOM 400 treatment. The incidences of potentially clinically relevant weight gain and loss (≥7% change from baseline) at the last visit of the open-label treatment phase were 12.5% and 7.6%, respectively. The incidences of patients having normal fasting laboratory values at baseline and abnormal values at any post-baseline assessment were low: glucose (4.7%), triglycerides (9.5%), and total cholesterol (2.5%). Mean change from baseline in serum prolactin values at last visit was −0.46±4.30 ng/mL in males and −0.44±4.73 ng/mL in females,

while 4.8% of females and 4.3% of males showed elevations in prolactin values that were potentially clinically relevant (>1×ULN, upper limit of the normal range) at any post-baseline assessment.

Conclusions: Long-term treatment with AOM 400 mg was safe and well tolerated by patients with schizophrenia, and the therapeutic effect was maintained, as indicated by the high completion rate and high rates of maintained stability. The modest mean increases in weight and the low rates of potentially clinically relevant weight gain, elevation in prolactin values, and fasting metabolic markers further support a favorable metabolic profile for AOM 400 in long-term treatment. This research was supported by Otsuka Pharmaceutical Development & Commercialization, Inc, and H. Lundbeck A/S.

Learning Objectives

1. To understand the impact of long-term treatment with aripiprazole once-monthly on metabolic parameters in patients with schizophrenia.
2. To describe changes in laboratory measures during long-term maintenance treatment of schizophrenia with aripiprazole once-monthly.

Literature References

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T81. EFFECTS OF RATER CHANGE ON INCREASED PANSS SCORE VARIABILITY

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[1]Bracket

Abstract Introduction: We have previously established identical scorings (all 30 PANSS items identical across consecutive visits within a subject) associated with a rater change between the visits as a strong marker of poor data quality (Kott and Daniel, 2014). In the current analysis we examine the potential impact of rater change between consecutive visits on excessive variability in the data. Is rater change associated with unexpectedly large changes in the PANSS score?

Methods: We have analyzed data from 10 large global double blind schizophrenia clinical trials. For the purposes of analysis we operationalized 3 sets of criteria for defining unexpectedly large changes in the total PANSS score between consecutive visits: A) changes > 20 points, B) magnitude of total PANSS change identified as an outlier using the Tukey's method with cutoffs set to 1.5 times the interquartile range and C) same as B) but cutoffs set to 3 times the interquartile range.

We defined the "different rater group" as all visits where there was a change in PANSS rater between consecutive visits. We calculated the proportions of large changes as defined above (A-C) and using the chi-square test of independence estimated whether there was a significant difference in the proportions of large across visit PANSS changes between the same rater and different raters groups. In addition, we calculated odds ratios with confidence intervals comparing the odds of large PANSS change as defined above (A-C) in the rater change group vs. the same rater group.

Results: Of 79,969 visits collected, 46,652 were evaluable. Rater change occurred 3,887 (8.33%) times. We identified 943 (2.02%) large changes using definition A of large total PANSS changes, 3,358 (7.2%) using definition B, and 698 (1.5%) using definition C. The chi-square test of independence rejected the null hypothesis for all 3 definitions of large changes indicating that the proportions of large changes are not independent of the rater group (same vs. different rater group). The odds ratios for the "different rater group" vs. "the same rater group" for each of the large change definitions were 1.58 (1.29-1.92), 1.63 (1.46-1.81) and 1.79 (1.45-2.23) respectively.

Discussion: Our previous analyses identified identical scorings across consecutive visits with associated rater change as a marker of poor data quality. In the current analysis we established that rater change is also associated with an increase in PANSS data variability. There is an ongoing discussion in the field whether having the same subject rated by different raters improves data quality diminishing expectation bias. Our results indicate that rater change between visits is associated with an increased risk of poor data quality. The risk may be manifest in a loss of variability between visits consistent with raters sharing scores or with an increased level of variability consistent with changes in interview and scoring technique. In summary, both, lack of variability and increased variability in the PANSS data associated with a rater change may be consistent with poor data quality and should be investigated further with available methodologies such as review of recorded interviews or comparison of rater and computer scoring.

Learning Objectives
1. Attendees will become familiar with the effect of rater change on PANSS variability.
2. Attendees will become familiar with identification of risk factors associated with rater change.

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T82. COMPARISON OF RELAPSE-PREVENTION STUDIES OF ANTIPSYCHOTIC MEDICATIONS DEVELOPED FOR ADMINISTRATION DAILY, ONCE PER MONTH, AND ONCE EVERY 3 MONTHS

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Abstract Purpose: To compare time to first relapse of schizophrenia symptoms in subjects randomly withdrawn to placebo after stabilization in 3 different relapse-prevention studies with 3 formulations of paliperidone: oral extended-release (ER) paliperidone, once-monthly paliperidone palmitate (PP1M) long-acting injectable (LAI), and once-every-3-months PP (PP3M) LAI.

Content: 3 different formulations of paliperidone are available. 3 studies provide insight into different windows for reinstituting treatment if these therapies are discontinued.

Methodology: 3 similarly designed, randomized, double-blind (DB), placebo-controlled, relapse-prevention studies of oral paliperidone (N=628; NCT00086320), PP1M (N=951; NCT00111189), and PP3M (N=620; NCT01529515) were conducted sequentially over 10 years. All enrolled subjects were diagnosed with schizophrenia (per DSM-IV) and had similar inclusion/exclusion and relapse criteria. Subjects were stabilized during a flexible-dose open-

label (OL) phase of variable duration and randomly assigned to either continue on a fixed dose of active drug or switch to placebo during a DB relapse-prevention phase. Primary endpoint for each study was time to relapse, estimated using the Kaplan-Meier method. Risk reduction among placebo arms across studies was examined using Cox proportional hazards models. All studies were terminated early for efficacy after the interim analysis when a prespecified number of relapses were observed.

Results: 101, 203, and 145 patients were included in the placebo arms for the analysis of oral paliperidone ER, PP1M, and PP3M studies. Risk (hazard) of relapse of placebo-treated subjects in the PP1M vs oral paliperidone studies was 0.441 (95% confidence interval [CI], 0.313-0.620; p<0.001), suggesting a 56% reduction in risk of relapse with the PP1M study. Risk of placebo-treated subjects in the PP3M vs oral studies was 0.212 (95% CI, 0.140-0.320; p<0.001), suggesting a 79% reduction in risk of relapse with the PP3M study. When comparing studies of the 2 LAI formulations, risk of relapse of placebo-treated subjects in the PP3M vs PP1M studies was 0.480 (95% CI, 0.334-0.691; p<0.001), suggesting a 52% reduction in risk of relapse with the PP3M study. Median time to relapse (days) was significantly longer following discontinuation of PP3M (395; 95% CI, 274-not reached) vs discontinuation of PP1M (172; 95% CI, 134-222) or oral paliperidone (58; 95% CI, 42-114) (p<0.0001: PP3M vs PP1M, PP3M vs oral paliperidone, and PP1M vs oral paliperidone).

Limitations: In addition to the differences in apparent elimination half-life among paliperidone formulations, differences in design and conduct across the 3 studies may have contributed to the observed variations in median time to first relapse for subjects switched to placebo.

Importance: This post-hoc analysis suggests that following randomized discontinuation after OL stabilization, the reduction in the unadjusted risk of relapse across studies was greater with subjects continuing on PP3M vs PP1M or oral paliperidone. These differences are likely due to variations in the apparent plasma-elimination half-life of paliperidone for each formulation. In subjects vulnerable to relapse (eg, patients living in an underserved settings with difficulty accessing healthcare), treatment with PP3M confers the longest residual protection (with a median duration of 395 days) following sudden discontinuation.

Support: Janssen Scientific Affairs LLC.

Learning Objectives
1. To understand how different modified-release formulations of the same antipsychotic molecule (paliperidone) can impact relapse risk in patients with schizophrenia
2. To understand how an investigational long-acting injectable formulation of paliperidone palmitate administered once every 3 months (PP3M) can fit into the treatment paradigm of patients with schizophrenia given the extended median time patients were free of symptomatic relapse after sudden discontinuation of treatment

Literature References
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T84. SUBJECTIVE AND OBJECTIVE MEASUREMENT OF MEDICATION ADHERENCE IN SERIOUS MENTAL ILLNESS

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Abstract Purpose: Poor adherence to medication is a well-established problem in psychiatric patients and has been consistently associated with poor health outcomes (Weiden et al., 2004). Despite this, deviations from adherence remain very difficult to detect in practice. Measurement options for medication adherence tend to be classified as objective (eg, blood plasma levels) or subjective (patient-report) (Sajatovic et al., 2010). In this study, we aimed to examine the relationship between both subjective and objective measurement types in patients diagnosed with serious mental illness.

Methodology: This open-label observational study enrolled 47 patients with a current diagnosis of bipolar I disorder (n=15) or schizophrenia (n=32) who had been treated with approved indicated doses of oral aripiprazole for ≥2 weeks. During a clinical site visit, blood samples for pharmacokinetic (PK) analysis were collected (4 PK measures at hour 0, 1, 2, and 3) and patients were asked to complete the Morisky 8-item Medication Adherence Scale (MMAS8). Patient variables known to potentially impact PK were also determined (eg, age, weight, CYP2D6 poor metabolizer phenotypes). (NCT02050854)

Results: Relative adherence levels derived from PK results (objective measure) were not statistically correlated with the aggregate MMAS8 scores (subjective measure). However, relative adherence levels were statistically correlated with one MMAS8 question ("When you travel or leave home, do you sometimes forget to bring along your medication(s)?" and possibly with another MMAS8 question.

Importance: Although this study employed well-controlled experimental conditions for PK sampling, such a method requires specific pharmacometric expertise and may be challenging in an outpatient setting. The current study design could be employed with different populations to elucidate the composite of self-reported individual questions most strongly associated with objective measures. The lack of correlation between the objective measure of adherence and the total score of the MMAS8 is noteworthy and suggests that having more questions in a scale for a clinical condition may add to noise rather than specificity.

Learning Objectives
1. Under controlled experimental conditions, the objective and subjective measurements of adherence did not correlate in SMI patients.
2. Practically, objective adherence monitoring via plasma samples may be arduous to implement in clinical practice.

Literature References
1. Weiden PJ, Kozma C, Grogg A, Locklear J: Partial compliance and risk of rehospitalization among California Medicaid patients with schizophrenia. Psychiatr Serv 2004; 55:886-891
2. Sajatovic M, Velligan DI, Weiden PJ, Valenstein MA, Ogedegbe G: Measurement of psychiatric treatment adherence. J Psychosom Res 2010; 69:591-599

T85. EFFICACY OF BREXPIPRAZOLE (OPC-34712) ON PANSS ITEMS AND MARDER FACTOR SCORES: A META-ANALYSIS OF TWO PIVOTAL STUDIES IN SCHIZOPHRENIA

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Abstract Background: Brexpiprazole is a rationally designed serotonin-dopamine activity modulator (SDAM) that is a partial agonist at 5-HT1A and dopamine D2 receptors at similar potency, and an antagonist at 5-HT2A and noradrenaline alpha1B/2C receptors [1]. It is under review by the FDA as monotherapy for schizophrenia and adjunctive treatment for MDD. The aim of this post-hoc analysis was to evaluate the efficacy of brexpiprazole across a spectrum of schizophrenia symptoms using the five previously validated PANSS-derived Marder factor scores: positive, negative, disorganized thoughts, uncontrolled hostility/excitement, and anxiety/depression [2].

Methods: The post-hoc analysis was performed on the pooled data from 2 pivotal 6-week, double-blind, placebo controlled studies of patients with schizophrenia who were randomly assigned to fixed once-daily doses of brexpiprazole 2 mg (n=359), 4 mg (n=359) or placebo (n=358) (NCT01396421 and NCT01393613). An additional treatment group was included in each study (0.25 mg and 1.0 mg) to evaluate the lower dose range; these doses were not included in the meta-analysis.

The analysis evaluated the efficacy of brexpiprazole on the PANSS total score, the PANSS-derived Marder factor scores, and on the PANSS single items. The data were analyzed using a mixed model repeated measures (MMRM) approach with pooled placebo groups.

Results: Pooled brexpiprazole 4 mg and 2 mg were each superior to placebo in change from baseline in PANSS total score at week 6 (least square mean difference [LSMD] versus placebo: -6.69, p<0.0001 and -5.46, p=0.0004, respectively). The LSMD vs placebo at week 6 was also significant (p<0.05) for brexpiprazole 4 mg and 2 mg on all five Marder factor scores. On the PANSS single items, the LSMD vs placebo at week 6 was significant (p<0.05) on 22 out of 30 items for brexpiprazole 4 mg and on 13 out of 30 items for brexpiprazole 2 mg. There were no common TEAEs (≥5% and twice the rate of placebo).

Conclusion: Results of the pooled analysis of 2 pivotal studies showed consistent efficacy of brexpiprazole 4 mg and 2 mg dose, across the spectrum of symptoms associated with schizophrenia; treatment with brexpiprazole showed superiority over placebo on PANSS total score, across all five PANSS Marder factors and on many PANSS single items. However, improvement during the treatment of acute psychosis can lead to secondary improvements in other domains of psychopathology. In addition, treatment with brexpiprazole was well tolerated.

Learning Objectives
1. To understand the effects of brexpiprazole across a spectrum of schizophrenia symptoms.
2. To understand the tolerability of brexpiprazole in patients with acute exacerbation of schizophrenia

Literature References
1. Maeda K, Sugino H, Akazawa H et al. Brexpiprazole I: In vitro and in vivo characterization of a novel serotonin-dopamine activity modulator. J Pharmacol Exp Ther. 2014;350:589-604.
2. Marder SR, Davis JM, Chouinard G. The effects of risperidone on the five dimensions of schizophrenia derived by factor analysis: combined results of the North American trials. J Clin Psychiatry 1997; 58:538-546.

T86. SCIENTIFIC BRAIN TRAINING PROGRAMS ON COGNITION, SOCIAL COGNITION AND FUNCTIONING: COMPARISON OF COGNITIVE REMEDIATION PROGRAMS IN SEVERE MENTAL ILLNESS

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Abstract Background: Cognitive deficits are a major determinant of social and occupational dysfunction in schizophrenia. Cognitive domains such as memory and problem-solving skills have important links to ability to live and work independently in the community. Unfortunately, both memory and problem-solving abilities are particularly impaired in schizophrenia. Cognitive remediation strategies designed to improve cognitive functioning have recently been introduced into treatment programs for people with psychiatric illnesses, and have already shown ability to improve cognitive functioning. The current study is designed to evaluate computerized cognitive skills training for improving memory and problem-solving skills in patients with schizophrenia by assessing neurocognitive change from baseline to endpoint.

Methods: Patients with schizophrenia who are receiving inpatient and outpatient clinical services were recruited for study participation. Patients were evaluated on a standardized battery of neuropsychological assessments and a brief assessment of functional skills and clinical symptoms at screening and at the endpoint. Patients were randomized to a structured computerized cognitive skills training (COGPACK Alone, Posit Science Brain Fitness Alone, COGPACK + Mind Reading (Social Cognition software), Posit Science Brain Fitness + Mind Reading) for 2 hours a week for 12 weeks. Patients not randomized to MRIGE will participate 2 hours computerized cognitive exercises (COGPACK or Posit Science Brain Fitness) per week.

Results: A total of 75 patients were enrolled to date; 13 are active patients, and 49 were randomized. There were no significant differences at baseline between groups. The mean level of education was 10.75 (1.65) years for the COGPACK group and 12.07 (2.14) years for the Posit Science group. Mean PANSS score at baseline was 74.10 (11.14) and 74.28 (8.69) for the COGPACK and Posit Science group, respectively. Results showed a significant increase in scores on the MCCB MATRICS MSCEIT Social Cognition task for the Posit Science group (T-Score = 26.08 (6.45) to 33.67 (9.59)) compared to the COGPACK (T-Score = 38.55 (11.91) to 35.64 (12.04)) group from baseline to endpoint (12 weeks), $F(1,21) = 11.004$, $p = 0.008$. Additionally, there was a significant improvement in the global cognitive index for the Posit Science group (20.54 (9.30) at baseline to 24.31 (9.71) at endpoint) compared to COGPACK (23.33 (7.28) to 24.89 (8.78)). There was a significant improvement for global cognitive index for all groups combined (Mean baseline = 15.77 (10.54), Endpoint = 18.64 (10.47); $F(1,21) = 3.025$, $p = 0.047$), and for Working Memory (Mean baseline = 21.35 (12.38) Endpoint = 25.26 (10.95); $F(1,22) = 6.31$, $p = 0.02$. No significant differences were observed in emotion recognition (ER-40, DSCB) or social functioning (PSP) tasks.

Conclusions: Our results suggest that in the treatment of cognitive deficits in schizophrenia, both therapy methods tend to be equally efficacious, with Posit Science showing greater improvements in social cognition. We suggest that future research should not restrict its focus to the efficacy, effectiveness and efficiency of these therapy methods but should also attempt to establish which subjects are more likely to benefit from one method or the other.

Learning Objectives
1. The audience will be able to learn more about different programs used as interventions in cognitive remediation and how these programs and their mechanisms of action work in individual subjects with severe mental illness.
2. The audience will be able to understand what outcomes can be achieved beyond cognitive changes, such as changes in functional and social outcomes and if cognitive remediation has an affect on these secondary outcomes.

Literature References
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Wance D, Herrmann E. Improving social cognition in schizophrenia: a pilot intervention combining computerized social cognition training with cognitive remediation. Schizophr Bull. 2013 May;39(3):507-17. doi: 10.1093/schbul/sbs120.

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persistent mental illness. Psychiatr Serv. 2008 Mar;59(3):241-7. doi: 10.1176/appi.ps.59.3.241. PubMed PMID: 18308903.

T87. SECONDARY EFFECTIVENESS OUTCOMES IN QUALIFY, A HEAD-TO-HEAD CLINICAL STUDY OF ARIPIPRAZOLE ONCE-MONTHLY AND PALIPERIDONE PALMITATE IN SCHIZOPHRENIA

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Abstract Introduction: The QUALIFY study compared treatment effectiveness of aripiprazole once-monthly 400 mg (AOM 400) and paliperidone palmitate once-monthly (PP) in patients with schizophrenia. Here we report secondary endpoints.

Methods: QUALIFY was a 28-week open-label, rater-blinded, head-to-head study (NCT01795547) of AOM 400 and PP (flexible dosing 50-150 mg/month as paliperidone [EU and Canada], 78–234 mg/month as paliperidone palmitate [US]). Patients were randomized to conversion to oral aripiprazole or oral paliperidone (3 weeks), then initiated AOM 400 or PP treatment according to labels (5 weeks); injections continued every 4 weeks for 20 weeks. The primary endpoint was change from baseline (BL) to week 28 in the Heinrich-Carpenter Quality-of-Life Scale (QLS) total score. Pre-specified secondary endpoints included the Investigator's Assessment Questionnaire (IAQ), Clinical Global Impression–Severity (CGI-S) scale, Work Readiness Questionnaire (WoRQ), QLS domain scores, and primary and secondary endpoints in age-stratified subgroups (≤35 or >35 years).

Results: The mean (±SE) dose was 387±3.4 mg AOM and 110±3.6 mg PP as paliperidone at week 24. At week 28, significantly greater improvements with AOM 400 vs PP were found for CGI-S (LSM treatment difference: -0.28, 95%CI:[-0.48;-0.09], p=0.004) and IAQ (LSM treatment difference:-1.49 (95%CI:[-2.94;-0.049], p=0.043). WoRQ total scores showed significantly greater improvement with AOM 400 vs PP from BL to week 28 (LSM difference: -1.16, 95%CI:[-1.96,-0.37], p=0.004), and 26.4% of patients on AOM 400 vs 12.2% on PP changed from 'No' to 'Yes' in readiness to work (odds ratio: 2.67, 95%CI:[1.39;5.14], p=0.003). Improvements from BL to week 28 in QLS domain scores of intrapsychic foundations were significantly greater with AOM 400 vs PP. Treatment differences in the remaining QLS domains (interpersonal relations, instrumental role, and common objects and activities) favored AOM 400 vs PP without reaching significance. In patients ≤35 years, improvements from BL to week 28 in QLS total score, IAQ total score, and CGI-S scores were significantly greater with AOM 400 vs PP (LSM differences [95%CI], QLS: 10.68, [0.70;20.66], p=0.037; IAQ: -2.65, [-5.28;-0.02], p=0.048; CGI-S: -0.44, [-0.83;-0.06], p=0.026). In patients >35 years, numerically greater improvements with AOM 400 vs PP were

observed (LSM differences [95%CI], QLS: 2.81, [-2.02;7.63], p=0.25; IAQ:-1.02, [-2.77;0.73], p=0.25; CGI-S:-0.22, [-0.44;0.01], p=0.061).

Conclusions: Significant improvements on functioning and symptoms as measured by IAQ, CGI-S, WoRQ, and intrapsychic foundations of the QLS support superiority on the primary endpoint and a greater overall effectiveness for AOM 400 vs PP. In patients ≤35 years, significantly greater improvements with AOM 400 vs PP were consistently seen across effectiveness outcomes, suggesting that AOM 400 treatment at a younger age may confer better treatment outcomes than PP in patients with schizophrenia.

Learning Objectives
1. To describe the QUALIFY study, a novel head-to-head study of 2 LAIs in patients with schizophrenia
2. To understand the secondary results of the QUALIFY study, a head-to-head, randomized, open label study comparing real world effectiveness of aripiprazole once-monthly to paliperidone palmitate in patients with schizophrenia

Literature References
1. Heinrichs DW, Hanlon TE, Carpenter WT, Jr. The Quality of Life Scale: an instrument for rating the schizophrenic deficit syndrome. Schizophr Bull. 1984;10(3):388-98.
2. Potkin SG, Bugarski-Kirola D, Edgar CJ, Soliman S, Le Scouiller S, Kunovac J, Miguel Velasco E, Garibaldi GM. Psychometric evaluation of the Work Readiness Questionnaire in schizophrenia. CNS Spectr. 2014 Oct 1:1-8.

T88. EFFECT OF ARIPIPRAZOLE LAUROXIL ON METABOLIC AND ENDOCRINE PROFILES, AND RELATED SAFETY CONSIDERATIONS IN ACUTE SCHIZOPHRENIA

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Abstract Background: Antipsychotic medication use is often associated with weight gain and adverse metabolic side effects with the severity of side effects varying by drug. Aripiprazole lauroxil (AL), a long-acting injectable aripiprazole, has demonstrated safety and efficacy in treating schizophrenia in a double-blind, placebo-controlled 12-wk trial. Effects of AL on weight, metabolic and endocrine profiles, and related safety outcomes were examined.

Methods: 622 patients were randomized to AL 441 mg, AL 882 mg or placebo IM, once monthly. Changes in weight, BMI, fasting blood glucose, serum lipids, glycosylated hemoglobin (HbA1c) and prolactin at the end of 12-wk were assessed. Shifts in metabolic parameters from normal to abnormal and the incidence of related adverse events (AE) were evaluated.

Results: Baseline BMI (mean±SD) was 27.7±5.3, 27.3±5.7 and 27.0±5.1 in the AL 441 mg, 882 mg and placebo groups. Weight increased by 0.7±3.9, 0.9±3.7 and 0.01±3.6 kg in the AL 441 mg, 882 mg and placebo groups over 12-wk. The percent of patients with weight increases ≥7% was 9.7% for AL 441 mg, 8.7% for 882 mg and 5.8% for placebo. Change in fasting glucose was -0.0±19.0, -1.3±15.8 and 2.7±29.5 mg/dL for AL 441 mg, 882 mg and placebo. Baseline HbA1c values were <5.7% and exhibited minimal change over time. Change in fasting triglycerides was -9.0±95.7, -10.3±78.5 and 8.2±82.1 mg/dL for AL 441 mg, 882 mg and placebo. Shifts in total cholesterol from normal to borderline/high were observed in more patients in the AL 441 mg group than placebo, 19.8% vs. 9.8%, which was not different from the 882 mg group, 9.4%. Shifts in LDL cholesterol from normal to borderline/high were closer

for 882 mg and placebo, 22.2% and 17.2%, but were higher in the AL 441 mg group, 28.3%. Shifts in all other metabolic parameters were similar across groups. Related AEs were reported in 2.4%, 1.4% and 2.4% of patients in the AL 441 mg, 882 mg and placebo groups. Change from baseline in prolactin was -8.7±22.7, -7.38±21.1 and 3.1±31.8 ng/mL for the AL 441 mg, 882 mg and placebo groups.

Conclusion: AL was well-tolerated with a generally benign metabolic profile. Similar changes were observed in the AL treatment and placebo groups for metabolic parameters with only modest weight gain in the treatment groups. No meaningful dose related changes in fasting glucose, HbA1c or serum lipids were observed. Both AL doses were associated with reductions in mean prolactin levels from baseline whereas placebo treatment was not.

Learning Objectives
1. To compare the effects of aripiprazole lauroxil treatment on metabolic parameters.
2. To review the effects of aripiprazole lauroxil on prolactin levels.

Literature References
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T89. THE EFFECT OF BREXPIPRAZOLE (OPC-34712) IN ADULT OUTPATIENTS WITH EARLY-EPISODE SCHIZOPHRENIA: AN EXPLORATORY STUDY

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Abstract Background: The progressive nature of schizophrenia during the early stages of the disease allows residual and persistent symptoms to accumulate, such that patients experience a continuing loss of functioning [1]. There is a need for a new treatment of schizophrenia that optimizes symptom control in patients with early episode schizophrenia without tolerability trade-offs that affect the patient's ability to remain on treatment and maintain meaningful social interactions. Brexpiprazole is a rationally designed serotonin-dopamine activity modulator (SDAM) that is a partial agonist at 5-HT1A and dopamine D2 receptors at similar potency, and an antagonist at 5-HT2A and noradrenaline alpha1B/2C receptors [2]. The purpose of this open-label study (NCT02013622) was to investigate the effects of flexibly dosed brexpiprazole in the improvement of outpatients with early-episode schizophrenia through the assessment of social functioning, efficacy, and tolerability.

Methods: Patients 18 to 35 years old with early-episode schizophrenia (start of first schizophrenia episode ≤ 5 years before the time of study were enrolled and received open-label brexpiprazole up to 4 mg/day, for 16 weeks. During the first 2 to 4-week period, brexpiprazole was cross-titrated with previous antipsychotic medications. The primary efficacy endpoint was PANSS Total Score change from baseline to Week 16. Other outcomes were change from baseline to Week 16 in in CGI-S score, change from baseline to Week 16 in the Personal and Social Performance (PSP) scale, and in the Specific Level of Functioning in Schizophrenia (SLOF). Safety outcome variable included adverse events, physical examinations, vital signs, body weight, clinical laboratory tests, ECGs, SAS, AIMS, BARS and C-SSRS.

Results: A total of 49 patients were treated with brexpiprazole, and of these 25 (51%) patients completed 16 weeks of treatment. At baseline, the mean PANSS total score was 70.6, indicating that the patients were relatively stable. Improvements were observed in PANSS total score from baseline to Week 16 (least square mean change: -10.2, p<0.0001). In addition, PANSS results were supported by CGI-S and CGI-I scores. There was also an improvement of social function as seen in PSP (p=0.0003) and SLOF (p=0.0002) scales and of sleep as measured by PSQI (p=0.0177). Brexpiprazole was well tolerated with no unexpected safety signals compared with that observed in pivotal trials [3, 4].

Conclusion: Treatment with brexpiprazole may represent a novel and effective strategy for treatment of patients with early-episode schizophrenia.

Learning Objectives
1. To understand the effect of brexpiprazole in patients early episode schizophrenia.
2. To understand the effect of brexpiprazole on social functioning in relatively stable patients whose positive symptoms are controlled.

Literature References
1. Lieberman JA, Perkins D, Belge A et al. The early stages of schizophrenia: speculations on pathogenesis, pathophysiology, and therapeutic approaches. Bio Psychitry. 2001;50:884-897.
2. Maeda K, Sugino H, Akazawa H et al. Brexpiprazole I: In vitro and in vivo characterization of a novel serotonin-dopamine activity modulator. J Pharmacol Exp Ther. 2014;350:589-604.
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T90. ILOPERIDONE AS A LONG-TERM MAINTENANCE TREATMENT: RESULTS FROM A PLACEBO-CONTROLLED RANDOMIZED WITHDRAWAL STUDY

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Abstract   Background: Iloperidone, a mixed D2/5HT2 antagonist, was approved by the US FDA for the treatment of schizophrenia in 2009 based on short-term acute efficacy studies. The purpose of this study was to evaluate the safety and effectiveness of long-term flexible dosing of iloperidone for maintenance treatment of schizophrenia.
Methods: Study subjects were adults with schizophrenia who were first treated with open-label iloperidone 12mg/day given as 6mg BID and then stabilized for a further 14-24 weeks with a flexible-dose iloperidone regimen as per investigator judgment ranging between 8-24mg/day daily dose (given BID). Subjects who remained clinically stable for at least 12 weeks entered the relapse prevention phase and were randomized 1:1 to either continue on the same flexible dose regimen of iloperidone or to withdraw from iloperidone to matched placebo in a double-blinded fashion. Subjects were followed for up to 26 weeks and were withdrawn upon showing signs of relapse or impending relapse. A pre-defined unblinded interim analysis (IA) was conducted utilizing a group sequential testing procedure with an O'Brien-Fleming stopping

boundry after 68 relapse or impending relapse events were observed. The primary outcome was time-to-relapse or impending relapse with event criteria defined in the protocol prior to first subject enrollment.

Results: Of the 635 subjects entering the stabilization phase, 303 (48%) met the criteria for the double-blind relapse prevention phase, with 153 subjects randomized to continue with iloperidone and 150 to switch to placebo. The study was stopped early after 68 events were observed and an IA showing that iloperidone was more effective than placebo in relapse preventions (log rank test: $p<0.0001$), with estimated relapse rates at the end of the double-blind relapse prevention phase of 63.4% (KM est.) for the placebo group compared to 20.4% (KM est.) for those staying on iloperidone. The mean time to relapse based on KM estimates was 71 days for placebo and 139 days for iloperidone subjects, with a Cox regression hazard ratio estimate of 4.7 (95% CI: 2.7-8.3) favoring iloperidone ($p<.0001$). The most common adverse events (AEs) suspected to be related to iloperidone in the stabilization phase were dizziness, somnolence and dry mouth. There were no iloperidone treatment-related adverse events with a frequency >2% and higher than placebo in the double-blind relapse prevention phase. There were no notable differences in serious adverse events or incidence of clinically notable abnormalities in hematology or chemistry parameters except that 4.5% and 2.6% of patients had elevations in blood urea nitrogen and LDL, respectively, on iloperidone versus none on placebo.

Conclusion: These results showed that flexible dosing of iloperidone in long-term use (up to 26 weeks, with a preferred dose range of 12-16 mg/day) was safe and effective in preventing relapse or impending relapse in patients with schizophrenia. The analysis of safety indicated no new safety signals with respect to long-term use of iloperidone.

Learning Objectives
1. Describe long-term efficacy of iloperidone.
2. Describe the long-term safety of iloperidone.

Literature References
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T91. PRIOR HOSPITALIZATION AND TREATMENT EFFECT SIZE IN SCHIZOPHRENIA: A MODERATOR ANALYSIS

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Abstract Objective: Responsiveness to treatment has been associated with stages of illness in schizophrenia, with greater treatment response at earlier stages of illness. The objective of this study was to assess if diminished treatment responsiveness is associated with relapse and the number of prior hospitalization in schizophrenia.

Methods: A post-hoc analysis was performed on pooled data from four 6-week, double-blind, placebo-controlled trials for which PANSS (LOCF) data were available. Subjects hospitalized with an acute exacerbation of schizophrenia were randomly assigned to treatment with fixed, once-daily doses of lurasidone 40 mg (n=353), 80 mg (n=402), 120 mg (n=288), 160 mg (n=121), or placebo (n=566). ANCOVA model was applied to compare mean changes from baseline in PANSS total among patients with and without prior hospitalization.

Results: Baseline PANSS total was comparable between the lurasidone (95.8, n=1544) and the placebo (96.2, n=566) groups. In patients who had no prior hospitalization (n=330, 16%), treatment effect size (Cohen's d) was 0.86 (mean change -27.5 in the lurasidone group versus -12.1 in the placebo group). Treatment effects sizes were 0.34 in patients who had 1 prior hospitalization (n=256, 12.2%), 0.55 in patients who had 2 prior hospitalization (n=269, 12.8%), 0.48 in patients who had 3 prior hospitalization (n=253, 12.1%), 0.41 in patients who had 4 or more prior hospitalization (n=987, 47.1%). Statistical interaction test showed that the number of prior hospitalizations was a moderating variable for treatment effect size, with significant difference between treatment effect and prior hospitalizations (0 versus 1 or more) (p=0.015).

Conclusions: Our findings suggest that patients with a history of relapse and prior hospitalization in schizophrenia have diminished treatment responsiveness compared to those with no prior hospitalization. Relapse prevention may be crucial in achieving optimal response including recovery in patients with schizophrenia.

Learning Objectives
1. To learn about staging of illness in schizophrenia.
2. To learn about the relationships of relapse and number of prior hospitalizations with response to lurasidone treatment.

Literature References
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T92. THE NATIONAL PREGNANCY REGISTRY FOR ATYPICAL ANTIPSYCHOTICS: EFFECTS OF FETAL EXPOSURE ON RISK FOR MAJOR MALFORMATIONS

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Abstract Background: Atypical antipsychotics are widely used by reproductive-age women to treat a spectrum of psychiatric illnesses. Despite widespread use of this class of agents in women of childbearing potential, reproductive safety data across these medicines are sparse. The National Pregnancy Registry for Atypical Antipsychotics (NPRAA) at Massachusetts General Hospital was established in 2008 to address this knowledge gap.

Website: www.womensmentalhealth.org/pregnancyregistry

Toll-free number: 1-866-961-2388

Methods: 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) 2-3 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: 1) rates of major malformations in infants, 2) birth weight, 3)gestational age at delivery, 4) miscarriage rates, and 5) delivery complications. Data on maternal health outcomes, including weight gain across pregnancy and evidence of gestational hypertension/diabetes, are also obtained. Neonatal information regarding extrapyramidal symptoms (EPS) and withdrawal symptoms are systemically collected from pediatric medical records. Potential major malformations are identified and relevant records are sent to a dysmorphologist blinded to drug exposure for adjudication.

Results: As of December 2014, total enrollment in the Registry was 487 women: 353 women in the exposed group and 134 women in the comparison group. The overall drop-out and loss to follow-up rate of subjects in the exposed and comparison groups combined was 12.7%. The proportion of study subjects for whom medical records were obtained was 82.2%. A total of 303 women have completed the study and were eligible for inclusion in the analysis. Of 214 live births with first trimester exposure to atypical antipsychotics, three (N=3) major malformations were confirmed. Of the 89 control group live births, one (N=1) major malformation was confirmed. The absolute risk of major malformations was 1.4% for infants exposed to an atypical during the first trimester and 1.1% for unexposed infants. The odds ratio for major malformations was 1.25 (0.13, 12.19) comparing exposed to unexposed infants, not reaching statistical significance.

Discussion: The NPRAA offers a systematic way to collect prospective reproductive safety information which informs the care of women who may use atypical antipsychotics to sustain psychiatric well-being. This preliminary analysis indicates a low 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. These preliminary findings suggest that atypical antipsychotics taken as a class do not appear to confer the level of teratogenic risk seen with major teratogens such as valproic acid.

Learning Objectives
1. Provide an updated estimate of the relative risk for major malformations in infants exposed in utero to atypical antipsychotics.
2. Describe the estimated frequency with which extrapyramidal and withdrawal symptoms are observed in newborns exposed to atypical antipsychotics during the third trimester of pregnancy.

Literature References
1. Cohen LS, Viguera AC, McInerney KA, et al.: Establishment of The National Pregnancy Registry for Atypical Antipsychotics. Journal of Clinical Psychiatry 2015; in press.
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T93. MAJOR DEPRESSIVE DISORDER AND THE ROLE OF ANXIETY IN ESTABLISHING BIOMARKERS FOR CLINICAL CARE USING FMRI OF EMOTION CONFLICT REGULATION: RESULTS FROM THE EMBARC STUDY

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Abstract Background: Major Depressive Disorder (MDD) has been associated with abnormalities in regulating emotional conflict (Etkin & Schatzberg, 2011). Similar abnormalities have been found in those suffering from anxiety disorders (Etkin & Schatzberg, 2011; Etkin & Wagner, 2007). The ventral anterior cingulate cortex (vACC) and amygdala have been most commonly implicated in these abnormalities. In the present work, we sought to investigate emotion conflict regulation in a large sample of early onset MDD, taking into account the role anxiety plays in their emotion regulation processing.

Methods: Participants consisted of 40 healthy controls (HC) and 100 patients with early onset MDD before starting medication as part of the multisite EMBARC study (http://embarc.utsouthwestern.edu/), a two phase, randomized, placebo-controlled trial. Participants were between 18-65 years of age. They were scanned at one of four sites, and the event-related emotion conflict task was acquired. Analyses to compare HC and MDD patients, with high- or low-anxiety (MDD-HiAnx; MDD-LoAnx) were performed on behavior and brain function using SPSS and SPM, respectively.

Results: Results show performance on the task to be equivalent between HC, MDD-LoAnx and MDD-HiAnx. SPM maps revealed several clusters in regions of interest to differ between the groups for reactivity or regulation of emotional conflict. For reactivity, the right insula showed higher activity in MDD-HiAnx than MDD-LoAnx. Whereas, with regulation, the vACC showed higher activity in MDD-LoAnx than MDD-HiAnx group. These results are in line with previous work.

Conclusion: The present work provides evidence that anxiety can moderate the regulation of emotion conflict in MDD, and should be considered when investigating biomarkers for treatment response. The final EMBARC sample, along with their outcomes data, will be used in follow-up to the present work to identify if the currently identified markers are useful in predicting treatment response as early as one-week from starting antidepressant care.

Learning Objectives
1. To connect clinical measures to biomarker data to better phenotype major depressive disorder.
2. To translate new findings in biomarker research into knowledge for clinical care practices.

Literature References
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2. Etkin A, Wager TD: Functional neuroimaging of anxiety: a meta-analysis of emotional processing in PTSD, social anxiety disorder, and specific phobia. Am J Psychiatry 2007; 164:1476– 1488.

T94. DO PSYCHIATRIC INPATIENTS WHO REPORT AGGRESSION AND IMPULSIVITY ALSO SCORE HIGHER ON THE SHEEHAN-SUICIDALITY TRACKING SCALE?

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Abstract   Introduction: Identifying risk factors for suicidal behavior offer clinicians the opportunity to intervene and reduce their patients' risk of self-harm. Aggression and impulsivity have been associated with suicide attempts in the general population (1). Similarly, in the psychiatric inpatient population, suicide attempts have been linked to aggression (2) and impulsivity (3). We examined whether there was an interactive relationship between aggression and impulsivity on suicidal behavior as assessed by the Sheehan Suicidality Tracking Scale (S-STS).

Methods: Adult psychiatric inpatients (n = 199) completed the S-STS (4) and an investigator-designed Risk Assessment Measure (RAM). Participants reported their suicidal behavior in the past month on the S-STS and reported whether they engaged in aggressive behavior and/or impulsive behavior in the past month on the RAM. We ran a two-way ANOVA to examine the effects of aggression and impulsivity on the S-STS suicidal behavior score.

Results: About 40% (n = 80) of participants reported that they had been aggressive towards others in the past month and about 65% (n = 130) reported that they had been engaged in impulsive behavior in the past month. There was no significant interaction effect between aggression and impulsivity, $F(1, 3) = 1.66$, $p = 0.20$. The interaction term was removed from the analysis and a second two-way ANOVA was conducted. There was a significant main effect of impulsivity, $F(1, 2) = 12.01$, $p = 0.001$; those reporting impulsive behavior in the past month scored significantly higher on the S-STS suicidal behavior scale. There was no significant main effect of aggression on suicidal behavior, $F(1, 2) = 0.72$, $p = 0.40$.

Discussion: Previous studies of adult psychiatric inpatients have demonstrated that aggression and impulsivity are risk factors for suicide attempt. In this sample of adult psychiatric inpatients, impulsivity, but not aggression, was linked to higher score on a standardized suicide assessment of suicidal behavior and no interaction effect was observed. Two previous studies of psychiatric inpatients failed to find a significant relationship between aggression and suicidal behavior (5; 3). This could be due to different methodologies used in assessing aggressive behavior, or perhaps differences in aggression are not accompanied by differences in suicidal behavior. Nevertheless, our findings suggest that clinicians should be mindful of their patients' impulsive tendencies when assessing for their risk for suicidal behavior.

Learning Objectives
1. Examine relationship between suicidal behavior, aggression, and impulsivity in an inpatient psychiatric setting utilizing a standardized suicide assessment.
2. Contribute to literature on risk factors for suicidality.

Literature References
1. Wang L; He CZ; Yu YM; Qiu XH; Yang XX; Qiao ZX; Sui H; Zhu XZ; Yang YJ: Associations between impulsivity, aggression, and suicide in Chinese college students. BMC Public Health 2014; 14: 551. doi: 10.1186/1471-2458-14-551
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T95. EFFICACY AND SAFETY OF BREXPIPRAZOLE (OPC-34712) AS ADJUNCTIVE TREATMENT IN MAJOR DEPRESSIVE DISORDER: META-ANALYSIS OF TWO PIVOTAL STUDIES

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Abstract   Background: Despite sufficient availability of different classes of antidepressants, approximately 50% of patients with MDD do not achieve a response to antidepressants treatment [1]. Brexpiprazole is a rationally designed serotonin-dopamine activity modulator (SDAM) that is a partial agonist at 5-HT1A and dopamine D2 receptors at similar potency, and an antagonist at 5-HT2A and noradrenaline alpha1B/2C receptors [2]. The efficacy, safety and tolerability of adjunctive brexpiprazole were evaluated in patients with major depressive disorder (MDD) and inadequate response to antidepressant treatments (ADTs), based on pooled data from two pivotal phase III studies.

Methods: Patients with MDD and inadequate response to 1–3 ADTs were enrolled and received single-blind ADT for 8 weeks. Patients with inadequate response after this prospective phase were randomized to ADT+brexpiprazole or ADT+placebo for 6 weeks. Both studies included fixed doses (2mg [Study 1: NCT01360645]; 1mg and 3mg [Study 2: NCT01360632]). Primary efficacy endpoint was the change in MADRS total score from baseline to week 6. As the two studies had a similar design, a meta-analysis was performed with pooled placebo groups.

Results: Adjunctive brexpiprazole showed greater improvement at week 6 than adjunctive placebo in MADRS total score (least square mean difference to placebo+ADT [n=360]: 1mg+ADT [n=204]: -2.02, p=0.0018; 2mg+ADT [n=164]: -2.35, p=0.0007; 3mg+ADT [n=196]: -2.54, p=0.0001). The most frequent adverse events included akathisia (4.4%, 7.4%, 13.5%, 1.7%), weight increase (6.6%, 8.0%, 5.7%, 1.9%), tremor (4.0%, 2.1%, 5.2%, 2.2%) and somnolence (4.0%, 4.3%, 5.7%, 0.5%), in the brexpiprazole 1mg+ADT (n=226), 2mg+ADT (n=188), 3mg+ADT (n=229) and pooled placebo+ADT groups (n=411), respectively.

Conclusion: Data from adequate and well-controlled clinical studies provide evidence that brexpiprazole is efficacious as adjunctive treatment in MDD patients with an inadequate response to ADTs. All doses of adjunctive brexpiprazole were well tolerated, with notably low levels of sedating or activating (i.e., akathisia, restlessness, anxiety, insomnia) side effects.

Learning Objectives
1. To understand the efficacy of adjunctive brexpiprazole to antidepressants in patients with major depressive disorder.
2. To understand the safety and tolerability of adjunctive brexpiprazole to antidepressants in patients with major depressive disorder.

Literature References

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T96. THE EFFICACY OF VORTIOXETINE IN THE TREATMENT OF PATIENTS WITH MDD IN SHORT-TERM PLACEBO-CONTROLLED STUDIES: A META-ANALYSIS OF 11 STUDIES

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Abstract   Purpose: Vortioxetine is approved for the treatment of major depressive disorder (MDD) [1, 2]. This analysis compares the efficacy of therapeutic doses of vortioxetine (5−20 mg/day) using data from 12 completed randomized double-blind placebo-controlled short-term clinical trials of adults with MDD.

Methods: Patient-level data from 12 studies were included in this analysis (NCT00672958, NCT00672620, NCT00735709, NCT01153009, NCT01163266, NCT01179516, NCT00839423, NCT00635219, NCT01140906, NCT00811252, NCT01422213, NCT01255787). Results are shown by study and as meta-analyses, which included 11 studies, excluding the study in elderly patients (NCT00811252). All patients were required to meet DSM-IV criteria for a major depressive episode for clinical trial inclusion. Estimated treatment difference in change in MADRS total score from baseline to endpoint was the primary efficacy outcome measure, using MMRM analysis based on the FAS (comprising all treated patients with ≥1 post-baseline MADRS assessment). Secondary outcome measures were: effects on depressive symptoms (MADRS single items) and on anxiety symptoms (HAM-A total score); response rate (≥50% reduction in baseline MADRS); remission rate (MADRS ≤10); and CGI-I score.

Results: In the adult MDD studies, 1515 patients were treated with placebo and 2732 with vortioxetine (5mg/day, n=840; 10mg/day, n=877; 15mg/day, n=344; 20mg/day, n=671). Patient characteristics were similar. The mean age was 44 years, the men-to-women ratio was approximately 1:2, and the median number of previous MDEs was 2. Meta-analysis supported the dose response found in individual studies. Mean difference in change in MADRS between placebo and vortioxetine was −2.3 (5mg, p=0.007), −3.6 (10mg, p<0.001), −2.6 (15mg, p=0.105) and −4.6 points (20mg, p<0.001). Vortioxetine demonstrated a broad clinical effect across MADRS single items and on the HAM-A total score. Clinical relevance was further shown by significant differences in response and remission rates (LOCF) and CGI-I scores for all vortioxetine doses. In the elderly study, vortioxetine (5mg/day) showed a significant improvement versus placebo in primary (−4.7 MADRS points) and secondary endpoints.

Conclusion: This meta-analysis found vortioxetine (5−20mg/day) efficacious in adult MDD patients, with increasing efficacy with increased dose. Consistency of the data and broad clinical effect are shown by secondary outcomes and efficacy in elderly patients.

Learning Objectives
1. To evaluate the short-term clinical efficacy of therapeutic doses of vortioxetine (5-20 mg/day) in adults with MDD.
2. To examine the dose-dependent clinical effect of vortioxetine in patients with MDD.

Literature References

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Wednesday, June 24, 2015

Poster Session II

W1. NO FOOD EFFECT FOR A NOVEL ORAL DISINTEGRATING TABLET FORMULATION OF EXTENDED-RELEASE METHYLPHENIDATE FOR THE TREATMENT OF ADHD

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Abstract Objective: Attention-deficit/hyperactivity disorder (ADHD) is a common condition that can profoundly impact daily living. Methylphenidate (MPH) is a commonly used ADHD treatment.1 Due to the shortcomings of the immediate release formulation of MPH (eg, short half-life requiring multiple doses, peaks and troughs in blood levels, compliance with BID/TID dosing), extended-release formulations of MPH have been developed.2 Currently available extended-release oral formulations of MPH are available as capsules or tablets, which may be challenging for patients who cannot or do not like to swallow capsules or tablets.1 Methylphenidate extended-release oral disintegrating tablets (MPH XR-ODT) may represent a more patient-friendly dosage form for patients who have difficulty swallowing tablets or capsules. Ideally, this dosage form could be taken either with or without food.

Methods: This was a single-dose, open-label, randomized, 2-period, 2-treatment crossover study. Healthy adult volunteers (≥18 years of age) fasted overnight (≥10 hours). In the morning, prior to dosing (2 x 30 mg of MPH XR-ODT), subjects either continued to fast (fasted group) or consumed a US Food and Drug Administration-standard high-calorie, high-fat breakfast (which was to be completed 5 minutes prior to dosing; fed group). A 7-day washout period separated each treatment period. Blood samples for pharmacokinetic (PK) analysis were collected predose through 36 hours postdose. The following PK parameters were calculated: maximum plasma concentration (Cmax), time to maximum plasma concentration (Tmax), the last quantifiable drug concentration (Clast), time of the last measurable concentration (Tlast), observed elimination rate constant (λz), half-life (t1/2), and overall systemic exposure (AUClast and AUCinf). No significant food effect was concluded if the 90% confidence intervals (CI) about the geometric mean ratios (Fed/Fasted) for Cmax, AUClast, and AUCinf were within the 80% to 125% interval. Safety was also assessed.

Results: Overall, the 24 subjects enrolled in the study were 50.0% male, 83.3% white, and had a mean (SD) age of 30.9 (±9.3) years. Twenty-three subjects completed the study. The PK parameters for total MPH (d-MPH + l-MPH) were comparable under fed and fasted conditions. The 90% CIs for total MPH about the geometric mean ratios (Fed/Fasted) for Cmax, AUClast, and AUCinf were all within the accepted 80% to 125% limits, consistent with no food effect. The most common treatment-emergent adverse events (TEAEs) were anxiety (in 4 fasted subjects [16.7%] and 4 fed subjects [17.4%]) and nausea (in 5 fasted subjects [20.8%] and 2 fed subjects [8.7%]). No TEAEs were related to abnormal laboratory evaluations or physical examinations. Mild or intermittent tachycardia was reported in 3 subjects (1 in the fasted condition and 2 in the fed condition).

Conclusions: Food intake did not significantly alter the rate of absorption of MPH or the extent of exposure to MPH from the MPH XR-ODT. This suggests that the MPH XR-ODT is a rugged formulation that can be taken with or without food. Taken together with other PK and clinical

efficacy and safety data for this formulation, MPH XR-ODT is a useful ADHD formulation, particularly for patients who have difficulty or do not like taking capsules or tablets.

Learning Objectives
1. Describe the effects of food on the rate and extent of absorption of novel methylphenidate extended-release oral disintegrating tablets.
2. Discuss how methylphenidate extended-release oral disintegrating tablets, a unique dosage form, provides a new treatment option for individuals with ADHD, including those who have difficulty swallowing or do not like to swallow tablets or capsules.

Literature References
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W2. THE CONTROLLED-RELEASE PROPERTIES AND EXPOSURE LEVELS OF A NOVEL ORALLY DISINTEGRATING TABLET FORMULATION OF AMPHETAMINE FOR TREATMENT OF ADHD ARE MAINTAINED IN THE PRESENCE OF ALCOHOL

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Abstract Objectives: There appears to be a strong correlation between attention-deficit/hyperactivity disorder (ADHD) and substance abuse, including alcoholism.1 ADHD is 5 to 10 times more prevalent in adult alcoholics, and children with ADHD are more likely to start drinking at an early age. Extended-release amphetamine (AMP) formulations are routinely used to manage ADHD, however, they should not be used with alcohol due to the risk of pharmacodynamic interactions. The pharmacokinetic (PK) properties of extended-release formulations of certain drugs (eg, certain opioids) are known to be altered in the presence of alcohol due to rapid release of high concentrations of drug product into the bloodstream, a phenomenon termed "dose dumping."2 However, the effect of alcohol on extended-release medications used for ADHD treatment is unknown.

Novel amphetamine extended-release oral disintegrating tablets (AMP XR-ODT) have been developed using a drug-loaded resin (drug-resinate) to facilitate drug ingestion (eg, can be taken without water, disintegrate in the mouth without chewing) and to provide a patient-friendly formulation for those who cannot or will not swallow a tablet or capsule. In order to examine the ruggedness of the drug-resinate formulation and the safety profile of AMP XR-ODT in the presence of alcohol, this in vivo study assessed the effects of increasing concentrations of ethanol on the rate and extent of absorption of amphetamine from AMP XR-ODT in healthy adults.

Methods: This was a randomized, single-dose, open-label, 4-period, 4-sequence, 4-treatment crossover study in healthy adult volunteers. After a ≥10-hour fast, volunteers (21-45 years old) were administered AMP XR-ODT (equivalent to 30 mg mixed amphetamine salts) followed by 240 mL of varying concentrations of alcohol (0%, 4%, 20%, or 40%). Treatments were separated by a 14-day washout period. Plasma concentrations of d- and l-amphetamine were assessed through 60 hours postdose. The following PK parameters were calculated: maximum plasma concentration (Cmax), time to maximum plasma concentration (Tmax), the last

quantifiable drug concentration (Clast), time of the last measurable concentration (Tlast), observed elimination rate constant ($\square$z), half-life (t1/2), and overall systemic exposure (AUClast and AUCinf). Safety was also assessed.

Results: Thirty-two healthy volunteers enrolled in the study (mean [SD] age 32.0 [±6.9] years, 90.6% male, 50.0% Caucasian); 27 completed all 4 treatments. The PK profiles of d-amphetamine and l-amphetamine were comparable across treatments. The 90% confidence intervals for the geometric mean ratios (0% alcohol compared to 4%, 20%, and 40% alcohol) for Cmax, AUClast, and AUCinf were within the accepted 80% to 125% limits, demonstrating no significant difference. Most adverse events (AEs) were mild or moderate, and there were no serious treatment emergent AEs.

Conclusions: Varying concentrations of alcohol (4%-40% ethanol) did not significantly alter the rate, extent of absorption, or exposure of amphetamine from AMP XR-ODT in healthy subjects. The results of this study indicate that the extended-release properties of AMP XR-ODT are maintained in the presence of ethanol, indicating that it is a rugged and potentially promising option for the treatment of ADHD.

Learning Objectives
1. Discuss the purpose of performing an in vivo interaction study to examine the oral bioavailability of an extended-release formulation of amphetamine in the presence of alcohol.
2. Describe the pharmacokinetic profile of amphetamine extended-release orally disintegrating tablets in the presence of 0%, 4%, 20%, and 40% ethanol in healthy adults.

Literature References
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W3. DOPAMINE TRANSPORTER GENE (DAT1) DOPAMINE RECEPTOR GENE (DRDR4), AND RESPONSE TO METHYLPHENDIATE AND ATOMOXETINE TREATMENT IN ADHD YOUTH

Thomas Hildebrandt[1], Emily Olsen[2], Edwin Cook Jr.[2], Jeff Bishop[3], Jeffrey Newcorn[1], Mark Stein[4]

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Abstract Both the dopamine transporter (DAT1) and dopeamine 4 receptor (DRD$) gene have been associated with risk for ADHD and evauated in clincial trials, with inconsistent findings. Previous studies have varied greatly in their subject selection and methodology. We have previously demonstrated an association between the 9/9 allele of DAT1 and poor response to methylphendiate, and sought to replicate this as well as examine DRD4 in children treated with methylphenidate (MPH) and Atomoxetine (ATX).

Participants in the first treatment block in the Methylphendiate-Atomoxetine Crosssover Study (MACRO) (n = 199) were genotyped for DAT1 10 repeat alleles and Drd4 7 repeatr alleles. For those treated with MPH first, the slope and intercept for those with the 9/9 genotype differed from the 9/10 and 10/10 genotype groups (p = .03).At 54 and 72 mg. MPH, youth withthe 9/9 genotype displayed a CGI-S change of 1 from baseline, as opposed rto changed

fropm 1.7-3 onthe CGI-S for the10/10 and 10/9 genotypes. DRD4 genotype was not associated with response to MPH or ATX.

In summary, children absent the 10 repeat allele display a less robust response to MPH than children with the more common genotypes. Further research is needed with larger samples of the 9/9 genotype to examine in more detail the relationship between genotybe, baseline severity, comorbidity, dose, tolerability, and treatment response. Given the low genotype frequency, consideration should be given to enriching or selecting samples based on genotype in future studies that eventually may inform clincial decision making.

Learning Objectives
1. Increase familiarity with candidate gene studies in ADHD based upon the drug targets of stimulant medications.
2. Highlight the complexity of evaluating pharamacogenetic effects in clinical trials and potential   reasons for inconsistent findings across studies.

Literature References
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W4. DOES THE PRESENCE OF ATTENTION DEFICIT HYPERACTIVITY DISORDER PREDICT TREATMENT FAILURE IN PATIENTS DIAGNOSED WITH MAJOR DEPRESSIVE DISORDER PRESCRIBED SSRIS?

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Abstract Background: At present, selective serotonin reuptake inhibitors (SSRIs) are the most commonly prescribed medication for the treatment of Major Depressive Disorder (MDD) in Canada. In many cases, despite adequate dose and duration of treatment, few patients achieve full remission resulting in residual symptoms, including cognitive impairment. Lack of remission may in part be explained by the high prevalence of comorbid psychiatric conditions, etiopathological heterogeneity and overlap, both within and across these conditions, as well as dysfunction of specific neural pathways that result in the symptomatic presentation. In recent years, Attention Deficit Hyperactivity Disorder (ADHD) has gained increased interest and acceptance as a valid diagnosis in the adult population. Still, many clinicians fail to adequately screen adult patients for ADHD during psychiatric assessment, despite the fact that it has been demonstrated that unreferred adolescents with a history of ADHD are significantly more likely to develop MDD in adulthood. Thus, the aim of this study was to assess the number of patients with undetected ADHD that were referred for treatment of MDD, and identify predictive correlates for treatment resistance in patients that met the criteria for ADHD and MDD.

Method: Data was collected from consecutive referrals (n=123) to a tertiary-care mood and anxiety clinic. Referrals were assessed for reason for referral, primary diagnosis, number of diagnoses and medication history. Intake diagnosis was formed by clinical-structured interview (Mini International Neuropsychiatric Interview Plus 6.0.0) and a semi-structured psychiatric interview by the treating physician. One-way analysis of variance and t-tests were performed to examine predictive factors related to presence of comorbidities, treatment resistance, and medication history. Data collection and analysis is currently ongoing.

Results: Results indicated that undetected ADHD was present in more than 28.4% of mood and anxiety disorder referrals and 22% of patients referred for treatment-resistant depression (TRD). Predictive factors of undetected ADHD included number of diagnoses ($p<0.005$), psychiatric medication history ($p<0.005$), and number of SSRIs prescribed ($p<0.05$). Whereas, the number of failed medications at intake ($p<0.005$), number of diagnoses ($p<0.005$), Social Anxiety Disorder ($p<0.006$) and SSRI failure ($p<0.005$) were predictive of the presence of ADHD in patients referred for TRD.

Conclusion: These results support previous findings that ADHD is a significant risk factor for the development of MDD. This study demonstrated that ADHD is often undetected in adult patients referred for MDD treatment and suggests that SSRI failure is a predictor of patients being diagnosed as treatment-resistant. This signifies the importance of accurate screening for premorbid conditions, and the need for further studies of behavioral and neurobiological markers in relation to treatment direction.

Learning Objectives
1. To understand the prevalence of undiagnosed ADHD in adult patients referred to a mood and anxiety disorders clinic.
2. To identify factors that might suggest the presence of ADHD in individuals referred for MDD labeled as treatment-resistant.

Literature References
1. Bond, D. J., Hadjipavlou, G., Lam, R. W., McIntyre, R. S., Beaulieu, S., Schaffer, A., & Weiss, M. (2012). The Canadian Network for Mood and Anxiety Treatments (CANMAT) task force recommendations for the management of patients with mood disorders and comorbid attention-deficit/hyperactivity disorder. Annals Clininal Psychiatry, 24(1), 23-37.
2. Meinzer, M. C., Lewinsohn, P. M., Pettit, J. W., Seeley, J. R., Gau, J. M., Chronis-Tuscano, A., & Waxmonsky, J. G. (2013). Attention Deficit-Hyperactivity Disorder in Adolescence Predicts Onset of Major Depressive Disorder through Early Adulthood. Depression and Anxiety, 30(6), 546–553.

W5. REVIEW OF ORAL COCAINE ALKALOID AS AGONIST THERAPY: A PROPOSAL ORIGINATED AND APPLIED IN PERU FOR SMOKED COCAINE (COCA PASTE) DEPENDENCE

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Abstract Aims: Oral cocaine as alkaloid have been used as agonist therapy for control cocaine dependence since the 1980s. We review the results of the use oral cocaine contained in coca tea or coca flour over 100 patients addicted to coca paste (cocaine formulation smoked mixed with tobacco in commercial cigarettes originated in Perú).

Methods: Bibliographic review of use of oral cocaine as therapy in cocaine addicts between 1980 and 2014, in Pubmed, Cochrane, CPDD meetings, Bolivian and Peruvian references.

Results: We found 6 studies (2 blind/28 subjects, and 4 open/83 subjects) treated with cocaine alkaloid contained in coca tea or coca flour, plus counsel and one with cocaine contained in coca leaf as chewing (without toxicological tests nor control group). Two of the first six studies, one blind and one open, were performed mixed with transdermal nicotine (40 subjects). Schedule with oral cocaine as agonist therapy showed statistically significant results compared with placebo (tea and flour matches in color and taste) in patients considered refractory to current treatments. The coca paste-addicted patients under double schedule cocaine-nicotine showed better results than the simple schedule (cocaine alkaloid alone). Both schedules were

statistically significant compared with placebo in maintained abstinence during the studies. Family and school/job data were collected for monitoring and control.

Conclusions: FDA no approved pharmacological treatment for cocaine addiction. Patients under oral cocaine schedules showed better results than control groups, without show illness nor abnormal behavior. Although urine test ever showed positive results to benzoylecgonine (BE), negative results indicate that the subject is not in complying with the treatment regimen. During the first days urine tests have a relative prove of abstinence, but after to obtain a BE average of subject under abstinence, higher level from BE average could indicated relapse. Positive statistically results warrants further research in regions where its medical uses is approved for other disorders.

Learning Objectives
1. We postulated (2009) a coca paste dependence as double dependence cocaine-nicotine, and simultaneous agonist treatment for both substances.
2. We postulated a concept of regional therapy with oral cocaine because only in the Andean regions can buy over the counter and without legal restrictions cocaine alkaloid containing in coca leaves and its modern industrial products as coca tea or coca flour, that could be an alternative for cocaine dependence treatment.

Literature References
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W6. STRESS-RELATED COGNITIVE DEFICITS: IMPLICATIONS FOR ANXIETY DISORDERS

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Abstract Numerous studies suggest that stressful experiences early in life can induce neurochemical, morphological, and physiological changes in the mammalian brain—changes that endure into adulthood and are closely linked with an increased risk of stress-related psychiatric disorders, including anxiety disorders, major depressive disorders (MDD) and post-traumatic stress disorder (PTSD). The basolateral amygdala (BLA) is a limbic structure in the brain which is known to be involved in emotional and stress responses, while the dentate gyrus (DG), a subfield of the hippocampus, is implicated in learning and memory. Together, the BLA-DG neuronal pathway is thought to be involved in the regulation of synaptic plasticity of emotional memories. In a previous study, we reported neonatal stress resulted in significantly greater long-term potentiation (LTP, a cellular mechanism for memory formation and consolidation) compared to control. The aim of the present study, however, is to assess whether an acute stress has any impact on brain circuits responsible for emotional memories. Preliminary results indicate acute stress has the overall effect of depotentiating LTP in all animals tested. However, depotentiated LTP in stressed animals was much larger than in controls, indicating acute stress has a more profound effect on LTP in animals with prior exposure to stress as neonates. These results are consistent with previous reports of long-lasting alterations in assembly of neural circuits involved in emotion and the regulation of the stress response in animals that experienced chronic stress early in life. Finally, these findings may have clinical implications in terms of acute stress promoting deficits in cognitive functions in populations already at risk for anxiety, depression and PTSD.

Learning Objectives After attending this talk, you should be able to:

1. Understand how animal models of neurological disorders can be useful in the study such diseases.
2. Make use of appropriate knowledge to connect stress to several affective disorders impacting a large segment of the population.

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W7. DIFFERENTIAL OLFACTORY SENSITIVITY IN COMBAT VETERANS WITH AND WITHOUT PTSD

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Abstract Background: Posttraumatic stress disorder (PTSD) is characterized by highly-emotional memories of traumatic events. Given that odors can enhance the retrieval of autobiographical memories, trigger physiological arousal, and precipitate trauma-related flashbacks, it is reasonable to hypothesize that odors, and trauma-related odors in particular, may play a significant role in the pathophysiology of PTSD. In this preliminary study therefore, we sought to examine self-reported, odor-elicited distress in combat veterans, with and without PTSD, and healthy controls.

Methods: Fifty-two combat veterans with (CV+PTSD) and without (CV-PTSD) PTSD and twenty-one healthy controls (HC) completed the olfactory questionnaire (OQ) which gathered information pertaining to hedonic valence and ability to elicit distress/relaxation for a range of odor categories and the individual odors within those categories.

Results: The CV+PTSD (N=30; M/F=28/2; Age: M=33.4, SD=11.0) and CV-PTSD (N=22; M/F=21/1; Age: M=30.0, SD=7.0) groups were comprised of almost all men of similar age. The HC group was mainly female and older than both veteran groups (N=21; M/F=6/15; Age: M=47.0, SD=12.7). A main effect of diagnosis on the frequency of which odor categories were rated to elicit distress was revealed for "burning", "flammables", "garbage", and "human body fluids/excretions". Group comparisons revealed that CV+PTSD reported a higher prevalence of distress to "flammables" (i.e. fuel) compared to HC [40% vs. 4.8%, $\chi2$ (1, N=51) = 8.08, p=.004] and a significantly higher prevalence of distress to "burning" compared to both HC (93.3% vs. 61.9%, $\chi2$ (1, N=51) = 7.74, p=.005) and CV-PTSD (93.3% vs. 54.5%, $\chi2$ (1, N=52) = 10.76, p=.001). In contrast, lower prevalence rates of distress for human body fluids/excretions-related odors were reported in the veteran groups compared to HC [CV+PTSD=80.0%, CV-PTSD=68.2%, HC=100%; CV+PTSD vs. HC: $\chi2$ (1, N=51) = 4.76, p=.029; CV-PTSD vs. HC: $\chi2$ (1, N=43) = 7.98, p=.005]. A main effect of diagnosis was also revealed for both "unpleasant" (F2,70=3.77, p=.028) and "pleasant" (F2,70=9.46, p<.001) odor groups. Compared to HC, combat veterans with and without PTSD rated both pleasant and unpleasant odors significantly more neutral.

Conclusion: This is the first study to survey the emotional impact of nine different odor categories (burning-, death/decay-, drug -, food-, flammable-, floral-, garbage-, human body fluids/excretions-, and environmental-related odors) as well as the individual odors within these categories in civilians and combat veterans with and without PTSD. While veterans with

PTSD reported a higher prevalence of distress to fuel and burning-related odors compared to healthy civilians, the only odor category that distinguished combat veterans with versus without PTSD was burning-related odors. In contrast to the increased sensitivity to burning-related and fuel odors, combat veterans with and without PTSD reported significantly less sensitivity to a large number of pleasant and unpleasant, non-combat-related, odors. A possible explanation for the increased sensitivity to burning-related and fuel odors with decreased sensitivity to a large number of other odors might be the co-occurrence of attentional bias toward threat odors with selective ignoring of distractor odors. Working together, these processes may optimize survival.

Learning Objectives
1. To describe differences in odor-elicited distress between combat veterans both with and without PTSD and healthy controls.
2. To provide a possible explanation for the differences in sensitivity to odors between combat veterans and healthy controls.

Literature References
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W8. POST HOC ANALYSES OF ANXIETY MEASURES IN ADULT PATIENTS WITH GENERALIZED ANXIETY DISORDER TREATED WITH VILAZODONE

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Abstract Introduction: Generalized anxiety disorder (GAD) is characterized by a broad range of psychic and somatic symptoms. Many patients do not adequately respond to current treatments and new medications are needed to improve the management of GAD. Vilazodone, a selective serotonin reuptake inhibitor and 5-HT1A partial agonist, approved for the treatment of major depressive disorder in adults, is being investigated for the treatment of GAD. In 3 double-blind, randomized, placebo-controlled GAD trials, vilazodone was superior to placebo on the primary efficacy outcome, change in total score on the 14-item Hamilton Anxiety Rating Scale (HAMA). Post hoc analyses of pooled data from these 3 trials evaluated the efficacy of vilazodone across GAD symptom domains.

Methods: Data from the 3 GAD studies were pooled for analysis: 1 fixed-dose study of vilazodone 20 mg/d and 40 mg/d (NCT01629966) and 2 flexible-dose studies of vilazodone 20-40 mg/d (NCT01766401, NCT01844115). All vilazodone doses were combined for analyses. Post hoc analyses evaluated mean change from baseline to Week 8 in the HAMA total score, Psychic (items 1-6, 14) and Somatic (items 7-13) Anxiety Subscale scores, and individual HAMA item scores in the intent-to-treat (ITT) population using a mixed-effects model for repeated measures; effect sizes (ES) were estimated using least squares mean differences (LSMDs). HAMA response (≥50% improvement from baseline in total score) and remission (total score ≤7) rates and associated odds ratios (OR) were analyzed using a logistic regression model.

Results: The pooled ITT population comprised 618 placebo patients and 844 vilazodone patients. Mean baseline scores on the Psychic (14) and Somatic (10) Anxiety Subscales indicated that patients generally had greater levels of psychic anxiety than somatic anxiety. Vilazodone- compared with placebo-treated patients had significantly greater improvements in HAMA total score (LSMD=-1.83; P<.0001; ES=0.26), Psychic Anxiety Subscale score (LSMD=-1.21; P<.0001; ES=0.28), and Somatic Anxiety Subscale score (LSMD=-0.63; P=.0012; ES=0.19). Significantly greater improvements for vilazodone compared with placebo were seen on all HAMA psychic anxiety items (P value range: <.0001 to <.0280; ES range: 0.13 to 0.32), except insomnia. For somatic anxiety items, significantly greater improvements were observed for vilazodone versus placebo on all items (P value range: .0005 to .0134; ES range: 0.15 to 0.20), except gastrointestinal symptoms and genitourinary symptoms. The vilazodone group relative to the placebo group showed significantly higher rates of HAMA response (47.5% vs 38.7%; P=.0008; OR=1.44) and remission (26.7% vs 20.6%; P=.0061; OR=1.42).

Conclusions: In this post hoc pooled analyses, vilazodone patients compared with placebo patients showed significantly greater improvement in HAMA total score, HAMA Somatic and Psychic Anxiety Subscale scores, and on 11 of 14 HAMA items. These results suggest that vilazodone showed broad efficacy across the diverse range of psychic and somatic symptoms associated with GAD.

Learning Objectives At the conclusion of this session, participants should be able to:
1. Identify individual psychic and somatic anxiety symptoms associated with generalized anxiety disorder and understand the need for broad efficacy in treating the disorder.
2. Evaluate the efficacy of vilazodone across the individual symptom domains of generalized anxiety disorder.

Literature References
1. Thase ME, Chen D, Edwards J, Ruth A: Efficacy of vilazodone on anxiety symptoms in patients with major depressive disorder. Int Clin Psychopharmacol 2014;29:351-356
2. Allgulander C: Generalized anxiety disorder: A review of recent findings. J Exp Clin Med 2012;4:88-91

W9.   TRAUMA AND PTSD PREDICT VIOLENCE IN URBAN CIVILIANS

Jeff Sanders[1], Cindy Gillikin[1], Kerry Ressler[1]

[1]Emory University

Abstract   Objective: A longstanding question in psychiatric research is whether a history of psychological trauma and Post-Traumatic Stress Disorder (PTSD) are associated with violent behavior. This relationship is especially important to understand within inner city areas, where violence and PTSD are both prevalent.   In this study we examined whether the experience of trauma and PTSD by inner city civilians predicted violent behavior.

Method: Data were collected from over 1900 primary care patients in a large inner city hospital setting. We assessed childhood trauma history with the Childhood Trauma Questionnaire (CTQ) and adult trauma history with the Traumatic Events Inventory (TEI). PTSD symptoms were measured with the PTSD Symptom Scale (PSS) and violent behaviors were measured with the Behavior Questionnaire (BQ). Using these measures, we examined the prevalence of violent behavior and if childhood or adult trauma exposure predicted this violence. We further studied if PTSD symptoms predicted violence.

Results: Trauma, PTSD and aggressive behavior were prevalent in the inner city. Both childhood and adult trauma and PTSD symptom burden were predictive of perpetrating interpersonal violence. This effect was found in both genders and was maintained after controlling for other pertinent variables such as demographics and presence of depression.

Conclusions: Our findings point to a dysregulation of violent behavior that may be a consequence of trauma and PTSD. These data indicate that effective PTSD interventions within inner city settings may help to reduce community violence.

Learning Objectives
1. To appreciate the high levels of violence that are characteristic of the inner city and to appreciate its relationship to childhood and adult trauma and PTSD.
2. To appreciate how effective PTSD screening and intervention may have help to reduce the 'cycle of violence' in the inner city.

Literature References
1. Donley S, Habib L, Jovanovic T, Kamkwalala A, Evces M, Egan G, et al. Civilian PTSD symptoms and risk for involvement in the criminal justice system. J Am Acad Psychiatry Law. 2012;40(4):522-9.
2. Elbogen EB, Johnson SC, Wagner HR, Sullivan C, Taft CT, Beckham JC. Violent behaviour and post-traumatic stress disorder in US Iraq and Afghanistan veterans. Br J Psychiatry. 2014;204:368-75.

W10. COMBINED NEUROCOGNITIVE AND EEG BIOMARKERS TO ASSESS EFFECTS OF CNS DEPRESSANTS AND STIMULANTS

Robin Johnson[1], Shani Waninger[1], Aaron Kemp[1], Maja Stikic[1], Stephanie Korszen[1], Chris Berka[1]

[1]Advanced Brain Monitoring

Abstract Chronic sleep deprivation has reached epidemic levels in the US, with up to 10% of Americans suffering from some level of insomnia, and more than 30% sleeping less than 6 hours a night. The effects of this sleep loss have a significant impact on quality of life, and they lead to increased public health and safety risks, as well as economic productivity losses. Several pharmaceutical approaches are utilized to cope with the consequences of chronic sleep loss, including CNS depressants that can combat insomnia. This class of drugs often facilitates initial sleep onset, but comes at the price of disrupting sleep architecture, often leading to less restful/recovery sleep. Alternatively, stimulant drugs can be used to promote attention and vigilance to counteract the effects of sleep loss, without targeting sleep itself. While this approach has shown short-term efficacy, stimulant use can have negative consequences that may impact functioning, and thus safety (including next day drowsiness).

Developing assessments that can determine which drug class/type is present in an individual is a crucial first step for: identifying functional risks and consequences for future drug development, aiding in public health and safety assessments, and supporting "individualized" medicine approaches. Current methods rely upon subjective questionnaires and neurocognitive testing, so the use of EEG-based biomarkers shows promise in developing objective, unobtrusive biomarker for drug identification. Past studies have established characteristic EEG-based features for different stimulant and depressant drugs, and this study herein considered EEG recordings in combinations with neurocognitive testing results (i.e., CogState).

The findings presented are based upon an analysis of EEG data and CogState results from a drug time-response study in which subjects (n=14) received the following doses on 4 separate visits, in a randomized order: 1) placebo pill, 2) 100mg modafinil PO, 3) 20mg

methylphenidate PO, and 4) 1mg lorazepam PO. Resting state EEG (eyes open and eyes closed) was acquired prior to drug administration, and then at time = 2hrs, 4hrs, and 6hrs. Additionally, subjects completed the CogState test at baseline and after each EEG recording. For analysis, EEG-based features included PSDs (both bandwidth and individual Hz bins) and wavelets. A series of 2-,3-, and 4-way linear and quadratic discriminant function analyses were applied to determine the best model for identifying drug condition. A series of 2-way lDFAs were found to be the most effective and accurate in defining the drug state, and these results achieved a classification accuracy of approximately 84% overall.

Additionally, regressions were examined for the following conditions: cognitive testing results only, EEG metrics only, and cognitive testing combined with EEG. Results indicate that cognitive testing results alone explain, at best, only 2-4% of the variance. EEG-based features, on the other hand, explain up to 65% of the variance – a value which did not improve when combining the cognitive results. EEG performed best at time = 2hrs, which corresponds to peak activity, supporting the ability for EEG to prove useful in both detecting drug presence, as well as drug effect levels. Performance measures were also considered, but the only significant finding was a slower reaction time for the lorazepam condition vs. modafinal, as well as for lorazepam vs. methylphenidate.

Learning Objectives
1. Developing assessments that can determine which drug class/type is present in an individual is a crucial first step for: identifying functional risks and consequences for future drug development, aiding in public health and safety assessments, and supporting "individualized" medicine approaches.
2. Current methods rely upon subjective questionnaires and neurocognitive testing, so the use of EEG-based biomarkers shows promise in developing an objective, unobtrusive biomarker for drug identification.

Literature References
1. Chapotot, F., et al., Distinctive effects of modafinil and d-amphetamine on the homeostatic and circadian modulation of the human waking EEG. Psychopharmacology, 2003. 166(2): p. 127-138.
2. Saletu, B., P. Anderer, and G.M. Saletu-Zyhlarz, EEG topography and tomography (sLORETA) in the classification and evaluation of the pharmacodynamics of psychotropic drugs. Clinical EEG and neuroscience, 2006. 37(2): p. 66-80.

W11. AUDITORY P300 IN PATIENTS WITH MAJOR DEPRESSION TREATED WITH QUETIAPINE (SEROQUEL®): A PRELIMINARY STUDY

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Abstract Background: Only 30%-55% of major depresive disorder patients achieve a remission state at the end of acute selective serotonine reuptake inhibitor or selective norepinephine reuptake inhibitor treatment (1). Several lines of evidence suggest that quetiapine may have an antidepressant effects while some clinical trials found that quetiapine reduced the depressive symptoms considerably. On the contrary, the view of some experts is

that the antidepressant effect of quetiapine may not be superior to that of other antidepressants (2).

Objectives: We recorded event-related potentials (ERPs) in patients with major depression before and after treatment with quetiapine (Seroquel®), to investigate: 1. the drug's effects on the amplitude of P300, and; 2. The relationship between P300 amplitude and the severity of depression. Methods Auditory oddball stimulus discrimination paradigms were presented to patients (N = 10) before and after 8 weeks treatment with quetiapine. The 2-stimulus auditory oddball paradigm used a standard tone (400 Hz, 80 dB, 75%) and a target tone (700 Hz, 80 dB, 25%). The patients' psychopathology severity was initially evaluated applying the Hamilton Depression Rating Scale (HAM-D) and likewise re-evaluated after treatment. Results: After quetiapine treatment we observed that the patients' P300 amplitude increased over their original baseline activity in central regions ($p < 0.05$)

Conclusions: In our study group these findings are clear evidence that the amplitude of P300 for auditory tasks increases after quetiapine treatment. Based on these results, we suggest that the atypical antipsychotic quetiapine may improve some aspects of cognitive domains in patients with major depression. After treatment with quetiapine, there were significant correlations between the severity of the symptoms and the auditory-evoked P300 amplitudes for central electrodes.

Bibliography: 1. Thase ME, Entsuah AR, Rudolph RL. Remission rates during treatment with venlafaxine or selective serotonin reuptake inhibitors. The British journal of psychiatry : the journal of mental science. 2001 Mar;178:234-41. PubMed PMID: 11230034. 2. Maneeton N, Maneeton B, Srisurapanont M, Martin SD. Quetiapine monotherapy in acute phase for major depressive disorder: a meta-analysis of randomized, placebo-controlled trials. BMC psychiatry. 2012;12:160. PubMed PMID: 23017200. Pubmed Central PMCID: 3549283.

Learning Objectives We recorded event-related potentials (ERPs) in patients with major depression before and after treatment with quetiapine (Seroquel®), to investigate:
1. The drug's effects on the amplitude of P300, and;
2. The relationship between P300 amplitude and the severity of depression.

Literature References
1. Thase ME, Entsuah AR, Rudolph RL. Remission rates during treatment with venlafaxine or selective serotonin reuptake inhibitors. The British journal of psychiatry : the journal of mental science. 2001 Mar;178:234-41. PubMed PMID: 11230034.
2. Maneeton N, Maneeton B, Srisurapanont M, Martin SD. Quetiapine monotherapy in acute phase for major depressive disorder: a meta-analysis of randomized, placebo-controlled trials. BMC psychiatry. 2012;12:160. PubMed PMID: 23017200. Pubmed Central PMCID: 3549283.

W12. ASSOCIATION OF OBESITY AND INFLAMMATORY MARKER LEVELS WITH TREATMENT OUTCOME FROM A STUDY OF ADJUNCTIVE L-METHYLFOLATE CALCIUM IN MDD PATIENTS WITH INADEQUATE RESPONSE TO SSRIS

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Abstract Background: Adjunctive treatment with l-methylfolate (Deplin®) significantly improved treatment outcomes in patients with major depressive disorder (MDD) and an inadequate response to antidepressants relative to placebo in an earlier trial. This exploratory

analysis evaluated baseline levels of specific cytokines, CRP, leptin, adiponectin, and body mass index (BMI) on l-methylfolate treatment response.

Methods: Adults with MDD and an inadequate response to an antidepressant were eligible. Patients were randomized according to the Sequential Parallel Comparison Design (SPCD) to Placebo-Placebo, Placebo-l-methylfolate (15 mg/day) or l-methylfolate (15 mg/day) during two 30-day phases. Treatment effect from both phases relative to placebo was estimated from baseline concentrations of individual biomarkers (IL-1α, -1β, IL-2, -4, -5, -6, -8, -10, -12 (p70), -13, and -17, TNFα, and IFNγ, leptin, adiponectin), BMI, and combinations. The effects of individual biomarkers above and below the median were assessed.

Results: Change in HAMD-28 in the total sample from baseline was greater with l-methylfolate vs. Placebo (pooled treatment effect -2.74, 95% CI -4.99, -0.48, p=0.017) overall and greater for those with baseline BMI ≥30 kg/m2 (pooled treatment effect -4.6, 95% CI -7.22, -1.98, p=0.001), but not BMI <30. Pooled mean differences for baseline levels of individual markers above median were significant (l-methylfolate vs. Placebo) for TNFα, IL-8, CRP, and leptin and for combinations of BMI ≥30 kg/m2 with elevated levels of TNFα, IL-6, IL-8, CRP, and leptin (pooled treatment effect -6.31 to -3.98 [p≤0.05]).

Conclusions: Inflammatory and obesity-related factors were associated with greater symptom improvement with l-methylfolate. Combinations of BMI ≥30 kg/m2 and specific factors predicted improved response to l-methylfolate in MDD patients with an inadequate antidepressant response.

Learning Objectives Participants will:
1. Better understand the relationships between inflammation, obesity, and depression.
2. Gain an improved appreciation of the effect of l-methylfolate and response to antidepressants in obese patients with systemic inflammation.

Literature References
1. Shelton R.C., Miller A.H, Eating ourselves to death (and despair): The contribution of adiposity and inflammation to depression. Progress in Neurobiology 2010, 91, 275-299.
2. Papakostas G.I., Shelton R.C., Zajecka J.M., Etemad B., Rickels K., Clain A., Baer L., Dalton E.D., Schoenfeld D., Pencina M., Meisner A., Bottiglieri T., Nelson E., Mischoulon D., Alpert J.E., Barbee J.G., Lydiard B., Zisook S., Fava M. L-methylfolate as adjunctive therapy for selective serotonin reuptake inhibitor-resistant major depressive disorder: results of two randomized, double-blind, parallel-sequential trials. Am J Psychiatry 2012, 169, 1267-1274.

W13. IMPLEMENTING PHARMACOGENETIC TESTING INTO A PSYCHIATRY RESIDENCY TRAINING CLINIC: A QUALITY IMPROVEMENT PROJECT

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Abstract Background: Genetic testing has made individualized treatment possible in the fields of immunology and oncology. In psychiatry, the STAR-D study found a high non-response rate to an initial antidepressant trial and a high rate of adverse side effects. It has been postulated that this may be explained by individual differences in drug metabolism due to variations in cytochrome p450 enzymes, suggesting that a more individualized approach to treatment may also be useful in psychiatry. Recently, several commercial genetic tests have become available to assess an individual's genotype for the major cytochrome p450 enzymes responsible for psychotropic drug metabolism including CYP2D6, CYP2C19, CYP2C9, CYP3A4, and CYP2B6. In addition, genetic tests are also available to assess folate metabolism, serotonin

transporter gene SLC6A4 to assess response time for SSRI's, and the HTR2A serotonin receptor Type 2A gene to predict adverse drug reactions with certain SSRIs. Despite the potential for pharmacogenetic testing to guide treatment decisions and optimize dosing, psychiatrists have been slow to implement this testing into their clinical practice, often citing unfamiliarity with available tests and cost as limiting factors. The purpose of this quality improvement project was to test the feasibility and utility of implementing pharmacogenetic testing into an outpatient psychiatry residency training clinic in a community based hospital.

Method: After researching several commercially available genetic testing options, we established an account with a FDA approved company that has been supported by clinical studies published in peer review journals*. Clinic patients were considered for testing due to treatment resistant depression, a history of multiple failed med trials, or sensitivity to multiple psychotropics. After obtaining informed consent for genetic testing, noninvasive DNA samples were obtained during a routine office visit. Pharmacogenetic test results were then shared with the patient at their next follow-up appointment. Data was collected over 6 months from November 2014 thru April 2015.

Results: To date, over 30 outpatients, ranging in age from 18-73 have completed pharmacogenetic testing. Insurance carriers have included Medicare, Medicaid and commercial private insurance. Over half of our outpatient psychiatry residents (60%) have implemented pharmacogenetic testing into their practice, compared to 25% of faculty attending physicians. Patients have consistently reported satisfaction with their test results, and clinicians have found the results useful in making clinical treatment decisions.

Conclusions: Pharmacogenetic testing may provide valuable information to the patient and clinician. Given the availability of testing and increased coverage by insurers, it may be feasible to implement pharmacogenetic testing into clinical practice. One important caveat to pharmacogenomics testing in our clinic is patient heterogeneity, as 95% of tests performed were on Caucasian patients. In addition, as this was an initial quality improvement project and not a clinical research project, it remains to be determined in future studies whether or not pharmacogenomic testing in our clinic will result in improved outcomes, i.e. faster recovery from depression, decreased adverse effects from medications, and/or reduced cost of treatment.

*DISCLAIMER: Drs. de Julio and Stevenson do not endorse any specific genetic assay nor do they have any financial involvement in any such assay.

Learning Objectives
1. Identify clinical indications, feasibility and limitations of outpatient pharmacogenetic testing.
2. Improve clinician familiar (both resident and attending physicians) with current pharmacogenetic tests and be able to interpret test results.

Literature References
1. Trivedi, M.H., Rush, A.J., Wisniewski, S.R., Nierenberg, A.A., Warden, D., Ritz, L., Norquist, G., Howland, R.H., Lebowitz, B., McGrath, P.J., Shores-Wilson, K., Biggs, M.M., Balasubramani, G.K., Fava, M.: Evaluation of Outcomes With Citalopram for Depression Using Measurement-Based Care in STAR*D: Implications for Clinical Practice. An J Psychiatry 2006; 163: 28-40.
2. Hall-Flavin, D.K., Winner, J.G., Allen, J.D., Carhart, J.M., Proctor, B., Snyder, K.A., Drews, M.S., Eisterhold, L.L., Geske, J., Mrazek, D.A.: Utility of integrated pharmacogenomic testing to support the treatment of major depressive disorder in a psychiatric outpatient setting. Pharmacogenetics and Genomics 2013; 231 (10): 535-548.

W14. IDENTIFYING PSYCHIATRIC DISORDERS IN YOUNG ADULTS IN PRIMARY AND SECONDARY CARE: HOW DO BIPOLAR DISORDERS DIFFER? RESULTS FROM A 10-YEAR STUDY

Catherine Duclos[1], Sybille Saury[2], Andrée Daigneault[3], Jean Paquet[1], Serge Beaulieu[3]

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Abstract Objectives: In a recent study evaluating the diagnostic agreement between primary care general practitioners (GPs) and secondary care psychiatrists, we showed that agreement between reason for referral and diagnosis of bipolar disorder (BD) was poor (0.35 95% CI [0.31, 0.38]), and that the frequency of BD was low, representing only 6.1% of all patients referred to secondary care. Given that BD is often accompanied with long diagnostic delays, and therefore often missed in young adults, the present study aimed at juxtaposing BD prevalence and diagnosis to that of other psychiatric disorders in young adults, in a secondary care setting.

Methods: The study was conducted at Hôpital du Sacré-Coeur de Montréal's shared-care evaluation program, which establishes/clarifies psychiatric diagnoses requested mainly from GPs. Reasons for referral and primary psychiatric diagnosis were compiled for all 18-25 year-old patients assessed from 1998 to 2010, from the overall pool of 10,492 patients. GP-psychiatrist agreement was established for BD, major depressive disorders (MDD), anxiety disorders (AD), personality disorders, and psychotic disorders, using Cohen's Kappa coefficient (K). Ks and their 95% confidence intervals (CI) were compared to identify differences between groups. Given that patients suffering from substance abuse were referred directly to specialized medical facilities, substance use disorders were not included in our study.

Results: Among the 18-25 year-old patients of our sample (n=1062, 39.7% men), the most common reasons for referral were MDD (n=454), AD (n=361), and personality disorders (N=323), while BD was suspected in only 87 of referrals. BD was less frequently diagnosed (5.4%) than the other disorders evaluated in this study. Personality disorders (32.6%) were by far the most frequent diagnosis, followed by AD (16.3%) and MDD (15.0%). Overall, AD, personality disorders, and psychotic disorders were associated with a significantly greater GP-psychiatrist agreement (AD: K=0.42, 95% CI [0.37,0.48]; personality disorders: K=0.72, 95% CI [0.69,0.76]; psychotic disorders: K=0.60, 95% CI [0.51,0.68]) than for BD (K=0.30, 95% CI [0.20,0.41]) and MDD (K=0.24 [0.19,0.29]). Whereas MDD had significantly lower K than all other disorders, including BD, personality disorders had a significantly higher K than all other disorders in the study.

Conclusions: Our study showed that referrals to a secondary care psychiatrist for suspicion of BD are much less frequent than referrals for suspicion of personality disorders, AD, or MDD. Personality disorders were much more frequently diagnosed than any other disorder, which could partly be explained by the young age of our sample and the higher proportion of women (60.3%). Our study also suggests that among 18-25 year-olds, GP-psychiatrist agreement is poor for BD and MDD. Given that a depressive episode is present in both BD and MDD, and is the most common reason for referral in our study, these results may suggest that GP's and psychiatrist don't share a common agreement on what constitutes a depressive condition. Moreover, young adults may have more non-specific symptoms given that their disorder is at its onset, therefore hindering the diagnostic process.

Keywords: bipolar disorders, anxiety, depression, personality disorders, diagnosis, secondary care

Learning Objectives

1. To better understand the diagnostic agreement between primary care general practitioners (GPs) and secondary care psychiatrists for young adults suffering of bipolar disorders.

Literature References

1. Daigneault A, Duclos C, Saury S, Paquet J, Dumont D, Beaulieu S. Diagnosis of bipolar disorder in primary and secondary care: What have we learned over a 10-year period? Journal of affective disorders. 2014;174c:225-232.

W15. LURASIDONE IN THE LONG-TERM TREATMENT OF PATIENTS WITH BIPOLAR I DISORDER: RESPONDER AND REMITTER STATUS DURING A 24-WEEK OPEN-LABEL EXTENSION STUDY

Terence A. Ketter[1], Joyce Tsai[2], Robert Silva[2], Hans Kroger[2], Josephine Cucchiaro[2], Antony Loebel[2]

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Abstract Introduction: Lurasidone has demonstrated efficacy in the short-term treatment of bipolar depression.1-3 The aim of the current analysis was to evaluate responder status after 6 months of extension treatment in patients completing an initial short-term study.

Methods: Patients with bipolar I depression who completed 6 weeks of double-blind, placebo-controlled treatment with either lurasidone monotherapy (1 study) or adjunctive therapy with lithium or valproate (2 studies), were treated for 6 months with flexible doses of lurasidone, 20-120 mg/d, in an open-label extension study (N=813; monotherapy, 38.9%; adjunctive therapy, 61.1%). Post-hoc observed case analyses were performed to determine the proportion of patients exhibiting a change, from open-label baseline to Month 6, in their depression status among one of 4 outcome categories: non-responder (<50% improvement), responder (≥50% improvement), remitter (Montgomery-Asberg Depression Rating Scale [MADRS] <12), and relapse (MADRS ≥20 for 2 consecutive assessments or discontinuation due to a depression-related adverse event or due to insufficient clinical response).

Results: A total of 68.4% of patients completed the extension study. At extension baseline, the proportion of patients who met a priori responder and remitter criteria, respectively, were similar among patients initially randomized to monotherapy (56.3% and 44.9%) and adjunctive therapy (51.1% and 45.7%). Among extension baseline responders, a low proportion of patients met relapse criteria during 6 months of treatment among patients initially randomized to monotherapy and adjunctive therapy (10.2% and 10.2%, respectively); while the proportion of responders and remitters increased on both monotherapy (90.3% and 83.7%, respectively) and adjunctive therapy (83.2% and 77.2%, respectively). Among patients who were non-responders at extension baseline, a majority had converted to responder status at the end of 6 months in both the monotherapy (83.0%) and adjunctive therapy (73.0%) groups. Among responders at extension baseline in the monotherapy (56.3%) or adjunctive therapy (51.1%) groups, the vast majority were responders at Month 6 in both the monotherapy (96.1%) and adjunctive therapy (91.4%) groups. Among remitters at extension baseline, the vast majority were remitters at Month 6 in both the monotherapy (95.1%) and adjunctive therapy (91.0%) groups. In addition, among responders at extension baseline (who did not meet remitter criteria), 79.2% in the monotherapy group and 66.7% in the adjunctive therapy group showed sufficient improvement at Month 6 to meet remitter criteria.

Conclusions: Lurasidone appears to be an effective long-term treatment for patients with bipolar depression, with low rates of relapse after 6 months of treatment. The majority of

patients who did not meet responder criteria at the start of the extension study improved and became responders by 6 months, and the majority of baseline responders achieved remission by 6 months.

ClinicalTrials.gov Identifiers: NCT00868959

Learning Objectives
1. After completion of this presentation, the reader will have a better understanding of the efficacy of lurasidone in the long-term management of bipolar depression.
2. After completion of this presentation, the reader will have a better understanding of the likelihood that additional treatment with lurasidone will convert acute responders to remission status.

Literature References
1. Loebel A 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.
2. Loebel A 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.

W16. CATEGORICAL IMPROVEMENT ACROSS MANIA SYMPTOMS: POOLED ANALYSES OF CARIPRAZINE PHASE II/III TRIALS

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Abstract Introduction: Bipolar mania is characterized by a wide spectrum of symptoms. Antipsychotics are a first-line treatment option for bipolar mania, although many patients fail to achieve full remission with currently available therapies. Cariprazine, a dopamine D3/D2 receptor partial agonist with preferential binding to D3 receptors, has demonstrated efficacy in 3 positive Phase II/III clinical trials in patients with manic or mixed episodes associated with bipolar I disorder. Previous analyses showed that cariprazine was associated with significantly greater mean changes versus placebo on all YMRS single items. Evaluating mean change from baseline in a group of patients, however, may not represent clinically meaningful improvements in individual symptoms. This pooled post hoc analysis assessed clinically relevant symptom improvement in individual YMRS items by evaluating the percent of patients that shifted from a more severe symptom category at baseline to a less severe category at end of study.

Methods: Pooled 3-week data (N=1037) from 3 double-blind, randomized, placebo-controlled trials (NCT00488618, NCT01058096, NCT01058668) were analyzed. All cariprazine doses (3-12 mg/d) were pooled. For categorical shift analyses, the percentage of patients that shifted from at least moderate severity (YMRS item score ≥ 2 [items scored 0-4] and ≥ 4 [items scored 0-8]) at baseline to mild/no symptoms (score <2 [0-4 items] and <4 [0-8 items]) at Week 3 were determined for all 11 YMRS items. Additional analyses included the percentage of patients that shifted from at least moderate to mild/no symptoms concurrently on all 4 core YMRS symptoms (irritability, speech, content, and disruptive-aggressive behavior) and the percentage of patients with mild/no symptomatology at endpoint concurrently on all 11 items.

Results: The percentage of patients that shifted from moderate or worse severity at baseline to mild/no symptoms at Week 3 was significantly higher for cariprazine versus placebo on each of the YMRS single items. Odds ratios (OR) ranged from 1.6 (increased motor activity-energy)

to 2.7 (irritability); all P<.001. Category shifts on all 4 YMRS core items concurrently were observed in a significantly greater percentage of cariprazine- (50.5%) versus placebo-treated (29.1%) patients (OR=2.43; P=.0002). The percentage of patients with mild/no symptoms on all 11 YMRS items at endpoint was also significantly higher in the cariprazine group (22.5%) compared with the placebo group (13.5%) (OR=1.85; P=.0004).

Conclusions: In this novel post hoc YMRS category shift analysis, a significantly greater proportion of cariprazine-treated patients compared with placebo-treated patients showed clinically meaningful categorical improvements on all 11 YMRS symptom domains. These results suggest that cariprazine is associated with clinically meaningful improvements across a broad spectrum of mania symptoms in patients with bipolar disorder.

Learning Objectives
1. At the conclusion of this session, participants should understand the use of a novel YMRS categorical shift analysis to demonstrate clinically meaningful improvement in symptoms of mania associated with bipolar disorder.
2. At the conclusion of this session, participants should be able to evaluate the efficacy of cariprazine in improving mania symptoms by assessing shifts from more to less severe YMRS categories.

Literature References
1. Durgam S, Starace A, Li D, Migliore R, Ruth A, Nemeth G, Laszlovszky I: The efficacy and tolerability of cariprazine in acute mania associated with bipolar I disorder: a phase II trial. Bipolar Disord 2015;17:63-75.
2. Sachs GS, Greenberg WM, Starace A, Lu K, Ruth A, Laszlovszky I, Nemeth G, Durgam S: Cariprazine in the treatment of acute mania in bipolar I disorder: A double-blind, placebo-controlled, Phase III trial. Journal Affective Disord 2014;174C:296-302.

W17. EFFECT OF LURASIDONE ON METABOLIC PARAMETERS IN PATIENTS WITH BIPOLAR DEPRESSION

John W. Newcomer[1], Joyce Tsai[2], Andrei Pikalov[2], Hans Kroger[2], Josephine Cucchiaro[2], Antony Loebel[2]

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Abstract Introduction: Patients with bipolar disorder are at a higher risk of developing metabolic syndrome compared with untreated subjects. The aim of the current analysis was to evaluate the extent to which treatment with lurasidone was associated with clinically relevant shifts in body mass index (BMI) and metabolic laboratory values in patients with bipolar depression.

Methods: Data were analyzed from 3 studies in patients with bipolar depression who were randomized to 6 weeks of double-blind, placebo-controlled treatment with lurasidone (20-120 mg/d), either as monotherapy (one study, N=499), or adjunctive therapy with lithium (Li) or valproate (VPA; two studies, combined N=694). Patients completing these three 6-week studies continued to receive 6 months of treatment with lurasidone 20-120 mg/d in an open-label extension study (N=813). Normal, borderline, or abnormal BMI or laboratory values, respectively, were defined as follows for BMI (18.5- 25 vs 25- 30 vs ≥30 kg/m2), cholesterol (<170 vs 170 to <200 vs ≥200 mg/dL), triglycerides (<90 vs 90 to <130 vs ≥130 mg/dL), LDL (<110 vs 110 to <130 vs ≥130 mg/dL), glucose (<100 vs 100 to <126 vs ≥126 mg/dL), and HbA1c (<5.7% vs 5.7% to 6.4% vs >6.4%). The proportions of patients who shifted between

normal and borderline-or-abnormal values were analyzed, from double-blind baseline to Week 6, and from double-blind baseline to Month 6 of the extension study.

Results: At Week 6 in the monotherapy study, the proportion of patients treated with lurasidone vs placebo, respectively, who shifted from normal-to-borderline/abnormal were as follows for BMI (7.5% vs. 4.9%), cholesterol (25.4% vs 15.2%), triglycerides (30.4% vs 38.6%), LDL (21.0% vs 25.0%), and glucose (20.6% vs 17.4%). The proportion of patients treated with lurasidone vs placebo, respectively, who shifted from borderline/abnormal-to-normal were as follows for BMI (2.2% vs. 1.1%), cholesterol (13.3% vs 9.3%), triglycerides (18.1% vs 20.0%), LDL (16.9% vs 16.9%), and glucose (48.3% vs 39.4%). The shift pattern was similar among patients treated in the adjunctive therapy study. At Month 6 of the extension study, among patients initially randomized to monotherapy, the proportion of patients on lurasidone who shifted from normal-to-borderline/abnormal vs borderline/abnormal-to-normal, respectively, were as follows for BMI (12.5% vs. 1.5%), cholesterol (22.4% vs 8.1%), triglycerides (33.0% vs 19.7%), LDL (30.0% vs 23.2%), and HbA1c (16.1% vs 28.1%). At Month 6 of the extension study, among patients initially randomized to adjunctive therapy, the proportion of patients on lurasidone who shifted from normal-to-borderline/abnormal vs borderline/abnormal-to-normal, respectively, were as follows for BMI (22.2% vs. 4.5%), cholesterol (35.0% vs 14.4%), triglycerides (45.9% vs 15.3%), LDL (32.2% vs 21.1%), and HbA1c (12.6% vs 41.0%).

Conclusions: These data add to the substantial and growing body of information regarding the metabolic safety of lurasidone.

Clinicaltrials.gov identifier: NCT00868699, NCT00868452, NCT00868959.

Sponsored by Sunovion Pharmaceuticals Inc.

Learning Objectives
1. After completion of this presentation, the reader will have a better understanding of the prevalence of abnormal metabolic parameters in patients with a diagnosis of bipolar depression.
2. After completion of this presentation, the reader will have a better understanding of the effect of long-term treatment with lurasidone on weight and metabolic parameters.

Literature References
1. Loebel A 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.
2. Executive summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III).. JAMA. 2001;285:2486-97.

W18. PHARMACOLOGICAL TREATMENT OF DEPRESSION IN CHILDREN AND ADOLESCENTS: SWITCHING VS. AUGMENTING

Zainab Zia[1], Zohra Chahal[1], Taryn Mayes[1], Catherine Karni[1], Graham Emslie[1]
[1]UT Southwestern Dallas

Abstract Background: Major depressive disorder (MDD) is a serious and chronic illness among youth. While several antidepressants have demonstrated efficacy in this population, remission rates remain low2. The Sequenced Treatment Alternatives to Relieve Depression (STAR *D) study in adults demonstrated that 1 in 3 depressed patients who were not in remission using an antidepressant responded to medication augmentation, and 1 in 4 responded to switching antidepressants. No study has examined clinical characteristics or outcomes of switching vs. augmentation in resistant depression in youth.

Methods: Data are based on patients evaluated in the Outpatient Depression Clinic of Children's Health. At each visit, psychiatrists complete the Quick Inventory of Depression Symptoms for Adolescents (QIDS-A), and medication management is based on the Children's Medication Algorithm Project (CMAP)1. Treatment decisions and visit frequency are based on patient need. Between July 2012 and December 2014, 226 patients entered the clinic with primary diagnosis of depression; 192 patients had QIDS-A ≥11 at baseline and had at least 2 visits.

Results: Most patients in this clinical sample were female (70%) and non-Hispanic Caucasian (57.3%), with a mean age of 14.0 ±2.2. Over half (55%) were not on any antidepressant medication at the initial evaluation.

One-third of the sample either switched antidepressants or were augmented during their treatment course (20% switch, 17% augmentation). There were no demographic differences between those who remained on the same treatment vs. those who were switched/augmented. Youth who were switched/augmented were more likely to already be on an antidepressant at the first visit (55.6% vs. 38.6%; p<.05), and had more severe QIDS-A depression scores (16.0 ±3.0 vs. 15.0 ±3.2; p<.05). The length of depressive episode was also approximately 1 month longer, although this was not statistically significant. The presentation will also examine differences in characteristics of switching vs. augmenting both at baseline and at the time of treatment change, and will explore outcomes for these strategies.

Conclusions: In this clinical sample one third either switched antidepressant or augmented with another medication. Youth who were switched or augmented had slightly more severe depression and were more likely to already be on an antidepressant than those who remained on the initial medication.

Learning Objectives
1. To utilize data from a specialty depression clinic to identify characteristics of treatment non-response in youth treated for depression.
2. To examine differences in clinical characteristics in non-responders who had medication augmentation vs. switch.

Literature References
1. Texas Consensus Conference Panel on Medication Treatment of Childhood Major Depressive Disorder. Texas Children's Medication Algorithm Project: update from Texas Consensus Conference Panel on Medication Treatment of Childhood Major Depressive Disorder. Hughes CW, Emslie GJ, Crismon ML, Posner K, Birmaher B, Ryan N, Jensen P, Curry J, Vitiello B, Lopez M, Shon SP, Pliszka SR, Trivedi MH; Journal of the American Academy of Child & Adolescent Psychiatry 2007, 46:6, 667-686.
2. Remission and residual symptoms after short-term treatment in (TADS). Kennard BD, Silva S, Vitiello B, et al. J Am Acad Child Adolesc Psychiatry 2006, 45:12, 1404-1411.
3. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. Rush AJ, Trivedi MH, et al. Am J Psychiatry 2006, 163:11, 1905-1917.

W19. WHAT CAN DATA MONITORING TELL US ABOUT WHERE TO FOCUS EFFORTS TO REMEDIATE PROBLEMATIC SCORING OF THE POSITIVE AND NEGATIVE SYNDROME SCALE?

Nina Engelhardt[1], Kristy Wolanski[1], Francisco Burger[1], Matt Masotti[1], Christian Yavorsky[1], Guillermo DiClemente[1]

[1]CRONOS

Abstract Objective: To evaluate how the frequency and distribution of recognized categories of scoring inconsistencies identify where to focus rater remediation efforts.

Background: Many pharmaceutical companies are supporting the use of prospective data monitoring (DM) of outcome measures in CNS trials. Such programs identify inconsistencies and errors in scoring that are believed to affect the reliability and accuracy of ratings.' Despite widespread use of DM, little has been published that characterizes the frequency of errors during the course of the trial and their distribution.

Methods: DM data was sampled from a large global schizophrenia trial consisting of PANSS assessments reviewed for scoring inconsistencies. We found that most of the errors in PANSS assessments fell into the following categories: Low Variability, Clinically Improbable Score Pattern, Inconsistent Item Relationships, and Large Score Change. Assessments were categorized as having low variability if a large percentage of PANSS items were scored identically for the same subject across visits or for multiple subjects. Remaining categories included Clinically Improbable Score Pattern (the tendency to consistently assign the same score to several or all items within a scale), Inconsistent Item Relationships (lack of association among items within a scale or across scales that measure similar constructs), Large Score Change (at least a 40% decrease from screening in PANSS total score at specific study visits) and Other. Some scoring inconsistencies reflected sufficient risk to data quality to necessitate a phone call with the rater to determine scoring rationale and to remediate where appropriate. The sample consisted of 10 countries, 68 raters, and 150 calls which addressed a total of 227 unique PANSS assessments.

Results: The most frequent scoring problem was Inconsistent Item Relationships, which represented 38% of the sample. Low Variability, Clinically Improbable Score Pattern, Large Change Score, and Other were 31%, 20%, 6%, and 7% of the sample, respectively. The distribution of scoring inconsistencies was different among and within the 10 countries in our sample.

Conclusion: The distribution of categories of PANSS scoring inconsistencies in a schizophrenia trial illustrate that certain problematic scoring behaviors occur more frequently than others and may also be less amenable to change. Inconsistent Item Relationships was the most frequent scoring inconsistency and the least susceptible to change, as represented by number of calls per rater. Large Change Score, a relatively infrequent problem, was associated with the fewest number of calls per rater, suggesting this problem was more easily remedied. More complex problems, such as Inconsistent Item Relationships and Clinically Improbable Score Pattern, may require adjunct rater tools and more frequent calls. Comparison of problematic scoring categories from other researchers' PANSS data[2,3] may enable refinement and standardization of these categories. Future efforts to characterize the frequency and distribution of scoring inconsistencies in larger samples may provide a rationale for targeting certain rater behaviors both prior to and during study implementation.

Learning Objectives
1. Identify broad categories of scoring inconsistencies in the PANSS that may pose a threat to data quality in randomized controlled clinical drug trials.
2. Identify which categories of scoring inconsistencies may require greater input to remediate.

Literature References
1. Khan, A, Yavorsky, WC, Liechti, S, DiClemente, G, Rothman, B, Opler, M, DeFries A, Jovic,S: Assessing the sources of unreliability (rater, subject, time-point) in a failed clinical trial using items of the Positive and Negative Syndrome Scale (PANSS) J Clin Psychopharmacol 2013; 33:109-117

2. Daniel, DG, Kott, A: Risk based data quality monitoring utilizing data analytics and recorded PANSS Interviews in Global Schizophrenia Trials Poster presented at the 10th Anniversary International Society of Clinical Trial Methodology (ISCTM) Meeting, Washington,D.C., 18-20 February 2014

3. Use of algorithms/flags to identify clinical inconsistency 10th Anniversary International Society of Clinical Trial Methodology (ISCTM) Working Group, Washington, D.C., 18-20 February 2014

W20. PSYCHOMETRIC PROPERTIES OF THE DYNAMIC SOCIAL COGNITION BATTERY (DSCB) IN PATIENTS WITH SEVERE MENTAL ILLNESS

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Abstract Background: Social cognition has been broadly studied in autism spectrum disorders, and include impairments in: (a) affect perception; (b) social perception; (c) attributional style; and (d) Theory of Mind (ToM). Social cognition as a target for future pharmacotherapy has the potential to provide meaningful functional improvements in schizophrenia (Sz) and affective disorders, and has become a high priority for developing future psychosocial and pharmacological treatments. Studies examining processes of social cognition have traditionally relied upon the use of static (photographic or written) stimuli in order to assess facial displays of emotion and ToM which are dynamic by nature. There is a growing evidence of specialized brain systems that are preferentially activated by "biological motion" stimuli (including moving faces) giving further support to the need for dynamic stimuli. A comprehensive battery using dynamic video images may be a better predictor and more sensitive to change of social cognition in research trials.

Methods: A battery of video images was developed based on constructs from the Social Cognition Psychometric Evaluation (SCOPE) study and focused on emotion perception, attributional style and theory of mind (ToM). The battery was administered to 84 subjects with schizophrenia who had a baseline PANSS score of ≥ 60 and 41 subjects without schizophrenia or related disorders were enrolled. Construct, divergent, and convergent validity with the FEIT, ER- 40, MSCEIT. Confirmatory factor analysis was employed to examine model- fit for each scale using multiple indices including: chi- square index, comparative- fit index (CFI), goodness- of- fit index (GFI), and the root mean square error of approximation (RMSEA). Reliability properties were also examined (ICC and Cronbach's alpha).

Results: The reliability and factorial validity of each scale is supported: fit indices suggest each model to be an adequate- to- exact fit to the data; internal consistency was acceptable- to- good ($\alpha = 0.81$); rank order repeatability was strong (ICC = 0.82). Convergent and concurrent validity with FEIT, ER- 40, and MSCEIT was > 0.67. Accuracy rates for emotion perception and ToM were higher for the DSCB than for the FEIT, ER- 40 and MSCEIT. Social cognition was also a better predictor of instrumental functioning as measured by the UPSA-Brief, and social functioning as measured by the PSP.

Conclusions: Results support the reliability validity of the DSCB social cognitive scales relating to patients with schizophrenia. As such, the developed scale have utility for identifying potential social cognitive correlates of schizophrenia behavior, mediators of behavior change and validity testing of theoretical models based on social cognition in the population.

Learning Objectives
1. The audience will be able to understand the differences between static scales currently being used to measure social cognition and dynamic scales.

2. The audience will be presented with reliability, validity, item functioning data for a novel scale encompassing four RAND areas of social cognition (Emotion Perception, Emotion Identification, Theory of Mind and Attributional Style).

Literature References

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W21. DESIGN OF THE SCHIZOPHRENIA DISEASE RECOVERY EVALUATION AND MODIFICATION (DREAM) STUDY

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Abstract   Purpose: To describe the unique study design and key innovations of the Disease Recovery Evaluation and Modification (DREaM) study.

Content: For patients with recent-onset schizophrenia, recurrent relapses and persistent cognitive deficits can contribute to clinical and functional deterioration. Therefore, providing adequate treatment within the first 5 years following the onset of symptoms represents a critical period in the pathophysiology of the disease. Long-acting injectable (LAI) antipsychotics may be an effective treatment option for recently diagnosed patients with schizophrenia because they provide certain knowledge of adherence. However, few comparative effectiveness studies between LAIs and oral antipsychotics (OAs) in this population have been completed. The objective of the DREaM study is to compare the efficacy of paliperidone palmitate (PP) once-monthly and once-every-3-month (PP3M) LAI formulations vs OAs in disease progression and the potential for disease modification in patients with recent-onset schizophrenia. Data supporting disease modification will be based on a totality-of-evidence approach that evaluates the course and pathophysiology of the illness with measures of symptoms, functioning, and biological change.

Methodology: The DREaM study is a prospective, matched-control, randomized, open-label, flexible-dose study in subjects with recent-onset schizophrenia or schizophreniform disorder that will compare disease progression and disease modification following treatment with PP or OAs. The DREaM study includes 3 treatment phases: 2-month open-label run-in (Part 1), 9-month disease progression (Part 2), and 9-month extended disease progression/modification (Part 3). After completing run-in with paliperidone extended-release (or other OA) treatment, patients will be randomized in a 1:2 ratio to flexible-dose PP or OAs, respectively. After 9 months, the OA group will be further randomized 1:1 to PP or continued on flexible-dose OAs. Changes in cognition, patient functioning, and volume of brain intracortical myelin will all be assessed as measures of disease progression (Parts 2 and 3) and modification (Part 3). The primary endpoint to establish evidence of disease progression will be time to first treatment failure. Treatment failure will be defined as psychiatric hospitalization due to worsening symptoms; deliberate self-injury, suicide ideation, or violent behavior; new arrest/incarceration; discontinuation of antipsychotic treatment due to inadequate efficacy or safety; treatment supplementation with another antipsychotic; or increase in psychiatric services. Approximately 250 subjects will be randomly assigned for this study. Analysis will require distinct approaches to each of the major endpoints related to symptoms, functioning, and biological changes for establishing evidence of disease progression and modification.

Importance: Key innovations of the DREaM study include randomized matched-control of patients with a randomized delayed-start design. It is anticipated that study results based on these design parameters will permit identification of important insights into disease progression and potential disease modification in recent-onset schizophrenia. The study will evaluate whether LAI treatment with PP can slow disease progression and possibly modify disease course compared to OAs by tracking changes in cognition, functioning, and brain imaging.

Learning Objectives
1. To educate participants on the study design and key innovations of the DREaM study.
2. To evaluate the role of long-acting injectable antipsychotics compared to oral antipsychotics in preventing treatment failure and slowing disease progression in patients with recent-onset schizophrenia

Literature References
1. Fu, D.J., Bossie, C.A., Sliwa, J.K., Ma, Y.W., Alphs. (2014). L. Paliperidone palmitate versus oral risperidone and risperidone long-acting injection in patients with recently diagnosed schizophrenia: a tolerability and efficacy comparison. Int. Clin. Psychopharmacol. 29 (1), 45-55.
2. Bartzokis. G., Lu, P.H., Raven, E.P., et al. (2012). Impact on intracortical myelination trajectory of long acting injection versus oral risperidone in first-episode schizophrenia. Schizophr. Res. 140 (1-3), 122-128.

W22. A NOVEL, DISEASE-SPECIFIC SCORING ALGORITHM FOR THE CLINICAL GLOBAL IMPRESSION SCALE (CGI) IN DOWN SYNDROME

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Abstract Background: The Clinical Global Impression Scale (CGI) has been widely used as an outcome measure in pharmacological clinical trials for psychiatric disorders, including affective illnesses, schizophrenia and related disorders. Despite its widespread use, the CGI receives criticism due to its ambiguous scoring criteria, unstable reliability, and because CGI ratings may be too general to provide meaningful information about patient status or treatment response. The CGI also has a fixed administration across disparate disorders, negatively affecting its psychometric properties regard to key features of a particular condition. This is especially problematic in studies of neurodevelopmental disorders – such as Down syndrome (DS) – that violate key assumptions underlying the CGI (namely, that the disease under examination is potentially reversible—reflecting normal behaviors) and to account for the high variability in observed impairments. In order to clarify what the rating actually means for these populations, the CGI requires a higher level of standardization with regard to scoring methods and the ways in which the domains for assessment and anchors are conceptualized. To date no such scoring method exists for Down syndrome. The aim of this work was to examine the psychometric properties of a novel standardized CGI scoring system for use in phase 2/3 clinical trials with DS populations.

Methods: Primary impairment in functional and adaptive behaviors in Down syndrome includes communication, independence, appropriate socialization behavior and difficulties with executive function. Therefore "speech", "activities of daily living", "social functioning" and "non-compliance" were proposed as anchors for assessment in determining a global score of severity and improvement or deterioration. The CGI was added to a standard battery of outcome measures in a non-drug, longitudinal, multi-center, multi-national study evaluating the suitability of neurocognitive tests and functioning scales for the measurement of cognitive

and functioning changes in individuals with Down Syndrome. The duration of the study for each individual was between 24 and 27 weeks. Tests included CGI, ADAMS at Screening, CELF-2, CELF-4, BRIEF-P and VABS-II. Descriptive and comparative data analyses were performed.

Results: A total of 90 subjects were enrolled with a mean age of 18.23 years (SD = 23.27; Range = 12 – 30 years). There were 82 CGI-S and CGI-I ratings completed at screening. The CGI-S and CGI-I scores at W4 and W24 were correlated (r = 0.402 and r = 0.400, respectively), and the indirect improvement measures obtained from their differences were highly correlated with the direct CGI-I scores (r = 0.603). At screening, the CGI-S Communication/Speech, Social Functioning and Appropriateness, and Stubborn and non-compliant domains correlated significantly and positively with the ADAMS Total Social avoidance score (r = 0.400, 0.272 and 0.294, respectively) supporting construct validity. Similarly, the CELF Expressive Score significantly and negatively correlated with the CGI-S Communication/Speech domain (r = - 0.469, p = 0.037). The CGI-I global score correlated significantly and negatively with the VABS-II at Day 1, W4 and W24.

Conclusions: The CGI developed for Down Syndrome (DS) is a valid clinical outcome measure suitable for studies of DS. It offers a number of advantages including its established utility in clinical research, sensitivity to change, utility across diagnostic groupings, and consistency with neurocognitive measures in a DS population.

Learning Objectives
1. Measurement
2. Clinical Trials

Literature References
1. Raykov T. Evaluation of scale reliability for unidimensional measures using latent variable modeling. Measurement and Evaluation in Counseling and Development. 2009, 42,223–232.
2. Hollander et al (2010). Divalproex Sodium vs Placebo for the Treatment of Irritability in Children and Adolescents with Autism Spectrum Disorders. Neuropsychopharmacology, 35:990-998.

W23. REGIONAL DISTRIBUTION OF SCORING ERRORS IN RATING THE CLINICAL GLOBAL IMPRESSION SCALE IN GLOBAL SCHIZOPHRENIA CLINICAL TRIALS

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Abstract Introduction: The Clinical Global Impression Scale (Guy, 1976) is used to assess global illness severity in a variety of disorders. CGI ratings are vulnerable to error because of their subjectivity and the requirement that the current rating period be compared to an earlier point in time (CGI-I and CGI-C). In schizophrenia trials the problem is compounded by the multidimensional nature of schizophrenia symptoms. We have previously demonstrated that error rates in rating in clinical trials may be reduced in association with monitoring and intervention. (1) We hypothesized that cultural variation in perceptions of which schizophrenic symptoms are most globally important would lead to geographic differences in disparities between the CGI and PANSS and potentially between the CGI-S and CGI-I.

Method: Utilizing centralized, blinded data quality monitoring of CGI assessments in ten international schizophrenia clinical trials (79,500 visits), pre-defined patterns were utilized to detect inconsistencies in the relationship between the CGI-I and changes from baseline in the PANSS total score and CGI-S scores, respectively. Sites with unusually high error rates were

subsequently subjected to more intensive scrutiny. Chi-2 analysis was used to compare error rates by country and region.

Results: For inconsistencies between the CGI and PANSS the overall association of geographic region and error rate was statistically significant (chi-2 (4) = 345.6, p<0.001). In ascending order the proportion of visits in which pre-defined error criteria for inconsistencies were flagged were Eastern Europe (.057, n=15,853 visits), North America (.087, n=10,676 visits), Asia (.097, n=7,085 visits), South America (.124, n= 5,711 visits), Western Europe (.129, n=5,711 visits).

For inconsistencies between the CGI-S and CGI-I the overall association of geographic region and error rate was statistically significant (chi-2 (4) = 261.3, p<0.001). In ascending order the proportion of visits in which pre-defined error criteria for inconsistencies between the CGI-S and CGI-I were flagged were Eastern Europe (.038, n=22,339 visits), South America (.057, n= 9,454 visits), North America (.059, n=15,025 visits), Asia (.071, n=11,728 visits), Western Europe (.088, n=3,761 visits).

Discussion: Errors in scoring the CGI are relatively common and vary in frequency by geographical region. Discrepancies between the CGI and PANSS were more common than discrepancies between the CGI-S and CGI-I. The regional differences seen in discrepancies between the total PANSS score and CGI-S may reflect cultural differences in perceptions of which symptomatic or functional domains are most troubling.

Learning Objectives
1. Understand errors made in scoring the CGI in schizophrenia clinical trials.
2. Understand geographic and cultural influences on scoring errors in schizophrenia clinical trials.

Literature References
1. Daniel, DG, Busner J, McNamara C: Ongoing Monitoring and Feedback Decreases Error Rates and Improves Internal Consistency of PANSS Ratings in an International Clinical Trial. Poster presentation, International Society Clinical Trials Methodology, Autumn Conference, Baltimore, MD, Oct 13-14, 2010.
2. Daniel, DG and Kott, A: How Do US Clinical Research Sites Compare with Rest of World in Interview and Ratings Quality? Poster presentation at 166th Annual Meeting of the American Psychiatric Association, May 18-22, 2013, San Francisco, CA.

W24. THE FIRST STUDY: FAMILY INTERVENTION IN RECENTLY DIAGNOSED PATIENTS WITH SCHIZOPHRENIA

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Abstract Purpose: To evaluate the impact of a psychosocial education and skills training program provided to caregivers of patients with schizophrenia.

Content: The burden of schizophrenia is high, not only for patients but for caregivers. When integrated into the treatment plan, family education and training has been shown to have a positive impact on individuals with psychosis and their caregivers. Caregiver skill training and psychoeducation can make caregivers more effective, active participants in patient recovery, thereby enhancing chances of better outcomes.

Methodology: Family Intervention in Recent onset Schizophrenia Treatment (FIRST) is a randomized, open-label, parallel-group study designed to evaluate the overall effect of caregiver psychoeducation and skills training on the number of patient treatment failures (ie,

psychiatric hospitalization, psychiatric emergency department or crisis center visit, mobile crisis unit intervention, arrest/incarceration, or suicide or suicide attempt) compared to usual care in patients diagnosed with schizophrenia, schizoaffective disorder, or schizophreniform disorder over a 12-month period. The FIRST study includes a professional, clinician-provided service that delivers individualized psychoeducation and skills training to caregivers via interactive, real-time technology. Approximately 300 patients aged 18 to 35 years with a diagnosis of schizophrenia, schizoaffective disorder, and schizophreniform disorder and their caregivers (grouped in patient/caregiver pairings) will be randomly assigned to one of 2 treatment groups: 1) caregivers receiving psychoeducation and skills training and 2) caregivers receiving routine psychosocial support (available at the research sites as part of the usual psychosocial support). Patients in both treatment groups will receive routine clinical treatment as directed by the treating physician. The randomization will be stratified by the type of antipsychotic treatment patients are receiving at screening (paliperidone palmitate [PP] or oral antipsychotic treatment [OAT]). Enrollment will target approximately 50% of patients (n=150) who are currently receiving PP at screening. It will enable exploratory analyses to assess the effect of psychoeducation and skills training in patients receiving PP or OAT. Patient-caregiver pairs will be followed for 12 months following baseline assessments.

Hypotheses: The primary hypothesis is that when caregivers receive psychoeducation and skills training, patients with schizophrenia, schizoaffective disorder, and schizophreniform disorder will have fewer treatment failures compared with patients whose caregivers receive no additional training. The secondary hypothesis focuses on the role of psychoeducation and skills training in reducing caregiver burden and distress.

Importance: This study will assist in educating psychiatrists on the role of psychoeducation and skills training provided to families and caregivers who support patients recently diagnosed with schizophrenia, schizoaffective disorder, and schizophreniform disorder.

Learning Objectives
1. Describe the role of psychoeducation and skills training for families and caregivers of patients recently diagnosed with schizophrenia who are being administered antipsychotics.
2. Identify how a caregiver education and training program can help improve outcomes of patients who have been recently diagnosed with schizophrenia, schizoaffective disorder, and schizophreniform disorder.

Literature References
1. Fu, D.J., Bossie, C.A., Sliwa, J.K., Ma, Y.W., Alphs, L. (2014). Paliperidone palmitate versus oral risperidone and risperidone long-acting injection in patients with recently diagnosed schizophrenia: a tolerability and efficacy comparison. Int. Clin. Psychopharmacol. 29 (1), 45–55.
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W25. WHO IS PARTICIPATING IN CLINICAL TRIALS?

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Abstract Trust and the incidence of volunteerism in clinical research are declining. "Over the past 25 years, as the volume of clinical research has grown dramatically, we have as a

community failed to engage the public and prospective volunteers in the process."(Getz, 2014). People volunteer to participate in clinical trials for different reasons. Some volunteer because they want to help advance medical knowledge. Others have tried all available treatments for their condition without success. In a 2000 Harris Poll of cancer clinical trial participants, 76 percent of the respondents said they participated because they believed that the trial offered the best quality of care for their disease. Helping other people and receiving more and better attention for their own specific disease were other reasons cited. People should not, however, be tempted to enroll in a clinical trial simply because a potential treatment is being offered free during a study, or because of the promise of money, says David Banks, an FDA pharmacist. However, healthcare cost and employment issues are driving patients into seeking alternative healthcare possibilities. More people are unable to meet deductibles of their insurance plans or drugs are not being covered by their plans even if they do have insurance coverage. In addition, there continue to be people without insurance, such as contract workers and independent contractors, the socioeconomic disadvantaged, those between or jobs, and there are people with a host of other reasons that cause them difficulty in obtaining affordable health care.

These phenomena may be helping the patient diversity represented in clinical trials. It's important to test medical products in the people they are meant to help. In the past, most new drug testing had been done on white men. Groups such as women, blacks, and Hispanics often were not adequately represented. It's important to test medical products in a wide variety of people because drugs can work differently in people of various ages, races, ethnicity, and gender. The FDA seeks to ensure that people from many different groups are included in clinical trials.

Three free standing research centers questioned who was currently seeking to participate in clinical trials. They wanted to look at education, age, race and gender of current patients seeking to participate in clinical trials, along with marital status and employment status. This information not only answered the question of who is willing to join clinical trials but also important information on where to target marketing and education on clinical trials.

Learning Objectives
1. What are the major reasons that subjects join clinical trials?
2. What are the factors that might be affecting the demographics of those who seek to join clinical trials?

Literature References
1. Getz, Ken (2014) The Gift of Participation: A Guide to Making Informed Decisions About Volunteering for a Clinical Trial. Jerian Publishing; 2nd edition
2. Bain, LJ (2005). Crossroads in Clinical Trials. NeuroRx, 2(3), 525-528.

W26. A NEW PLATFORM TO IMPROVE QUALITY OF PANSS AND MADRS ADMINISTRATION

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[1]MedAvante

Abstract Introduction: Strategies are needed to improve quality of rater administration of many psychiatric instruments. The SCI-PANSS and the SIGMA (MADRS) are two of the most commonly used measures of psychopathology. To improve quality of rater administration, multi-level interventions (i.e., real-time clinical guidance and scoring assistance, immediate access to study data) were developed for a new electronic source (eSource) data capture and monitoring investigative study platform. To analyze the benefits, we chose one type of intervention, incompatible item scores, and tested them against recently collected clinical trial

data. The PANSS is a complex scale with different scoring rules and conventions for each item and requires raters to consult several sources during administration and scoring, a cumbersome process that can impede the interview and is prone to errors. Similarly, administration of the MADRS is often performed in an inconsistent manner because raters must consider six possible levels of intensity and frequency for every item, each with unique description, rating guidelines, scoring anchors and conventions. A strategy that simplifies the interview process for raters could decrease errors and increase interrater reliability in SCI-PANSS and SIGMA administration.

Methods: Extensive training experience (over 25,000 SCI-PANSS and over 39,000 SIGMA central assessments completed) has demonstrated the most common sources of error in administration. An e-platform was developed with automated scoring alerts triggered by these sources of error in addition to links to scoring anchors, item descriptions, and bases for rating to provide clinical guidance as the interview is being administered and scored. One type of error, incompatible item score pairs (16 pairs for PANSS and three for MADRS) was selected to analyze a subset of SCI-PANSS assessments (n = 288 from 79 site-based raters) and SIGMA assessments (n=1200 from 111 site raters) that were recorded for centralized over-read. The site raters' scores were analyzed to determine how many items would have triggered at least one alert to incompatible scores.

Results: 135 of the SCI-PANSS assessments (47%) would have triggered at least one alert to a potential scoring inaccuracy affecting subscale and total scores. 58 site raters (73%) would have seen at least one alert with the use of the eSource platform. 77 of the SIGMA assessments (6.4%) would have triggered alerts and 44 site raters (40%) would have seen at least one.

Conclusion: The PANSS and the MADRS are significantly different instruments in terms of number of items and construct overlap, but the scoring accuracy of both improves if incompatible item scores are flagged. Many other such interventions that help ensure proper administration and scoring using the eSource platform with multi-level clinical guidance for psychiatric instruments can reduce scoring errors that contribute to poor interrater reliability, which can compromise the ability to detect a positive signal.

Learning Objectives
1. To learn about a new strategy for improving the quality of site-based clinical ratings on measures of psychopathology.
2. To learn the frequency of scoring errors in one data sample.

Literature References
1. Kay SR, Opler LA, Fiszbein A. (2006). Positive and Negative Syndrome Scale (PANSS) Technical Manual. New York, NY: Multi-Health Systems.
2. Williams JBW, Kobak KA. (2008). Development and Reliability of the SIGMA: A structured interview guide for the Montgomery-Asberg Depression Rating Scale (MADRS). British Journal of Psychiatry, 192, 52-58.

W27. INCREASING USAGE OF SEDATIVE ANTIDEPRESSANTS IN LONG-TERM CARE HOMES AMONG ELDERLY WITH DEMENTIA: A POPULATION-BASED TIME-SERIES ANALYSIS

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Abstract Objective: To examine temporal changes in the prescriptions of sedative antidepressants (mirtazapine, trazodone and tricyclics), other psychotropic agents as well as psychotropic polypharmacy among older adults with dementia living in long-term care homes. Design: A population-based cross-sectional time-series analysis using linked health administrative databases. The study timeframe was divided into 37 intervals of 3 months (quarters) each starting from January 1, 2004 to March 31, 2013. Time series analysis was used to assess temporal trends and and project future utilization from April 1, 2014 to March 31, 2017.

Setting: Ontario, Canada.

Participants: For each quarter, older adults (≥ 65 years of age) living in a long-term care home with a documented diagnosis of dementia in the 5 years preceding the start of the quarter were identified.

Main outcome measures: The proportion of patients prescribed various classes of psychotropic medications and the proportion of patients prescribed 2 or more unique drug classes were calculated for each interval. Psychotropic medications included sedative and non-sedative antidepressants, benzodiazepines, conventional and atypical antipsychotics, cognitive enhancers, and antiepileptic drugs.

Results: The study population increased by 21% over the study period, from 49,251 in 2004 to 59,785 in 2013, while patient demographics and comorbidity status remained stable. The majority of patients (ranging from 75% to 79%) were prescribed at least one psychotropic medication throughout the study period. Sedative antidepressants prescriptions increased drastically from 17% in 2004 to 31% by 2013 ($p < 0.001$) and is projected to increase to 37% (95% CI: 35.6% - 37.9%) by 2017. Benzodiazepine use decreased significantly from 28% to 17% ($p < 0.0001$) and is projected to reach 8% (95% CI: 3.1% - 12.9%) in 2017. Atypical antipsychotic use declined significantly from 38% to 34% ($p < 0.0001$) during the same period and is projected to reach 31% (95% CI: 24.9% - 37.2%) in 2017. The proportion of patients on two or more psychotropic classes increased significantly in this period from 42% to 50% ($p < 0.001$).

Conclusions: Use of sedative antidepressants has increased over the last decade, despite the lack of evidence on their effectiveness or safety. The rise in psychotropic polypharmacy is also concerning as it poses risks of adverse outcomes, including cognitive impairment, falls and fractures; and such use should be discouraged.

Learning Objectives At the end of the session the participant will be able to:
1. Appreciate the usage of sedative antidepressants in patients with dementia living in long term care setting.
2. Appreciate the usage of psychotropic polypharmacy in this population.

Literature References
1. Valiyeva E, Herrmann N, Rochon PA, et al. Effect of regulatory warnings on antipsychotic prescription rates among elderly patients with dementia: a population-based time-series analysis. CMAJ 2008;179(5): 438-46
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W28. PREDICTORS OF RESPONSE TO ANTIPSYCHOTIC TREATMENT IN BEHAVIORAL AND PSYCHOLOGICAL SYMPTOMS WITH DEMENTIA - ANALYSIS OF THE CATIE-AD DATA

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Abstract Introduction: Antipsychotic drugs are frequently, albeit controversially, used to manage behavioral and psychological symptoms with dementia (BPSD). However, it still remains unclear as to which factors could serve as predictors of response to antipsychotic treatment, which was investigated in the present analysis.

Methods: Data used in the analyses were derived from the subjects who presented with a score of one or more in the Neuropsychiatric Inventory (NPI) or the Brief Psychiatric Rating Scale (BPRS) at baseline and were treated with risperidone, olanzapine, or quetiapine in Phase 1 of the Clinical Antipsychotic Trials in Intervention Effectiveness with Alzheimer's Disease (CATIE-AD). To examine factors associated with response at week 8, binary logistic regression analyses that included dementia subtypes (i.e. paranoid, misidentification, mixed, and non-psychotic), antipsychotic medications used, adherence to medications (i.e. adherence level of <76%, 76-100%, and >100%), gender, age groups (i.e. age ≤69, 70-74, 75-79, and ≥85), race, and reduction in the NPI and BPRS total scores at week 2, respectively, were conducted. With regard to the definition of response, (1) a score reduction of ≥25% in the BPRS or NPI or (2) one MCID (minimal clinically important difference defined as a half of SD) were adopted, respectively. Next, the prediction performance of binary classification in early improvement at week 2 (i.e. presence or absence) for response at week 8 was examined. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and predictive power of the consecutive cut-off points in increments of 5% between 5% and 25% in the NPI total and BPRS total scores at week 2 were calculated, respectively. These analyses were conducted for active drugs altogether and separately by means of the following two statistical methods: Available-Case (AC) analysis and Last Observation Carried Forward (LOCF).

Results: 242 subjects (risperidone, n=72; olanzapine, n=90; quetiapine, n=80) and 245 subjects (risperidone, n=74; olanzapine, n=90; quetiapine, n=81) were included for the analyses for the NPI and BPRS, respectively. The total score reduction at week 2 was the only one factor that was significantly associated with subsequent response at week 8 in the results with all analytic approaches (e.g. AC analyses using one MCID for the definition of response (NPI: odds ratio [OR], 1.16; 95% confidence interval [CI], 1.09-1.24; p<0.05; BPRS: OR, 1.22; 95% CI, 1.11-1.35; p<0.05)). The prediction performance of binary classification of early improvement showed that sensitivity and NPV were generally high whereas specificity and PPV were relatively low. For example, sensitivity, NPV, specificity, and PPV of the 5% cut-off as early improvement for the prediction of response (i.e. one MCID) in the BPRS at week 8, using AC method, were 0.84, 0.73, 0.54, and 0.70, respectively.

Conclusions: Early non-improvement at week 2 with antipsychotic treatment can be a strong predictor of subsequent non-response at week 8 in the treatment of BPSD. Evaluating patients early in the course of treatment with antipsychotic drugs can help identify non-responders who could exhibit unwanted adverse effects with continuous exposure and may benefit from alternative therapeutic approaches.

Learning Objectives
1. To understand what factors can predict response to antipsychotic treatment in patients with behavioral and psychological symptoms with dementia (BPSD).

2. To learn the impact of a certain degree of improvement at week 2 with antipsychotic drugs on subsequent response to those drugs at week 8 in patients with BPSD.

Literature References
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2. Lopez OL, Becker JT, Chang YF, Sweet RA, Aizenstein H, Snitz B, Saxton J, McDade E, Kamboh MI, DeKosky ST, Reynolds CF, 3rd, Klunk WE. The long-term effects of conventional and atypical antipsychotics in patients with probable Alzheimer's disease. Am J Psychiatry. 2013;170:1051-1058.

W29. NOCTURNAL WAKEFULNESS IS ASSOCIATED WITH NEXT-DAY SUICIDAL IDEATION IN MAJOR DEPRESSION AND BIPOLAR DISORDER: A PROPOSED WARNING SIGN AND ACUTE INDICATOR OF RISK

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Abstract Background: Self-reported sleep disturbances may confer elevated risk for suicidal ideation, attempts, and death. Epidemiological reports have linked difficulties with sleep with death by suicide, even when controlling for the effects of depression (1,2). By comparison, little research has evaluated sleep disturbance as an acute physiological risk factor for suicidal thoughts using objective methods such as polysomnography (PSG).

Aims: To investigate the relationship between nocturnal wakefulness in association with next-day suicidal ideation using overnight PSG assessment.

Method: Participants with Major Depressive Disorder (MDD) or Bipolar Disorder (BD) (n = 65) underwent overnight PSG monitoring. All participants were in a current depressive episode; MDD patients were medication-free for at least two weeks and BD patients were on therapeutic levels of lithium or valproate. The Hamilton Depression Rating Scale (HAM-D) was administered the morning after PSG recording to assess next-day suicidal ideation, depression symptom severity, and subjective sleep disturbances. The Montgomery Asberg Depression Rating Scale (MADRS) and the Scale for Suicide Ideation (SSI) was used to replicate significant results.

Results: A generalized linear mixed model found a significant time-by-ideation interaction, indicating greater nocturnal wakefulness at 4 AM among participants with suicidal ideation. Increased time awake during the 4 AM hour (4:00 to 4:59) was significantly associated with elevated suicidal thoughts the next day (standardized β = .31, p = .008). This relationship persisted after controlling for age, gender, diagnosis, and severity of depressive symptoms. Results were replicated using the MADRS suicide item and SSI.

Conclusions: Greater nocturnal wakefulness, particularly in the early morning hours, was significantly associated with next-day suicidal thoughts. PSG documented sleep disruption at specific times of night may represent an acute warning sign of suicidal ideation that warrants additional research.

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

1. Describe a promising objectively-defined biomarker for suicide risk, independent of depressive symptoms.
2. Summarize the research literature linking sleep disturbance and suicide risk.

Literature References
1. Bernert RA, Turvey CL, Conwell Y, Joiner TE, Jr. Association of poor subjective sleep quality with risk for death by suicide during a 10-year period: a longitudinal, population-based study of late life. JAMA Psychiatry. 2014; 71:1129-1137
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W30. FAMILY CULTURAL CONFLICT, MAJOR DEPRESSIVE EPISODE, AND MENTAL HEALTH SERVICE UTILIZATION AMONG LATINOS

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Abstract   In effort to better understand Latinos' underutilization of mental health services, this study examines the association of family cultural conflict (FCC) and use of mental health services among Latinos according to whether they have experienced a Major Depressive Episode (MDE). The National Latino and Asian American Study is a nationally representative household survey carried out in the U.S. in 2002-2003 that focuses on mental health disorders and mental health service utilization (MHSU). Secondary data analysis was conducted using data from the NLAAS, restricted to Latinos (N=2,554). Results indicate that only 8% of the Latino population report having used at least one source of MHSU in the past year, 16% of those with a MDE. For Latinos with a MDE, as family cultural conflict increases the likelihood of MHSU decreases. The findings highlight the need for research to expand work on the influence of culture and values among Latinos' MHSU.

Learning Objectives
1. Explain what family cultural conflict is among Latinos in the United States.
2. Assess/Recognize the role of the family system among Latinos in need of mental health care.

Literature References
1. Alegria, M., Shrout, P.E., Woo M., Guarnaccia, P., Sribney, W., Vila, D., Polo, A., Cao, Z., Mulvaney-Day, N., Torres, M., & Canino, G. (2007). Understanding differences in past-year psychiatric disorders for Latinos living in the U.S. Social Science and Medicine, 65(2): 214-230.
2. Chang, J., Natsuaki, M. N., & Chen, C. (2013). The importance of family factors and generation status: Mental health service use among Latino and Asian Americans. Cultural Diversity and Ethnic Minority Psychology, 19(3), 236–247. doi:10.1037/a0032901

W31. ADJUNCTIVE BREXPIPRAZOLE (OPC-34712) IN PATIENTS WITH MAJOR DEPRESSIVE DISORDER AND ANXIETY SYMPTOMS: AN EXPLORATORY STUDY

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Abstract Background: Anxiety symptoms are common in patients with major depressive disorder (MDD) and are associated with greater severity, impaired functioning, and less favorable outcomes [1]. Brexpiprazole is a rationally designed serotonin-dopamine activity modulator (SDAM) that is a partial agonist at 5-HT1A and dopamine D2 receptors at similar potency, and an antagonist at 5-HT2A and noradrenaline alpha1B/2C receptors [2]. The objective of this open-label study was to explore the effects of adjunctive brexpiprazole in patients with MDD and anxiety symptoms (NCT02013531).

Methods: Patients with MDD and anxiety symptoms (HAM-A ≥20) with an inadequate response to current ADT were enrolled and received open-label ADT+brexpiprazole 1 to 3mg/day (2mg/day target dose) for 6 weeks. Efficacy endpoints included change in clinician-rated MADRS and HAM-A total score from baseline to Week 6, and change in the 92-item patient-rated Kellner Symptom Questionnaire (KSQ, range 0 to 92) total score from baseline to Week 6.

Results: A total of 37 patients were treated with brexpiprazole+ADT, and of these 32 (86.5%) patients completed 6 weeks of treatment. At baseline, the mean MADRS total score was 30.3 (SD: 5.1), the mean HAM-A total score was 27.0 (SD: 5.05), and the mean KSQ total score was 55.9 (SD: 13.0), indicating that the patients had moderate to severe symptoms of depression and anxiety. Improvements were observed in MADRS total score from Baseline to Week 6 in patients treated with brexpiprazole+ADT (least square mean change: -19.6, 95% CI [-22.7;-16.6]) and in HAM-A total score (least square mean change: -17.8, 95% CI [-20.3;-15.3]). In addition, the KSQ total score also improved from baseline to Week 6 (mean change -29.4). Adjunctive brexpiprazole was well tolerated; the incidence of activating adverse events (akathisia, restlessness, agitation, anxiety, and insomnia) was low (≤5%) and no clinically relevant changes in the mean laboratory test values, vital signs, or ECG parameter values were observed.

Conclusion: Adjunctive treatment with brexpiprazole may represent a novel and effective strategy for treatment of patients with MDD and symptoms of anxiety showing an inadequate response to ADT.

Learning Objectives
1. To understand the effect of adjunctive brexpiprazole in patients with major depressive disorder and anxiety symptoms.
2. To understand the safety and tolerability of brexpiprazole in patients with major depressive disorder and anxiety symptoms.

Literature References
1. Fava M, Alpert JE, Carmin CN et al. Clinical correlates and symptom patterns of anxious depression among patients with major depressive disorder in STAR*D. Psychol Med. 2004;34(7):1299-1308.
2. Maeda K, Sugino H, Akazawa H et al. Brexpiprazole I: In vitro and in vivo characterization of a novel serotonin-dopamine activity modulator. J Pharmacol Exp Ther. 2014;350:589-604.

W32. THE ROLE OF THE KYNURENINE PATHWAY IN SUICIDALITY IN ADOLESCENT MAJOR DEPRESSIVE DISORDER

Kailyn Bradley[1], Julia Case[1], Omar Khan[1], Thomas Ricart[1], Amira Hanna[1], Carmen Alonso[2], Vilma Gabbay[1]

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Abstract Introduction: The neuroimmunological kynurenine pathway (KP) has been implicated in major depressive disorder (MDD) in adults and adolescents, most recently in

suicidality in adults (1, 2). The KP is initiated by the enzyme indoleamine 2,3-dioxygenase (IDO), which degrades tryptophan (TRP) into kynurenine (KYN) en route to neurotoxins. Here, we sought to specifically examine the KP in relation to suicidality in depressed adolescents. We hypothesized that depressed adolescents at high risk for suicide would exhibit elevated IDO, KYN and 3-hydroxyanthranilic acid (3-HAA), and decreased TRP. Methods: The KP was assessed in 20 adolescents with MDD at high risk for suicide—composed of past attempters and those who expressed active suicidal intent—30 non-suicidal depressed youth, and 22 healthy controls (HC). Plasma levels of TRP, KYN, 3-HAA, and IDO (indexed by KYN/TRP) were measured. Results: Adolescents with MDD at high risk for suicide showed decreased TRP compared to both non-suicidal depressed adolescents and HC [$F_{(2,67)} = 4.70$, $p = 0.012$]. Suicidal adolescents also showed elevated KYN/TRP compared to both non-suicidal depressed adolescents and HC [$F_{(2,67)} = 3.25$, $p = 0.045$]. Findings became more significantly pronounced when excluding medicated participants, wherein there was also a positive correlation between KYN/TRP and suicidality [ρ ($n = 11$) $= 0.63$, $p = 0.038$]. Finally, depressed adolescents with a history of suicide attempt differed from acutely suicidal adolescents with respect to disease severity ($p = 0.003$), anhedonia ($p = 0.012$), and suicidality ($p = 0.001$), but not KP activation (all $p > 0.05$). Conclusions: Our findings suggest a possible specific role of the KP in suicidality in depressed adolescents, while illustrating the clinical phenomenon that depressed adolescents with a history of suicide attempt are similar with respect to KP activation to acutely suicidal youth and are at increased risk for completion of suicide.

Learning Objectives
1. To assess the kynurenine pathway in relation to suicidality in depressed adolescents.
2. To understand the dimensional relationship between the kynurenine pathway and suicidality in adolescent depression.

Literature References
1. Bay-Richter, C., Linderholm, K.R., Lim, C.K., Samuelsson, M., Träskman-Bendz, L., Guillemin, G.J., Erhardt, S., Brundin, L., 2015. A role for inflammatory metabolites as modulators of the glutamate N-methyl-D-aspartate receptor in depression and suicidality. Brain, Behavior, and Immunity 43, 110-117.
2. Erhardt, S., Lim, C.K., Linderholm, K.R., Janelidze, S., Lindqvist, D., Samuelsson, M., Lundberg, K., Postolache, T.T., Träskman-Bendz, L., Guillemin, G.J., Brundin, L., 2013. Connecting inflammation with glutamate agonism in suicidality. Neuropsychopharmacology 38, 743-752.

W33. CLINICAL AND PHARMACOGENETIC OUTCOMES OF A DOUBLE-BLIND ANTIDEPRESSANT TREATMENT STUDY IN MEXICAN-AMERICANS

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Abstract Objective: We compare the effectiveness of fluoxetine and desipramine treatment in a prospective double-blind pharmacogenetics study in Mexican-Americans and examine the role of whole-exome functional gene variations in their antidepressant response. Method: 232 Mexican-Americans who met DSM-VI diagnostic criteria for major depressive disorder (MDD) were randomly assigned to an 8-week of double-blind desipramine (50-200 mg/day) or fluoxetine (10-40 mg/day) treatment after a one-week placebo lead-in period. Outcome measures included the Hamilton Depression (HAM-D), Hamilton Anxiety and Center for

Epidemiological Rating Scales, and Beck Depression Inventory. Whole exome genotyping data were obtained for 36 remitters and 29 non-responders at week 8.

Results: Our analysis showed fluoxetine treatment produced greater HAM-D score reduction, higher response/remission rates, shorter time to response/remission, and lower incidences of anticholinogeric and cardiovascular side effect events when compare to desipramine treatment. Pharmacogenetics analysis showed that a variation in Chromosome 6 achieved exome-wide significance for treatment remission (P=1.98x10-06; FDR=0.05). This variant is located in a brain methylated DNA immunoprecipitation sequencing site suggesting that it might be involved in epigenetic regulation of neuronal gene expression. Conclusions: Compared with desipramine, fluoxetine treatment showed a more rapid reduction of HAM-D score and lower incidence of side effects in a population comprised primarily of first generation Spanish speaking only Mexican-American individuals with MDD. Our pharmacogenetics approach strongly implicates the role of functional variants in antidepressant treatment response. Further, independent studies are needed for replication and validation.

Learning Objectives
1. To understand different treatment outcomes with antidepressant treatment in Mexican-Americans.
2. To learn of new genetic findings with the potential to predict antidepressant treatment outcomes.

Literature References
1. Dong C, Wong M-L, Licinio J. Sequence variations of ABCB1, SLC6A2, SLC6A3,SLC6A4, CREB1, CRHR1 and NTRK2: association with major depression and antidepressant response in Mexican-Americans. Molecular Psychiatry 2009;14:1105-1118.
2. Wong M-L, Dong C, Andreev V, Arcos-Burgos M, Licinio J. Prediction of susceptibility to major depression by a model of interactions of multiple functional genetic variants and environmental factors. Molecular Psychiatry 2012;17:624-633.

W34. ASSOCIATION BETWEEN STIGMA AND DEPRESSION OUTCOMES AMONG CHINESE AMERICAN IMMIGRANTS IN A PRIMARY CARE SETTING

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Abstract Purpose: Stigma has been proposed to be a major underlying factor contributing to lower rates of mental health service utilization among racial/ethnic minorities in the U.S.. Yet surprisingly little research has specifically explored associations between stigma, race/ethnicity, and psychiatric morbidity. This study aims to assess the impact of stigmatizing attitudes on depression outcomes among a psychiatrically underserved, immigrant Chinese American population. Methods: 190 Chinese immigrants with major depressive disorder were enrolled in a trial of culturally sensitive collaborative care for depression. Participants' self-reported stigma regarding their symptoms was assessed at study entry using the Explanatory Model Interview Catalogue, and depressive symptoms were assessed with the Hamilton Depression Rating Scale (HAM-D). Multivariable linear regression was used to assess the association between baseline stigma score and change in HAM-D score, adjusting for potential confounders. Results: Higher stigma scores at baseline were significantly associated after adjustment with attenuated change in HAM-D score at 6 months (p=.049). Conclusions: Stigma has a directly harmful effect on depression outcomes, even after individuals have been accurately diagnosed within a culturally sensitive community health center and agreed to

treatment. These results support further research into interventions targeting stigma to improve mental health outcomes among minority populations.

Learning Objectives

1. Understand the methodological challenges of assessing illness beliefs, including stigma that can impact on help-seeking behaviors and course of illness.
2. Describe the association between baseline self-stigma regarding depression and change in depression symptoms over a 6-month period.

Literature References

1. Alegria M, Chatterji P, Wells K, Cao Z, Chen C, Takeuchi D, Jackson J, Meng X: Disparity in Depression Treatment Among Racial and Ethnic Minority Populations in the United States. Psychiatric Services 2008; 59:1264-1272
2. Yang L, Kleinman A, Link B, Phelan J, Lee S, Good B: Culture and stigma: Adding moral experience to stigma theory. Social Science & Medicine 2007; 64:1524-1535

W35. THE EFFECT OF ADJUNCTIVE BREXPIPRAZOLE (OPC-34712) ON DEPRESSIVE SYMPTOMS IN PATIENTS WITH IRRITABILITY: RESULTS FROM POST-HOC ANALYSES

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Abstract Background: Irritability is common in patients with major depressive disorder (MDD) and is associated with greater overall severity and impaired functioning [1]. Brexpiprazole is a rationally designed serotonin-dopamine activity modulator (SDAM) that is a partial agonist at 5-HT1A and dopamine D2 receptors at similar potency, and an antagonist at 5-HT2A and noradrenaline alpha1B/2C receptors [2]. The objective of these post-hoc analyses was to assess the effects of adjunctive brexpiprazole treatment compared to monotherapy with an antidepressant treatment (ADT) in patients with MDD and irritability, and an inadequate response to ADT. The results were based on data from two phase III clinical studies [3].

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 after this prospective phase were randomized to ADT+brexpiprazole or ADT+placebo for 6 weeks. Both studies included fixed doses (2mg [Study 1: NCT01360645]; 1mg and 3mg [Study 2: NCT01360632]). Based on the self-rated IDS item 6 score, the patients were categorized as patients with irritability (IDS item 6 score≥1) or without irritability (IDS item 6 score=0). The efficacy endpoint was the change in MADRS total score from baseline to Week 6 in patients with irritability or without irritability. The analyses were conducted using a Mixed Model Repeated Measure (MMRM) approach with pooled placebo groups.

Results: Adjunctive brexpiprazole showed greater improvement than adjunctive placebo in the MADRS total score in patients with irritability (least square mean difference to placebo+ADT [n=306]: 1mg+ADT [n=179]: -2.18, p=0.0023; 2mg+ADT [n=140]: -2.09, p=0.0074; 3mg+ADT [n=180]: -2.55, p=0.0.004) as well as in patients without irritability (least square mean differences to placebo+ADT [n=75]: 1mg+ADT [n=32]: -1.55, p=0.3240; 2mg+ADT [n=35]: -3.04, p=0.0496; 3mg+ADT [n=33]: -2.60, p=0.0912). Irritability was not associated with an increased incidence of activating adverse events (akathisia, restlessness, agitation, anxiety, and insomnia).

Conclusion: In these post-hoc analyses, adjunctive treatment to antidepressant with brexpiprazole was superior to antidepressant monotherapy in reducing depressive symptoms in patients with irritability. There was no evidence of an increased incidence of activating adverse events.

Learning Objectives
1. To understand the effect of adjunctive brexpiprazole on depressive symptoms in patients with irritability who demonstrated inadequate response to antidepressants.
2. To understand the safety of adjunctive brexpiprazole in patients with MDD and irritability.

Literature References
1. Fava M, Hwang I, Rush AJ et al. The importance of irritability as a symptom of major depressive disorder: results from the National Comorbidity Survey Replication. Molecular Psychiatry. 2010;15:856-867.
2. Maeda K, Sugino H, Akazawa H et al. Brexpiprazole I: In vitro and in vivo characterization of a novel serotonin-dopamine activity modulator. J Pharmacol Exp Ther. 2014;350:589-604.
3. Thase ME, Youakim JM, Skuban A et al. Efficacy and safety of adjunctive brexpiprazole (OPC-34712) in major depressive disorder: results of two pivotal clinical studies. Neuropsychopharmacology. 2014;39:S357. Poster T100.

W36. COMBINATIONS OF BUPRENORPHINE AND SAMIDORPHAN MODULATE GLUTAMATE AND GABA TRANSMISSION IN THE MEDIAL PREFRONTAL CORTEX AND VENTRAL HIPPOCAMPUS OF MALE WISTAR RATS

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Abstract   Background: ALKS 5461 is a balanced opioid modulator which represents a novel treatment for depression that combines buprenorphine (BUP), a partial mu agonist, with samidorphan (SAM), a potent mu antagonist. ALKS 5461 was recently studied as adjunctive therapy in subjects having an inadequate response to antidepressants in a phase 2, sequential parallel comparison design trial, and was found to be superior to placebo on a range of primary and secondary measures of depressive symptoms (Ehrich et al., 2014). We previously described that combinations of BUP and SAM modulated mesolimbic monoaminergic systems, and produced antidepressant-like behavioral effects in rats (Deaver et al., ASCP 2014). These non-clinical microdialysis studies were designed to further investigate the effects of BUP, alone and in combination with SAM, on extracellular concentrations of glutamate (Glu) and γ-Aminobutyric acid (GABA) in the medial prefrontal cortex (mPFC) and ventral hippocampus (vHIPP) of male Wistar rats.

Results: BUP significantly increased extracellular Glu levels within the mPFC between one and four hours after drug administration. The maximal increase in mPFC Glu produced by BUP was approximately 190% above baseline levels. Concurrent administration of SAM dose-dependently attenuated, but did not completely block the effects of BUP on Glu concentrations in the mPFC. Neither BUP given alone, nor in combination with SAM, affected mPFC concentrations of GABA.

In the vHIPP, extracellular Glu concentrations did not change following treatment with BUP alone, nor in combination with SAM. Extracellular concentrations of GABA in the vHIPP increased slightly over time in the vehicle group. Administration of BUP alone did not

decrease concentrations of GABA. However, administration of low a dose of SAM with BUP decreased average GABA concentrations between hours two and three, whereas a higher dose of SAM with BUP did not.

Discussion: Dysregulation of the endogenous opioid system has been postulated to play an important role in mood disorders (Berrocoso et al., 2009). Exogenous opioids, including ALKS 5461, have been shown to have beneficial effects in treating depression. In these studies, BUP produced a delayed increase in extracellular concentrations of mPFC Glu, which was modulated, but not completely blocked, by SAM. The combination of BUP with the lower dose of SAM also decreased vHIPP GABA concentrations. Given the temporal pattern, the effects of BUP and SAM on amino acids in the mPFC and vHIPP likely occur via indirect pathways. In addition to the effects reported here, we previously found that the combination of BUP (0.1 mg/kg) and SAM (0.3 mg/kg) modulated mesolimbic monoaminergic systems, decreased immobility time in the forced swim test and increased saccharine consumption in nonclinical rat models. Taken together, these results indicate that balanced modulation of monoaminergic and amino acid neurotransmitter systems, including Glu, may contribute to the efficacy of ALKS 5461 in the treatment of depression.

Learning Objectives
1. Participants will learn about the pharmacology of a new drug combination, buprenorphine and samidorphan, a potential novel treatment for major depressive disorder.
2. Participants will learn about the utility of modulating buprenorphine activity to yield potential drug candidates with decreased risk of abuse, yet maintained efficacy.

Literature References
1. Ehrich E, Turncliff R, Du Y, Leigh-Pemberton R, Fernandez E, Jones R, Fava M. Evaluation of Opioid Modulation in Major Depressive Disorder. Neuropsychopharmacology . 12-18-2014.
2. Berrocoso E, Sanchez-Blazquez P, Garzon J, Mico JA. Opiates as antidepressants. Curr.Pharm.Des 15[14], 1612-1622. 2009.

W37. COMPARATIVE ASSESSMENT OF VORTIOXETINE OR ESCITALOPRAM ON THE SYMPTOMS OF TESD IN WELL-TREATED MDD PATIENTS PREVIOUSLY TREATED WITH SSRIS

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Abstract   Purpose: Patients with major depressive disorder (MDD) often report symptoms of sexual dysfunction despite being well treated with SSRIs for mood symptoms [1]. This analysis evaluates sexual functioning in well-treated MDD patients experiencing treatment-emergent sexual dysfunction (TESD) with their current SSRI therapy who directly switch to vortioxetine or escitalopram, as measured by the Changes in Sexual Functioning Questionnaire Short-Form (CSFQ-14) [2].

Methods: In this 8-wk, randomized, double-blind, head-to-head clinical study (NCT01364649) well-treated MDD patients receiving SSRIs (citalopram, paroxetine, or sertraline) and experiencing TESD were directly switched to vortioxetine 10mg or escitalopram 10mg for Wk 1, and escalated to 20mg for Wk 2. Investigators could adjust dose (10 or 20mg) at Wks 2, 4, or 6. Sexual functioning was evaluated by changes in CSFQ-14, with sub-group analyses based on gender, age, and baseline TESD severity.

Results: Of 447 patients enrolled, 348 completed 8 wks of treatment (vortioxetine, 169/225 [75.1%]; escitalopram, 179/222 [80.6%]). Patients were well treated with their current SSRI (baseline MADRS: 7.90; 8.33) but experienced significant TESD (baseline CPFQ: 36.5; 36.3). CSFQ-14 improvements at Wk 8 were greater in patients switched to vortioxetine (n=165, Δ+8.8 [0.64]) than escitalopram (n=173, Δ+6.6 [0.64]), with a mean difference of +2.2 in favor of vortioxetine (95% CI: 0.48-4.02, P=0.013; MMRM). Switching to vortioxetine yielded improvements in all 5 dimensions of sexual functioning with statistical superiority compared to escitalopram on 4/5 (pleasure P=0.015; desire/frequency P=0.010; desire/interest P=0.058; arousal/erection P=0.042; orgasm/ejaculation P=0.026; MMRM). Vortioxetine was also statistically superior compared to escitalopram in all 3 phases of sexual functioning at Wk 8 (desire P=0.022; arousal P=0.042; orgasm P=0.026; MMRM). All measured individual symptoms of sexual functioning improved for patients switching from SSRI therapy, with clinically significant superiority for vortioxetine compared to escitalopram on 8 of 14 items, and numerical superiority for the other 6 items. Sexual functioning improvements were independent of age, gender, and baseline TESD severity.

Conclusion: Vortioxetine was statistically superior to escitalopram in improving SSRI-induced TESD at Wk 8, as measured by changes in CSFQ-14 scores and improvements in all measured symptoms of sexual dysfunction associated with previous SSRI therapy, with statistical superiority in sexual functioning on 4 of 5 clinically relevant dimensions and all 3 phases.

Learning Objectives
1. To compare changes in SSRI-induced TESD between treatments after switching to vortioxetine or escitalopram.
2. To evaluate the clinical impact of switching MDD patients experiencing TESD to vortioxetine.

Literature References
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W38. LEVOMILNACIPRAN ER TREATMENT IN ADULT MDD PATIENTS IN A RECURRENT DEPRESSIVE EPISODE OR IN THE FIRST DEPRESSIVE EPISODE

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Abstract Background: Levomilnacipran extended-release (LVM ER) is a serotonin and norepinephrine reuptake inhibitor that is approved for the treatment of major depressive disorder (MDD) in adults. The majority of adults with MDD have recurrent episodes. Although some studies have reported poorer treatment outcomes in patients with a history of prior episodes, others have found similar outcomes between first-episode patients and those in a recurrent depressive episode. To explore the effects of LVM ER in patients with first-episode or recurrent MDD, post hoc analyses were conducted using pooled data from 5 randomized, placebo (PBO)-controlled clinical trials.

Methods: Patients in the studies (4 US, 1 non-US) were randomized to receive 8 or 10 weeks of double-blind treatment with LVM ER (40-120 mg/d) or PBO. In patients with available episode-related data (N=2451), 2 main subgroups were identified for post hoc analyses: patients in a recurrent depressive episode and patients in the first depressive episode (any episode duration). Based on available data (US studies only), a subgroup of antidepressant (ADT)-naïve patients in the first episode (duration <12 months) was also evaluated. In each of these subgroups, mean changes from baseline to end of treatment in Montgomery-Åsberg

Depression Rating Scale (MADRS), Hamilton Rating Scale for Depression (HAMD), and Sheehan Disability Scale (SDS) total scores were analyzed using a last observation carried forward approach. In addition, the percentage of patients with MADRS response, defined as ≥50% total score improvement from baseline, was analyzed in the recurrent and first-episode subgroups from the 5 studies.

Results: Approximately 80% of patients in the 5 studies were in a recurrent MDD episode. In patients with recurrent or first-episode MDD, least squares mean differences (LSMDs) between treatment groups indicated significantly greater improvements with LVM ER compared with PBO in MADRS (recurrent, -2.9, P<.0001; first, -2.6, P=.0137), HAMD (recurrent, -1.6, P=<.0001; first, -2.1, P=.0039); and SDS (recurrent, -2.3, P<.0001; first, -2.0, P=.0105) total scores. A similar magnitude of LVM ER treatment effects vs PBO was found in ADT-naïve first-episode patients (n=152 for MADRS and HAMD analyses), although sample sizes were too small to reach statistical significance (LSMD: MADRS total, 3.1, HAMD total, 1.9; SDS total, 2.3; all P>.05 vs PBO). MADRS response rate was significantly greater with LVM ER vs PBO in patients with recurrent (44.4% vs 33.5%; P<.0001) and first- episode MDD (44.5% vs 35.0%; P=.0228).

Conclusions: The treatment effects of LVM ER on depressive symptoms (MADRS and HAMD total scores) and functional impairment (SDS total score) were similar in patients with recurrent MDD and those in their first MDD episode, including patients who had not received prior ADT treatment.

Learning Objectives
1. To familiarize clinicians with the antidepressant effects of levomilnacipran ER in adults with first-episode or recurrent MDD.
2. To explore how MDD diagnosis (first episode vs recurrent) might affect improvements in functional impairment.

Literature References
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W39. EFFICACY AND SAFETY OF CARIPRAZINE AS ADJUNCTIVE THERAPY IN MAJOR DEPRESSIVE DISORDER: A DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED STUDY

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Abstract Introduction: Atypical antipsychotics are often used adjunctively in patients with major depressive disorder (MDD) who have an inadequate response to antidepressant treatment (ADT) alone. Cariprazine, a potent dopamine D3 and D2 receptor partial agonist with preferential binding to D3 receptors, is in clinical development for the treatment of schizophrenia, bipolar mania, and bipolar depression. Cariprazine is also being investigated as adjunctive treatment for patients with MDD who have inadequate response to standard ADT.

Methods: This was an 8-week, Phase 2b, randomized, double-blind, placebo-controlled, flexible-dose study of cariprazine in adults with MDD (NCT01469377). Patients with a current depressive episode and documented ongoing inadequate response to standard ADT were

randomized (1:1:1) to treatment with placebo, or cariprazine 1-2 mg/d or 2-4.5 mg/d to be administered adjunctively with current ADT. The primary and secondary efficacy outcomes were mean change from baseline to Week 8 in Montgomery-Åsberg Depression Rating Scale (MADRS) and Sheehan Disability Scale (SDS) total scores, respectively, analyzed using a mixed-effects model for repeated measures (MMRM); P values were adjusted for multiple comparisons. MADRS single items were evaluated post hoc. Safety assessments included adverse events (AEs), clinical laboratory tests, vital signs, and electrocardiograms.

Results: The intent-to-treat population comprised 808 patients (placebo=264; cariprazine: 1-2 mg/d=273, 2-4.5 mg/d=271); 83% of patients completed the study (placebo=88%; cariprazine: 1-2 mg/d=83%, 2-4.5 mg/d=77%). The least squares mean difference (95% confidence interval) (LSMD [95% CI]) in MADRS total score change from baseline to Week 8 was statistically significant in favor of cariprazine 2-4.5 mg/d versus placebo (-2.2 [-3.7, -0.6]; adjusted P=.0114); LSMD for cariprazine 1-2 mg/d versus placebo (-0.9 [-2.4, 0.6]) was not statistically significant (adjusted P=.2404). For cariprazine 2-4.5 mg/d versus placebo, significantly greater improvements were seen on multiple MADRS single items (Sadness [Apparent and Reported], Reduced Appetite, and Inability to Feel [P<.01 each]) and the MADRS Core 6 Subscale (P=.0079); for cariprazine 1-2 mg/d versus placebo, significantly greater improvement was seen on the Inability to Feel item (P=.0044). At Week 8, LSMD versus placebo for decrease in SDS total score was not statistically significant for cariprazine 1-2 mg/d (-1.1 [-2.5, 0.3], adjusted P=.2404) or 2-4.5 mg/d (-1.4 [-2.8, 0.0], adjusted P=.1140). AEs were reported in 59%, 69%, and 78% of patients in the placebo and cariprazine 1-2 and 2-4.5 mg/d groups, respectively. AEs reported in ≥10% of any treatment group were akathisia (22%), insomnia (14%), and nausea (13%) in the cariprazine 2-4.5 mg/d group and headache (13%) in the placebo group.

Discussion: In adults with MDD and inadequate response to standard ADT, adjunctive cariprazine 2-4.5 mg/d produced significantly greater improvement in depressive symptoms relative to placebo and was generally well-tolerated.

Learning Objectives At the conclusion of this session, participants should be able to:
1. Evaluate the efficacy and tolerability of cariprazine as an adjunctive treatment for patients with major depressive disorder who have inadequate response to standard antidepressant therapy.
2. Evaluate the efficacy of cariprazine across depression symptom domains in patients with major depressive disorder.

Literature References
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2. Han C, Wang SM, Kato M, Lee SJ, Patkar AA, Masand PS, Pae CU: Second-generation antipsychotics in the treatment of major depressive disorder: current evidence. Expert Rev Neurother 2013;13:851-870.

W40. THE ASSOCIATION BETWEEN SCHOOL BULLYING AND DEPRESSION: EVIDENCE FROM TWINSSCANCHINA STUDY

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Abstract Background: Recently, the prevalence of depression in adolescents has been found to be rising in China. Evidence from Western population has suggested that both genetic and environmental factors are involved in developing of adolescent depression symptoms (1).

Furthermore, the association between school bullying and depression has been reported by line of studies in Western population (2), which indicates school bullying victimization will increase level of depression and suicidal thoughts. As in China, school bullying phenomenon is also quite worrying and has shown to be exacerbated in recent years, it is important to increase the public awareness of school bullying and its negative impact on mental health in adolescents. However, little research has addressed this issue in Chinese population. Therefore, the purpose of present study is to investigate whether school bullying experience will predict the depression in Chinese adolescents, and furthermore, how genetic and/or environmental factors influence the level of depression based on subclinical Chinese population.

Methods: In this pilot study, 72 healthy Chinese twins, including 29 monozygotic (MZ) twins and 43 dizygotic (DZ) twins, were recruited. High school bullying history was measured by Retrospective Bullying Questionnaire (RBQ) which covered six types of victimization, including two physical (beaten/hit/kicked, stolen from), two verbal (nicknames, threatened), and two social (lies/gossip, excluded). The symptom of depression was measured by the Symptom Checklist 90-R (SCL-90-R), which was a self-reported clinical rating scale. Data analysis was carried out by multilevel linear model utilizing maximum likelihood estimation rationale.

Results: The mean age of the twins is 17 years old, with 66.3% female and 33.7% male. There is no significant difference in the mean level of depression between MZ twins (M=7.92, SD=8.46) and DZ twins (M=6.43, SD=6.08). In both types of twins, totally 19 participants (16.4%) have suffered one type of bullying (beaten/hit/kicked, or stolen from, or nicknames, or threatened, or lies/gossip, or excluded), 18 participants (15.5%) have suffered two types of bullying, 10 participants (8.6%) have suffered three types of bullying, and 9 participants (7.8%) have suffered four types of bullying. No participant suffering five or six types of bullying is detected in our dataset. Multilevel linear modelling has revealed school bullying experience significantly predicting depression level (b=1.3, P=0.001) in Chinese adolescents. Furthermore, genetic factor explains 47% of the variation in depression symptoms in Chinese adolescents, while common environmental and non-shared environmental factors explain 25% and 28%, separately.

Discussion: In this pilot study based on Chinese twin adolescents, consistently with Western population, high school bullying experience has demonstrated a significant association with depression, with more bullying experience predicting higher level of depression symptoms. Moreover, the depression has shown moderate heritability in Chinese adolescents, which is in line with findings in Western population (47% in Chinese population vs 44% in Western population) (1). Additionally, both common and non-shared environmental factors are identified to be significant contributors to individual differences in depression symptoms, which highlight the importance of exploring environmental risk factors to understand the mechanism of mental health problems. In conclusion, our findings suggest that school bullying acts as an environmental risk factor contributing to developing depression in Chinese adolescents. As our research is an ongoing one, further study employing larger sample size would be used to confirm these findings.

Learning Objectives
1. To investigate whether school bullying experience will predict the depression in Chinese adolescents.
2. To investigate how genetic and/or environmental factors influence the level of depression based on subclinical Chinese population.

Literature References
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W41. THE SAFETY AND TOLERABILITY OF VORTIOXETINE IN TREATING ADULTS WITH MAJOR DEPRESSIVE DISORDER FOR 52 WEEKS WITH OPEN-LABEL TREATMENT

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Abstract Purpose: Vortioxetine is approved for adults with major depressive disorder (MDD) [1, 2]. This analysis evaluated the long-term safety and tolerability of vortioxetine (5-20 mg/day) in 52-week open-label extension (OLE) trials of adult MDD patients.

Methods: Patient-level data from 5 vortioxetine OLE studies (NCT00761306, NCT00694304, NCT00707980, NCT01152996, NCT01323478) in MDD patients were pooled for safety and tolerability assessment. A total of 2405 patients participated and received vortioxetine (5-20 mg/day) in the OLE trials after completing a 6-8 week placebo-controlled study. Safety assessments were based on treatment-emergent adverse events (TEAEs), clinical laboratory values, ECGs, and vital signs during open-label treatment, using the baseline of lead-in studies as reference.

Results: Of the 2405 patients, 57.2% completed the 52-week treatment period (5-10 mg, 62.7%; 15-20 mg, 51.1%). Most patients were women (68.7%), >40 years (68.1%), with body mass index >25 kg/m2 (68.1%), and located in the US (59.2%). Most common (≥5%) primary reasons for study discontinuation were withdrawal of consent (11.2%), TEAEs (8.5%), loss to follow-up (7.6%), and lack of efficacy (5.8%). A total of 70.3% (5-10 mg) and 79.5% (15-20 mg) of patients reported TEAEs, with 6.0% (5-10 mg) and 10.8% (15-20 mg) discontinuing due to a TEAE. Discontinuation due to nausea was low but higher with higher doses (5-10 mg, 0.8%; 15-20 mg, 2.7%). Of all patients, 2.9% reported a serious AE (SAE). Suicidal ideation (0.2%) and suicide attempt (0.2%) were the only SAEs occurring in >0.1% of patients. One death, not attributed to treatment, occurred. Common TEAEs (≥10%) were nausea (5-10 mg, 15.5%; 15-20 mg, 24.5%), headache (13.0%; 13.1%), and nasopharyngitis (11.2%; 6.7%), which were all transient. There were no clinically significant trends in clinical laboratory values, ECGs, or vital sign parameters. Mean weight increase over the 52-week treatment period was <1 kg.

Conclusions: Vortioxetine was generally safe and well tolerated in MDD patients receiving open-label treatment for up to 52 weeks. Nausea was the only TEAE leading to discontinuation in ≥1% of patients, and was transient, with higher incidence at higher doses. Incidence of serious TEAEs was low, with no individual event reported in ≥1% of the total population.

Learning Objectives
1. To understand the long-term safety and tolerability of vortioxetine in adults with MDD.
2. To evaluate the long-term safety and tolerability of vortioxetine at different doses.

Literature References
1. Sanchez C, Asin KE, Artigas F. Pharmacol Ther. 2015;145:43-57.

2. Zhang J, Mathis MV, Sellers JW, Kordzakhia G, Jackson AJ, Dow A, Yang P, Fossom L, Zhu H, Patel H, Unger EF, Temple RJ. J Clin Psychiatry. 2014;[online ahead of print]:e1-e7. doi:10.4088/JCP.14r09164.

W42. PATTERNS OF IMPROVEMENT IN PATIENTS WITH ACUTE DEPRESSIVE EPISODES OF BIPOLAR I DISORDER AND BIPOLAR II DISORDER

Jamie Mullen[1], Catherine Datto[2], William Pottorf[2], Scott LaPorte[2], Charles Liss[2]
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Abstract   Introduction: Few studies of acute depressive episodes of bipolar disorder (BD) include patients with either BD type I or II. Five studies were examined of BDI and II patients treated with quetiapine (QTP; immediate and extended release), placebo, and either lithium or paroxetine to illustrate clinical patterns of response and safety profiles.

Methods: The primary results of the 5 randomized, 8-week, bipolar depression studies are reported elsewhere [1,2]. Here, efficacy and safety are examined according to BDI and II status. QTP 300 mg and 600 mg treatment arms were pooled because their efficacy was similar [1,2]. Efficacy assessments included MADRS, CGI-BP-S and HAM-A scores, and safety was assessed by adverse event (AE) and discontinuation adverse event (DAE) rates.

Results: BDI patients randomized to QTP totaled 1162, placebo 486, lithium 87 and paroxetine 74, while BDII patients randomized totaled 598, 231, 49 and 44, respectively. Demographic characteristics (sex, age and weight) and baseline severity of illness (MADRS, CGI-BP-S and HAM-A) were similar across treatment groups. In the first 4 weeks of treatment, BDII patients randomized to lithium demonstrated the slowest rates of symptom improvement, measured by change in MADRS total score. BDI and II patients randomized to QTP demonstrated fastest symptom improvement in the first 4 weeks. In the last 4 weeks of treatment, BDI or II patients randomized to placebo and paroxetine showed slower symptom improvement, while those treated with lithium nearly reached the symptom improvement achieved by those randomized to QTP. Similar patterns of response were seen for CGI-BP-S and HAM-A scores. For MADRS item changes, QTP showed greater improvement across BD subgroups and most items, but items 3, 5, 7 and 9 responded similarly well to lithium. Proportions of BDI patients reporting any AE were: QTP 76.7%, placebo 72.4%, lithium 54.0% and paroxetine 71.1%; and DAE rates were 9.9%, 3.8%, 5.7% and 11.8%, respectively. Proportions of BDII patients reporting any AE were 74.5%, 66.5%, 65.3% and 66.7%, respectively; and DAE rates were 14.2%, 4.1%, 10.2% and 4.4%. Patterns of AEs were consistent with the known side-effect profiles of these agents.

Conclusion: These subanalyses provide important insights on efficacy and safety in acute depressive episodes of BDI and II. BDII patients initially have a slower response to treatment, but by 8 weeks reach treatment improvement levels similar to BDI, with the exception of paroxetine in BDII patients. No clear pattern of tolerability differences was identified between BDI and BDII by randomized treatments.

Learning Objectives
1. At the conclusion of this presentation, the participant should be able to demonstrate knowledge and understanding of the efficacy and safety of quetiapine in patients with acute depressive episodes of bipolar I or bipolar II disorder.
2. At the conclusion of this presentation, the participant should understand that patients with bipolar II initially show a slower response than patients with bipolar I to quetiapine (and to lithium and paroxetine), but by 8 weeks reach similar treatment improvement levels.

Literature References

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2. Sanford M, Keating GM. CNS Drugs 2012; 26:435-60.

W43. PROVIDING FURTHER DETAILS ON THE EXPERIENCE OF SOMNOLENCE FOR PATIENTS WITH ACUTE DEPRESSIVE EPISODES TREATED WITH QUETIAPINE XR

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Abstract   Introduction: Number Needed to Harm (NNH) is an oversimplification of important safety information. Details regarding tolerability findings, and not simply the inverse of an adverse event (AE) incidence rate, can help provide prescribers/patients with appropriate expectations when considering treatment choices. This analysis provides details of the experience of somnolence (the most common AE with quetiapine) in patients taking quetiapine extended release (QXR) for acute depressive episodes in studies of bipolar disorder (BD) and adjunct treatment of major depressive disorder (MDD).

Methods: For this analysis, somnolence is the expression of one of two AE preferred terms according to MedDRA: somnolence or sedation. Acutely depressed patients with MDD in two studies were randomized to adjunct treatment with QXR 150 mg (n=315) or 300 mg (n=312) or placebo (n=309) [1]. In a separate study, acutely depressed patients with BDI or II were randomized to QXR 300 mg (n=137) or placebo (n=140) [2]. The timing of AEs, severity, duration, rates of discontinuation, and influence on the Montgomery-Åsberg Depression Rating Scale (MADRS) efficacy scale were evaluated.

Results: The combined proportions of patients with somnolence in the adjunct MDD studies were 35.6%, 42.3% (QXR 150 mg and 300 mg, respectively) and 7.8% (placebo). In the BD study, somnolence rates were 51.8% for QXR 300 mg and 12.9% for placebo. The majority of patients on QXR reported the AE as mild to moderate severity (MDD studies: 84.8% and 83.3% for QXR 150 and 300 mg; BD study: 88.7% for QXR 300 mg). The proportions of patients who discontinued due to somnolence in the MDD studies were 4.8%, 8.0%, and 0.3%, for QXR 150 mg, 300 mg, and placebo, respectively. For the BD study these discontinuation rates were 10.2% for QXR 300 mg and 0.0% for placebo. In both MDD and BD studies, patients with and without the experience of somnolence saw important improvements in their MADRS total scores when treated with QXR compared to placebo.

Conclusion: Quetiapine XR has a well-established efficacy and safety profile. The experience of somnolence associated with this medication is typically mild to moderate and often resolves with continued treatment, but in some patients can result in treatment discontinuation. Additionally, acutely depressed patients treated with adjunct QXR for MDD or monotherapy for BD have similar improvements in mean MADRS total score with or without the presence of somnolence. It is important to provide prescribers/patients with tolerability details that can facilitate treatment decision-making.

Learning Objectives

1. At the conclusion of this presentation, the participant should be able to demonstrate knowledge and understanding of the experience of somnolence during treatment with quetiapine XR in patients with acute depressive episodes of MDD (as adjunct to ongoing antidepressants) or bipolar type I or II disorder.

2. At the conclusion of this presentation, the participant should understand that the experience of somnolence associated with quetiapine XR is typically mild to moderate and often resolves with continued treatment, but in some patients can result in treatment discontinuation.

Literature References

1. Bauer M, El-Khalili N, Datto C, et al. J Affect Disord 2010; 127:19-30.
2. Suppes T, Datto C, Minkwitz M, et al. J Affect Disord 2010; 121:106-115.

W44. METHYLPHENIDATE AUGMENTATION FOR TREATMENT RESISTANT DEPRESSION IN AN ELDERLY PATIENT WITH MENINGIOMA

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Abstract Purpose: Elderly patients with treatment resistant depression and multiple comorbidities are challenging. Suicidal thoughts and vegetative symptoms require rapid response. Brain tumors limit the use of electroconvulsive therapy. We report an elderly male with history of depression, poor eating and sleeping and suicidal thoughts who was treated with methylphenidate augmentation and showed a significant response.

Methods: An 89 year old white male was admitted on 12/12/14 with depression, anxiety, poor appetite and sleep, hopelessness and helplessness, weight loss, suicidal thoughts and plans and hearing voices. Patient denied previous suicidal attempts. His medical history included CHF, HTN, DM. He was on mirtazapine 45 mg, zolpidem 5 mg, risperidone 0.5 mg and buproprion 150 mg PO daily. Risperidone was discontinued and patient started on aripriprazole 5 mg daily. He continued to be depressed with suicidal thoughts. CT scan of head showed left occipital meningioma and calcified right intraconal mass. Buproprion was discontinued and patient started on methylphenidate 5 mg PO daily on 12/30/14 and titrated to 5 mg PO TID over 2 weeks. Patient showed significant improvement. He started eating better. Suicidal thoughts resolved. Patient's clinical status was assessed by HAMD, CGI and GDS.

Results: The CGI-S was 7 on admission and continued to be 7 on 12/29/14 and the CGI-I was 4. The HAMD score was 16 and GDS 13 on 12/29/14 and 9 and 8 on 1/21/15. The CGI-S improved to 2 and the CGI-I to 1. Patient tolerated the methylphenidate without any side effects.

Conclusions: Patient's diagnosis and treatment were complicated by medical comorbidities, advancing age and meningiomas of the brain which limited our treatment options including electroconvulsive therapy. This patient who has not responded to adequate doses of mirtazapine, buproprion and risperidone / aripriprazole did show significant improvement with methylphenidate augmentation in 2 weeks.

Learning Objectives

1. Treating elderly patients with depression.
2. Treating elderly patients with comorbidities and treatment resistant depression.

Literature References

1. Subramoniam Madhusoodanan, Diana Goial. Rapid resolution of depressive symptoms with methylphenidate augmentation of mitarzapine in an elderly depressed hospitalized patient: a case report. Clin. Pract. (2014) 11 (3), 283-288
2. Lavretsky et al.Methylphenidate-enhanced antidepressant response to citalopram in the elderly: a double-blind, placebo controlled pilot trial. Am. J. Geriatr. Psychiatry 14(2), 181-185 (2006)

W45. THE METABOLIC TOLERABILITY PROFILE OF ADJUNCT BREXPIPRAZOLE (OPC-34712) IN MAJOR DEPRESSIVE DISORDER

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Abstract   Background: Some atypical antipsychotics are associated with metabolic adverse effects, including weight gain, impaired glucose metabolism and dyslipidemia [1]. Brexpiprazole is a rationally designed serotonin-dopamine activity modulator (SDAM) that is a partial agonist at 5-HT1A and dopamine D2 receptors at similar potency, and an antagonist at 5-HT2A and noradrenaline alpha1B/2C receptors [2]. The metabolic profile of brexpiprazole was evaluated in patients with major depressive disorder (MDD), based on data from two phase III studies (NCT01360645 and NCT01360632) [3] and two large long-term open-label studies (NCT01360866 and NCT01447576).

Methods: In two short-term studies, patients with MDD and inadequate response to antidepressants (ADTs) were enrolled and received single-blind ADT for 8 weeks. Patients with inadequate response after this prospective phase were randomized to ADT+brexpiprazole or ADT+placebo for 6 weeks. Both studies included fixed doses (2mg in one study and 1mg and 3mg in the other study). The long-term studies were open-label, 52-weeks, flexible-dose (0.5 to 3mg/day and 0.25 to 3mg/day) studies with brexpiprazole+ADT. The long-term studies enrolled de novo patients, patients who had completed one of the two pivotal studies, as well as patients who had completed one of two phase II studies. Metabolic parameters included weight, glucose, and lipid metabolism-related laboratory measurements.

Results: In the short-term studies, mean change in weight from baseline to Week 6 was 1.4kg, 1.4kg, 1.6kg, and 0.3kg for the 1mg, 2mg, 3mg brexpiprazole+ADT and placebo+ADT groups, respectively. In the long-term study, the mean change in weight from baseline to Week 52 was 3.1kg. An increase in weight of $\geq 7\%$ at any visit was seen in 4.9%, 4.8%, and 2.2% of brexpiprazole+ADT 1mg, 2mg, and 3mg patients vs 1.9% of placebo+ADT patients in the short-term studies and in 29.5% of the patients treated with brexpiprazole+ADT in the long-term study.

For fasting metabolic parameters, mean changes from baseline to last visit in the short-term studies were (brexpiprazole+ADT 1mg, 2mg, and 3mg vs placebo+ADT): total cholesterol 0.70, 2.60, and 1.49 vs -0.06mg/dL; high-density lipoprotein cholesterol 1.12, 1.21, and 2.07 vs 0.56mg/dL; low-density lipoprotein cholesterol -1.50, 1.37, and -0.77 vs -1.18mg/dL; triglycerides 3.21, -0.83, and 2.20 vs -2.27mg/dL; and glucose -0.75, -0.40, and 0.70 vs 0.92mg/dL. Mean changes from baseline to Week 52 in the long-term studies were: total cholesterol 0.12mg/dL; high-density lipoprotein cholesterol -3.21mg/dL; low-density lipoprotein cholesterol 0.26mg/dL; triglycerides 16.91mg/dL; and glucose 4.61mg/dL.

Conclusion: A moderate weight increase was observed on brexpiprazole with no clinically relevant changes in lipid profiles or other metabolic parameters observed. Results from the long-term study were consistent with those of the short-term pivotal studies and confirmed the good tolerability of brexpiprazole.

Learning Objectives

1. To understand the short term metabolic effects of adjunctive brexpiprazole in patients with MDD.
2. To understand the long term metabolic effects of adjunctive brexpiprazole in patients with MDD.

Literature References
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W46. DELAY IN USE OF ADJUNCT ATYPICAL ANTIPSYCHOTIC TREATMENT FOR MAJOR DEPRESSIVE DISORDER IS ASSOCIATED WITH HIGHER PHYSICIAN OFFICE VISITS AND COSTS

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Abstract Background: Major Depressive Disorder (MDD) has a lifetime prevalence of 16% and is associated with high economic burden. Antidepressant monotherapy, commonly the first treatment option for newly diagnosed MDD, frequently fails to result in remission. Following 2 or more trials of monotherapy antidepressants, the probability of remission has been reported as ≤25% [1], increasing the risk of chronic disease. Despite the documented efficacy of adjunct antipsychotics, anecdotal evidence suggests physicians delay their use beyond 2 previous monotherapy antidepressant failures. To identify treatment strategies that help reduce the number of physician office visits and related costs in managing MDD patients, it is important to understand the consequence of delaying the use of adjunct atypical antipsychotics (AAs). Such treatment strategies may be especially valuable given the increasing push for physician reimbursement from 'fee-for service' to 'outcome-based' contractual arrangements.

Methods: Using administrative claims data from the Truven Health MarketScan® Commercial Database 1/1/2008–7/1/2011, this study investigated the association between timing of adjunctive AA treatment and healthcare utilization and costs. Patients ≥18 years with ≥1 MDD diagnosis claim (ICD-9-CM code 296.2x, 296.3x, 311.xx) and ≥1 antidepressant prescription claim (index) were included. Patients were also required to have ≥1 additional non-index antidepressant prior to treatment with an oral adjunct AA. Continuous health plan enrollment was required ≥6 months prior to index and for 24 months during follow up. Days from index to first adjunct AA treatment were recorded and patients were classified as receiving adjunct AAs in year 1 or 2. Healthcare utilization and costs for outpatient office visits were measured during the 24-month follow up. Bivariate analyses were stratified by adjunct AA treatment in year 1 vs year 2 (Chi-square for categorical values and t-tests and ANOVA for continuous variables). Generalized Linear Models were used for multivariate analyses, adjusting for all demographics and clinical characteristics. Recycled prediction method was used to generate predicted outcomes for each month post-index.

Results: A total of 1,156 patients met study requirements; 675 (58%) received adjunct AAs within year 1 of initiating monotherapy antidepressant, and 481 (42%) in year 2. Patients with adjunct AAs in year 1 were more likely to be male (p=0.0069) and to have a psychiatric specialist visit 30 days prior to adjunct treatment (p=0.0175). In a bivariate analysis, patients with adjunct AAs in year 1 had fewer outpatient office visits (13.8 vs 16.3; p=0.0013) and

lower corresponding costs ($1,442 vs $1,779; p=0.0004). A multivariable analysis indicated that increased delay to AA adjunct treatment was significantly associated with increased outpatient office visits over the 24-month follow up (13.0 for patients with adjunct AAs at month 0 increasing to 17.5 for those at month 24) and with associated costs.

Conclusions: Delay in adjunct AA treatment was significantly associated with increased outpatient office visits and costs. With increasing responsibility for physicians to manage patient care with limited resources, early adjunctive use of efficacious and tolerable AAs may serve as a valuable treatment strategy for patients with MDD.

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Learning Objectives
1. To investigate the importance of earlier vs later antipsychotic adjunct therapy in patients with major depressive disorder.
2. To determine a correlation of early antipsychotic adjunct therapy and reduced healthcare utilization and cost.

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W47. CERC-301: AN ORAL NR2B SPECIFIC NMDA ANTAGONIST BEING DEVELOPED FOR THE TREATMENT OF MAJOR DEPRESSIVE DISORDER WITH POTENTIAL FOR A RAPID ONSET OF ANTIDEPRESSANT EFFECT

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Abstract   There is a significant unmet medical need for rapidly acting treatment of subjects with severe major depressive disorder (MDD) who have not adequately responded to antidepressant therapy. Current antidepressants require weeks to achieve full efficacy, may have significant side effects and still fail in a high percentage of subjects. Rapid reduction of severe depression is important to reduce the need for hospitalization and risk of self-harm and mortality. Considerable clinical and preclinical evidence suggests drugs that block the N methyl-D-aspartate (NMDA) receptor complex result in a rapid onset of antidepressant response in chronic stress animal models of depression and in patients who are resistant to available antidepressants. The potential utility of NMDA receptor blockers for psychiatric disease is broad, including MDD, bipolar depression and obsessive-compulsive disorder. Some core symptoms of depression, such as suicidality, may be uniquely sensitive to NMDA receptor blockade, thus potentially providing a lifesaving treatment effect.

CERC-301, a highly selective, orally bioavailable, N-methyl-D-aspartate (NMDA) receptor subunit 2B (NR2B), also referred to as Glutamate NMDA receptor subunit epsilon-2 (GluN2B) antagonist. CERC-301 previously showed signs of promise in a five patient, Phase 1B cross-over pilot study of treatment resistant depression, with daily doses up to 8 mg demonstrating improvement in the 17-item Hamilton Depression Rating Scale (HDRS-17), the Beck Depression Inventory (BDI) but not on the Montgomery-Asberg Depression Rating Scale (MADRS). Two additional clinical studies were completed by Cerecor in 2014, Clin301-200-A and Clin301-201.

Clin301-200-A was a 7 day, randomized, double-blind, placebo-controlled, parallel-group, safety, pharmacokinetic, and pharmacodynamic study of CERC-301 in cohorts of young, intermediate and elderly healthy subjects (total N=48). Daily doses of 8, 12, 16 and 20 mg were explored, providing the safety database to enable future outpatient studies of CERC-301 at up to 20 mg daily. Clin301-201 was a Phase 2a randomized, double-blind, placebo-controlled, study of 8mg of CERC-301 in the adjunctive treatment of subjects with severe depression and recent active suicidal ideation despite antidepressant treatment, using Sequential Parallel Comparison Design (SPCD) to evaluate the antidepressant effects of CERC-301, and was designed to confirm the 8mg efficacy signal observed in the earlier pilotcross-over study. The study population was enriched for subjects with recent active suicidal ideation. CERC-301 was administered daily at a dose of 8mg for 28 days and did not meet its primary endpoint of a change in the HDRS-17 at day 7. Results from both Clin301-200-A and Clin301-201 have been used to design the next Phase 2 efficacy study. Clin301-203 is a Phase 2, randomized, double-blind, placebo-controlled, sequential parallel study of CERC 301 in the treatment of subjects with severe depression despite antidepressant treatment and is designed to study higher doses than 8mg versus placebo administered every 7 days. Data will be presented from both Clin301-200-A and Clin301-201 as will the design of the planned Phase 2 study, Clin301-203.

W48. MAJOR DEPRESSIVE DISORDER WITH MIXED FEATURES: CLINICAL CHARACTERISTICS OF PATIENTS ENTERED IN A MULTIREGIONAL PLACEBO-CONTROLLED STUDY

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Abstract Introduction: Major Depressive Disorder (MDD) with mixed features (subthreshold hypomania) has been identified as a distinct nosological entity in the DSM-5. Failure to address subthreshold hypomania within the context of MDD can adversely affect the clinical course of the disorder (Zaninotto et al., 2014). We identified the predominant manic symptoms at baseline as part of a multiregional, placebo-controlled study involving patients with MDD with mixed features.

Methods: This study was done as part of the subject selection approval process for a clinical trial called RESOLVE 1: A randomized, 6-week, double-blind, placebo-controlled, flexible-dose, parallel group study of lurasidone for the treatment of major depressive disorder with mixed features (Clinicaltrials.gov NCT01421134). All eligible patients were required to have a diagnosis of MDD, current Major Depressive Episode, and 2-3 protocol-specified manic symptoms (consistent with DSM 5 criteria) for at least 2 weeks or more prior to screening. Eligible patients were randomized 1:1 to either lurasidone (flexible doses of 20 mg/d, 40 mg/d, 60 mg/d) or placebo once daily for 6 weeks. 44 clinical trial sites located in Russia, Serbia,

Ukraine, United Kingdom, and the United States participated in the study between April 2011 and October 2014.

Results: 211 subjects were enrolled in the study. Sixty two subjects were enrolled from the United States, 4 from the United Kingdom, 52 from Serbia, 62 from the Ukraine, and 31 from the Russian clinical trial sites. The mean total MADRS score was 33.2 ± 4.2 (SD) and the mean total HAM-A score was 16.9 ± 6.4 (SD) with no significant differences in scores in the US compared to Europe. The MADRS items of apparent sadness, reported sadness, reduced sleep, and concentration difficulties were associated with the highest mean item scores (4.1 ± 0.8, 4.4 ± 0.7, 4.3 ± 1.1, and 4.0 ± 0.9, respectively). The mean total YMRS score was 12.4 ± 5.0 in the U.S. compared to 10.0 ± 4.1 in Europe (t= 3.56; p= 0.0004). Overall, the YMRS items of decreased need for sleep, increased rate or amount of speech (talkativeness), and irritability were associated with the highest item mean scores (2.0 ± 0.9, 2.1 ± 2.1, and 1.9 ± 1.4, respectively). Of the 211 subjects, 133 subjects (63.0%) endorsed experiencing 2 of the 7 protocol-specific manic symptoms within the minimum 2 week interval required for the study; whereas 78 subjects (37.0%) endorsed 3 manic symptoms. Flight of ideas (racing thoughts) and increased talkativeness (pressured speech) were endorsed more than 60% of time as one of the manic symptoms.

Discussion: We identified flight of ideas (racing thoughts) and increased talkativeness (pressured speech) as the most frequent manic symptoms meeting eligibility criteria in this acutely depressed population. Our findings are consistent with observed manic symptoms identified in another "mixed" depression population (Koukopoulos et al., 2013). Individual MADRS item analyses revealed depressed mood, reduced sleep and concentration difficulties as the most prominent symptoms during screening. In this analyses, irritability and distractibility (concentration difficulties) were also reported as often as flight of ideas and increased talkativeness and co-existed within the mixed depression population.

Learning Objectives
1. To identify the predominant clinical characteristics of a population of patients meeting protocol specified criteria for Major Depressive Disorder with mixed features.
2. To identify the most frequently endorsed symptoms on the MADRS and YMRS in a multiregional population of patients meeting protocol specified criteria for Major Depressive Disorder with mixed features.

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W49. RELATIVE EFFICACY AND TOLERABILITY OF VORTIOXETINE VERSUS COMMONLY USED ANTIDEPRESSANTS FOR MAJOR DEPRESSIVE DISORDER: A META-REGRESSION OF CLINICAL TRIALS

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Abstract Purpose: Vortioxetine, a novel antidepressant with a multimodal mechanism of action, is approved for the treatment of adults with major depressive disorder (MDD) [1]. This

extension of a recently published meta-analysis [2] compares the efficacy and tolerability of vortioxetine with seven marketed antidepressants commonly used in the US.

Methods: Indirect comparisons using meta-regression, an extension of random-effects meta-analysis, were performed using data from 54 double-blind, placebo-controlled Phase 3 pivotal studies identified in a systematic review (N=18,312 patients). To ensure study comparability, only the experimental drug and placebo arms were included in primary analyses. Study-level standardized mean differences to placebo were regressed on active treatment to compare efficacy and tolerability of vortioxetine with branded (levomilnacipran, vilazodone, desvenlafaxine) and generic (duloxetine, escitalopram, sertraline, venlafaxine) antidepressants. Efficacy was defined as change from baseline on the Montgomery-Åsberg Depression Rating Scale or the Hamilton Depression Rating Scale after 6−12 weeks of treatment. Tolerability was defined as the withdrawal rate due to any adverse event.

Results: Standardized mean differences for vortioxetine compared with the selected antidepressants (negative estimates favor vortioxetine) were: duloxetine, 0.10 (95% confidence interval [CI]: -0.12, 0.32); escitalopram, -0.04 (95% CI: -0.32, 0.24); sertraline, -0.02 (95% CI: -0.39, 0.34); venlafaxine, 0.14 (95% CI: -0.11, 0.39); levomilnacipran, -0.05 (95% CI: -0.28, 0.19); vilazodone, -0.23 (95% CI: -0.53, 0.06); and desvenlafaxine, 0.04 (95% CI: -0.16, 0.23). Significantly lower withdrawal rates were observed for vortioxetine versus sertraline, venlafaxine, and desvenlafaxine (all P<0.05). No statistically significant differences in withdrawal rates were observed between vortioxetine and duloxetine, escitalopram, levomilnacipran, or vilazodone.

Conclusion: These findings indicate that vortioxetine offers a combination of efficacy and tolerability in MDD at least comparable to other antidepressants marketed in the US.

Learning Objectives
1. To compare the efficacy profile of vortioxetine with seven commonly used antidepressants marketed in the US.
2. To compare the tolerability profile of vortioxetine with seven commonly used antidepressants marketed in the US.

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W50. OPEN BOARD

W51. DEUTERIUM-MODIFIED DEXTROMETHORPHAN AND ULTRA LOW-DOSE QUINIDINE (AVP-786; D6 DM/Q): RESULTS OF A PHASE 1 SEQUENTIAL DRUG INTERACTION TRIAL WITH PAROXETINE AND DULOXETINE IN HEALTHY SUBJECTS

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Abstract Background: AVP-786 (d6-DM/Q) is a combination of deuterated dextromethorphan (d6-DM) and ultra-low dose quinidine (Q) being studied as an adjunctive therapy in major depression. Deuterium, a non-radioactive stable isotope of hydrogen, is ubiquitous in the environment, including water. Avanir has shown that DM deuteration significantly reduces susceptibility to CYP2D6 enzyme metabolism in nonclinical and clinical studies. Combining d6-DM with quinidine (Q), a CYP2D6 inhibitor, increases d6-DM bioavailability. This phase

1 study evaluated the pharmacokinetic (PK) interactions between AVP-786 (d6-DM 30 mg and Q 4.75 mg BID), and paroxetine (PRX; 20 mg/d) or duloxetine (DUL; 20 mg BID). Both PRX and DUL are CYP2D6 substrates and inhibitors, and both are approved for treatment of depression. Concurrent use with AVP-786 in clinical trials or following approval would be likely.

Methods: Single-center, open-label, sequential drug interaction study in healthy volunteers (aged 18–50 years, BMI 18-30 kg/m2, genotyped as extensive metabolizers of CYP2D6). Subjects enrolled in 1 of 4 groups (N=14 each): Group 1, PRX days 1–20, AVP-786 days 13–20; Group 2, AVP-786 days 1–20, PRX days 9–20; Group 3, DUL days 1–13, AVP-786 days 6–13; Group 4, AVP-786 days 1–13, DUL days 9–13. Pharmacokinetic parameters, including AUC, Cmax, Tmax, t½, Cmin and Tmin, were derived using non-compartmental methods for relevant analytes (d6-DM, d3-dextrorphan (d3-DX), Q, and PRX or DUL). Single vs combined administration were compared in each group using geometric mean ratios of Cmax and AUC0-12 (AUC0-24 for paroxetine) with 90% confidence intervals. Safety and tolerability were also assessed.

Results: Of 56 subjects enrolled, 50 completed the study (n=11, 14, 14, and 11 in Groups 1, 2, 3, and 4, respectively). In Group 1, AVP-786 coadministration increased steady-state systemic exposure (AUC) of PRX 1.64 fold and Cmax 1.49 fold vs PRX alone. Likewise, in Group 2, PRX coadministration increased the AUC and Cmax of the AVP-786 components d6-DM (2.18 fold and 1.81 fold) and Q (1.33 fold and 1.25 fold) with a corresponding decrease in exposure to the d3-DX metabolite (AUC decrease 28.4%; Cmax decrease 32.9%) compared with AVP-786 alone. In Group 3, AVP-786 coadministration increased steady-state systemic exposure (AUC) of DUL 1.84 fold and Cmax 1.68 fold vs DUL alone. In Group 4 DUL did not appreciably affect the d6-DM or Q component of AVP-786 nor the d3-DX metabolite.

The percentages of subjects reporting any AE on monotherapy vs. combination therapy were: Group 1: 50% vs. 83%, Group 2: 64% vs. 93%, Group 3: 43% vs. 50% and Group 4: 50% vs. 50%. The most commonly reported AEs in Groups 1 and 2 (AVP-786 and PRX) were dizziness, diarrhea, nausea. The most commonly reported AEs in Groups 3 and 4 (AVP-786 and DUL) were fatigue and muscle tightness. Clinical laboratory tests, vital signs, and ECG assessments showed no clear safety differences between treatments.

Conclusions: This phase 1 study showed that AVP-786 coadministration increased systemic exposure to PRX (~1.6 fold) and DUL (~1.8 fold) compared with either drug alone. Likewise, PRX increased exposure (~2.2 fold) to the d6-DM, component of AVP-786 with a corresponding decrease (~28%) in d3-DX metabolite exposure; Q exposure was modestly increased (~33%). DUL did not appear to affect exposure to d6-DM, its metabolite or Q.

Learning Objectives
1. Evaluate the drug-drug interaction potential of AVP-786 (deuterated dextromethorphan and ultra-low dose quinidine) when combined with paroxetine or duloxetine, two approved antidepressants that are metabolized by and inhibit CYP2D6.
2. Evaluate safety and tolerability of monotherapy compared with combined administration of AVP-786 and paroxetine or duloxetine in healthy volunteers.

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W52. MOTIVATION/ENERGY, FUNCTIONAL IMPAIRMENT, AND FUNCTIONAL HEALTH IN ADULTS WITH MDD TREATED WITH LEVOMILNACIPRAN ER

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Abstract Background: Decreased motivation and energy, impaired daily functioning, and reduced functional health are common complaints in patients with major depressive disorder (MDD). The effects of levomilnacipran extended-release (ER) on these symptom domains were evaluated in a Phase 3 trial using the 18-item Motivation and Energy Inventory (MEI), Sheehan Disability Scale (SDS), and 36-item Short-Form Health Survey (SF-36), respectively. Data from this 8 week, randomized, double-blind, placebo-controlled study were analyzed post hoc to explore the relationship between motivation/energy, functional health, and functional impairment.

Methods: Levomilnacipran ER (40-120 mg/d) effects on motivation/energy were analyzed based on changes from baseline to Week 8 in MEI total and subscale (social, cognitive) scores. Median MEI total scores at baseline were used to define patients with "low" and "high" levels of motivation/energy (≤ 28 and >28, respectively) before treatment. In each MEI subgroup, mean change from baseline to Week 8 was analyzed for SDS scores (total, subscales [work/school, social life, family/home life]) and SF-36 scores (Mental Component Summary [MCS], Physical Component Summary [PCS], 8 individual domains). Trellis plots of individual patient data were performed to explore the correlation between MEI total, SDS total, and SF-36 summary scores at baseline.

Results: At Week 8 in the overall population (N=429), the least squares mean difference (LSMD) for levomilnacipran ER vs placebo was significant for improvements on MEI total and subscale scores (total=5.05, P=.038; social=1.47, P=.045; cognitive=2.08, P=.021). LSMDs for levomilnacipran ER vs placebo on SDS total and subscale score changes were significant in the low MEI subgroup (total=-3.9, P<.001; work=-1.3, P=.002; social= 1.2, P=.002; family=-1.5, P<.001), but not the high MEI subgroup. The low MEI subgroup also had significantly greater improvements with levomilnacipran ER vs placebo on the SF 36 MCS (LSMD=5.50, P=.009) and 7 SF 36 domains (physical functioning, role-physical, general health, vitality, social functioning, role-emotional, mental health; all P<.05). No significant results for SF-36 score changes were found in the high MEI subgroup. Trellis plots suggested a moderate correlation between MEI total and SDS total scores at baseline; a stronger correlation was seen between baseline MEI total and SF 36 MCS scores.

Conclusions: This post hoc analysis showed that patients with lower motivation/energy at baseline experienced significant improvements in functional impairment and functional health after 8 weeks of flexible-dose treatment with levomilnacipran ER 40-120 mg/d compared with placebo. Correlation analyses suggest that motivation/energy may be related to functional impairment and functional health in patients with MDD, particularly in the domains more strongly associated with mental health.

Learning Objectives

1. To emphasize the importance of identifying and treating MDD patients who have decreased levels of motivation/energy.
2. To familiarize clinicians with the effects of levomilnacipran ER on motivation/energy and to highlight the impact of motivation/energy on functional impairment and health.

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W53. SWITCHING FROM INADEQUATE ADJUNCTIVE TREATMENT OPTIONS TO BREXPIPRAZOLE ADJUNCTIVE TO ANTIDEPRESSANT: AN OPEN-LABEL STUDY ON THE EFFECTS ON DEPRESSIVE SYMPTOMS AND COGNITIVE AND PHYSICAL FUNCTIONING

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Abstract Background: Brexpiprazole is a serotonin-dopamine activity modulator (SDAM) that is a partial agonist at 5-HT1A and dopamine D2 receptors at similar potency, and an antagonist at 5-HT2A and noradrenaline alpha1B/2C receptors [1]. The efficacy, tolerability and safety of brexpiprazole as adjunctive treatment in patients with major depressive disorder (MDD) were demonstrated in two pivotal studies [2]. The objective of this study was to investigate the effect of brexpiprazole on depressive symptoms in patients not responding to augmentation of their current antidepressants with several different classes of adjunctive therapy.

Methods: A 6-week open-label, single arm study to evaluate switching from other adjunctive treatments to brexpiprazole adjunctive to antidepressants. Patients 18 to 65 years of age were enrolled who had an inadequate response to a medication adjunctive to their base antidepressant (aripiprazole, quetiapine, bupropion, other antidepressants, or stimulants), and previous failure (same or earlier episode) to an adequate dose and duration of antidepressant monotherapy. Efficacy was measured by change from baseline in total score of the MADRS and cognitive and physical functioning questionnaire (CPFQ); safety and tolerability were also assessed regularly.

Results: Out of 61 enrolled, 51 patients (83.6%) completed 6 weeks of treatment with adjunctive brexpiprazole. Mean baseline scores were 29.6 for MADRS and 29.3 for CPFQ; scores were similar across prior adjunctive therapy. The overall mean change from baseline in MADRS was -17.3 (p<.0001), and ranged from -12.8 (p<.0001) for patients switched from adjunctive aripiprazole (n=12) to -19.5 (p<.0001) for patients switched from combination antidepressants (n=12). Mean change from baseline in CPFQ overall was -9.2 (p<.0001), and ranged from -5.6 (p<.0178) for patients switched combination antidepressant (n=12) to -13.3 (p=.0003) for patients switched from adjunctive stimulants (n=6). The most common treatment emergent adverse event was fatigue (9/61, 14.8%), no other adverse events were reported at rates higher than 10%.

Conclusion: After switching to brexpiprazole from a range of therapies adjunctive to their base antidepressant, patients showed marked improvement in depressive symptoms and self-reported improvements in cognitive and physical functioning. Tolerability was similar to what was observed in other larger, placebo-controlled clinical studies.

Learning Objectives
1. To understand the effect of switching from other medications adjunctive to antidepressants to adjunctive brexpiprazole in patients with major depressive disorders.
2. To understand the use of cognitive and physical functioning questionnaire in patients being treated for major depressive disorder.

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W54. ADJUNCTIVE BREXPIPRAZOLE (OPC-34712) IN YOUNG PATIENTS WITH MDD WHO ARE WORKING OR AT SCHOOL: AN EXPLORATORY STUDY

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Abstract Background: MDD is associated with impairments across multiple domains of patient functioning [1]. The optimal outcome for a patient with MDD, particularly in young patients is a full recovery from the major depressive episode and preservation of social functioning including holding a job [2]. There is a need for a new treatment of MDD that optimizes symptom control in young patients that are not associated with tolerability issues affecting the patient's ability to remain on treatment. Brexpiprazole is a rationally designed serotonin-dopamine activity modulator (SDAM) that is a partial agonist at 5-HT1A and dopamine D2 receptors at similar potency, and an antagonist at 5-HT2A and noradrenaline alpha1B/2C receptors [3]. The purpose of this open-label study (NCT02013609) was to investigate the effects of flexibly dosed brexpiprazole in the improvement of symptoms in young adults with major depressive disorder who have not responded adequately to their current antidepressants and/or who are in school or working.

Methods: Patients 18 to 35 years old who had an inadequate response treatment history to at least 1 ADT and who were working 20 hours or more or who were students taking 6 credit hours or more, were enrolled and received open-label brexpiprazole adjunctive the their current antidepressant, for 12 weeks. Brexpiprazole was initiated at 0.5 mg/day in week 1, 1 mg/day for week 2, and increased to the target dose of 2 mg at the end of week 2, after which the dose could be increased to 3 mg/day, or decreased to 1 mg/day. The primary efficacy endpoint was change from baseline to Week 12 in the MADRS Total Score. Other outcomes were change from baseline to Week 12 in CGI-S, change from baseline to Week 12 in the Sheehan Disability Scale (SDS) scale, and the Work Limitations Questionnaire (WLQ). Safety outcome variable included adverse events vital signs, body weight, ECGs, SAS, AIMS, BARS and C-SSRS.

Results: A total of 47 patients were treated with adjunctive brexpiprazole, and of these 29 (61.7%) patients completed 12 weeks of treatment. Mean MADRS total score was 28.3 at baseline, indicating that the patients had mild to moderate depression symptoms. Improvements were observed in MADRS total score from Baseline to Week 12 (LS mean change: -18.1, $p < .0001$), which was supported by an improvement of -2.0 on the CGI-S. There

was also a general improvement of function as seen in SDS mean score (LS mean change: -3.74, p <.0001), including in the work/school subscale (LS mean change: -3.5, p <.0001). On the WLQ, specific to functioning at work or at school, there were robust improvements on all subscales. Brexpiprazole was well tolerated with no unexpected safety signals compared with that observed in pivotal trials [4].

Conclusion: Treatment with brexpiprazole may represent a novel and effective strategy for treatment of young adults with MDD who have an inadequate response to their antidepressant and who are working or at school.

Learning Objectives
1. To understand the efficacy of brexpiprazole in young adults with MDD who have an inadequate response to their antidepressant and who are working or at school.
2. To understand the effect of brexpiprazole on work/school, productivity and social function in young adults with MDD who have an inadequate response to their antidepressant and who are working or at school.

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W55. PHARMACOTHERAPY RELAPSE PREVENTION IN BODY DYSMORPHIC DISORDER: A DOUBLE-BLIND PLACEBO-CONTROLLED TRIAL

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Abstract Objective: Body Dysmorphic Disorder (BDD), an often-delusional preoccupation with perceived defects in one's physical appearance, is a distressing, impairing, and common disorder. SRIs appear to be selectively efficacious for BDD, including delusional BDD. However, very few pharmacotherapy studies have been conducted, and all studies have been short-term (≤4 months). No continuation treatment or relapse prevention studies have been conducted. We report on the first relapse prevention study in BDD. For the study's primary aim, we compared time to BDD relapse and relapse rates in responders to acute open-label escitalopram treatment who were subsequently randomized to placebo vs. continuation treatment with escitalopram for six additional months. The acute treatment phase is also of interest, because few prior acute-phase studies have been done in BDD, and all contained relatively small samples (N=15-34 medication-treated subjects).

Method: Across 2 sites, 100 adults with DSM-IV BDD were treated openly for 14 weeks with escitalopram (Phase 1). Fifty-eight escitalopram responders were then randomized to double-blind continuation treatment with escitalopram or switched to placebo for six additional months (Phase 2). Outcome measures were the BDD-YBOCS (primary outcome), Brown Assessment of Beliefs Scale (BABS), HAM-D, LIFE-RIFT (psychosocial functioning), and Q-LESQ Short

Form (quality of life). For the study's primary aim, Kaplan-Meier survival curves were generated to examine group differences in time to relapse (and proportion relapsing). Cox's proportional hazards regression was used to test for treatment effects. Random effects regression models examined change in secondary outcome measures.

Results: Phase 1 (acute-phase treatment): 67% of treated subjects and 81% of completers achieved response of BDD (p<.0001). Median time to first response was 7.9 weeks (95% confidence interval: 6.9-8.9). Significant improvement from baseline to the last phase 1 visit was attained on the BDD-YBOCS, BABS, HAM-D, LIFE-RIFT, and Q-LES-Q (all p's<0.0001). Phase 2 (placebo-controlled discontinuation phase): Time to relapse was significantly longer with escitalopram than placebo (hazard ratio=2.74, 95% CI=1.01-8.62, p=.047). Kaplan-Meier estimates of the 26-week relapse proportions were .48 for the placebo group versus .19 for the escitalopram group. There were no statistically significant between-group differences in BDD severity, depressive symptoms, psychosocial functioning, or quality of life. During six additional months of continuation treatment with escitalopram, there was no statistically significant change in BDD-YBOCS scores for subjects receiving medication.

Conclusions: Continuation-phase escitalopram was effective in delaying time to relapse, and a higher proportion of placebo-treated subjects relapsed compared to escitalopram-treated patients. BDD symptom severity did not significantly change with six additional months of escitalopram treatment following acute response.

Learning Objectives
1. To learn about results from the first relapse prevention study in body dysmorphic disorder.
2. To learn about results from the first study of continuation phase pharmacotherapy in body dysmorphic disorder.

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W56. PRECLINICAL EVIDENCE SHOWING THAT LISDEXAMFETAMINE (LDX) PREVENTS COMPULSIVE AND PERSEVERATIVE BEHAVIOUR ASSOCIATED WITH BINGE EATING

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Abstract Background: Binge-eating disorder (BED) is a psychiatric condition characterised by compulsive, perseverative bouts of excessive consumption of palatable foods. LDX, a prodrug of d amphetamine, is approved to treat ADHD and is being evaluated in BED (1). Rats given irregular, limited access to chocolate develop robust binge-eating (BE) and LDX decreases chocolate bingeing (2). We have investigated whether BE rats show compulsive and perseverative responding when given access to chocolate and the influence of LDX on these behaviours.
Methods: Thirty-four adult, female, Wistar rats were given continuous access to chow and water. BE rats were given intermittent access to chocolate over 28 days. Non-binge (NB) controls were presented with an empty pot on these occasions. BE and NB rats were trained to perform the basic conditioned avoidance response (CAR) test in a 2-chamber shuttle box, ie

presentation of a tone/light stimulus warned of a mild foot shock 10s later if they did not relocate to the adjacent compartment. After CAR training, a chocolate-filled jar was put in 1 compartment of the shuttle box. When the rat entered this chamber, the conditioning stimulus was presented after a variable interval followed 10s later by a foot shock if the rat did not leave. Residence in the "safe" chamber without the pot did not initiate a trial and no foot shocks were given. LDX (0.8 mg/kg po [d-amphetamine base]) was tested. Results are mean ± SEM (n=14-17 rats/group).

Results: BE rats consumed 35.2 ± 5.2 kJ of chocolate in the test. Trials were only initiated by a rat entering the compartment with the pot. BE rats spent 309 ± 14 sec in the chocolate-paired compartment (~74% of the session) compared with 237 ± 10 sec (~20%) for NB controls (p<0.05). BE rats responded to the warning and left before receiving a foot shock (avoidance) in 78% of the trials compared with 98% for NB rats (p<0.01). The % of trials where BE rats received foot-shocks before leaving the compartment (esc

Learning Objectives
1. Determine whether BE rats show compulsive and perseverative behaviours.
2. Investigate whether LDX reduces compulsive and perseverative responding in BE rats.

Literature References
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W57. TIME COURSE OF THE EFFECTS OF LISDEXAMFETAMINE DIMESYLATE IN TWO PHASE 3 RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIALS IN ADULTS WITH BINGE EATING DISORDER

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Abstract Background: In 2 phase 3, randomized, placebo (PBO)–controlled trials, lisdexamfetamine dimesylate (LDX) reduced binge eating days/week (primary endpoint) in adults with protocol-defined moderate to severe binge eating disorder (BED). Here, LDX time course effects on secondary endpoints are reported.
Methods: Two 12-week, double-blind, PBO-controlled trials randomized (1:1) adults meeting DSM-IV-TR BED criteria (study 1, N=383; study 2, N=390) to PBO or LDX (50 or 70 mg). Clinical Global Impressions–Improvement (CGI-I) scores were assessed at each postbaseline visit and dichotomized (improved [very much improved/much improved] or not improved [minimally improved to very much worse]). Using daily binge eating diaries, binge eating episodes/week and 1-week binge eating responses (100%, 95%–75%, 74%–50%, and ≤49% reductions in binge eating episodes/week) were derived at each visit. Body weight was measured at each visit. Yale-Brown Obsessive-Compulsive Scale Modified for Binge Eating (Y-BOCS-BE) scores were assessed at baseline and weeks 4, 8, and 12/early termination (ET). For binge eating episodes/week and 1-week binge eating response, P-values are unadjusted and presented for descriptive purposes only; these endpoints were not part of the testing hierarchy.

Results: The full analysis set in studies 1 and 2 included 374 (PBO, 184; LDX, 190) and 350 (PBO, 176; LDX, 174) participants, respectively. The percent of participants improved on the CGI-I with LDX was numerically greater at week 1 (PBO vs LDX: study 1, 23.0% [42/183] vs 47.9% [90/188]; study 2, 21.8% [38/174] vs 39.3% [68/173]) through week 10 and statistically greater at week 12/ET (PBO vs LDX: study 1, 47.3% [87/184] vs 82.1% [156/190]; study 2, 42.9% [75/175] vs 86.2% [150/174]; both P<0.001). Mean±SD baseline binge eating episodes/week (PBO vs LDX) were 5.96±2.551 vs 6.42±2.962 in study 1 and 6.62±3.797 vs 6.40±3.463 in study 2; least squares (LS) mean (95% CI) treatment differences numerically favored LDX at week 1 (study 1: −1.73 [−2.28, −1.18]; study 2: −1.65 [−2.23, −1.07]) and all visits, including week 11/12 (study 1, −1.77 [−2.24, −1.30]; study 2, −2.23 [−2.77, −1.69]; both P<0.001). Percentages of participants exhibiting 1-week binge eating response reductions of 100% with LDX were numerically greater at week 1 (PBO vs LDX: study 1, 7.7% [14/183] vs 21.8% [41/188]; study 2, 2.9% [5/174] vs 9.8% [17/173]) through week 12/ET (PBO vs LDX: study 1, 26.6% [49/184] vs 47.1% [88/187]; study 2, 23.0% [40/174] vs 54.6% [95/174]). The LS mean (95% CI) treatment difference in percent change from baseline body weight was numerically greater with LDX at week 1 (study 1, −1.48 [−2.02, −0.95]; study 2, −1.56 [−2.00, −1.13]) through week 10 and statistically greater at week 12 (study 1, −6.35 [−7.17, −5.54]; study 2, −5.41 [−6.39, −4.44]; both P<0.001). Mean±SD baseline Y-BOCS-BE total scores (PBO vs LDX) were 21.51±4.745 vs 21.78±4.886 in study 1 and 21.52±4.840 vs 21.12±4.411 in study 2; LS mean (95% CI) treatment differences numerically favored LDX at week 4 (study 1: −6.53 [−8.09, −4.98]; study 2: −7.12 [−8.65, −5.60]) and week 8 and were statistically greater at week 12 (study 1, −7.40 [−8.93, −5.88]; study 2, −7.94 [−9.51, −6.36]; both P<0.001).

Conclusions: LDX produced greater global improvement and reductions in binge eating behavior, body weight, and the obsessive-compulsive features of BED than PBO in adults with moderate to severe BED. Clinical improvement was observed by week 1 and maintained through week 12.

Learning Objectives
1. To understand the time course of lisdexamfetamine dimesylate treatment effects on measures related to global symptom improvement, binge eating behavior, and obsessive-compulsive features in adults with moderate to severe binge eating disorder.
2. To understand the time course of lisdexamfetamine dimesylate treatment on body weight in adults with moderate to severe binge eating disorder.

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W58. ADHERENCE TO TREATMENT WITH ANTIPSYCHOTIC MEDICATIONS AMONG PATIENTS WITH SCHIZOPHRENIA, MAJOR DEPRESSIVE DISORDER, OR BIPOLAR DISORDER

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Abstract Background: Medication nonadherence is common among patients with psychiatric disorders, as is comorbid substance abuse. The objectives of this analysis were to identify rates of potential nonadherence among patients prescribed antipsychotic agents and to assess the use of nonprescribed medications and/or illicit substances in these patients.

Methods: A retrospective review was conducted utilizing a database of urine samples submitted to the laboratory from patients prescribed antipsychotic medications. Samples were classified as positive for the antipsychotic if either parent and/or metabolite(s) were confirmed, or negative for the antipsychotic if neither parent nor metabolite(s) were detected. Samples were also evaluated for the presence of illicit substances (marijuana metabolite [THCA] and/or cocaine metabolite [benzoylecgonine]) and selected prescription medications that were unknown to the prescribing physician (based on the medication list submitted to the laboratory by the ordering clinician). Antipsychotic medications were tested using liquid chromatography/tandem mass spectrometry. Other drugs were tested using mass spectrometry confirmation only after a positive immunoassay result. Results are presented as the aggregate of all eligible samples.

Results: A total of 3609 eligible urine samples were analyzed from patients who were prescribed antipsychotic medications and had a diagnosis of schizophrenia (n=1561 samples), major depressive disorder (MDD; n=686 samples), or bipolar disorder (BD; n=1362 samples). Men provided the majority of schizophrenia samples (64.6%) compared with 37.8% of MDD samples and 39.7% of BD samples. Average age was 43.9 years (diagnostic groups combined). Among the schizophrenia samples, the most commonly prescribed antipsychotics were risperidone (18.2%), paliperidone (15.2%), and olanzapine (12.9%) compared with aripiprazole (31.3%), quetiapine (26.5%), and risperidone (17.6%) for the MDD samples and quetiapine (26.9%), aripiprazole (18.9%), and risperidone (16.4%) for the BD samples. The proportion of urine samples that tested negative for a prescribed antipsychotic medication was 32.8% for MDD, 27.2% for BD, and 19.0% for schizophrenia, which was significantly higher in both MDD (odds ratio [OR], 2.1; 95% confidence interval [CI], 1.7-2.6) and BD (OR, 1.6; 95% CI, 1.3-1.9) compared with schizophrenia samples. A medication of which the prescribing physician was unaware (ie, opiate, synthetic opioid, benzodiazepine) and/or an illicit substance (ie, marijuana, cocaine) was detected in significantly more samples from MDD patients (42.7%; OR, 2.1; 95% CI, 1.7-2.5) or BD patients (35.2%; OR, 1.5; 95% CI, 1.3-1.8) relative to schizophrenia patients (26.5%).

Conclusions: Results of this retrospective analysis of urine samples from patients with serious mental illness indicate that potential antipsychotic medication nonadherence and substance misuse may be even greater among patients with MDD or BD than those with schizophrenia. Urine drug monitoring of psychiatric patients may identify potential medication nonadherence and signals of potential substance abuse, thereby prompting interventions to address these issues and enhance treatment outcomes.

Learning Objectives
1. Understand the relative rates of potential nonadherence to treatment with antipsychotic medications among patients diagnosed with schizophrenia, major depressive disorder, or bipolar disorder.
2. Recognize the extent to which nonprescribed medications and illicit substances are used by psychiatric patients being treated with antipsychotic medications.

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W59. EPIDEMIOLOGY AND ECONOMIC BURDEN OF SEROTONIN SYNDROME WITH CONCOMITANT USE OF SEROTONERGIC AGENTS IN THE U.S. CLINICAL PRACTICE

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Abstract Objectives: To examine the prevalence and incidence of serotonin syndrome (SS) over time as well as the economic burden of SS with concomitant use of serotonergic agents (SAs) in the U.S. clinical practice in two different populations.

Methods: Adult (age ≥18 years) patients prescribed SAs were identified using Veterans Health Administration (VHA) (01OCT2008-30SEPT2012) database and IMS PharMetrics Plus (01JAN2010-31DEC2013) database (commercially insured population). Patients with continuous health plan enrollment 12 months prior to the index date, defined as the first SA prescription claim date, were included and followed until death, disenrollment or the end of the study period. Patient cohort assignment was based on drug exposure: Single monoamine oxidase inhibitor (MAOI), MAOIs in combination with other SAs, single non-MAOI SA, and multiple non-MAOI SAs (two, three, four, and five or more SAs). Patients may have had more than one SS event (International Classification of Diseases, 9th Revision, Clinical Modification [ICD-9-CM] code 333.99) and were assigned to cohorts based on drug exposure type. Outcomes of interest were annual incidence and prevalence of SS events and related health care utilization and costs. Poisson regression was used to estimate the adjusted SS incidence relative risk (IRR).

Results: A total of 3,349,984 veterans and 11,818,956 commercially insured patients were identified. The incidence rate of SS among patients prescribed SAs decreased over time from 0.19% in 2009 to 0.07% in 2012 in the VHA population, and from 0.17% in 2010 to 0.09% in 2013 in the IMS population. Overall SS prevalence decreased during the 4-year study period. Compared to patients prescribed one non-MAOI SA, the highest SS IRR was observed in two cohorts: 1) patients prescribed MAOIs in combination with SAs (VHA: 3.37 [95% confidence interval (CI): 2.47-4.60]; IMS: 5.49 [95%CI: 4.33-6.97]) and 2) patients prescribed ≥5 non-MAOI SAs (VHA: 5.49 [95% CI: 4.93-6.11]; IMS: 5.77 [95% CI: 5.30-6.28]). Inpatient visits accounted for 0.88% and 4.35% of all SS events in the IMS and VHA populations, respectively and the rate of inpatient visits increased as the number of non-MAOI SAs increased, from 0.24% in the one non-MAOI SA cohort to 6.93% in the cohort of ≥5 non-MAOI SAs in the IMS population. A similar trend was seen in the VHA population. The median cost per SS-related inpatient visit was $10,792 among IMS patients and $8,765 in VHA patients.

Conclusion: The analysis suggests that the incidence and prevalence of SS among patients using SAs in veterans and commercially insured populations are low, and there is increased risk of any SS event and SS-related hospitalization as more SAs are taken concomitantly. This data provides physicians with additional information about the risk of SS associated with prescribing SAs.

Learning Objectives

1. Identify epidemiological patterns of serotonin syndrome including annual prevalence and incidence for the general populations and among patients taking serotonergic agents.
2. Examine the prescribing practices of concomitant medications associated with serotonin syndrome.

Literature References

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W60. EFFECTS OF LISDEXAMFETAMINE DIMESYLATE ON FUNCTIONAL IMPAIRMENT MEASURED ON THE SHEEHAN DISABILITY SCALE IN ADULTS WITH MODERATE TO SEVERE BINGE EATING DISORDER: RESULTS FROM TWO PLACEBO-CONTROLLED TRIAL

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Abstract Background: In 2 phase 3, randomized, placebo (PBO)–controlled trials, lisdexamfetamine dimesylate (LDX) reduced binge eating days/week (primary endpoint) in adults with moderate to severe binge eating disorder (BED). In these trials, LDX functional impairment effects were also assessed with the Sheehan Disability Scale (SDS; exploratory endpoint).

Methods: Two 12-week, double-blind, PBO-controlled trials randomized (1:1) adults meeting DSM-IV-TR BED criteria (trial 1, N=383; trial 2, N=390) to PBO or LDX (50 or 70 mg). The SDS (assessed at baseline, week 6, and week 12/early termination [ET]) measures work/school, social life/leisure activity, and family life/home responsibilities impairment on scales ranging from 0 to 10 (mild, 1–3; moderate, 4–6; marked, 7–9; extreme, 10); total score ranges from 0– 30. Days lost from work/school were also assessed. Mixed-effect models for repeated measures assessed treatment differences in SDS total score changes from baseline at week 12; unadjusted P-values are included for descriptive purposes only as the SDS was not part of the hierarchical testing strategy.

Results: In trials 1 and 2, mean±SD baseline SDS total score was 10.81±7.536 and 11.33±7.330 with PBO and 10.52±7.212 and 10.88±7.809 with LDX, respectively. Least squares (LS) mean±SEM changes from baseline total score at week 12 in trials 1 and 2 were –4.96±0.429 and –5.04±0.405 with PBO and –7.76±0.421 and –8.74±0.398 with LDX, respectively (LS mean [95% CI] treatment differences: trial 1, –2.80 [–3.98, –1.61]; trial 2, –3.70 [–4.81,–2.58]; both P<0.001). Mean±SD baseline work/school impairment scores were 3.1±2.70 and 3.1±2.53 with PBO and 2.9±2.55 and 3.1±2.74 with LDX in trials 1 and 2, respectively. LS mean±SEM changes from baseline at week 12 were –1.3±0.14 and –1.3±0.14 with PBO and –2.2±0.14 and –2.4±0.14 with LDX in trials 1 and 2, respectively (LS mean [95% CI] treatment differences: trial 1, –0.8 [–1.2, –0.4]; trial 2, –1.1 [–1.5,–0.7]). Mean±SD baseline social life/leisure activity impairment scores were 4.2±2.93 and 4.3±3.02 with PBO and 4.0±2.91 and 4.1±3.01 with LDX in trials 1 and 2, respectively. LS mean±SEM changes from baseline at week 12 were –2.0±0.16 and –1.9±0.16 with PBO and –3.0±0.16 and –3.3±0.15 with LDX in trials 1 and 2, respectively

(LS mean [95% CI] treatment differences: trial 1, −1.0 [−1.4, −0.5]; trial 2, −1.4 [−1.8, −1.0]). Mean±SD family life/home responsibilities impairment scores were 3.5±2.69 and 3.9±2.76 with PBO and 3.6±2.66 and 3.6±2.82 with LDX in trials 1 and 2, respectively. LS mean±SEM changes from baseline at week 12 were −1.6±0.16 and −1.8±0.14 with PBO and −2.6±0.15 and −3.1±0.14 with LDX in trials 1 and 2, respectively (LS mean [95% CI] treatment differences: trial 1, −1.0 [−1.4, −0.5]; trial 2, −1.3 [−1.7, −0.9]). The baseline mean±SD number of days lost from work/school in the last week was 0.4±1.08 and 0.5±1.38 days with PBO and 0.3±0.87 and 0.4±1.03 days with LDX in trials 1 and 2, respectively; mean±SD change from baseline at week 12/ET in the number of days lost from work/school was −0.2±1.06 and −0.3±1.23 days with PBO and −0.1±1.08 and −0.4±1.11 days with LDX in trials 1 and 2, respectively.

Conclusions: In both trials, adults with moderate to severe BED exhibited mild to moderate functional impairment across all SDS domains at baseline. At week 12, numerically larger functional impairment reductions were observed with LDX vs PBO for SDS total and domain scores; LDX also produced greater reductions in days lost from work/school.

Learning Objectives
1. To understand the functional impairments in adults with moderate to severe binge eating disorder (BED) who participated in clinical trials of lisdexamfetamine (LDX), as measured by the Sheehan Disability Scale (SDS).
2. To understand the effect of LDX compared with placebo on functional impairment, as measured by the SDS, in adults with mild to moderate BED.

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W61. THE NEUROPROTECTIVE EFFECT OF ERYTHRINA VELUTINA STANDARDISED EXTRACT ON AMINO ACID LEVELS IN MOUSE HIPPOCAMPUS

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Abstract Introduction: The decrease in cerebral blood flow below 16ml of blood per 100g/min fact that the brain occurs in ischemic stroke, is a critical event that results in a series of functional, structural and biochemical culminating in irreversible neuronal death changes. Given the difficulty of truly effective drugs in the treatment of stroke in this study suggest a possible neuroprotective effect of standardized extract of E. velutina since species of this genus has shown significant action in the central nervous system. In anticonvulsant action, we observed a possible neuroprotective effect of the extract, which was detected a ratio of suppression of seizure and consequent cell death 1. Aims: The purpose of the present work was to study the effects of standardized extract of Erythrina velutina (SEEV) in the determination of amino acids in mice brain undergoing global cerebral ischemia (ISQ). Methods: The animals (swiss mice, males, 30-35 g) were subjected to transient cerebral ischemia by occlusion of both carotid arteries during 30 minutes and treated for 5 days with SEEV 200 or 400 mg/kg and Memantine (MEM) 10 mg/kg, 2 or 24 hours (2 or 24h) after ischemia. The same procedure

was done in false-operated group (FO) + dimetilsufóxido (DMSO) with the exception of clamping the carotid arteries. On day 6 after induction of ischemia, the animals were subjected to sacrificed and dissected brains on ice the hipocampus (HC), determination of glutamate (GLU), and gamma-amino-butirico acid (GABA). Statistical analysis were performed using two-way ANOVA considering significant when $p<0.05$. Results: The results show there was an increase in the amount of glutamate in the HC of ischemic animals treated with DMSO (ISQ + DMSO : 280,3 ± 46,2) compared to the control group (FO + DMSO : 45,0 ±7,7) . The amount GLU was reduced by both doses of SEEV (ISQ + SEEV 200mg 24h : 37,2 ±8,6) and (ISQ + SEEV 400mg 24h :11,6 ±3,4) with only 24 hours. Regarding the inhibitory amino acid in the HC groups (ISQ + MEM 10mg 24h: 468,0±63,9) and (ISQ+ SEEV 400mg 24H - 280,8 ± 73,0) showed a significant increase in GABA concentrations when compared to ischemic control (ISQ + DMSO - 109,3± 19,9). Conclusion: Our results indicate the interference the GABAergic system can lead to neuroprotection and that the decrease in glutamate levels, can improve neuronal injury.Therefore, it is possible to suggest that standardized extract of Erythrina velutina is a promising tool for the alternative treatment the cerebral ischemia, but more studies are needed to confirm this potential of this drug.

Learning Objectives
1. The purpose of the present work was to study the effects of standardized extract of Erythrina velutina (SEEV) in the determination of amino acids in mice brain undergoing global cerebral ischemia (ISQ).

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W62. EVALUATION OF CYTOCHROME P450 PHENOTYPES AND POTENTIAL IMPLICATIONS IN THE TREATMENT OF SERIOUS MENTAL ILLNESS

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Abstract   Background: Genetic variations in cytochrome P450 (CYP450) drug metabolizing superfamily of enzymes, specifically CYP2D6, CYP2C19, and CYP3A4/3A5 enzymes, can influence the effectiveness and tolerability of commonly prescribed psychiatric medications, such as antidepressants, antipsychotics, and anxiolytics. This analysis explored the distribution of variations in CYP450 phenotypes that can have potential implications in the treatment of serious mental illness.

Methods: Buccal swab DNA collected from a random sampling of patients was analyzed to detect single nucleotide polymorphisms (SNPs) contained in five CYP450 genes (CYP2C9, CYP2C19, CYP2D6, CYP3A4, and CYP3A5) and copy number variations (CYP2D6 gene) using the GenetAssist™ (Ameritox Ltd., Baltimore, MD) pharmacogenetic panel and TaqMan® real-time PCR technique (Thermo Fisher Scientific Inc., Waltham, MA). The genotypes were determined using AlleleTyper™ software (Thermo Fisher Scientific Inc., Waltham, MA). Phenotypes were assigned as ultra-rapid metabolizer (UM), extensive/normal metabolizer (EM), intermediate metabolizer (IM), and poor metabolizer (PM) based on the genotypes and published guidelines.

Results: Among the 165 patients included in this study, three CYP2C9 (*2, *3, and *8), five CYP2C19 (*2, *4B, *6, *8, and *17), fourteen CYP2D6 (*2A, *3, *4, *4N, *5, *9, *10, *17, *29, *35, *36, *41, *78, and *91), 2 CYP3A4 (*1B and *22), and five CYP3A5 (*1D, *3, *3B,

*6, and *7) allelic variants were detected. The majority of the patients had EM phenotype for CYP2C9 (UM, 0; EM, 85.5%; IM, 12.7%, PM: 1.8%), CYP2D6 (UM, 1.8%; EM, 89.7%; IM, 3.6%; PM, 4.8%; IM/EM, 0.6%), and CYP3A4 (EM, 100%) functions. However, for the CYP2C19 function, only 41.2% of patients had EM phenotype and 33.9% of patients had UM phenotype (IM, 23.6%; PM, 1.2%). Furthermore, for the CYP3A5 activity, only 1.8% of patients had EM phenotype (UM, 0; IM, 18.8%; PM, 79.4%). Sixty-nine (41.6%) of the samples had abnormality (UM or PM phenotypes) in at least one of the pathways, excluding CYP3A5.

Conclusions: Although the majority of the population had IM/EM phenotypes for the five CYP450 genes assessed, there were considerable genetic variations in these genes indicating differences in their drug metabolizing properties in this patient population. The frequencies of genotypes found in the five CYP450 genes in this study are in accordance with previously published results. This genetic variation can have potential implications to treatment success and tolerability of psychiatric medications. Pharmacogenetic testing can be an effective tool in the treatment of mental illness to help guide pharmacotherapy when clinicians are faced with challenging situations. Clinicians who are considering treatment changes for those difficult-to-treat patients (ie, patients who are not responding to current therapy, who are having significant adverse events, or who require a high dose of medication) can utilize pharmacogenetic testing optimally in conjunction with objective behavioral assessments and urine drug monitoring.

Sponsored by Ingenuity Health, a service of Ameritox Ltd.

Learning Objectives
1. Assess the frequency of genotypic and phenotypic variations of 5 cytochrome P450 genes (CYP2C9, CYP2C19, CYP2D6, CYP3A4, and CYP3A5) in a patient population.
2. Recognize the potential impact of genetic variations in cytochrome P450 genes on the treatment of mental illness.

Literature References
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W63. WEIGHT CHANGE AND CARDIOMETABOLIC RISK WITH ANTIPSYCHOTIC POLYPHARMACY: META-ANALYSIS SHOWING IMPROVED OUTCOMES WITH CERTAIN ARIPIPRAZOLE COMBINATIONS

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Abstract Background: While antipsychotic cotreatment (APC), used frequently in clinical practice, has been criticized for lack of evidence and additive adverse effects, open label data suggest that some combinations might improve cardiometabolic risk.
Objectives: To investigate the cardiometabolic effects of specific APCs.

Methodology: Data from randomized placebo controlled trials (RPCTs) of APC versus placebo in schizophrenia were meta-analyzed using random effects models. Primary outcome

was change in weight or BMI. Secondary outcomes included other cardiometabolic and psychopathology outcomes. For dichotomous data relative risk (RR) and for continuous data Hedges's g was calculated as effect size measures, each with 95% Confidence Intervals (CIs), and with number-needed-to-treat (NNT) and standardized/weighted mean difference (SMD/WMD) as appropriate.

Results: Eight RCPTs (n=786) lasting 8-16 weeks were analyzed. Compared with placebo, adding aripiprazole to clozapine or olanzapine (N=3, n=283) was the only APC associated with significant weight loss [SMD=-0.54 (CI:-0.78,-0.30), p<0.0001; WMD=-1.69kg (-2.79,-0.59, p=0.003], greater weight loss >7% [N=1, n=206, RR:4.93 (CI:1.48,16.42), p=0.009; NNT=9 (CI:6-25)] and significant reduction in total cholesterol [N=2, n=246, SMD=-0.43 (CI:-0.68,-0.18), p=0.0009)], LDL-cholesterol [N=2, n=241, SMD=-0.34 (CI:-0.57,-0.11), p=0.002)] and triglycerides [N=3, n=273, SMD=-0.35 (CI:-0.70,-0.00), p=0.05)], but not of HDL-cholesterol (p=0.95) or glucose (p=0.41). No significant cardiometabolic effects were found with risperidone or fluphenazine augmentation of clozapine (N=3, n=119), aripiprazole augmentation of quetiapine or risperidone (N=1, n=290) or aripiprazole augmentation of haloperidol (N=1, n=54). No significant changes were found regarding total psychopathology (p=0.25-0.94), positive symptoms (p=0.30-0.99) or negative symptoms (p=0.19-0.94) with any APCs. Side effects were not significantly different with placebo vs APC, except for significant prolactin decrease when adding aripiprazole to clozapine (p=0.0005) or quetiapine/risperidone (p<0.0001), while adding risperidone to clozapine raised prolactin significantly (p<0.0001].

Conclusion: Specific APCs differ in their cardiometabolic safety. Short-term addition of aripiprazole to a high metabolic risk antipsychotic (olanzapine, clozapine), but not to a medium risk (quetiapine, risperidone) or low risk (haloperidol) antipsychotic significantly improved body weight and lipid parameters. Adding risperidone or fluphenazine to clozapine did not have any beneficial effect and none of the combinations benefited or worsened psychopathology or short-term adverse effects, except for increased prolactin when adding risperidone to clozapine, while aripiprazole addition to clozapine, quetiapine or risperidone lowered prolactin.

Importance: The preliminary results from this meta-analysis suggest that certain aripiprazole cotreatments could improve weight and cardiometabolic outcomes.

Specific Findings: We hope to present change data on weight, metabolic parameters and change in psychopathology scores observed with antipsychotic cotreatment. We hypothesize based on results from the analysis, that certain antipsychotic cotreatments can improve cardiometabolic outcomes.

Learning Objectives
1. To investigate the cardiometabolic effects of specific Antipsychotic cotreatments.
2. To assess improved cardiometabolic outcomes with certain Antipsychotic cotreatments.

Literature References
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W64. COMPARATIVE POSOLOGICAL RESULTS FOR 3 FORMULATIONS OF PALIPERIDONE USED IN THE MANAGEMENT OF PATIENTS WITH PSYCHOTIC DISORDERS

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Abstract Purpose: To summarize differences in the results of clinical trials supporting the posology of 3 different formulations of paliperidone for the management of schizophrenia and schizoaffective disorder.

Content: With the introduction of a long-acting injectable formulation of paliperidone palmitate (PP) that is administered once every 3 months (PP3M), 3 different formulations of paliperidone are now available. It is important for clinicians to understand how each formulation fits into the management of schizophrenia.

Methodology: Available data from different clinical trials were used to compare key considerations around the use of the 3 paliperidone formulations—oral paliperidone extended-release (ER), long-acting injectable PP once-monthly (PP1M), and long-acting injectable PP3M—in patients with schizophrenia. Similar analyses from these trials were compared regarding the use of these medications for the acute, stabilization, and maintenance treatment of psychotic disorders.

Results: Both paliperidone ER and PP1M can be used for the acute treatment of schizophrenia or schizoaffective disorder as monotherapy or adjunctive to antidepressants and/or mood stabilizers. PP3M is indicated for use in patients with schizophrenia who have been previously stabilized on PP1M. The recommend dose of paliperidone ER is 6 mg, which can be titrated from 3-12 mg as needed. For PP1M, the initial dose on day 1 is 234 mg; on day 8 the dose is 156 mg (both day 1 and day 8 doses are administered in the deltoid muscle), followed by 39-234 mg (deltoid or gluteal muscle) per month thereafter. Previous oral antipsychotics can be discontinued at the time of treatment initiation. For PP3M, it is recommended that patients are adequately treated on PP1M for at least 4 months prior to administration. The dose of PP3M (administered in the deltoid or gluteal muscle) is derived from the PP1M dose multiplied by 3.5 (ie, for a total of 273-819 mg). For PP1M the dosing window is ±4 days for the second initiation dose and ±7 days for the maintenance doses. For PP3M the dosing window is ±2 weeks on exceptional occasions. To avoid an incomplete administration and ensure a homogeneous suspension both PP1M and PP3M should be shaken vigorously for at least 10-15 seconds within 5 minutes before administration. The median terminal elimination half-lives for paliperidone ER, PP1M, and PP3M within their indicated dose ranges have been demonstrated to be approximately 23 hours, 25-49 days, and 84-95 days (deltoid injections)/118-139 days (gluteal injections), respectively.

Implications: Despite providing the same molecule, paliperidone's various formulations have unique posological attributes. It is critical that clinicians understand these different attributes when using the 3 different formulations for the treatment and management of patients.

Support: Janssen Scientific Affairs LLC.

Learning Objectives
1. To educate participants on the 3 different formulations of paliperidone for the management of schizophrenia and schizoaffective disorder.
2. To educate participants on how each formulation of paliperidone fits into the acute, stabilization, and maintenance treatment of schizophrenia and schizoaffective disorder.

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W65. EFFECTS OF BITOPERTIN ON BIOMARKER MEASURES OF COGNITIVE DYSFUNCTION IN ADULTS WITH SCHIZOPHRENIA AND SCHIZOAFFECTIVE DISORDER: RESULTS FROM A PH1B, DOUBLE BLIND, PLACEBO CONTROLLED PARALLEL ARM STUDY

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Abstract Background: Schizophrenia-like deficits in electrophysiology measures, specifically decreases in mismatch negativity (MMN) and N1, are inducible by ketamine challenge in healthy volunteers, suggesting that they may serve as indices of NMDA dysfunction in schizophrenia. Targeting the allosteric glycine site of the NMDA receptor has been proposed as an approach to enhance NMDA receptor functioning in schizophrenia. This study assessed whether treatment with bitopertin, a selective, orally active inhibitor of the glycine transporter 1, reduced deficits in MMN.

Methods: Patients with schizophrenia or schizoaffective disorder (aged 18-65) clinically stable on antipsychotic treatment were randomized 3:2 to adjunctive, 6-week treatment with bitopertin 10mg or placebo. MMN, N1, P300 and VEP were obtained at baseline and week 6. Standard assessments were used to measure symptoms, including the PANSS.

Results: 29 patients (96.6% male) were randomized: 17 to bitopertin 10mg and 12 to placebo. The bitopertin group failed to show reduction from baseline compared to placebo in all MMNs; adjusted mean change (95%CI) in MMN amplitude (μV): duration (early): bitopertin: 0.76 (0.16, 1.36), placebo: -0.02 (-0.67, 0.63); duration (late): bitopertin: 0.49 (-0.04, 1.01), placebo: -0.30 (-0.86, 0.27); pitch: bitopertin: 0.35 (-0.22, 0.92), placebo: 0.90 (0.28, 1.51); intensity: bitopertin: 0.13 (-0.28, 0.53), placebo 0.59 (0.15, 1.03). Treatment with bitopertin did not demonstrate improvement in other endpoints when compared to placebo. The incidence of adverse events was low and similar in bitopertin and placebo groups.

Conclusions: This small study does not provide evidence that bitopertin 10mg enhances NMDA receptor functioning, consistent with negative phase III results.

Learning Objectives
1. Participants will understand the potential of electrophysiological measures, some of which are related to NMDA receptor functioning, as biomarkers of clinical effects in patients with schizophrenia.
2. Participants will be aware of the results of a proof-of-mechanism study with a selective, orally active inhibitor of the glycine transporter 1 (GLYT1).

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W66. EFFICACY OF CARIPRAZINE VERSUS PLACEBO ACROSS SCHIZOPHRENIA SYMPTOM DOMAINS: POOLED ANALYSES FROM 3 PHASE II/III TRIALS

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Abstract   Introduction: Schizophrenia is a complex disorder associated with diverse symptoms (eg, positive, negative, mood) and cognitive impairment. New antipsychotics with broad efficacy across the range of symptoms may improve the management of schizophrenia and enhance patient outcomes. Cariprazine is a potent dopamine D3 and D2 receptor partial agonist with preferential binding to D3 receptors. The efficacy, safety, and tolerability of cariprazine in the treatment of schizophrenia were supported in 3 Phase II/III studies. A pooled analysis evaluated the efficacy of cariprazine across the range of schizophrenia symptoms.

Methods: Data from 3 randomized, placebo-controlled trials were pooled. Studies were generally similar in design and included 6 weeks of double-blind treatment; the primary efficacy measure in all studies was the Positive and Negative Syndrome Scale (PANSS). All cariprazine dose groups (1.5 to 9 mg/d) were combined for analyses. Efficacy across symptom domains was evaluated using PANSS-derived Marder factor groupings (anxiety/depression, disorganized thought, negative symptoms, positive symptoms, uncontrolled hostility/excitement), PANSS cognitive factor, and PANSS single items. Change from baseline in factor scores and individual PANSS item scores were evaluated based on least squares mean differences (LSMDs) between cariprazine and placebo using a mixed-effects model for repeated measure approach; results were not adjusted for multiple comparisons. Effect sizes were calculated for all comparisons.

Results: The pooled study population comprised 442 placebo and 1024 cariprazine patients. Cariprazine was significantly superior to placebo on all PANSS Marder factors (anxiety/depression, P=.0015; other Marder factors, P<.0001) and the PANSS cognitive factor (P<.0001). Effect sizes for cariprazine versus placebo were: Marder factors—anxiety/depression (-0.21), disorganized thought (-0.47), negative symptoms (-0.39), positive symptoms (-0.37), uncontrolled hostility/excitement (-0.34); PANSS cognitive factor (0.48). Cariprazine- versus placebo-treated patients showed significantly greater improvement on 26 of 30 PANSS single items (3 of 4 items in the anxiety/depression factor [anxiety, tension, and depression; all P<.01], all 7 disorganized thought factor items [all P<.05], all 4 uncontrolled hostility/excitement factor items, 6 of 7 negative symptoms factor items [all items except motor retardation, P<.001], 6 of 8 positive symptoms factor items [all except somatic concern and grandiosity, P<.01], and all 5 cognitive factor items [all P<.001]). Statistical significance versus placebo was not reached for 4 PANSS items (somatic concerns, guilt feelings, motor retardation, and grandiosity). Effects sizes for PANSS single items that showed statistical significance ranged from -0.15 (mannerisms and posturing) to -0.44 (conceptual disorganization).

Discussion: In this pooled analyses, cariprazine- versus placebo-treated patients demonstrated significantly greater improvement on all Marder factors and the PANSS cognitive factor. Cariprazine was significantly superior to placebo on most PANSS single items. Results suggest that cariprazine has efficacy across the broad range of symptoms associated with schizophrenia; however, improvements in symptom domains can be secondary to improvement in psychosis during the treatment of acute schizophrenia.

Learning Objectives At the conclusion of this session, participants should be able to:
1. Identify the diverse range of mood symptoms and impairments associated with schizophrenia.
2. Evaluate the efficacy of cariprazine across the spectrum of symptoms associated with schizophrenia in this study.

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W68. SAFETY, TOLERABILITY, AND PHARMACOKINETICS OF A NOVEL PDE10A INHIBITOR -TAK-063 - FOLLOWING MULTIPLE DOSING IN SUBJECTS WITH STABLE SCHIZOPHRENIA AND HEALTHY JAPANESE SUBJECTS

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Abstract Background: TAK-063 selectively inhibits phosphodiesterase 10A (PDE10A), which hydrolyzes both cyclic adenosine monophosphate and cyclic guanosine monophosphate. PDE10A inhibition may aid schizophrenia treatment by modulating, indirectly or directly, the effects of glutamatergic and dopaminergic systems. The objective was to characterize the safety, tolerability, and pharmacokinetics (PK) of TAK-063 following repeated dosing.

Methods: This was a randomized, double-blind, placebo-controlled, multiple-dose study in stable schizophrenia subjects washed out of their current antipsychotic medications (n=47) and healthy Japanese subjects (n=30). Ten subjects per cohort were enrolled and randomized to either TAK-063 or placebo (8 active and 2 placebo). Schizophrenia subjects were dosed once daily (QD) 3, 10, 20, 30, and 100 mg and Japanese subjects were dosed 3, 10 and 20 mg TAK-063 QD in the fed state using tablets for 7 days. Safety assessments were recorded throughout; serial plasma and urine samples were collected on days 1 and 7 with pre-dose plasma samples on days 4, 5 and 6.

Results: TAK-063 was safe and generally well tolerated in both groups. There were no serious adverse events (AE) or deaths. Most AEs were of mild or moderate intensity. Somnolence, the most frequent AE in both treatment groups, was especially prevalent in schizophrenia subjects following 100 mg QD. Extrapyramidal syndrome (EPS), mainly dystonia, was observed in 14 schizophrenia subjects and 1 Japanese subject treated with TAK-063. EPS was also observed in one schizophrenia subject in the placebo group. No clinically significant changes in the physical examination, clinical laboratory tests or ECGs were observed. Blood pressure and pulse rate parameters were consistent with treatment emergent AEs of orthostatic tachycardia

and orthostatic hypotension and were similar between placebo and treatment groups. In the two groups, PK was broadly similar; in addition to TAK-063, a metabolite, M-I, was also quantified and exhibited a similar profile to TAK-063. TAK-063 was absorbed with a median Tmax of 1.5 to 4 hours. Cmax and AUC24 values of TAK-063 and M-I increased in a dose related manner up to 30 mg in schizophrenia subjects and in Japanese subjects up to 20 mg with modest accumulation upon repeat dosing. At doses of 30 to 100 mg, the increase in exposure was less than dose proportional. Renal clearance was a minor elimination route (<0.1% of dose).

Discussion: TAK-063 was safe and well tolerated in schizophrenia and Japanese subjects at all doses tested; somnolence was the most commonly observed AE. At equivalent doses, reports of EPS were higher in subjects with schizophrenia than in healthy Japanese subjects, despite similar PK between groups. At doses of 30 to 100 mg, the increase in exposure was less than dose proportional likely due to solubility-limited oral bioavailability.

Learning Objectives
1. Understand early clinical safety and tolerability results of TAK-063, a novel PDE-10A inhibitor in development for the treatment of schizophrenia.
2. Understand the pharmacokinetics of TAK-063 following multiple daily doses in schizophrenia patients and healthy Japanese subjects.

Literature References
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W69. AN ANTIPSYCHOTIC TREATMENT THAT DELIVERS PALIPERIDONE PROVIDES A 3-MONTH DOSING INTERVAL: AN ASSESSMENT OF A RELAPSE-PREVENTION TRIAL

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Abstract Purpose: To present the efficacy and safety data from an international, placebo-controlled, relapse-prevention study (NCT01529515) of a formulation of paliperidone palmitate (PP) with a 3-month dosing interval in patients with schizophrenia with distinct baseline characteristics.

Content: Given the extended apparent elimination half-life of paliperidone, an investigational, long-acting, injectable formulation of PP provides a 3-month dosing interval (PP3M). This opens the potential for effective antipsychotic treatment with administration 4 times per year.

Methodology: Adults with schizophrenia (per DSM-IV-TR) were stabilized with PP once-monthly (PP1M) in an open-label (OL) 17-week transition phase, followed by a single PP3M injection in an OL 12-week maintenance phase. Qualifying subjects were then randomly assigned to PP3M or placebo in a double-blind (DB) relapse-prevention phase. An interim analysis of the efficacy data after 42 relapse events was overseen by an independent data-monitoring committee (IDMC). Time to relapse of PP3M vs placebo was assessed using the Kaplan-Meier method (with a log-rank test for treatment difference). The final efficacy data were further evaluated using Cox proportional hazards models after adjusting for age group

(18-25, 26-50, 51-65, and >65 years), sex (male, female), and OL baseline body mass index (BMI) category (normal: <25 kg/m2; overweight: ≥25 kg/m2 to <30 kg/m2; obese: ≥30 kg/m2).

Results: A total of 506 patients entered the study, and 305 (60.3%) were randomly assigned to PP3M (n=160) or placebo (n=145). At the interim assessment, PP3M was associated with a significant delay in relapse of psychotic symptoms compared to placebo (2-sided log-rank test, p<0.001). The Cox analysis showed a 3.45-fold greater risk of relapse with placebo vs PP3M (hazard ratio [HR], 3.45; 95% confidence interval [CI], 1.73-6.88; p=0.0004). Based on this interim analysis, the IDMC recommended early study termination for evidence of efficacy. Final study results were consistent with the interim analysis (HR: 3.81; 95% CI, 2.08-6.99; p<0.0001). These findings were consistent regardless of age, sex, or BMI (p<0.0001, regardless of factor included in the model). Common treatment-emergent adverse events more frequently reported after DB baseline by subjects receiving PP3M vs placebo included weight gain (8.8% vs 3.4%), headache (8.8% vs 4.1%), nasopharyngitis (5.6% vs 1.4%), and akathisia (4.4% vs 0.7%).

Importance: In patients with schizophrenia initially treated with PP1M, PP3M significantly delayed relapse of psychotic symptoms compared to placebo. These results support the use of this formulation of paliperidone in patients with schizophrenia with a need for injections and associated patient-level assessments of adherence only 4 times per year.

Support: Janssen Pharmaceuticals Inc.

Learning Objectives
1. To understand the role of a long-acting injectable formulation of paliperidone palmitate (PP) with a 3-month dosing interval (PP3M) in the treatment of patients with schizophrenia with distinct baseline characteristics.
2. To understand how PP3M can significantly delay relapse of psychotic symptoms in patients with schizophrenia regardless of baseline characteristics.

Literature References
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W70. EFFICACY AND SAFETY OF BREXPIPRAZOLE (OPC-34712) AS MAINTENANCE TREATMENT IN ADULTS WITH SCHIZOPHRENIA: A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY

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Abstract Background: Brexpiprazole is a serotonin-dopamine activity modulator that is a partial agonist at 5-HT1A and dopamine D2 receptors at similar potency, and an antagonist at 5-HT2A and noradrenaline alpha1B/2C receptors [1]. The efficacy and safety of brexpiprazole

for the treatment of adults experiencing an acute exacerbation of schizophrenia was demonstrated in two 6-week phase 3 trials [2,3]. The objective of this study was to evaluate the efficacy, safety, and tolerability of brexpiprazole compared with placebo as maintenance treatment in adults with schizophrenia [NCT01668797].

Methods: Patients experiencing an acute exacerbation (PANSS total score >80) of schizophrenia were cross-titrated from current antipsychotic treatment(s) to brexpiprazole over a period of 1 to 4 weeks if required, before entering a 12 to 36 weeks single-blind stabilization phase on brexpiprazole (1 to 4 mg). Stability of symptoms was defined as: 1) Outpatient status, and 2) PANSS total score ≤70, and 3) A score of ≤4 on PANSS items P02, P03, P06, G09, and 4) CGI-S ≤4, and 5) No current suicidal behavior, and 6) No violent or aggressive behavior. Patients with stable symptoms over a period of 12 consecutive weeks and on stable dose of brexpiprazole for at least the last 4 weeks were then randomized to the stabilization dose of brexpiprazole or placebo for up to 52 weeks (maintenance phase). The primary efficacy endpoint was the time from randomization to exacerbation of psychotic symptoms/impending relapse which was defined as any of the following criteria: 1) CGI-I score ≥5 and an increase on any of PANSS items P02, P03, P06, G09 to a score of >4 (with an absolute increase of ≥2 on that specific item since randomization or with an absolute increase of ≥4 on the combined four PANSS items), or 2) Hospitalization due to worsening of psychotic symptoms, or 3) Current suicidal behavior, or 4) Violent or aggressive behavior.

Results: The study was terminated early by an Independent Data Monitoring Committee because efficacy was demonstrated by the first pre-planned interim analysis. A total of 464 patients entered the stabilization phase, of whom 202 achieved stabilization and were randomized to brexpiprazole (n=97) or placebo (n=105). The primary analysis showed beneficial effect of brexpiprazole relative to placebo on the time to exacerbation of psychotic symptoms / impending relapse (log-rank test: hazard ratio=0.292, p<0.0001). There was a statistically significant difference in the relapse rate between brexpiprazole and placebo groups (13.5% vs 38.5%, p<0.0001). During the stabilization phase, 9.3% of patients were withdrawn due to adverse events. During the maintenance treatment phase the withdrawal rates due to adverse events were 6.2% and 11.5% in the brexpiprazole and placebo groups, respectively.

Conclusion: Brexpiprazole was effective in preventing exacerbation of psychotic symptoms/impending relapse in patients with schizophrenia and was generally well tolerate

Learning Objectives
1. To understand the efficacy of adjunctive brexpiprazole as maintenance treatment in adults with schizophrenia.
2. To understand the safety and tolerability of adjunctive brexpiprazole as maintenance treatment in adults with schizophrenia.

Literature References
1. Maeda K, Sugino H, Akazawa H, et al. Brexpiprazole I: In vitro and in vivo characterization of a novel serotonin-dopamine activity modulator. J Pharmacol Exp Ther 2014; 350:589-604.
2. Correll C, Skuban A, Youakim JM, et al. Brexpiprazole for the treatment of acute schizophrenia: a randomized, controlled trial. Neuropsychopharmacology 2014; 39:S474. Poster W3.
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W71. LONGITUDINAL ANALYSIS OF THE INDIVIDUAL PLACEBO RESPONSE FROM DOUBLE-BLIND CLINICAL STUDIES USING THE MATRICS

CONSENSUS COGNITIVE BATTERY (MCCB) IN COGNITIVE IMPAIRMENT ASSOCIATED WITH SCHIZOPHRENIA

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Abstract Introduction: The MATRICS Consensus Cognitive Battery (MCCB) was developed to provide an assessment of cognitive impairment and measure change in clinical trials for Cognitive Impairment Associated with Schizophrenia (CIAS). While pivotal trials are expected to be 24 weeks in duration to characterize the benefit risk of an investigational product to treat (CIAS), earlier clinical studies such as proof of concept (POC) or dose-ranging trials may be of shorter duration. It is therefore important to understand the natural history progression and variability of the MCCB over relatively brief periods of time in order to more confidently design and power early-stage clinical trials. These data will assist in informing early development decision-making in drug development for CIAS. The objective of this analysis was to characterize the time course of the MCCB in placebo subjects with CIAS.

Methods: The individual-level data in the placebo arm from 8 randomized, double-blind clinical studies were combined into a single dataset consisting of 514 subjects (n=1773 total observations). Sampling times on MCCB ranged from 4 to 24 weeks. Median age of the combined dataset was 45 years old and ranged from 18 to 65 years. Median baseline MCCB composite score was 27.0 units.

A nonlinear mixed effects model for the time course of the MCCB composite T-score was constructed using R software (v3.12). The time to maximal placebo (PBOmax) effect was characterized by an exponential rate constant. The effects of baseline MCCB composite score, age and gender on PBOmax were assessed. In addition, the effect of having a screening MCCB assessment prior to baseline was explored as a binary covariate on the magnitude of placebo effect. Model fit and inclusion of covariates was determined using likelihood ratio tests and goodness of fit diagnostics. Inter-individual level random effects on PBOmax were nested within study level random effects. Random effects were modeled as additive given the nature of the scale.

Results: The maximal placebo effect (PBOmax) was estimated to be 1.80 (SE=0.279) units (which is similar to previous reports1,2). Baseline MCCB and age were found to be significant covariates in the model. Gender was not a significant covariate in the model. The effect of having a screening MCCB assessment prior to baseline failed to improve the model fit. Given the minimal data in the early portion of the time curve to inform the parameter estimation, the rate constant has a fair amount of uncertainty associated with the estimate. The exponential rate constant was estimated to be 7.2 (95% CI: 3.5, 15) weeks-1, and the corresponding time to the steady state maximal placebo effect ranges from 0.3 to 1.4 weeks. This estimate of time to steady state is very rapid, is influenced by the curve equation, and may suggest a threshold type effect. Additional data in the early phase of the time course would be required to further refine the early portion of the curve.

Conclusions: A non-linear model based on individual-level data was generated to characterize the MCCB time course in placebo subjects with CIAS. Both baseline MCCB and age were found to be significant on the maximal placebo effect. Though the 95% CI for the placebo rate constant was wide, the output of the model suggests a relatively rapid time to the steady state maximal placebo effect. While it is recognized that different mechanisms of action may have different time course of effect, ensuring a comprehensive understanding of the MCCB placebo time course will enable early decision-making in drug development for CIAS.

Learning Objectives

1. To understand the time course of placebo conditions on cognitive change in patients with schizophrenia.
2. To learn the time course of specific changes in the MATRICS Consensus Cognitive Battery in clinical trials for patients with schizophrenia.

Literature References

1. Gaudreault F, Tan B, Liu J, Chen D. Model-Based Meta-Analysis of Longitudinal MATRICS Consensus Cognitive Battery (MCCB) for Cognitive Impairment Associated with Schizophrenia (CIAS). J Pharmacokinet Pharmacodyn. 2014; 41: s87-s88.
2. Umbricht D, Keefe R, Murray S, et al. A randomized, placebo-controlled study investigating the nicotinic α7 agonist, RG3487, for cognitive deficits in schizophrenia. Neuropsychopharmacology, 2014; 39: 1568-1577.

W72. DIFFERENTIAL ACTIVATION OF IMMUNE/ INFLAMMATORY RESPONSE RELATED CO-EXPRESSION MODULES IN THE HIPPOCAMPUS ACROSS THE MAJOR PSYCHIATRIC DISORDERS

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Abstract Schizophrenia, bipolar disorder and major depression are common and extremely disabling disorders thought to be caused by an interaction of genetic and environmental factors. Despite extensive research efforts the molecular mechanisms underlying the pathophysiology of these disorders remain to be determined. Gene co-expression network analysis has recently provided insight into the molecular mechanisms underlying the pathophysiology of these disorders. We performed co-expression network analysis to identify co-expression modules associated with the major psychiatric disorders by using RNA-Seq data of all the genes in the hippocampus and by pooling the data from each disease group with the controls. To further explore gene-gene interactions that may differ between disease group and controls we generated separate co-expression networks for each disease group independently and for controls independently. Two immune/inflammation related co-expression modules were associated with disease status when built from RNA-seq data from schizophrenia and controls combined. The correlation between immune-related modules and schizophrenia was replicated using microarray data from an independent tissue collection. Immune/inflammation related co-expression modules were also built when using RNA-seq data from bipolar disorder cases alone or from major depression cases alone but where not preserved when using only data from control cases. IL23R was a hub gene in the module generated for bipolar disorder cases, and C1QA, C1QB and C1QC were hub genes in the module built from major depression cases. Moreover, there was no overlap in the genes that comprise the immune/inflammation response-related modules across the different disorders. Thus there appears to be differential activation of the immune/inflammatory response, as determined by the co-expression of genes that is associated with the major psychiatric disorders and which may also be associated with the abnormal neuropathology in each disorder.

Learning Objectives

1. Participants will be able to explore co-expression modules that were associated with major psychiatric disorders.
2. Participants will be able to compare co-expression modules from each disease group to those from controls.

Literature References
1. Hwang Y, Kim J, Shin JY, Kim JI, Seo JS, Webster MJ et al. Gene expression profiling by mRNA sequencing reveals increased expression of immune/inflammation-related genes in the hippocampus of individuals with schizophrenia. Translational psychiatry 2013; 3: e321.
2. Langfelder P, Horvath S. WGCNA: an R package for weighted correlation network analysis. BMC Bioinformatics 2008; 9: 559.

W73. LONG-ACTING INJECTABLE VS ORAL ANTIPSYCHOTICS FOR HOSPITALIZATION PREVENTION IN SCHIZOPHRENIA: A SYSTEMATIC REVIEW AND META-ANALYSIS OF COHORT STUDIES

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Abstract Background: Long-acting injectable antipsychotics (LAIs) are hoped to reduce relapse rates in comparison to oral antipsychotics (OAPs), however, our meta-analysis of randomized controlled trials1) did not find such an advantage. A subsequent meta-analysis of mirror-image studies2) did show significant superiority of LAIs over OAPs. Given such inconsistent results, non-randomized, but parallel comparison of LAIs and OAPs; i.e. cohort studies are a third design to explore the comparative effectiveness of LAIs.

Methods: Meta-analysis of cohort studies comparing LAIs and OAPs. Co-primary outcomes were hospitalization risk (proportion of patients who were hospitalized) and the hospitalization rate (number of hospitalization per person-year). Secondary outcomes included hospitalization days and all-cause discontinuation.

Results: Across 37 cohort studies (n=59053), patients on LAIs had similar risk of hospitalization (N=27, n=31512, risk ratio=0.932, 95%CI: 0.818, 1.061, p=0.287, I2=82.9%) and similar rate of hospitalization (N=10, 34176 person-years, rate ratio=0.778, 95%CI: 0.588, 1.031, p=0.081, I2=94.3%) compared with patients on OAPs. There was also no significant difference between two arms in hospitalization days (N=8, n=10276, Hedge's g=-0.044, 95%CI: -0.20, 0.11, I2=83.9%), however, patients on LAIs were less likely to discontinue the treatment (N=11, n=22715, risk ratio=0.758, 95%CI: 0.638, 0.899, p=0.001, I2=91.9%). Based on reported patient characteristics patients on LAIs were more severely ill and/or chronic compared to patients on OAPs (N=17, n=30149, Hedges' g=0.193, 95%CI: 0.020, 0.367, p=0.029).

Conclusions: Based on cohort studies, which are more representative of real-world clinical practice than RCTs, patients on LAIs had similar risk/rate of hospitalization compared with patients on OAPs. Patients on LAIs were more severe and/or chronic than patients on OAPs. Therefore, there might be a conservative bias influencing the results.

Learning Objectives
1. To understand the complexities of clinical trials comparing long acting injectable and oral antipsychotics.
2. To understand the difference of the results with different methodological approach.

Literature References
1. Kishimoto T, Robenzadeh A, Leucht C, Leucht S, Watanabe K, Mimura M, Borenstein M, Kane JM, Correll CU. Long-acting injectable vs oral antipsychotics for relapse prevention in schizophrenia: a meta-analysis of randomized trials. Schizophr Bull. 2014;40(1):192-213.

2. Kishimoto T, Nitta M, Borenstein M, Kane JM, Correll CU. Long-acting injectable versus oral antipsychotics in schizophrenia: a systematic review and meta-analysis of mirror-image studies. J Clin Psychiatry. 2013;74(10):957-65.

W74. ROLE OF FGF14 IN THE INHIBITORY CIRCUITRY UNDERLYING COGNITIVE PROCESSING

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Abstract Cognitive processing is highly dependent on the functional integrity of gamma-amino-butyric acid (GABA) interneurons in the brain. These cells regulate excitability and synaptic plasticity of principal neurons balancing the excitatory/inhibitory tone of cortical networks. Reduced function of parvalbumin (PV) interneurons and disruption of GABAergic synapses in the cortical circuitry results in desynchronized network activity associated with cognitive impairment across many psychiatric disorders, including schizophrenia, and bipolar disease. Yet, the mechanisms underlying these complex phenotypes are still poorly understood. Here, we show that in animal models genetic deletion of fibroblast growth factor 14 (Fgf14), a resident protein of the axonal initial segment (AIS), a regulator of neuronal excitability and synaptic transmission, and an emerging brain disease-associated factor, leads to loss of PV interneurons in the CA1 hippocampal region, a critical area for cognitive function. Strikingly, this cellular phenotype associates with decreased expression of glutamic acid decarboxylase 67 (GAD67) and vesicular GABA transporter (VGAT) at GABAergic presynaptic puncta and coincide with loss in frequency and amplitude of spontaneous and miniature inhibitory synaptic events in CA1 pyramidal neurons, reduced in vivo gamma frequency oscillations and impaired working memory. Altogether these phenotypes recapitulate salient molecular, cellular, functional and behavioral features associated with cognitive impairment in complex brain disorders, adding FGF14 to the repertoire of potential risk factors for psychiatric disorders.

Learning Objectives
1. Identify new potential mechanisms controlling cognitive function.
2. Introduce new biomarkers/drug development targets.

Literature References
1. Lewis DA, Curley AA, Glausier JR, Volk DW. Cortical parvalbumin interneurons and cognitive dysfunction in schizophrenia. Trends Neurosci. 2012;35:57-67.
2. Hsu WC, Nilsson CL, Laezza F. Role of the axonal initial segment in psychiatric disorders: function, dysfunction, and intervention. Frontiers in psychiatry. 2014;5:109.

W75. LURASIDONE TREATMENT RESPONSE IN PATIENTS WITH SCHIZOPHRENIA ASSESSED USING THE DSM-5 DIMENSIONS OF PSYCHOSIS SEVERITY SCALE

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Abstract Background: The 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) provides a "Clinician-Rated Dimensions of Psychosis Symptom Severity"

assessment (Section III: Emerging Measures and Models). The objective of this analysis was to evaluate lurasidone treatment response using this dimensional approach.

Methods: Data were derived from a 6-week, placebo and active-controlled trial of lurasidone in hospitalized patients with an acute exacerbation of schizophrenia. The standard 7 point scale (1=Absent to 7=Extreme) for each PANSS item was mapped on to the 5 point scale for each domain of the Clini¬cian-Rated Dimensions of Psychosis Symptom Severity assessment in the DSM-5 (0=Not present, 1=Equivocal, 2 = Mild, 3=Moderate, 4=Severe). Scores for each DSM-5 psychosis domain were obtained from the average of non-missing individual items in the domain. Cognitive impairment and mania symptom domains were excluded from this analysis.

Results: Of the 482 patients including in this analysis, most had moderate severity symptoms at acute study baseline including hallucinations (70%), delusions (86%), disorganized speech (67%), and negative symptoms (79%); mild (41%) to moderate (35%) abnormal psychomotor behavior, and mild (36%) to moderate (38%) depression. Both lurasidone (160 mg/d or 80 mg/d) and quetiapine XR (600 mg/d) showed significantly greater improvement (vs. placebo) at study endpoint on the 6 domains of psychosis symptoms assessed.

In patients with at least moderate severity negative symptoms at study baseline (n=360), the higher lurasidone 160 mg/d dose group had significantly greater treatment effect size (0.86) compared to the lower lurasidone 80 mg/d dose group (0.52) (p<0.05). In patients with at least moderate severity level of depression symptoms at study baseline (n=181), the higher lurasidone dose group (1.26) and the quetiapine XR 600 mg/d group (1.0) had significantly greater effect size than the lower lurasidone dose group (0.57) (p<0.05). For the other 4 psychosis domains, effect size was numerically greater in the higher lurasidone dose group compared to the lower dose group in patients with moderate to severe symptoms. Severity of negative or depressive symptoms at study baseline was a significant predictor of treatment response at week-6.

Discussion: Larger treatment effects were consistently observed for lurasidone 160 mg/d (versus 80 mg/d) in the treatment of moderate to severe psychosis symptoms. Lurasidone 80 mg/d was comparably effective to lurasidone160 mg/d for less severe symptoms. Dimensional assessment of symptom severity (per DSM-5) can aid understanding of the relationship between baseline symptom severity and treatment response across the various domains of psychotic illness.

Learning Objectives
1. To learn about the dimensional approach in the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5).
2. To learn about the "Clinician-Rated Dimensions of Psychosis Symptom Severity" assessment (Section III: Emerging Measures and Models) in DSM-5 and its relationship with lurasidone treatment response across the various domains of psychotic illness.

Literature References
1. Loebel A, Cucchiaro J, Xu J, et al, 2013b. Effectiveness of lurasidone vs. quetiapine XR for relapse prevention in schizophrenia: A 12-month, double-blind, continuation study. Schizophr Res. 147, 95-102.
2. Harvey PD, Siu CO, Hsu J, Cucchiaro J, Maruff P, Loebel A, 2013. Effect of lurasidone on neurocognitive performance in patients with schizophrenia: a short-term placebo- and active-controlled study followed by a 6-month double-blind extension. EurNeuropsychopharmacol.23, 1373-1382.

W76. OPTIMIZING RESPONSE TO LURASIDONE IN PATIENTS WITH ACUTE SCHIZOPHRENIA: A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF DOSING REGIMENS

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Abstract Objectives: To evaluate the efficacy of low-dose lurasidone in patients with an acute exacerbation of schizophrenia and to determine an effective treatment strategy for patients not achieving clinically meaningful improvement in Positive and Negative Syndrome Scale (PANSS) total score after 2 weeks of standard dosing.

Methods: This 6-week, randomized, placebo-controlled study enrolled adults (aged 18-75 years) diagnosed with schizophrenia and experiencing an acute exacerbation. Eligible patients were randomized in a 1:2:1 ratio to receive fixed-dose lurasidone 20 mg/d, 80 mg/d, or placebo. After 2 weeks, patients in the lurasidone 80-mg/d group classified as early nonresponders (<20% PANSS score decrease) were re-randomized in a 1:1 ratio to receive lurasidone 80 mg/d or 160 mg/d for the remaining 4 weeks.

Results: The intent-to-treat population comprised 411 patients (men, 63.7%; mean age, 40.8 years) randomized to lurasidone 20 mg/d (N=101), 80 mg/d (N=198), or placebo (N=112). At Week 6, lurasidone 20 mg/d did not differ significantly from placebo in PANSS total score change from baseline (-17.6 vs -14.5; P=0.26), whereas lurasidone 80 to 160 mg/d demonstrated significant reduction (-24.9; P<0.001; effect size [ES]=0.63) relative to placebo. At Week 2, 95 patients in the 80-mg/d group were classified as early nonresponders. In these early nonresponders to lurasidone 80 mg/d, titration to 160 mg/d (N=43) resulted in significantly greater improvement in PANSS total score from Week 2 to Week 6 compared with 4 additional weeks of treatment at the 80-mg dose (N=52; -16.6 vs -8.9; P=0.023; ES=0.52). The most common adverse events (AEs) occurring more often with lurasidone (dose groups combined) than placebo were akathisia (8.7% vs 1.8%), nausea (6.4% vs 3.6%), and vomiting (3.7% vs 0.9%), respectively. Rates of study discontinuation due to AEs were lower for lurasidone 20 mg/d (2.0%) and lurasidone 80 to 160 mg/d (4.0%) compared with placebo (7.1%).

Conclusions: Lurasidone 20 mg/d did not provide significant improvement compared with placebo, thus confirming lurasidone 40 mg/d as the minimally effective dose for the treatment of patients with acute schizophrenia. In early nonresponders to lurasidone 80 mg/d (at Week 2), dose escalation to 160 mg/d provided superior efficacy with no observed change in tolerability.

ClinicalTrials.gov identifier: NCT01821378.

Learning Objectives
1. Evaluate the efficacy of low-dose lurasidone (20 mg/d) in patients with an acute exacerbation of schizophrenia.
2. Determine an optimal treatment strategy for patients not achieving a clinically meaningful reduction in the Positive and Negative Syndrome Scale total score after 2 weeks of standard dose lurasidone treatment.

Literature References
1. Meltzer HY, Cucchiaro J, Silva R, et al: Lurasidone in the treatment of schizophrenia: a randomized, double-blind, placebo- and olanzapine-controlled study. Am J Psychiatry 2011; 168:957-967.

2. Loebel A, Cucchiaro J, Sarma K, et al: Efficacy and safety of lurasidone 80 mg/day and 160 mg/day in the treatment of schizophrenia: a randomized, double-blind, placebo- and active-controlled trial. Schizophr Res 2013; 145:101-109.

W77. OPEN BOARD

W78. INCIDENCE, ONSET, DURATION AND SEVERITY OF AKATHISIA WITH BREXPIPRAZOLE (OPC-34712) IN ACUTE SCHIZOPHRENIA: A POOLED ANALYSIS OF TWO PIVOTAL STUDIES

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Abstract Background: Antipsychotic treatment-induced akathisia may result in cognitive deficits, anxiety, and impaired coping [1]. Brexpiprazole is a rationally designed serotonin-dopamine activity modulator (SDAM) that is a partial agonist at 5-HT1A and dopamine D2 receptors at similar potency, and an antagonist at 5-HT2A and noradrenaline alpha1B/2C receptors [2]. Brexpiprazole shows partial agonism with lower intrinsic activity at the D2 receptor and stronger antagonism at the 5-HT2A receptor than the only currently available D2 partial agonist, aripiprazole, suggesting a relatively lower potential to induce D2 partial agonist-mediated adverse effects, e.g., akathisia. The occurrence of akathisia was evaluated in patients with acute schizophrenia, based on pooled data from two pivotal phase III studies. The efficacy and additional safety endpoints have been reported elsewhere [3, 4].

Methods: In two similarly designed studies, patients with acute schizophrenia were randomly assigned to fixed once-daily doses of brexpiprazole 2mg, 4mg or placebo (an additional treatment group was included in each study [0.25mg and 1.0mg] to evaluate the lower dose range; these doses were not included in the present analyses). Patients randomized to brexpiprazole received 1mg for Days 1 to 4 followed by 2mg from Day 5. Patients randomized to 2mg continued on 2mg whereas patients randomized to 4mg received their final dose from week 2 onwards. Treatment related adverse events were assessed by investigators at every study visits.

Results: The incidence of akathisia in the brexpiprazole groups appeared to be dose-dependent (2mg: 4.6% [17/368], 4mg: 6.9% [25/364]); the incidence of akathisia was 4.6% (17/368) in the placebo group. All the events were considered to be mild to moderate and did not lead to withdrawal of treatment. Most events of akathisia occurred during the first 3 weeks of treatment and seemed to be linked to dose increases. The 25th and 75th percentiles of akathisia duration were 8 and 26 days for brexpiprazole treated patients in these two pivotal studies.

Conclusion: Treatment with brexpiprazole was associated with a low rate of akathisia and appeared to be dose-dependent. The events of akathisia were mild or moderate and no patients withdrew from treatment due to akathisia.

Learning Objectives
1. To understand the frequency and severity of akathisia induced by brexpiprazole in patients with schizophrenia.
2. To understand the onset and duration of akathisia induced by brexpiprazole in patients with schizophrenia.

Literature References

1. Kim JH, Byun HJ. Association of subjective cognitive dysfunction with akathisia in patients receiving stable doses of risperidone or haloperidol. J Clin Pharm Ther. 2007;32(5):461-467.
2. Maeda K, Sugino H, Akazawa H et al. Brexpiprazole I: In vitro and in vivo characterization of a novel serotonin-dopamine activity modulator. J Pharmacol Exp Ther. 2014;350:589-604.
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4. Kane J, Skuban A, Youakim JM et al. A multicenter, randomized, controlled, phase III trial of fixed-dose brexpiprazole for the treatment of adults with acute schizophrenia. Neuropsychopharmacology. 2014;39:S357. Poster T101.

W79. EFFECTS OF LURASIDONE ON HOSTILITY IN PATIENTS WITH AN ACUTE EXACERBATION OF SCHIZOPHRENIA: A POOLED ANALYSIS OF FIVE SHORT-TERM STUDIES

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Abstract Objective: This analysis assessed the efficacy of lurasidone for reducing hostility in patients with an acute exacerbation of schizophrenia.

Methods: Patient-level data were pooled from 5 randomized, double-blind, placebo-controlled, 6-week studies of fixed-dose lurasidone (40-160 mg/d). The analysis included patients experiencing an acute exacerbation of schizophrenia with evidence of hostility (ie, a score of ≥2 on the Positive and Negative Syndrome Scale [PANSS] hostility item at study baseline). Change from baseline in the PANSS hostility item score was evaluated in lurasidone-treated patients compared with patients receiving placebo using a mixed-model repeated-measures analysis. The presence of positive symptoms of schizophrenia, somnolence, and akathisia were added to the model as covariates.

Results: At study baseline, 1148 patients met criteria for hostility (n=775 randomized to lurasidone; n=373 randomized to placebo). Patients were mostly men (72.8%), average age was 37.9 years, and 61.5% had ≥4 prior hospitalizations. Compared with placebo, lurasidone produced significantly greater reductions in the PANSS hostility item score from Week 1 (P=0.002) through Week 6 (P<0.001). After adjusting for change in the positive symptoms of schizophrenia, lurasidone resulted in significantly greater improvement in hostility relative to placebo from Week 2 (P=0.014) through Week 6 (P<0.05). After adjusting for the presence of somnolence and akathisia in addition to positive symptoms, lurasidone significantly reduced hostility compared with placebo at Week 2 and every subsequent assessment (P<0.05), except for Week 6 (P=0.077). Improvement in hostility (defined as ≥1 point decrease in the PANSS hostility item score) was observed in 63.1% of lurasidone-treated patients at Week 6 study endpoint (last observation carried forward) compared with 55.0% of patients receiving placebo (P<0.01; number needed to treat=13).

Conclusions: Lurasidone, dosed in the range of 40 to 160 mg/day, significantly reduced hostility relative to placebo in this analysis of short-term studies of patients with an acute exacerbation of schizophrenia. Improvement in hostility was observed even after adjusting for change in other positive symptoms of schizophrenia, as well as the presence of somnolence and akathisia.

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

Learning Objectives
1. Assess the efficacy of lurasidone for reducing hostility in patients with an acute exacerbation of schizophrenia in an analysis of short-term studies with once-daily dosing ranges of 40 to 160 mg.
2. Characterize improvement in hostility after adjusting for change in other positive symptoms, as well as somnolence and akathisia.

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W80. EFFECT OF LURASIDONE ON PROSOCIAL FUNCTIONING IN PATIENTS WITH SCHIZOPHRENIA: A POOLED ANALYSIS OF FIVE SHORT-TERM, PLACEBO-CONTROLLED STUDIES

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Abstract Objective: This analysis assessed the efficacy of lurasidone for improving prosocial behavior in patients with schizophrenia.

Methods: Patient-level data were pooled from 5 randomized, double-blind, placebo-controlled, 6-week studies of fixed-dose lurasidone (40-160 mg/d) in the treatment of patients with an acute exacerbation of schizophrenia. This analysis included patients who were randomly assigned to receive lurasidone or placebo and had data at baseline and at least 1 postbaseline assessment for the Positive and Negative Syndrome Scale (PANSS). The prosocial factor score was calculated as the sum of 6 PANSS item scores: active social avoidance, emotional withdrawal, passive social withdrawal, stereotyped thinking, hallucinatory behavior, and suspiciousness. Lower scores are indicative of better prosocial behavior. Mixed-model repeated-measures analysis was used to compare change from baseline in the prosocial factor score for patients receiving lurasidone versus placebo.

Results: A total of 1526 patients (lurasidone, n=1030; placebo, n=496) were included in the analysis. Most patients were men (73.0%); average age was 38 years. At baseline, mean score on the PANSS prosocial factor was 23.0 among lurasidone-treated patients and 23.2 in the placebo group. Least-squares mean change from baseline to Week 6 study endpoint was -6.3 in patients treated with lurasidone (dose groups pooled) and -3.7 in patients receiving placebo (P<0.001; effect size=0.57). Lurasidone (dose groups pooled) provided significantly greater improvement than placebo in the prosocial factor score beginning as early as Day 3/4 and continuing through the 6-week study period (P≤0.001). When each dose of lurasidone was analyzed separately, least squares mean change from baseline to Week 6 endpoint in the prosocial factor score was -5.9 for 40 mg/d, -6.3 for 80 mg/d, -6.1 for 120 mg/d, and -7.3 for 160 mg/d. All doses of lurasidone were superior to placebo from Week 1 (P≤0.001) through Week 6 (P<0.001), with effect sizes at Week 6 ranging from 0.49 for lurasidone 40 mg/d to 0.75 for lurasidone 160 mg/d. In these studies, the most common adverse events associated with lurasidone compared with placebo were akathisia (16.1% vs 4.6%), somnolence (12.6% vs 6.2%), and insomnia (10.5% vs 8.9%), respectively.

Conclusions: In this pooled analysis of short-term studies of patients with schizophrenia, lurasidone, at doses of 40 mg/d to 160 mg/d, produced significantly greater improvement than placebo in prosocial behavior. Effect sizes indicate that these were clinically meaningful differences, suggesting that lurasidone may improve social functioning in patients with schizophrenia.

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

Sponsored by Sunovion Pharmaceuticals Inc.

Learning Objectives
1. Characterize the efficacy of lurasidone in improving prosocial functioning in patients with schizophrenia using the Positive and Negative Syndrome Scale prosocial factor scores in short-term studies.
2. Assess efficacy in prosocial functioning for patients taking lurasidone doses of 40, 80, 120, and 160 mg/day versus placebo.

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W81. METABOLIC SYNDROME PREVALENCE IN PATIENTS WITH SCHIZOPHRENIA RECEIVING SHORT-TERM TREATMENT WITH LURASIDONE, OLANZAPINE, AND QUETIAPINE XR: A POOLED ANALYSIS

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Abstract Objective: This analysis evaluated the prevalence of metabolic syndrome in patients with schizophrenia during short-term treatment with lurasidone, olanzapine, and quetiapine XR.

Methods: Patient-level data were pooled from three phase 3, randomized, double-blind, placebo-controlled, 6-week studies of fixed-dose lurasidone (40-160 mg/d) in the treatment of patients with an acute exacerbation of schizophrenia. This analysis included patients who were randomly assigned to receive lurasidone, an active comparator (olanzapine 15 mg/d or quetiapine XR 600 mg/d), or placebo and had data to determine metabolic syndrome status. Metabolic syndrome was defined based on the updated National Cholesterol Education Program criteria (without using drug treatment criteria). Patients were classified as having metabolic syndrome if they met any 3 of the following 5 criteria: 1) elevated waist circumference ($\geq$102 cm for men, $\geq$88 cm for women), 2) elevated triglycerides ($\geq$150 mg/dL), 3) reduced high-density lipoprotein cholesterol (<40 mg/dL in men, <50 mg/dL in women), 4) elevated blood pressure (systolic $\geq$130 mm/Hg or diastolic $\geq$85 mm/Hg), and 5) elevated fasting glucose ($\geq$100 mg/dL). Logistic regression analysis adjusting for baseline metabolic syndrome status using a last observation carried forward (LOCF) approach was performed to determine statistical significance for between-group differences.

Results: A total of 1457 patients were randomly assigned to treatment (men, 72.0%; average age, 37.9 years), of whom 1203 had both baseline and post-baseline data for metabolic syndrome and are included in this analysis (lurasidone, n=703; olanzapine, n=105; quetiapine XR, n=96; placebo, n=299). At baseline, prevalence of metabolic syndrome was 19.1% for placebo, 21.6% for lurasidone, 21.0% for olanzapine, and 14.6% for quetiapine XR. Rates of metabolic syndrome at Week 6 study endpoint (LOCF) were 20.2% for placebo, 21.9% for lurasidone, 35.5% for olanzapine, and 38.4% for quetiapine XR, with significantly greater prevalence relative to placebo for olanzapine and quetiapine XR (both $P<0.001$). In patients without metabolic syndrome at baseline, the proportion who met criteria for metabolic syndrome after 6 weeks of treatment (LOCF) was 10.7% of patients receiving placebo, 9.4% of lurasidone-treated patients, 25.3% of olanzapine-treated patients, and 30.5% of quetiapine XR–treated patients.

Conclusions: This post hoc pooled analysis found marked differences between lurasidone and 2 other atypical antipsychotic agents in the prevalence of metabolic syndrome after short-term therapy (6 weeks). Patients were more likely to develop metabolic syndrome during treatment with olanzapine or quetiapine XR compared with lurasidone.

ClinicalTrials.gov identifiers: NCT00549718, NCT00615433, and NCT00790192.

Sponsored by Sunovion Pharmaceuticals Inc.

Learning Objectives
1. Evaluate the effect of short-term treatment with lurasidone on metabolic syndrome in patients with schizophrenia.
2. Compare the prevalence of metabolic syndrome in patients following short-term treatment with lurasidone to patients receiving short-term treatment with olanzapine or quetiapine XR.

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W82. A META-ANALYSIS OF PLACEBO-CONTROLLED TRIALS OF OMEGA-3 FATTY ACID AUGMENTATION IN SCHIZOPHRENIA: POSSIBLE STAGE-SPECIFIC EFFECTS

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Abstract Background: Omega-3 supplements have shown promise in clinical trials as an adjunctive treatment for schizophrenia. However, clinical efficacy across studies has been inconsistent. We conducted a meta-analytic assessment of the data and hypothesized that omega-3 augmentation may have differential efficacy at various stages of schizophrenia.

Methods: An online search was conducted using PubMed for placebo-controlled, randomized, double-blind, clinical trials (RCTs) using the terms "omega-3," "EPA," "eicosapentaenoic acid," "PUFA," "polyunsaturated fatty acid," "schizophrenia," "prodrome," "schizophreniform," and "schizoaffective." A meta-analysis was conducted on placebo-controlled trials only.

Results: 10 studies met the criteria for inclusion. Of these trials, six used the Positive and Negative Syndrome Scale (PANSS) as an outcome measure for patients in the chronic stage of

schizophrenia (N=319). A meta-analysis of these six studies indicated non-significant effects for omega-3 on Total PANSS scores (where weighted d=0.18, and when corrected for unreliability and range restriction, weighted d=0.11). In the remaining four trials, omega-3 had an adverse effect in the prevention of recurrence of symptoms after discontinuation of antipsychotic therapy (d=-0.58, N=33) and prevention of symptom worsening in acute exacerbation (d=-0.29, N=57). However, in first-episode patients (N=69), omega-3 decreased non-psychotic symptoms, decreased required antipsychotic medication dosage (d=.40), and improved early (6 week, d=0.52), but not late (12 week, d=0.06), treatment response rates. It was also significant in reducing both the conversion rate (d=0.57) and psychotic symptom severity in prodromal patients at very high risk for psychosis (d=0.7, N=81).

Conclusion: The data in this study suggest a differential benefit of omega-3 at various stages of schizophrenia, with higher efficacy in prodromal and first-episode patients as adjunct therapy to antipsychotic medications. Its efficacy for chronic schizophrenia appears questionable and Omega-3 fatty acid may in fact worsen acute exacerbations of chronic schizophrenia. The neurobiological and therapeutic implications of these findings are discussed.

Learning Objectives
1. Understanding the efficacy of omega-3 supplementation for the treatment of schizophrenia based on a meta-analysis of currently available clinical trials.
2. Understanding the neurobiological and therapeutic implications of omega-3 supplementation in patients with varying stages of schizophrenia.

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W83. ANTIPSYCHOTIC DOSE INCREASE OR STAY IN NON-RESPONDERS WITH SCHIZOPHRENIA: A DOUBLE-BLIND RANDOMIZED CONTROLLED TRIAL

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Abstract Background: While antipsychotic drugs play an indispensable role in the treatment of schizophrenia, there has been no clear consensus on how to deal with insufficient treatment response. Surprisingly, it still remains unclear as to whether antipsychotic doses should be further increased when they are already within recommended dose ranges and side effects are not problematic. There has been little evidence to support to go beyond the recommended doses; in fact, to our knowledge, only one study by Kinon et al. systematically addressed this question. In the randomized controlled trial, they found that the following three strategies were equivalently efficacious for patients who did not respond to 20 mg/d of fluphenazine: staying on 20 mg/d of fluphenazine, increasing the dose to 80 mg/d, and switching to 20 mg/d of haloperidol. However, those doses tested are too high to generalize to our today's practice. Moreover, newer antipsychotics were not validated. Therefore, we have been conducting a trial to compare efficacies between antipsychotic dose increase and keeping the same dose in patients with schizophrenia who did not respond to a moderate dosage of olanzapine or

risperidone. Furthermore, the impact of antipsychotic plasma concentrations and cytochrome P450 (CYP) gene polymorphism on treatment outcomes will also be examined.

Methods: This study is a 4-week double-blind randomized controlled trial. Patients with schizophrenia, schizoaffective disorder, or persistent delusional disorder (International Classification of Diseases, 10th Revision) who had been treated with olanzapine 10 mg/d or risperidone 3 mg/d for $\geq$ 4 weeks and presented with a total score of ≥ 60 in the Positive and Negative Syndrome Scale (PANSS) were included. Enrolled subjects were randomly allocated to either of the following two treatments. In the dose increase group, antipsychotic doses were increased to the maximum dose of the suggested dose ranges (i.e. olanzapine 20 mg/d or risperidone 6 mg/d) whereas in the same dose group antipsychotic doses were not changed (i.e. olanzapine 10 mg/d or risperidone 3 mg/d). The following assessments were performed at baseline and week 4: PANSS, Clinical Global Impression, Global Assessment of Functioning, Functional Assessment for Comprehensive Treatment of Schizophrenia, Targeted Inventory on Problems in Schizophrenia, Simpson-Angus Scale, Barnes Akathisia Rating Scale, Abnormal Involuntary Movement Scale, and plasma concentrations of olanzapine or risperidone. CYP gene polymorphisms were also examined with blood or saliva samples. Peak and trough dopamine D2 receptor occupancy levels by antipsychotics will be estimated from plasma drug concentrations and linked to treatment outcomes.

Results: One hundred and two subjects have participated in this study so far. In the preliminary analysis of 11 subjects conducted for safety evaluation, all subjects in both the increase group (n=7) and the same dose group (n=4) successfully completed all the study procedures. There were no significant differences in the change of the total PANSS score for 4 weeks between the increase and the same dose groups (-5.0 vs. -10.0, p=0.571). No serious adverse event has been observed.

Conclusion: Our preliminary findings suggest that patients with schizophrenia who present clinically significant psychopathology with a moderate dosage of antipsychotic drug may not benefit from antipsychotic dose increment. We will perform the final analysis of full data (N>100) at the time of presentation. Treatment outcomes will be examined in terms of subjects' clinical and characteristics as well as estimated dopamine D2 receptor occupancy levels and CYP gene polymorphisms.

Learning Objectives
1. To compare effectiveness of antipsychotic dose increase and continuation for patients with schizophrenia who failed to respond to a moderate dosage of antipsychotic drug.
2. To clarify who responds to dose increment in terms of clinical characteristics, psychopathology, antipsychotic plasma concentration, and cytochrome P450 gene polymorphism.

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W84. OPEN BOARD

W85. SAFETY, TOLERABILITY AND PHARMACOKINETICS OF TAK-063, A PDE10A INHIBITOR, AFTER A SINGLE DOSE IN HEALTHY JAPANESE AND NON-JAPANESE SUBJECTS

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Abstract Background: TAK-063 is in clinical development for the treatment of schizophrenia. TAK-063 selectively inhibits phosphodiesterase 10A (PDE10A), which hydrolyzes both cyclic adenosine monophosphate and cyclic guanosine monophosphate. Current evidence suggests that inhibition of PDE10A may be beneficial in the treatment of schizophrenia by modulating, indirectly or directly, the effects of glutamatergic and dopaminergic systems. The objective was to characterize the safety, tolerability, and pharmacokinetic (PK) profiles of TAK-063 administered as a single dose of oral suspension at escalating dose levels in healthy subjects.

Methods: This was a randomized, double-blind, placebo-controlled, single-dose study in healthy Japanese and non-Japanese subjects. Upon completion of inclusion and exclusion criteria, 84 subjects were enrolled in 6 cohorts (n=14 per cohort) and randomized to TAK-063 or placebo with 11 subjects (i.e., 5 Japanese, 6 non-Japanese) in each cohort receiving a single dose of TAK-063 (3, 10, 30, 100, 300, or 1000 mg) and 3 subjects (i.e., 1 Japanese, 2 non-Japanese) receiving a matching placebo under fasted conditions. Subjects receiving 100 mg TAK-063 also received 100 mg TAK-063 under fed conditions after a washout period. Safety assessments included adverse event (AE) reporting, clinical laboratory tests, physical examination, electrocardiogram (ECG), vital signs, and suicidal assessments. Serial plasma and urine samples were collected for determination of TAK-063 and M-I metabolite concentrations. PK parameters were derived using non-compartmental methods.

Results: Administration of TAK-063 was generally safe and well tolerated with no serious adverse events or deaths. The most common treatment-related AEs (TEAE) under fasted conditions for all TAK-063 doses combined were somnolence, postural orthostatic tachycardia, orthostatic hypotension, nausea, vomiting, dizziness, and headache. Under fasted conditions, plasma concentrations of TAK-063 and M-I peaked approximately 3 to 4 hours post-dose and subsequently declined (T½=15-25 hours) with renal elimination playing a minor role. Increases in exposure to TAK-063 and TAK-063 M-I were less than dose proportional. Under fed conditions, TAK-063 was more slowly absorbed and resulted in greater oral bioavailability of TAK-063 (up to 2-fold in Cmax and AUC values), relative to fasted conditions. No substantial differences were noted between Japanese and non-Japanese subjects in TEAE incidence or PK of TAK-063 and M-I.

Discussion: A single dose of TAK-063 (range 3 to 1000 mg) was well tolerated in Japanese and non-Japanese subjects. Somnolence was the most common adverse event and increased in frequency and intensity with increasing dose. Nonlinear pharmacokinetics was observed across the evaluated dose range for TAK-063; this is likely due to solubility-limited oral bioavailability, which was enhanced with the co-administration of food.

Learning Objectives
1. Become familiar with the mechanism of action of TAK-063, a PDE10A inhibitor in development for schizophrenia.
2. Review the Phase 1 safety and PK data for TAK-063 after a single dose.

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W86. DELTOID INJECTION OF ARIPIPRAZOLE ONCE-MONTHLY IN THE TREATMENT OF SCHIZOPHRENIA

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Abstract Introduction: The deltoid muscle is evaluated as an alternative site of administration to the gluteal site for aripiprazole once-monthly 400 mg (AOM 400), an extended release injectable suspension of aripiprazole for treatment of patients with schizophrenia.

Methods: Data from 2 open-label studies (Study 1, NCT01646827 and Study 2, NCT01909466) are used to compare deltoid and gluteal injections of AOM 400 in stable patients, aged 18-65 years, with a current diagnosis of schizophrenia. Study 1 was a randomized, single-dose, parallel-arm, relative bioavailability study comparing the pharmacokinetic (PK) parameters of AOM 400 after injection in the deltoid (N=17) compared with the gluteal muscle (N=18). Study 2 was a multiple-dose, parallel-arm study designed to evaluate the safety and tolerability of AOM 400 injections in the deltoid muscle, and to derive PK parameters following 5 monthly injections. Patients in study 2 were randomized to receive the first AOM 400 injection either in the deltoid (N=71) or gluteal (N=67) muscle followed by 4 monthly injections of AOM 400 (N=138) in the deltoid muscle.

Results: Administration of AOM 400 in the deltoid muscle was found to have a comparable safety and tolerability profile to administration in the gluteal muscle after single and multiple injections in 2 clinical studies. Treatment-emergent adverse events (TEAEs) in Study 1 were reported by 82.4% (14/17) and 100% (18/18) of patients after a single injection in the deltoid and gluteal muscle, respectively. TEAEs were reported by 81.2% (112/138) of patients after multiple injections in the deltoid muscle in Study 2; the most frequent TEAEs were injection site pain (27.5%, 38/138), weight increased (12.3%, 17/138), headache (11.6%, 16/138), toothache (8.0%, 11/138), upper respiratory tract infection (8.0%, 11/138), and akathisia (8.0%, 11/138), in line with the safety and tolerability profile of AOM 400 in gluteal injections. TEAEs resulting in study discontinuation occurred in 5.1% (7/138) of patients. The incidence of injection site pain after the first deltoid injection of AOM 400 was 25.4% (18/71) and decreased to 4/122 (3.3%), 1/109 (0.9%), 0/106 (0.0%), and 3/100 (3.0%) for the subsequent second, third, fourth, and fifth deltoid injections, respectively. There were no clinically relevant findings in vital signs, electrocardiogram, weight, extrapyramidal side effects, suicidality, or clinical laboratory values. Multiple injections of AOM 400 in the deltoid muscle resulted in comparable maximal- and minimal plasma concentrations and comparable exposures of aripiprazole measured as area under the curve compared with injections in the gluteal muscle as measured in earlier studies.

Conclusions: Administration of AOM 400 by injection in the deltoid muscle is a safe and well-tolerated alternative to the established gluteal injection. Based on the PK data after initial and multiple injections in the deltoid muscle, the efficacy of AOM 400 is expected to be comparable to injections in the gluteal muscle.

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

Learning Objectives
1. To understand the tolerability profile of aripiprazole once-monthly with gluteal and deltoid injections derived from two clinical studies using either single or multiple injections.

2. To understand the pharmacokinetic properties of gluteal and single or multiple deltoid injections of aripiprazole once-monthly.

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W87. ADVANCING THE CLINICAL DEVELOPMENT OF ITI-007: A NOVEL INVESTIGATIONAL TREATMENT FOR SCHIZOPHRENIA, BIPOLAR DEPRESSION AND BEHAVIORAL DISTURBANCES IN DEMENTIA

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[1]*Intra-Cellular Therapies*

Abstract Background: ITI-007 is a first-in-class investigational new drug that modulates serotonin, dopamine, and glutamate in a dose-dependent manner which allows for targeting different therapeutic indications at different doses. At low doses ITI-007 is predominantly a serotonin 5-HT2A 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, and inhibits serotonin reuptake.

Methods: ITI-007 was evaluated in a series of randomized, double-blind, placebo-controlled clinical trials utilizing different dose ranges. Low doses of ITI-007 were evaluated in patients with primary insomnia and in geriatric volunteers and elderly patients with dementia. Higher doses were evaluated in patients with schizophrenia. A number of a priori assessments were included to evaluate the effects of ITI-007 as well as provide a rich dataset on which to perform retrospective analyses on a broad array of symptom domains.

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. For patients with dementia, a dose of 9 mg ITI-007 was safe and 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. Moreover, 60 mg ITI-007 improved symptoms of depression as measured by the Calgary Depression Scale for Schizophrenia (CDSS) in an a priori defined subgroup of patients with schizophrenia and co-morbid depression. ITI-007 has been demonstrated to be safe and well tolerated across a broad dose range across all studies to date.

Discussion: ITI-007 is an investigational new drug and represents a new approach to the treatment of a broad array of psychiatric and neurological symptoms, with the effective dose range tailored to specific indications. Clinical studies are planned to evaluate ITI-007 in the low dose range for the treatment of behavioral disturbances in dementia. Higher doses (40 – 60 mg ITI-007) are being evaluated in a Phase 3 program for the treatment of schizophrenia. Additional studies are planned to evaluate ITI-007 for the treatment of bipolar depression and major depressive disorder.

W88. EFFECT OF ARIPIPRAZOLE LAUROXIL ON PERSONAL AND SOCIAL FUNCTIONING AND HEALTH-RELATED QUALITY OF LIFE AMONG PATIENTS WITH SCHIZOPHRENIA

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Abstract   Background: Patients with schizophrenia frequently experience psychosocial dysfunction and poor health-related quality of life, and these broader outcome domains may not be fully captured in standard symptom rating scales.

Methods: Personal and social functioning and health-related quality of life were assessed in a 12 week placebo controlled trial demonstrating the safety and efficacy of aripiprazole lauroxil (AL), a long-acting injectable aripiprazole, in treating schizophrenia. Patients (n=622) experiencing an acute exacerbation of schizophrenia were randomized to AL 441 mg, 882 mg, or placebo IM, once monthly, along with an initial 3 weeks of oral aripiprazole (15 mg) or matching oral placebo as per blinded assignment. All Patients started medication in the inpatient study unit but could be discharged after 2 weeks of observation as per clinical judgment. Assessments included change from baseline to the end of the 12 week treatment period in the Short-Form 36-Item Health Survey (SF-36) mental and physical component scores, change from baseline (first injection) to each post-baseline visit measured by the Personal and Social Performance (PSP) scale in all randomized subjects who received at least 1 dose of study drug and had at least 1 primary efficacy assessment using a last observation carried forward approach, and Kaplan Meier curves of time to study treatment retention.

Results: The Kaplan Meier curves of time to study retention demonstrated significantly greater duration of study retention in the AL groups vs. placebo (p<0.001): 114 (58.2%) for AL 441 mg, 114 (55.9%) for 882 mg vs. 82 (41.8%) for placebo. Baseline PSP scores indicated 'marked' to 'very severe' difficulties in functioning (mean range 48.6-50.9). The placebo-adjusted differences (mean±SE) in PSP scores demonstrated clinically meaningful and statistically significant improvement for the AL 441 mg and 882 mg groups throughout the 12 weeks of assessment (Day 29: 5.9±1.3 and 7.0±1.3, Day 57: 6.6±1.4 and 7.7±1.4, and Day 85: 7.8±1.4 and 9.0±1.4) (all p <0.001). The SF-36 mental component scores improved significantly with placebo-adjusted differences (mean±SE) of 2.6±1.2 (p<0.03) and 3.9±1.2 (p<0.002) in the AL 441 mg and 882 mg groups, respectively. The SF-36 physical component scores improved significantly in the AL 441 mg and 882 mg groups with placebo-adjusted differences of 1.8±0.8 (p<0.02) and 2.0±0.8 (p<0.01).

Conclusion: Both AL 441 mg and 882 mg have demonstrated efficacy and safety in treating symptoms of schizophrenia and are associated with significant improvements in personal and social functioning and health-related quality of life over the course of a 12 week placebo controlled trial.

Learning Objectives

1. Describe the effects of aripiprazole lauroxil treatment on quality of life and social functioning.
2. Identify the association of aripiprazole lauroxil treatment and study retention.

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W89. THE METABOLIC TOLERABILITY PROFILE OF BREXPIPRAZOLE (OPC-34712) IN ACUTE SCHIZOPHRENIA

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Abstract Background: Approximately one-third of new cases of diabetes in patients with schizophrenia were associated with use of olanzapine, risperidone, or quetiapine in a US Veterans Health Administration cohort [1]. Brexpiprazole is a rationally designed serotonin-dopamine activity modulator (SDAM) that is a partial agonist at 5-HT1A and dopamine D2 receptors at similar potency, and an antagonist at 5-HT2A and noradrenaline alpha1B/2C receptors [2]. The metabolic tolerability profile of brexpiprazole was evaluated in patients with acute schizophrenia, based on data from two pivotal phase III studies (NCT01396421 and NCT01393613) [3, 4] and two long-term open-label studies (NCT01397786 and NCT01649557).

Methods: In two similarly designed studies, patients with acute schizophrenia were randomly assigned to fixed once-daily doses of brexpiprazole 2mg, 4mg or placebo for 6 weeks (an additional treatment group was included in each study [0.25mg and 1.0mg] to evaluate the lower dose range; these doses are not presented). The long-term studies were open-label, 52-weeks, flexible-dose (1 to 4mg/day and 1 to 6mg/day) studies with brexpiprazole. The long-term studies enrolled de novo patients, patients who had completed one of the two pivotal studies, as well as patients who had completed a phase II study. Metabolic parameters included weight, glucose, and lipid metabolism-related laboratory measurements.

Results: In the short-term studies, mean change in weight from baseline to Week 6 was 1.7, 1.4, and 0.4kg for the 2mg, 4mg brexpiprazole and placebo groups, respectively. In the long-term studies, the mean change in weight from baseline to Week 52 was 2.0kg. An increase in weight of ≥7% at any visit was seen in 10.3% and 10.2% of brexpiprazole 2mg and 4mg patients vs 4.1% of placebo patients in the short-term studies and in 19.6% of the patients treated with brexpiprazole in the long-term studies. For fasting metabolic parameters, mean changes from baseline to last visit in the short-term studies were (brexpiprazole 2 and 4mg vs placebo): total cholesterol 2.22 and 2.97 vs -3.21mg/dL; high-density lipoprotein cholesterol 1.51 and 0.46 vs -1.78mg/dL; low-density lipoprotein cholesterol 0.36 and 2.35 vs -1.82mg/dL; triglycerides -1.39 and 0.75 vs 0.38mg/dL; and glucose -0.23 and 1.64 vs 0.42mg/dL. Mean changes from baseline to Week 52 in the long-term studies were: total cholesterol 3.89mg/dL; high-density lipoprotein cholesterol 1.81mg/dL; low-density lipoprotein cholesterol 0.52mg/dL; triglycerides 3.56mg/dL; and glucose 0.23mg/dL.

Conclusion: A moderate weight increase was observed after treatment with brexpiprazole with no clinically relevant changes in lipid profiles or other metabolic parameters observed. Results from the long-term study were consistent with those of the short-term pivotal studies and confirmed the good tolerability of brexpiprazole.

Learning Objectives
1. To understand the short term metabolic effects of brexpiprazole in patients with schizophrenia.
2. To understand the long term metabolic effects of brexpiprazole in patients with schizophrenia.

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W90. TOLERABILITY AND RESPONSE TO LOW DOSE GABAPENTIN AMONG MIDLIFE WOMEN WITH HOT FLASHES AND INSOMNIA

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Abstract Background: Hot flashes and night sweats, or vasomotor symptoms (VMS), are the most common complaint of the menopause transition, affecting up to three-quarters of women during midlife. VMS are strongly linked with sleep disturbance, with 70% of women with VMS reporting at least mild insomnia symptoms. Nighttime VMS and associated sleep disturbance prompt many midlife women to seek treatment for their symptoms, as disrupted sleep has a substantial impact on quality of life. Currently available VMS treatments include hormone therapy and SSRI/SNRI that have attendant safety concerns or side effect profiles, respectively, which can limit their use for this condition. The anticonvulsant gabapentin is FDA-approved for the treatment of neuropathic pain and epilepsy. Gabapentin (dosed three times a day) has also been shown to be more effective than placebo for reducing VMS in several randomized clinical trials. Treatment-emergent and typically dose-related side effects of this agent are dizziness, drowsiness, and unsteadiness. We now describe results of an open-label pilot study in which the tolerability of gabapentin administered at bedtime only was systematically investigated. Potential salutary effects on frequency of nighttime VMS specifically and associated sleep interruption were also examined.

Methods: Women between the ages of 40 and 65 were recruited from the Boston area by the Massachusetts General Hospital Center for Women's Mental Health and the Brigham and Women's Hospital Women's Hormones and Aging Research Program. Subjects were peri- or postmenopausal with a mean of two or more bothersome VMS per 24-hours during a two-week period of tracking. Four nighttime VMS per week were also necessary for study inclusion as was insomnia, determined as a score greater than 12 on the Insomnia Severity Index (ISI). Women were excluded if they reported use of: hormone therapy, hormonal contraceptives, prescribed therapy for VMS, or medications with known VMS efficacy (e.g., SSRI) regardless of the indication. Subjects were also excluded if they were experiencing current depression or had a lifetime diagnosis of psychosis or bipolar disorder. Interested subjects tracked VMS and sleep symptoms for two weeks to determine eligibility and to establish a stable baseline with respect to these symptoms. Eligible participants initiated open-label treatment with 100mg dosed at bedtime for one week, followed by 300mg for 3 weeks, and then 600mg for 3 weeks unless they experienced dose-limiting side effects.

Tolerability, insomnia symptoms, and VMS, as well as mood and quality of life, were assessed systematically at each study visit.

Results: Of 26 women eligible for the trial who initiated treatment (mean age 55.3 +/- 4.5 years), 20 tolerated the dose titration up to 600mg and completed the study. The 20 women who completed the treatment regimen experienced few side effects and little if any dizziness, drowsiness, or unsteadiness. Four (15.4%) of 26 eligible subjects dropped due to side effects after initiating treatment, including three who experienced morning drowsiness and nausea (two on 300mg and one on 100mg), and one who reported a mild rash and elected to discontinue. Bedtime dosing resulted in decreased nighttime VMS as well as reduced sleep disruption. For the 19 completers who have VMS data for both baseline and the final visit, the mean number of VMS per night fell from 3.5 at baseline (range 1.5-8.0) to 1.1 (range 0.0-3.9) during the final week of the intervention. Of these 19, 14 experienced a greater than 50% reduction in nighttime VMS over that period. The mean ISI score dropped from 15.6 (range 8-24) to 6.0 (range 0-18), with 18 out of 20 subjects scoring below the threshold for clinical insomnia (ISI <14) at the final visit, and 14 out of 20 subjects experiencing a greater than 50% drop in ISI score across the intervention.

Discussion: The preliminary data in this open-label study of 20 women support the need for larger, placebo-controlled trials of bedtime dosing of gabapentin for treatment of nighttime VMS and menopause-related sleep disturbance. Although this report describes a small sample of women treated in an uncontrolled fashion, the data reveal some promising trends with respect to tolerability and potential efficacy of low dose gabapentin when used for symptoms known to compromise quality of life for large numbers of midlife women. Due to the finite treatment options for women experiencing symptoms associated with the menopausal transition, maximizing the number of potential treatments with demonstrated efficacy has significant clinical implications.

Learning Objectives:
1. Assess the tolerability of bedtime-only dosing of low-dose gabapentin in midlife women with vasomotor symptoms and insomnia.
2. Preliminarily describe the effects of bedtime-only dosing of low-dose gabapentin on vasomotor symptoms and insomnia symptoms in peri- and postmenopausal women.

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W91. PHASE IIA STUDY OF A PROPRIETARY COMBINATION OF BUPROPION AND TRAZODONE FOR HYPOACTIVE SEXUAL DESIRE DISORDER (HSDD) IN PREMENOPAUSAL WOMEN: NOVEL RESPONDER AND REMITTER RESULTS

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Abstract Objectives. HSDD remains without approved pharmacotherapies, though one CNS agent, bupropion, is recommended. This study tested the efficacy and safety of "Lorexys," a proprietary combination of bupropion and trazodone, in premenopausal women.

Material and Methods: This was an open-label crossover study in non-depressed, otherwise healthy patients with DSM-IV-TR HSDD, aged 25-50 years, with four weeks per treatment.

With n=30 and 33% more Lorexys responders vs. bupropion, the power at alpha =0.05 was 80%. Four weeks of bupropion at 300 mg/day and a washout was followed by four weeks of Lorexys low-dose (LOR-low), ie, bupropion plus trazodone at doses lower than the labeled doses, followed by another washout and four weeks of Lorexys moderate-dose (LOR-mod; 2x LOR-low).The primary efficacy endpoint was Female Sexual Function Index Desire domain (FSFI-d); the key secondary was Female Sexual Distress Scale-Revised (FSDS-R). Analyses included % responders and % remitters from the first baseline, using standard definitions (see table) for FSFI-d and FSDS-R item 13 (FSDS-R-i13), plus Patient's Global Impression of Change (PGIC).

Results: Five patients (17%) discontinued for administrative reasons; one (4%) discontinued for adverse events, on LOR-mod. Table shows responder and remitter rates with LOR-mod; rates with LOR-low were intermediate and non-significant vs. bupropion:

Measure	Definition	LOR-mod	Bupropion	p-value on Fisher's Exact test, 2-tailed
RESPONDERS				
FSFI-d	+2	76%	38%	<0.01
FSDS-R-i13	-1	88%	45%	<0.01
PGIC	>=Mod.	58%	24%	<0.05
REMITTERS				
FSFI-d	>=5	58%	24%	<0.05
FSDS-R-i13	<=2	75%	32%	<0.01

Conclusion: Lorexys was highly superior to bupropion for premenopausal HSDD, favoring further development.

W92. EFFECT OF LURASIDONE DOSE ON COGNITIVE IMPAIRMENT IN PATIENTS WITH SCHIZOPHRENIA: POST-HOC ANALYSIS OF A LONG-TERM, DOUBLE-BLIND CONTINUATION STUDY

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Abstract Background: We previously reported that treatment with 160 mg/d of lurasidone improved cognitive performance in a manner superior to placebo, quetiapine XR 600 mg/d, and lurasidone 80 mg/d in a 6-week, randomized trial of patients with an acute exacerbation of schizophrenia. The objective of this post-hoc analysis was to evaluate the cognitive and functional performance of patients with final doses of lurasidone at 40/80 mg/d, 120 mg/d, and 160 mg/d compared to quetiapine XR 200-800 mg/d during the 6-month, double-blind continuation study that followed the acute trial.

Methods: Acutely admitted patients with schizophrenia were treated with one of two doses of lurasidone (80 or 160 mg/d), placebo, or 600 mg/d quetiapine XR in a 6-week acute treatment study. Following the acute study, placebo patients were switched to lurasidone with flexible dosing ranging from 40-160 mg/d. Lurasidone and quetiapine patients remained on their original treatment, which was dosed flexibly in a double-blind manner in the 12-month continuation study. Cognitive performance and functional capacity were assessed with the CogState computerized cognitive battery and the UPSA-B at baseline, week 6 (end of the acute

study), and at 3 months (week 19) and 6 (week 32) in the continuation study. Mixed effects model was applied to evaluate the cognitive and functional performance of patients with final doses of lurasidone at 40/80 mg/d, 120 mg/d, and 160 mg/d (by week 32), as compared to quetiapine XR 200-800 mg/d.

Results: Subjects receiving final doses of lurasidone 120 mg/d (n=77) and 160 mg/d (n=51) showed significantly greater improvement in overall cognitive performance compared to quetiapine XR 200-800 mg/d (n=85) at week 32, while those on last dose of 40/80 mg/d (n=23) showed a trend towards significance (p=0.06, n=23). Mean changes in neurocognitive composite z-score from pre-treatment baseline to endpoint were significant for the 3 lurasidone final dose groups, with composite change scores of scores of z=1.53, z=1.43, and z= 1.34 for the lurasidone 40/80 mg/d, 120 mg/d, and the 160 mg/d, respectively. In contrast, the change in neurocognitive composite z-score was not statistically significant in the overall quetiapine group (z=0.46), with none of the individual quetiapine doses showing any significant improvement. Functional capacity scores improved in all treatment groups.

Conclusion: Our findings indicate improved cognitive performance in patients treated with each of the doses of flexible-dose lurasidone 40-160 mg/d, compared to quetiapine XR 200-800 mg/d. All doses of lurasidone were superior to all doses of quetiapine for cognitive performance. The discrepancies in dose response compared to the 6-week study need to be further studied, but the benefits of lurasidone compared to quetiapine XR over the 6-month continuation study period were all statistically significant and the change scores were too substantial to be attributed to practice effects.

Learning Objectives
1. To learn about the effect of lurasidone dose on improving cognitive and functional performance in patients with schizophrenia.
2. To learn about the lurasidone dose response relationship and its role for optimizing treatment strategies to reduce cognitive impairment associated with schizophrenia.

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W93. ROLE OF BMI AS RISK OR PROTECTIVE FACTOR FOR SUICIDALITY AMONG ADULT PSYCHIATRIC INPATIENTS

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Abstract Introduction: Obesity and suicide are significant public health issues that have been increasing in prevalence in recent years. Several epidemiological studies suggest an inverse relationship between body mass index (BMI) and completed suicide, and between BMI and attempted suicide. However, others have found an increased risk of suicide attempt among those with high BMI. Few studies have examined BMI and suicidal ideation. Additionally, few studies have examined whether high BMI is a risk factor for suicidality in psychiatric inpatients

or have used a standardized suicide assessment. In the current study, we compared scores on a standardized suicide assessment between psychiatric inpatients of different BMI groups.

Methods: Patients (n = 199) completed the Sheehan Suicidality Tracking Scale (S-STS), a standardized suicide assessment which inquires about suicidal ideation and behavior which occurred in the past month. Patient height and weight were recorded by a nurse at admission and retrieved from the electronic medical record. BMI was calculated. Patients were classified as underweight, normal weight, overweight, or obese according to the Centers for Disease Control and Prevention (CDC) guidelines. We ran one-way ANOVAs to test for differences in score on the S-STS subscales (suicidal ideation, suicidal behavior) and in total score on the S-STS between the BMI groups.

Results: Admission height and weight were able to be retrieved from the electronic medical records of 87% of the sample (n = 174). Four percent of patients (n = 7) were underweight, 27% (n = 47) were of a normal weight, about 28% (n = 49) were overweight, and about 41% (n = 71) were obese. One-way ANOVAs revealed that the BMI groups differed on the S-STS suicidal ideation subscale score ($F(3,173) = 5.68$, $p = 0.001$) and on the total S-STS suicidality score ($F(3,173) = 4.67$, $p = 0.004$). The BMI groups did not differ on the S-STS suicidal behavior subscale score ($F(3,173) = 1.35$, $p = 0.26$). In order to examine differences between the BMI groups, we ran Tukey's HSD test. Obese individuals scored significantly higher than overweight individuals on the suicidal ideation subscale ($p < 0.001$) and the total suicidality score ($p = 0.002$). No other significant between-group differences emerged.

Discussion: Contrary to our prediction, we did not find that higher BMI was associated with lower score on the S-STS and the S-STS subscales. However, Wagner et al (2013) found that extremely obese individuals had significantly higher odds of suicide risk behavior and suicide attempt than those of a normal weight. The risk for suicidal ideation and behavior may be increased at both extremes of the BMI spectrum. Clinicians should emphasize the importance of maintaining a healthy body weight when treating the patient at risk for suicidal ideation and behavior.

Learning Objectives
1. Examine relationships between suicidal behavior, suicidal ideation, and body mass index in an inpatient psychiatric setting utilizing a standardized suicide assessment.
2. Contribute to literature on risk factors for suicidality.

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W94. DASOTRALINE FOR THE TREATMENT OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PROOF-OF-CONCEPT TRIAL IN ADULTS

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Abstract Introduction: Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterized by symptoms of inattention, hyperactivity and impulsivity associated with clinically significant impairment in functioning. ADHD has an early onset, but frequently persists, with a prevalence estimate of 4% in adults.1 Dasotraline is a novel compound that is a potent inhibitor of dopamine and norepinephrine transporters, and achieves stable plasma concentrations with once-daily dosing.2 The primary objective of the current study was to evaluate the efficacy of dasotraline for the treatment of adult patients with ADHD. Secondary objectives were to evaluate the safety of dasotraline, and to assess the relationship between the plasma concentrations of dasotraline, improvement in efficacy measures, and plasma concentrations of 3,4-dihydroxyphenylglycol (DHPG).

Methods: Adult outpatients meeting DSM-IV-TR criteria for ADHD (N=341) were randomized to 4 weeks of double-blind, once-daily treatment with dasotraline 4 mg/d, 8 mg/d, or placebo. The primary efficacy endpoint was change from baseline at Week 4 in the ADHD Rating Scale, Version IV (ADHD RS-IV) total score. Secondary efficacy endpoints included the Clinical Global Impression, Severity (CGI-S) scale, modified for ADHD symptoms.

Results: Least squares (LS) mean improvements at Week 4 in ADHD RS-IV total score were significantly greater for dasotraline 8 mg/d versus placebo (-13.9 vs -9.7; P=0.019), and non-significantly greater for 4 mg/d (-12.4; P=0.076). The LS mean improvements in modified CGI-S were significantly greater at Week 4 for dasotraline 8 mg/d versus placebo (-1.1 vs -0.7; P=0.013), and for 4 mg/d versus placebo (-1.1 vs -0.7; P=0.021). The most frequent adverse events reported were insomnia, decreased appetite, nausea, and dry mouth. Discontinuations due to treatment-emergent adverse events were 11.2% and 29.7% of patients in 4 mg/d and 8 mg/d treatment groups, respectively. No evidence of drug liking was observed on the Drug Effects Questionnaire for either dose of dasotraline, nor was any drug misuse or diversion detected through the Abuse Potential Monitoring Plan. In addition, no signs or symptoms of withdrawal were observed on the Physician Withdrawal Checklist for either dose of dasotraline. For the 4 mg/d and 8 mg/d doses, mean dasotraline plasma levels increased during the first 2 weeks of treatment, and then plateaued at Weeks 3 and 4. Plasma concentrations of DHPG decreased in the first week of treatment for both dasotraline doses, and then plateaued at Weeks 3 and 4.

Conclusions: The results of this study found once-daily dosing with dasotraline, a novel, long-acting dopamine and norepinephrine reuptake inhibitor, to have statistically and clinically significant effects in adults with ADHD. Dasotraline was generally well-tolerated, with higher rates of insomnia observed with 8 mg/d. Further evaluation of the clinical utility of dasotraline in ADHD is warranted.

Clinicaltrials.gov identifier: NCT01692782.

Sponsored by Sunovion Pharmaceuticals Inc.

Learning Objectives

1. After completion of this presentation, the reader will have a better understanding of the potential efficacy of dasotraline for the treatment of ADHD in adults.
2. After e completion of this presentation, the reader will have a better understanding of the short-term safety and tolerability of dasotraline in adults with ADHD who received fixed doses of dasotraline, without gradual dose escalation.

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W95. SWITCHING TO CLOZAPINE USING IMMEDIATE VS. GRADUAL ANTIPSYCHOTIC DISCONTINUATION: A PILOT, DOUBLE-BLIND, RANDOMIZED CONTROLLED TRIAL

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Abstract Background: Clozapine has been demonstrated to be clinically superior to other antipsychotics and used for treatment-resistant schizophrenia. While the issue of clozapine titration has frequently been addressed because of its numerous and potentially severe side effects, no study as of yet has assessed the comparability of gradual vs. immediate antipsychotic discontinuation in switching to clozapine.

Objective: The objective of this study was to compare effects of immediate and gradual antipsychotic discontinuation on clinical outcomes in patients with schizophrenia undergoing a switch to clozapine.

Method: This study represents a pilot, 8-week, double-blind, randomized controlled trial. Patients who met the following criteria were included in the study: (1) outpatients with schizophrenia or schizoaffective disorder; and (2) candidacy for a trial of clozapine, defined as an inadequate clinical response to > two antipsychotics and/or intolerable side effects. Patients were randomly assigned to immediate discontinuation (prior antipsychotics were discontinued at baseline) or gradual discontinuation (prior antipsychotics were reduced by 25% each week). For each group, clozapine was gradually increased to 300 mg/day. The following assessments were performed: the Brief Psychiatric Rating Scale (BPRS), Clinical Global Impression - Severity scale (CGI-S), Calgary Depression Scale for Schizophrenia, Drug Attitude Inventory, and Schedule for the Assessment of Insight for efficacy; and the Simpson-Angus Scale, Barnes Akathisia Rating Scale, Abnormal Involuntary Movement Scale, and UKU Side Effect Rating Scale for safety.

Results: A total of 33 patients were enrolled; 15 and 18 patients were assigned to the immediate and gradual discontinuation group, respectively. Three patients in the gradual discontinuation group discontinued the study due to side effects. While significant improvements were observed in the BPRS total and CGI-S scores after the switch to clozapine in both groups, no significant differences were found on any efficacy and safety measures between the two groups.

Conclusions: Findings suggest that (1) a switch to clozapine improves psychopathology in patients with treatment-resistant schizophrenia and (2) immediate and gradual antipsychotic discontinuation strategies are comparable regarding efficacy and safety when switching to clozapine in patients with schizophrenia. Due to the small sample size, larger-scale trials are needed to confirm the findings.

Learning Objectives
1. To learn effects of switching to clozapine on clinical outcomes in patients with schizophrenia.
2. To learn effects of immediate and gradual antipsychotic discontinuation on clinical outcomes in patients with schizophrenia undergoing a switch to clozapine.

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W96. THE RELATIONSHIP BETWEEN INSIGHT INTO ILLNESS AND COGNITION IN SCHIZOPHRENIA ACROSS THE ADULT LIFESPAN

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Abstract Objectives: Impaired insight into illness is common in schizophrenia and negatively influences medication adherence and treatment outcomes. Little is known about the trajectory of insight deficits across the lifespan in patients with schizophrenia. Insight impairment is associated with illness severity, and deficits in premorbid intellectual function (i.e. IQ), executive function, and memory. The available literature suggests the course of insight impairment follows a U-shaped curve, where insight impairment is severe during the first episode of psychosis, modestly improves over mid-life, and declines again in late-life. In a previous study focusing on patients aged 60 years or above, we found that illness severity and premorbid intellectual function, but not other clinical or cognitive factors accounted for variance in insight impairment. Using one large sample of participants with schizophrenia assessed at one site, we aimed to test whether similar relationships are observed across the lifespan.

Methods: We assessed insight into illness using the Positive and Negative Syndrome Scale (PANSS) item G12 and explored its relationship to illness severity (PANSS Total), premorbid intellectual function (Wechsler Test of Adult Reading, WTAR) and cognition in 171 participants with schizophrenia aged 18 to 79 (n=51 for 18-39 years; n=38 for 40-59 years; and n=82 for 60 or above). To accomplish this, bivariate Pearson correlations and a regression analysis were performed using PASW software (Released 2009. PASW Statistics for Windows, Version 18.0. Chicago: SPSS Inc.).

Results: Across the whole sample, impaired insight (PANSS item G12) was associated with age (r=0.21, p=0.005), PANSS Total (r=0.44, p<0.001) and subscale scores (r=0.28-0.45, p<0.001), premorbid intellectual function (WTAR; r=-0.35, p<0.001), education (r=-0.26, p<0.001), global cognition (MMSE; r=-0.31, p<0.001), information processing speed

(Repeatable Battery for the Assessment of Neuropsychological Status, RBANS digit-symbol coding; r=-0.29, p<0.001), executive function (Trail Making Test - B, TMT-B; r=0.34, p<0.001), and working memory (Letter Number Span, LNS; r=-0.32, p<0.001). However, only PANSS Total (B=5.88, p<0.001) and WTAR scores (B=-2.60, p=0.010) explained a proportion of the variance of insight impairment.

Conclusions: Our study demonstrates that across the adult lifespan, impaired insight is mostly explained by illness severity and premorbid intellectual function, and not by other cognitive functions. This is consistent with our previous findings in late-life. Our results highlight the importance of premorbid intellectual function as a strong predictor of insight across the lifespan and the potential benefit from early intervention, e.g. before the onset of the illness, to remediate the cognitive changes that occur prior to the manifestation of the schizophrenia syndrome. Early intervention is also supported by the findings that first episode and younger patients have significantly greater improvement in insight during a psychotic episode than multi-episode or older patients, which suggests these groups may have a greater capacity for developing insight into illness than those in later phases of schizophrenia.

Learning Objectives
1. To understand the relationship between impaired insight and cognition.
2. To understand the importance of early intervention, which may minimize insight impairment in schizophrenia, and ultimately lead to improved medication adherence and clinical outcomes.

Literature References
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