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Poster Session III
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W2. Treatment with Adjunctive Aripiprazole Results in Significant Improvement Compared with Continued Antidepressant Monotherapy in Patients with Mild, Moderate, and Severe Major Depressive Disorder

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Background: The severity of a patient's depressive symptoms may inform treatment decisions. However, current treatment guidelines are based on trial data that group patients of varying degrees of severity together. To better understand the appropriate patient for adjunctive aripiprazole in major depressive disorder (MDD), this post-hoc analysis pooled data from 3 similar, randomized trials,[1,2] and stratified patients based on published severity cut-offs on the Montgomery Åsberg Depression Rating Scale (MADRS).[3]

Methods: These trials enrolled patients with an inadequate response to 1-3 trials of antidepressant therapy (ADT). Each study had an 8-week prospective ADT phase (Phase B), followed by a 6-week randomized phase (Phase C) of adjunctive aripiprazole versus continued antidepressant monotherapy + placebo for patients with an inadequate response during the prospective phase. Inadequate response to ADT monotherapy was defined as $<50\%$ reduction in the 17-item Hamilton Rating Scale for Depression (HAM-D-17) total score, HAM-D-17 total score $\geqslant 14$, and Clinical Global Impressions-Improvement (CGI-I) score $\geqslant 3$. For this post-hoc analysis, patients were stratified at the beginning of Phase C by MADRS total score into 3 groups: mild (MADRS total score $\leqslant 24$), moderate (MADRS total score = 25-30), and severe (MADRS total score $\geqslant 31$). During Phase C, aripiprazole was flexibly dosed with a target of 10 mg/day. Patients were initiated at 5 mg/day (could decrease to 2 mg/day for tolerability) and increased to 10 mg/day (could decrease to 5 mg/day for tolerability) at the end of Week 1; the maximum dose was 20 mg/day. Change in MADRS total score for adjunctive aripiprazole and adjunctive placebo was assessed at the end of 6 weeks using last observation carried forward (LOCF).

Results: Baseline demographics across the three groups appeared similar. At the beginning of Phase C, in the aripiprazole group, 224 (41%), 206 (38%), and 110 (20%) patients were considered mild, moderate, or severe, respectively; in the placebo group, it was 191 (36%), 179 (34%), and 155 (30%) patients, respectively. At the end of 6 weeks, mean changes in MADRS total score between aripiprazole and placebo were significantly different in all three severity groups: mild -7.9 aripiprazole vs. -5.4 placebo ($P = 0.0005$); moderate -9.5 aripiprazole vs. -6.3 placebo ($P = 0.0001$); severe -11.9 aripiprazole vs. -7.4 placebo ($P = 0.0001$). Statistically significantly differences between aripiprazole and placebo first appeared at Week 1 (mild or severe) or Week 2 (moderate). In all three groups, the endpoint effect size of aripiprazole treatment was moderate (0.334-0.483). Similarly, mean percent improvement in MADRS total score between aripiprazole and placebo were significantly different in all three severity groups: mild -38% aripiprazole vs. -26% placebo ($P = 0.0008$); moderate -35% aripiprazole vs. -23% placebo ($P = 0.0001$); severe -35% aripiprazole vs. = 22% placebo ($P = 0.0002$). Adjunctive aripiprazole was well tolerated across the severity groups, with no trends in the proportion of patients reporting an adverse event (AE) based on severity; the most common AEs in the aripiprazole-treated groups were akathisia and restlessness.

Conclusions: In this pooled analysis, adjunctive aripiprazole resulted in significantly greater symptom improvement than placebo regardless of baseline severity. Change scores appeared greatest in the severe group but this may reflect the truncated range in the mild group. The greater response with adjunctive aripiprazole demonstrates the utility of this strategy to manage depression in a wide spectrum of patients.

References 1. Thase ME, et al. Examning the efficacy of adjunctive aripiprazole in major depressive disorder: a pooled analysis of 2 studies. Prim Care Companion J Clin Psychiatry. 2008;10:440-7.2. Berman RM, et al. Aripiprazole augmentation in major depressive disorder: a double-blind, placebo-controlled study in patients with inadequate response to antidepressants. CNS Spectr. 2009;14: 197-206.3. Kearns NP, et al. A comparison of depression rating scales. Brit J Psychiat. 1982;141:45-9.

Keywords: aripiprazole, depression, antidepressants, MADRS, treatment

Disclosure: J. Nelson, **Part 1:** Honoraria from Eli Lilly Global, Lundbeck, Otsuka Asia, Schering Plough/Merck (Asia); consultant for Bristol-Myers Squibb, Cenestra Health, Corcept, Covidien, Eli Lilly, Forest, Lundbeck, Medtronics, Merck, Mylan (Dey Pharma), Orexigen, Otsuka, Pfizer, Sunovion, served on advisory boards for Avanir, Bristol-Myers Squibb, Eli Lilly, Labopharm, Mylan (Dey Pharma), and Otsuka, **Part 2:** Honoraria from Eli Lilly Global, Lundbeck, Otsuka Asia, Schering Plough/Merck (Asia); consultant for Bristol-Myers Squibb, Cenestra Health, Corcept, Covidien, Eli Lilly, Forest, Lundbeck, Medtronics, Merck, Mylan (Dey Pharma), Orexigen, Otsuka, Pfizer, Sunovion, served on advisory boards for Avanir, Bristol-Myers Squibb, Eli Lilly, Labopharm, Mylan (Dey Pharma), and Otsuka, **Part 3:** n/a, **Part 4:** n/a; T. Stewart, **Part 1:** Speaker for Bristol-Myers Squibb Co., and Otsuka Pharmaceutical Co., Ltd.; A. Hatch, **Part 1:** Employee of Otsuka Pharmaceutical Development & Commercialization, Inc., **Part 2:** Employee of Otsuka Pharmaceutical Development & Commercialization, Inc.; K. Largay, **Part 1:** Employee of Otsuka Pharmaceutical Development & Commercialization, Inc., **Part 2:** Employee of Otsuka Pharmaceutical Development & Commercialization, Inc.; E. Bellochio, **Part 1:** Employee of Bristol-Myers Squibb Co., **Part 2:** Employee of Bristol-Myers Squibb Co., **Part 3:** Employee of Bristol-Myers Squibb Co.; S. Marler, **Part 1:** Employee of Bristol-Myers Squibb Co., **Part 2:** Employee of Bristol-Myers Squibb Co., **Part 3:** Employee of Bristol-Myers Squibb Co.; R. Baker, **Part 1:** Employee of Otsuka Pharmaceutical Development and Commercialization, Inc, **Part 2:** Employee of Otsuka Pharmaceutical Development and Commercialization, Inc, **Part 3:** Employee of Otsuka Pharmaceutical Development and Commercialization, Inc; J. Sheehan, **Part 1:** Employee of Bristol-Myers Squibb Co., **Part 2:** Employee of Bristol-Myers Squibb Co., **Part 3:** Employee of Bristol-Myers Squibb Co.; R. Berman, **Part 1:** Employee of Bristol-Myers Squibb Co., **Part 2:** Employee of Bristol-Myers Squibb Co.

W3. Genomic Predictors of Response to Antidepressant Treatment in Geriatric Depression Using Genome-wide Expression Analyses: A Pilot Study

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Background: Depression and antidepressant response are associated with leukocyte gene transcriptional alterations. The present pilot study examined immune cell gene expression with antidepressant treatment in geriatric depression.

Methods: Genome-wide transcriptional profiles were collected from peripheral blood leukocytes sampled at baseline and 16-week follow-up from 37 older adults with major depression who were

randomized to methylphenidate + citalopram; citalopram + placebo; or methylphenidate + placebo. Methylphenidate dose ranged between 10-40 mg per day, and citalopram dose was 20-40 mg per day. Genome-wide transcriptional profiling was carried out in the peripheral blood mononuclear cell samples obtained at baseline and post-intervention. Promoter-based bioinformatics analyses tested the hypothesis that observed transcriptional alterations were structured by transcription factors implicated in dopaminergic, serotonergic, and neuroplastic pathways.

Results: 25 responder and 12 non-responders gene expression profiles were analyzedIn the analyses of covariance controlling for treatment group, 2 gene transcripts showed systematic up-regulation in non-responders at baseline. Up-regulated genes at baseline in non-responders compared to non-responders included 1) CA1 carbonic anhydrase gene on chromosome 8 involved in reversible hydration of CO_2 and respiratory function (fold change 2.54; $P = 0.03$); 2) SNCA -alpha-synuclein gene implicated in Parkinson's disease that binds to dopamine transporter (fold change 2.1; $P = 0.03$). Additionally, promoter-based bioinformatic analysis of genes found to be upregulated by 1.2-fold indicated a reduction in CREB activity in responders versus non-responders over time in the entire sample and in the subgroup taking methylphenidate and placebo (both $p < .0001$, or Bonferroni-corrected $p < .05$).

Conclusions: The present results suggest a unique transcriptional signature in responders and non-responders to antidepressant treatment in the dopaminergic and metabolic pathways important for neurolplasticity and brain aging. Response to treatment in the overall sample and to methylphenidate was associated with a reduction in CREB activity in responders versus non-responders. Our results are novel in identifying potential biomarkers of response/nonresponse to an antidepressant treatment in geriatric depression, but will need to be replicated in larger samples with the use of additional specific biomarkers of the identified pathways.

Keywords: Genomic, microarrays, predicotrs of treatment response, antidperessant, gelriatric depression

Disclosure: H. Lavretsky, **Part 1:** Research grants from Forest Research Institute; Consulting fee from Lilly, Dey Pharmacuetical, **Part 4:** Forest Research Institute; A. Eskin, Nothing to Disclose; S. Nelson, Nothing to Disclose; S. Cole, Nothing to Disclose.

W4. The Acetylcholinesterase Inhibitor, Rivastigmine, but not Huperzine A, Improves Verbal Learning/Episodic Memory and Working Memory in Cocaine-dependent Volunteers

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Background: Long-term, high-dose cocaine use is a risk factor for the onset of neurocognitive impairment in humans. In a recent meta-analytic review of 15 studies that included 586 matched controls and 481 abstinent cocaine users, effect sizes of moderate or greater magnitude for attention, episodic memory, and working memory were reported (Jovanovski, 2005). These neurocognitive impairments have important implications with respect to day-to-day functioning; for example, the presence of cocaine-associated neurocognitive impairment is associated with poor treatment retention/increased treatment dropout. Not surprising, cocaine-associated neurocognitive impairment has been identified as an important target of treatment, and medications such as modafinil have demonstrated an indication vis-à-vis improvement on measures of working memory. Thus, given that cocaine—associated neurocognitive impairment is potentially amenable to treatment, this study sought to determine whether the acetylcholinesterase inhibitors rivastigmine or huperzine A could improve neurocognitive performance in cocaine-dependent individuals.

Methods: Seventy two cocaine-dependent individuals who were not seeking treatment at the time of enrollment in the study were randomly assigned to receive placebo ($n = 15$), rivastigmine 3 mg ($n = 14$), rivastigmine 6 mg ($n = 14$), huperzine A 0.4 mg ($n = 15$), or huperzine A 0.8 mg ($n = 14$). Urinanalysis was used to confirm abstinence from cocaine on the day of admission and during the next 7 days. The baseline neurocognitive assessment, which included measures of attention/information processing (as measured by the Continuous Performance Task), verbal learning episodic memory (as measured by the Hopkins Verbal Learning Test), and working memory (as measured by the Dual N-Back Task), was conducted immediately after the washout phase and prior to the administration of study medication (Day 0). The follow-up assessment was conducted on Day 8 after participants had received rivastigmine, huperzine A, or placebo for seven days (Day 2-8).

Results: Enrolled participants were primarily African-American, $\sim$41 years old, had $\sim$12 years of education, used cocaine for $\sim$16 years and $\sim$17 out of the last 30 days, and used $\sim$2 grams of cocaine per day via the smoked route of administration. Rivastigmine administration (6 mg) significantly improved performance on two measures of working memory span (mean n-back span, maximum n-back span) and improved performance on a verbal learning and memory task (HVLT total recall). Those participants randomized to 6 mg rivastigmine had significantly higher mean n-back span ($1.91 \pm .12$; Mean $\pm$ SEM) when compared to those randomized to placebo (1.55 ± 0.12; $p < 0.02$). In addition, those participants randomized to 6 mg rivastigmine had significantly higher max n-back span (2.64 ± 0.19) when compared to those randomized to placebo ($2.07 \pm .18$; $p < 0.03$). Furthermore, those participants randomized to 6 mg rivastigmine had significantly higher scaled total verbal learning HVLT scores (42.14 ± 2.45) when compared to those randomized to placebo (31.73 ± 2.37; $p < 0.001$). There were no differences between rivastigmine and placebo groups on measures of sustained attention/information processing and huperzine A did not modulate performance on measures of information processing speed, verbal learning/ episodic memory, or working memory.

Conclusions: This study provides additional data showing that cocaine-associated neurocognitive impairment, in a sample of long-term, high-dose cocaine users, can be remediated. Additionally, while this confirms that working memory impairments are amenable to treatment, this is to our knowledge, the first study to show that cocaine-associated memory impairment can be treated. These effects are likely relevant in the treatment of cocaine dependence, in which the remediation of impaired verbal learning, episodic, and working memory may be associated with improved treatment outcomes.

Keywords: cocaine; acetylcholinesterase inhibitor; neurocognition; verbal learning; working memory

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W5. Treatment of Depression with Botulinum Toxin A: A Randomized, Double-blind, Placebo Controlled Trial

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Background: In spite of advances in our understanding and treatment of major depressive disorder (MDD), many patients fail to achieve remission. Recently, it has been proposed that inhibition of frowning could be used as a treatment for MDD (Finzi et al., 2006). Preliminary studies have suggested that botulinum toxin treatment of frown muscles may help depression (Finzi et al., 2006, Wollmer et al., 2012). The corrugator (frown) muscle plays an essential role in the facial expressions of anger and sadness. Charles Darwin first suggested that muscle contractions involved in the formation of facial expressions contribute to emotional states and mood; William James elaborated on this concept, which has been confirmed experimentally, and is now known as the facial feedback hypothesis. Darwin also recognized that severely depressed individuals show corrugator muscle overactivity, which may result in the "omega sign." Botulinum toxin (BT) reversibly inhibits muscle contraction. When injected into the glabellar region, BT reversibly inhibits frowning for about three months. We have conducted a randomized, double-blind, placebo controlled trial of BT injection into the glabellar region as a treatment for MDD.
Methods: The study was IRB approved, and informed consent was given by all subjects. Male or female outpatients aged 18 to 65 years, with MDD, as diagnosed by the Structured Clinical Interview for Axis I DSM-IV Disorders (SCID), were eligible. Subjects were required to have a Montgomery-Asberg (MADRS) score $\geqslant$ 26 and a Clinical Global Impression – Severity (CGI) score $\geqslant$ 4 at screening Eligible subjects were randomly assigned at screening to receive either onabotulinumtoxinA(OBA) (Botox Cosmetic, Allergan) or placebo(PLB) (0.9%NaCl) injections in the glabellar region(Finzi et al., 2006). Women received 29 U of OBA and men, 40 U. All patients were assessed at randomization and after 3 and 6 weeks with the MADRS, Beck Depression Inventory II (BDI) and CGI. The primary outcome measure was response to treatment, as defined as a $\geqslant$ 50% decrease in MADRS score. Remission was defined as a MADRS score of 10 or lower along with a $\geqslant$50% decrease in score. Secondary outcomes were response to treatment in scores on BDI and CGI. Subjects at rest and maximal frowns were assessed photographically at the beginning and end of the study.
Results: 121 subjects were screened, of whom 84 subjects were randomized: 41 to OBA and 43 to placebo. Eight patients were excluded (4 patients in the OBA group for withdrawal of consent, and two in each group for protocol violations). One OBA subject was lost to follow-up after injection. 33 subjects in the OBA group and 41 in the placebo group completed all three visits. The two groups did not differ significantly on any of the demographic or clinical baseline variables. 91% of the OBA and 80% of the PLB subjects suffered from recurrent depression. The average number of antidepressants tried during subject lifetimes, were 2.2 for OBA, and 1.8 for PLB, and the mean duration of the current depressive episode was 27.9 months. As for the primary end point, MADRS scores at the six week visit versus baseline, there was a significant improvement in the OBA group compared to the PLB group; there was a 47.0% reduction in MADRS scores for OBA subjects, versus a 20.6% reduction for PLB (student's t test, $p<0.0004$). The OBA group showed a significant clinical improvement in depression, compared to the PLB group, over time, as measured by MADRS score, (ANOVA, $f=9.7$, $p<0.0028$, two-tailed); BDI-II score, (ANOVA, $f=5.7$, $p<0.019$, two-tailed.); and CGI score (ANOVA, $f=15.3$, $p<0.0002$, two-tailed.). The response rate for MADRS was 51.5% vs. 14.6%; $p<0.0009$ Fisher's exact test. The remission rate, as judged by MADRS, was significantly higher in the OBA group, 27.3%, than in the PLB group, 7.3%, $p<0.027$, Fisher's exact test. A decrease in the maximal ability to frown at 6 weeks (among all subjects) was correlated with MADRS response; $p<0.01$; Spearman coefficient. In the OBA group, there was a trend towards greater response ($\geqslant$50% decrease in MADRS score) with increasing baseline frown (N.S., $p<0.07$).
Conclusions: This is the first randomized, double-blind and placebo -controlled clinical trial to show that a single treatment of the glabellar region with OBA induces a strong and sustained alleviation of symptoms in a broadly defined group of people with MDD. The results are consistent with those of our earlier pilot study (Finzi et al.) and the prior smaller controlled study of BT in patients with refractory depression. Our study is also the first to show that subjects treated with OBA went into remission at a significantly higher rate than placebo subjects. The mechanism of action of OBA in helping depression is unknown, but our results support the facial feedback hypothesis and suggest that it can be utilized therapeutically. The results also support the concept of *emotional proprioception* (Finzi, 2013) whereby the brain continuously monitors the relative valence of salient facial expressions, which may be an important influence on mood.
Keywords: botulinum toxin depression clinical trial
Disclosure: E. Finzi, **Part 4:** Dr Finzi has received a use patent to treat major depression with botulinum toxin; N. Rosenthal, Nothing to Disclose

W6. Adjunctive Aripiprazole More Than Doubles the Rate of Early and Sustained Response across Multiple Measures in Patients with MDD Who Have an Inadequate Response to Antidepressant Monotherapy

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Background: Medications with rapid antidepressant effects address an unmet need in major depressive disorder (MDD), as it can take several weeks to determine if a given antidepressant will be effective for an individual patient. However, a rapid, transient effect alone does not address patients' longer-term needs. Therefore, we evaluated the early and sustained antidepressant effects of adjunctive aripiprazole in MDD. Early and sustained response (ESusR) is a particularly rigorous measure of efficacy because patients must respond early and at all subsequent time points. This post-hoc analysis investigated ESusR using both measures of symptoms (Montgomery Asberg Depression Rating Scale [MADRS]), total clinical progress from baseline (Clinical Global Impression-Improvement scale [CGI-I]) and a measure of clinical state versus other patients with depression (CGI-Severity scale [CGI-S]).
Methods: This pooled analysis of 3 similar studies,[1,2] enrolled patients with an inadequate response to 1-3 trials of antidepressant therapy (ADT). Each study had an 8-week prospective ADT phase (Phase B), then a 6-week randomized phase of adjunctive aripiprazole vs. adjunctive placebo (Phase C). In this analysis, ESusR was defined as a patient who had a response by one of 3 measures during Phase C ($\geqslant$50% improvement in MADRS total score; CGI-I or CGI-S scores of 1-2) at Week 2 and sustained that response at all subsequent visits (Weeks 3, 4, 5, and 6). In addition, because the literature presents inconsistent cut-offs for response on the CGI-S, we determined the most appropriate definition in this population.
Results: Among Week 2 MADRS Responders, the median and mode CGI-S scores at Week 2 were 2 (borderline mentally ill) for both adjunctive aripiprazole ($n=88$) and adjunctive placebo

(n = 42), while the median and mode CGI-S scores among Week 2 adjunctive aripiprazole (n = 299) and adjunctive placebo Non-responders (n = 345) were 4 (moderately ill). However, among Week 2 Responders and Non-Responders the distribution of CGI-S scores significantly differed between the aripiprazole and placebo treatment arms ($p < 0.0001$) and appeared to favor aripiprazole. The rates of ESusR by MADRS in the adjunctive aripiprazole and adjunctive placebo groups were 11.6% (45/387) and 5.4% (21/387), respectively ($P = 0.002$; relative risk [RR] = 2.2, 95% CI: 1.3, 3.5). Rates of ESusR by CGI-I in the adjunctive aripiprazole and placebo groups were 30.9% (120/389) and 15.3% (59/386), respectively ($P < 0.0001$; RR = 2.0, 95% CI: 1.5, 2.7). Rates of ESusR by CGI-S in the adjunctive aripiprazole and placebo groups were 13.6% (53/390) and 5.1% (20/389), respectively ($P < 0.0001$; RR = 2.6, 95% CI: 1.6, 4.3). Overall, 31.3% (121/386) of patients receiving aripiprazole responded by at least one measure of EsusR compared with 15.6% (60/384) of patients receiving placebo.

Conclusions: In this MDD population who failed previous ADT, a CGI-S cut-off of 2 constituted the most appropriate definition of response on this scale. The distribution of CGI-S scores among Week 2 responders appeared to favor aripiprazole. ESusR was demonstrated with adjunctive aripiprazole at a rate more than double compared with ADT monotherapy using a symptom scale and 2 global response measures. As expected, the response cut-off of MADRS improvement $\geqslant$50% was similar to a CGI-S score of 1-2. Both definitions appeared to be a more rigorous response definition than CGI-I 1-2. The magnitude of treatment effect across the three measures was similar. These similar results across three scales suggest aripiprazole reliably and robustly increases the proportion of patients who achieve ESusR.

References: 1. Thase ME, et al: Examining the efficacy of adjunctive aripiprazole in major depressive disorder: a pooled analysis of 2 studies. Prim Care Companion J Clin Psychiatry. 2008;10:440-7. 2. Berman RM, et al: Aripiprazole augmentation in major depressive disorder: a double-blind, placebo-controlled study in patients with inadequate response to antidepressants. CNS Spectr. 2009; 14:197-206.

Keywords: Aripiprazole, Depression, Response, Antidepressant, Clinical trial

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W7. A Randomized Controlled Crossover Trial of Ketamine in Obsessive-compulsive Disorder

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Background: Obsessive-compulsive disorder (OCD) is a leading cause of illness-related disability (1). First-line OCD pharmacological treatments lead to limited symptom relief and typically have a lag time of 6-10 weeks before clinically meaningful improvement (2). Identifying more effective pharmacological treatments with faster onset of action would be a major advance. Medications thought to modulate the glutamate system are a promising new class of pharmacological agents for the treatment of OCD (3-8). Ketamine, a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist, modulates glutamate and has been shown to have rapid anti-depressant effects in multiple studies (9-15). A recent case study of a unmedicated individual with OCD without comorbid depression who was given ketamine (0.5 mg/kg IV over 40 minutes) showed rapid anti-obsessional effects that persisted from 1 to 7 days post-infusion, long after the drug had cleared (16). A subsequent open trial of ketamine in ten individuals showed modest but significant improvement in OCD symptoms over days 1 to 3 following ketamine infusion compared to baseline; the majority of individuals with OCD in this study were taking multiple medications and had moderate to severe current comorbid depression (17). We investigated the effects of ketamine on individuals with OCD who were not currently on medications and did not have moderate to severe comorbid depression.

Methods: In a randomized, double-blind, placebo-controlled, crossover design, unmedicated adults (N = 10) with OCD received two intravenous infusions: one of saline and one of ketamine (0.5 mg/kg) over 40 minutes. These infusions were spaced at least 1 week apart; the order of each pair of infusions was randomized. To be eligible, participants were required to have at least moderate to severe OCD (Yale-Brown Obsessive-Compulsive Scale [YBOCS] score >16) with no or mild depression (Hamilton Depression Rating Scale [HDRS-17] <25), and endorse near-constant intrusive obsessions (>8 hours per day) (18, 19). To assess rapid changes in obsessions, the OCD visual analogue scale (OCD-VAS) was used at baseline, at 26, 90, 110, and 230 minutes and daily for 7 days post-infusion (16). To assess both obsessive and compulsive symptoms, the YBOCS scale, designed to be used to assess OCD symptoms at 1 week intervals, was used at baseline and 7 days post-infusion. To monitor depressive symptoms, the HDRS-17 was used at baseline and 1 and 3 days post-infusion. Response rate of obsessions was defined as a minimum of 35% improvement in obsessions (as measured by the OCD-VAS), and response rate for OCD symptoms was defined as a minimum of 35% reduction in OCD symptoms (as measured by the YBOCS).

Results: All ten participants completed the study. At baseline, participants had moderate to severe OCD symptoms (mean YBOCS 27.1 +/−3.4 SD, range: 22-34). On average, there was a significant rapid decrease in obsessions (as measured by OCD-VAS) which decayed over time and then reached a plateau. Responder rate (n = 10) of obsessions (as measured by OCD-VAS) at post-infusion time points were as follows: 90% at 3 hours, 80% at 1 day, 60% at 2 days, 50% at 3 days, and 50% until day 7. Responder rate (n = 10) for OCD symptoms (as measured by YBOCS) was 50% at day 7. Responder rate for OCD symptoms among the subset of patients (n = 5) who got the ketamine infusion first (and thus the effects of ketamine could be evaluated at both day 7 and day 14), was 40% at day 14. At baseline, participants had minimal depressive symptoms (mean HDRS 4.2 +/−5.6, range: 0-16). The average depressive symptoms of the 10 patients did decrease somewhat after the ketamine infusion (4.2 +/−5.6 to 1.8 +/−1.9, $F(2,17) = 3.38$, $p = 0.058$).

Conclusions: These data suggest that ketamine can rapidly relieve symptoms of OCD, and this effect can persist for at least one week in 50% of OCD patients with constant intrusive thoughts. A subset of individuals had relief for up to two weeks. Future research is needed to better understand the mechanism of ketamine's rapid anti-obsessional effect and persistant reduction in OCD symptoms, long after the drug has cleared. These insights will help inform the development of new treatment strategies for individuals suffering with OCD.

Keywords: Ketamine; Glutamate, Obsessive-Compulsive Disorder, Clinical Trial, Pharmacological Therapy

Disclosure: C. Rodriguez, Nothing to Disclose; L. Kegeles, **Part 4:** Research contract, Pfizer; Research contract, Amgen; A. Levinson, Nothing to Disclose; S. Marcus, Nothing to Disclose; H. Simpson, **Part 4:** research contract from Neuropharm; medication for research study from Janssen.

W8. Safety and Tolerability of Atomoxetine Hydrochloride in a Placebo-controlled Randomized Withdrawal Study in Adults with Attention-Deficit/Hyperactivity Disorder

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Background: Safety and tolerability of atomoxetine (ATX) were studied in the first double-blind (DB), placebo (PBO)-controlled, randomized withdrawal trial of ATX in adults with attention deficit/hyperactivity disorder (ADHD). Responders, who completed 24 wks of ATX treatment (TX), were randomized to an additional 25 wks of ATX or PBO.

Methods: The study was conducted at 152 outpatient sites in 18 countries. Patients (N = 2017; 60% from Europe), 18-50 yrs of age, with ADHD were enrolled into the study and received up to 12 wks of open-label (OL) ATX (40-100 mg/day). Responders were maintained on an ATX dose of 80 or 100 mg/day for an additional 12 wks of DB maintenance. Those who met response maintenance criteria were randomized to ATX (N = 266) or PBO (N = 258) for a 25-wk randomized withdrawal phase. Safety measures included discontinuation due to adverse events (AEs), serious AEs (SAEs), TX-emergent AEs (TEAEs), supine blood pressure (BP) and pulse, body mass index (BMI) and weight, electrocardiogram (ECG), the Columbia Suicide-Severity Rating Scale (C-SSRS), the Hamilton Anxiety Rating Scale–14 items (HAMA), and the Hamilton Depression Rating Scale-17 items (HAMD-17). For categorical variables, TX differences were compared with Fisher's exact test. For continuous variables, within-TX least-squares mean (LSMean) changes from baseline (BL) to endpoint (EP) were analyzed with a Wilcoxon signed-ranked test and between-TX LSMean changes from BL to EP were analyzed with analysis of covariance or analysis of variance.

Results: During the first 24 wks of ATX TX, no deaths occurred. Discontinuations due to AE with a frequency of $\geqslant$1% were nausea (2.4%) and fatigue (1.1%). TEAEs with a frequency of $\geqslant$5% were nausea (27.4%), headache (17.3%), dry mouth (17.0%), decreased appetite (14.6%), fatigue (13.0%), hyperhidrosis (9.0%), insomnia (8.8%), dizziness (8.5%), nasopharyngitis (6.8%), and somnolence (5.6%). Twenty-nine (1.4%) patients experienced 35 SAEs; 10 were judged by the investigator as related to study drug (alcohol abuse and 2 events of restlessness in 1 patient; haemorrhage and headache in 1 patient; 2 events of bradykinesia in 1 patient; suicidal ideation, palpitations, and auditory hallucination in 1 patient each). Changes from BL to EP in systolic BP (1.3 mmHg), diastolic BP (1.6 mmHg), pulse (5.4 bpm), BMI (−0.3 kg/mE2) and weight (−0.8 kg) were significant ($p < .001$). For ECG parameters, changes from BL to EP in heart rate (HR; 8.7 bpm), PR (−4.2 ms), QRS (0.4 ms), Fridericia's QT correction (QTcF; −0.1 ms) and, Bazett's QT correction (QTcB; 8.2 ms) were significant ($p < .05$). No patient had a QTcF or QTcB $>$500 ms, and no patient showed an increase from BL in QTcF and QTcB $>$60 ms. Suicide-related events as assessed by the C-SSRS were experienced by 2.8% of patients. Changes from BL to EP on HAMA (−0.8) and HAMD-17 (−0.3) total scores were significant ($p < .001$), but not clinically relevant. During the 25-wk, DB randomized withdrawal phase, 1 death of unconfirmed myocardial infarction occurred in a male patient on 100 mg ATX; the investigator was unable to assess the relatedness between this event and blinded study drug, OL ATX TX, or protocol procedures. The incidence of SAEs was similar between ATX and PBO (2.6% vs. 1.6%; $p = .545$). Frequencies of discontinuations due to AEs were similar between ATX and PBO overall (3.4% vs 1.9%; $p = .418$) and for each individual AE. The overall percentage of patients experiencing $\geqslant$1 TEAE(s) was significantly higher for ATX than PBO (47.0% vs 37.6%; $p = .034$), but there were no significant differences between ATX and PBO for any individual TEAE. There were significant, but relatively small differences between ATX and PBO in diastolic BP (−0.1 vs −2.3 mmHg; $p < .001$), pulse (−1.4 vs −5.3 bpm; $p < .001$), BMI (−0.1 vs 0.4 kg/mE2; $p < .001$) and weight (−0.2 vs 1.1 kg; $p < .001$). Changes from BL in QTcF (0.8 vs 2.3 ms) were not significantly different between ATX and PBO; however, there were significant differences ($p < .01$) between ATX and PBO for changes in HR (−2.6 vs −9.1 bpm), PR (0.2 vs 4.1 ms), and QTcB (−1.6 vs −5.9 ms). No patient had a QTcF and QTcB $>$500 ms, and no patient showed an increase from BL in QTcF and QTcB $>$60 ms. The relative frequencies of suicide-related events assessed by the C-SSRS were not significantly different between ATX and PBO (2.3% vs 1.2%). Changes from BL to EP in the HAMA (−0.3 vs 0.1) and HAMD-17 (0.0 vs 0.4) total scores were not significantly different between ATX and PBO.

Conclusions: This study demonstrated that ATX exhibited an acceptable safety profile in adults with ADHD during the first 24 wks of TX, and during an additional 25 wks of DB TX in the largest clinical trial of ADHD in adults to date.

Keywords: attention-deficit/hyperactivity disorder, adult, European, atomoxetine

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W9. Efficacy and Safety of Cariprazine in Acute Exacerbation of Schizophrenia: A Phase III, International, Randomized, Double-blind, Placebo-Controlled Trial

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Background: Cariprazine is a potent dopamine D_3-preferring D_3/D_2 receptor partial agonist antipsychotic in development for the treatment of schizophrenia and bipolar mania. With almost 10-fold greater selectivity for the dopamine D_3 receptor over the D_2 receptor, cariprazine has a unique pharmacological profile among antipsychotics. Along with high dopamine D_2 receptor affinity, high affinity at the dopamine D_3 receptor may result in clinical advantages such as beneficial effects on negative symptoms and improvements in cognitive functioning. Cariprazine has previously demonstrated efficacy in patients with acute exacerbation of schizophrenia in a phase II study. This phase III study (NCT01104779) evaluated the efficacy and safety of cariprazine 3-6 and 6-9 mg/d in patients with acute exacerbation of schizophrenia.
Methods: An international, randomized, double-blind, placebo-controlled fixed/flexible-dose study compared cariprazine 3-6 mg/d and cariprazine 6-9 mg/d with placebo. Patients with DSM-IV-TR-defined schizophrenia with a current psychotic episode <2 weeks' duration, and a Positive and Negative Syndrome Scale (PANSS) total score $\geqslant 80$ and $\leqslant 120$ were randomized (1:1:1) to receive placebo, cariprazine 3-6 mg/d, or cariprazine 6-9 mg/d. Patients received 6 weeks of double-blind treatment followed by 2 weeks of safety follow-up. Hospitalization was required for the screening period and at least the first 4 weeks of double-blind treatment. The primary efficacy parameter was the change from baseline to Week 6 in PANSS total score analyzed using a mixed-effects model for repeated measures (MMRM) approach on the modified Intent-to-Treat population (ITT), defined as patients who received at least 1 dose of study drug and had at least 1 postbaseline PANSS assessment. Sensitivity analyses using pattern-mixture model (PMM) and additional analysis using analysis of covariance (ANCOVA) with last observation carried forward (LOCF) approaches were performed. A matched parallel gatekeeping procedure was applied to control overall type 1 error rates for multiple comparisons. The secondary efficacy parameter was the change from baseline to Week 6 in Clinical Global Impressions-Severity (CGI-S) score analyzed similarly to the primary analyses. Additional efficacy measures included, in part, the PANSS positive and negative subscales, Negative Symptom Assessment (NSA-16), and Clinical Global Impressions-Improvement (CGI-I). Safety was evaluated by AEs, clinical laboratory values, vital signs, electrocardiograms (ECGs), extrapyramidal symptom (EPS), and akathisia scales.
Results: Of the 446 patients that were randomized and received treatment (Safety Population: placebo [n = 147], cariprazine 3-6 mg/d [n = 151], or cariprazine 6-9 mg/d [n = 148]), 60.5% completed the study. The most common reasons for discontinuation were withdrawal of consent (16.4%), insufficient therapeutic response (11.4%), and AEs (9.0%). The overall mean daily cariprazine dose ($\pm$ SD) was 4.22 ± 0.93 mg/d for the 3-6 mg/d group and 6.55 ± 1.43 mg/d for the 6-9 mg/d group. At Week 6, least squares mean difference (LSMD) and 95% confidence intervals (95%CI) in PANSS total score for cariprazine versus placebo was -6.8 (95% CI = -11.3, -2.4; adjusted $P = .0029$) for the 3-6 mg/d group and -9.9 (95% CI = -14.5, -5.3; adjusted $P < .0001$) for the 6-9 mg/d group. Significant improvement for cariprazine over placebo in PANSS total score was observed starting at Week 1 for the 6-9 mg/d group and at Week 2 for the 3-6 mg/d group. CGI-S scores were also significantly improved at Week 6 in both cariprazine groups compared with placebo (3-6 mg/d, LSMD = -0.3 [-0.6, -0.1]; adjusted $P = .0115$; cariprazine 6-9 mg/d, LSMD = -0.5 [-0.8, -0.3] adjusted $P = .0002$). On PANSS positive scores, both cariprazine groups showed significant improvement relative to placebo (3-6 mg/d, LSMD = -2.0 [-3.5, -0.6]; $P = .0074$; 6-9 mg/d, LSMD = -3.4 [-4.9, -1.8]; $P < .0001$). Cariprazine 6-9 mg/d demonstrated significant improvements over placebo on negative symptoms as measured by change in the PANSS negative (LSMD = -1.7 [-2.9, -0.4]; $P = .0095$) and NSA-16 total (LSMD = -3.4 [-6.0, -0.9]; $P = .0089$) scores. Both cariprazine groups also demonstrated significant improvement versus placebo on CGI-I scores. Discontinuations due to AEs were similar across groups. The most common AEs leading to discontinuation ($\geqslant 2\%$) were worsening of schizophrenia and psychotic disorder. Common ($\geqslant 5\%$ and twice the rate of placebo) treatment-emergent AEs (TEAEs) that occurred in both cariprazine groups were akathisia, EPS, and tremor. Common TEAEs in the cariprazine 3-6 mg/d group were constipation and diarrhea; common TEAEs in the cariprazine 6-9 mg/day group were restlessness, dyspepsia, vomiting, and increased weight. Mean changes in cholesterol, triglycerides, fasting glucose, and weight were small and similar between groups. Prolactin levels decreased in all treatment groups.
Conclusions: Cariprazine 3-6 mg/d and 6-9 mg/d demonstrated significant improvement relative to placebo on change from baseline to Week 6 on primary (PANSS total score) and secondary (CGI-S) parameters. Cariprazine was generally well tolerated, although the incidence of EPS and akathisia was greater for cariprazine compared with placebo.
Keywords: cariprazine, schizophrenia, clinical trial
Disclosure: S. Zukin, **Part 1:** Full time employee of Forest Research Institute, **Part 2:** Full time employee of Forest Research Institute, **Part 3:** Full time employee of Forest Research Institute; J. Kane, **Part 1:** Funding received from Advisory Board with Forest Laboratories, Inc.; A. Cutler, **Part 1:** Funding received from: Abbott, Acadia, Alkermes, AstraZeneca, Britol-Myers Squibb, Forest Laboratories, Inc., Genentech (Roche), Glaxo Smith Kline, Johnson & Johnson PRD, Eli Lilly, Lundbeck, Merck (including Organon, Schering-Plough), Novartis, Ortho-McNeil Janssen, Otsuka, Pfizer (including Wyeth), Sanofi, Shire, Sunovion (formerly DSP, Sepracor), Targacept, and Vanda, **Part 4:** Funding received from: Abbott, Acadia, Alkermes, AstraZeneca, Britol-Myers Squibb, Forest Laboratories, Inc., Genentech (Roche), Glaxo Smith Kline, Johnson & Johnson PRD, Eli Lilly, Lundbeck, Merck (including Organon, Schering-Plough), Novartis, Ortho-McNeil Janssen, Otsuka, Pfizer (including Wyeth), Sanofi, Shire, Sunovion (formerly DSP, Sepracor), Targacept, and Vanda; Y. Wang, **Part 1:** Full time employee of Forest Research Institute, **Part 2:** Full time employee of Forest Research Institute, **Part 3:** Full time employee of Forest Research Institute; O. Mokliatchouk, **Part 1:** Full time employee of Forest Research Institute, **Part 2:** Full time employee of Forest Research Institute, **Part 3:** Full time employee of Forest Research Institute; K. Nagy, **Part 1:** Full time employee of Gedeon Richter Plc, **Part 2:** Full time employee of Gedeon Richter Plc, **Part 3:** Full time employee of Gedeon Richter Plc; I. Laszlovszky, **Part 1:** Full time employee of Gedeon Richter Plc, **Part 2:** Full time employee of Gedeon Richter Plc, **Part 3:** Full time employee of Gedeon Richter Plc; S. Durgam, **Part 1:** Full time employee of Forest Research Institute, **Part 2:** Full time employee of Forest Research Institute, **Part 3:** Full time employee of Forest Research Institute.

W10. Rasagiline in the Treatment of the Persistent Negative Symptoms of Schizophrenia

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Background: There are no known effective pharmacological treatments for negative symptoms of schizophrenia. However,

previous studies with selegiline, a MAO-B inhibitor, suggest that this class of agents may be of benefit for this indication. The current study assessed whether the selective MAO-B inhibitor, rasagiline, was effective for persistent negative symptoms. In light of its mechanism of action, we also examined whether rasagiline would improve performance on cognitive measures, whose performance reflected prefrontal or striatal dopamine activity.
Methods: Sixty people with DSM-IV schizophrenia or schizoaffective disorder entered a 12-week, double-blind, placebo-controlled, randomized clinical trial. Participants were randomized to either: rasagiline 3 mg/day ($n = 31$) or placebo ($n = 29$). Participants were clinically stable and required to meet *a priori* criteria for persistent negative symptoms. The Scale for the Assessment of Negative Symptoms (SANS) total score was used to assess negative symptoms. The Brief Psychiatric Rating Scale positive symptom item total score was used to assess positive symptom change. The Calgary Depression Scale total score was used to assess depressive symptom change. The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS); N-Back test; a probabilistic learning task; and delayed discounting task were used to assess cognition.
Results: Participants randomized to rasagiline had a non-significantly greater reduction in SANS total score than those randomized to placebo ($F = 2.70$; $df = 41.2$; $p = 0.11$). The estimated magnitude of the group treatment differences increased over time. At week 12, the group difference in SANS total score: 3.42 ± 1.59, was significant ($t = 2.15$; $df = 37.3$; $p = 0.04$). The group difference at week 12 was largely driven by a reduction in the SANS Avolition score in the participants randomized to rasagiline ($t = 3.06$; $df = 49.0$; $p = 0.004$). There were no significant group differences on any of the other symptom measures. There were no significant group differences on the RBANS total score, or on any of the N-back, probabilistic learning, or delayed discounting tasks.
Conclusions: The results of the current study support the utility of MAO-B inhibitors for the treatment of negative symptoms, with an apparent selective benefit for avolition. The use of other non-pharmacological interventions may be required to enhance the therapeutic benefit of such agents. The results do not suggest that rasagiline is of any benefit for the cognitive impairments observed in people with schizophrenia. (clinicaltrials.gov, trial number: NCT00492336). Supported by the Stanley Medical Research Institute, NIDA Contract No1DA59909 (P.I. Deanna L. Kelly), and the Intramural Research Program, NIH, NIDA (David A. Gorelick).
Keywords: rasagiline, dopamine, negative symptoms, cognitive function, schizophrenia
Disclosure: R. Buchanan, **Part 1:** Advisory Boards: Amgen; Astellas; Janssen Pharmaceuticals, Inc.; NuPathe, Inc.; Pfizer; Roche; Takeda, Consultant: Abbott; Amgen; Bristol-Meyer-Squibb; En-Vivo; Pfizer; Takeda, Speakers Bureau: None, Major Stock Holder: None, Other, Pfizer: DSMB member, Otsuka: DSMB member, **Part 4:** Psychogenics; E. Weiner, Nothing to Disclose; D. Kelly, **Part 4:** Ameritox; Bristol-Myers-Squibb; R. McMahon, **Part 1:** Consultant: Amgen, **Part 4:** Psychogenics; J. Gold, **Part 1:** Consultant: Pfizer, Bristol Meyers Squibb, Glaxo-Smith-Kline, Merck, and Novartis; D. Gorelick, Nothing to Disclose.

W11. Effects of Suvorexant, an Orexin Receptor Antagonist, on Next Day Driving Performance in Healthy Volunteers

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Background: Suvorexant is a potent orexin receptor antagonist that is being developed for treatment of insomnia. In a previous study in elderly subjects ($\geqslant$ 65 years old), suvorexant (15 and 30 mg) did not produce clinically meaningful impairment of next-day driving performance as assessed by Standard Deviation of Lateral Position (SDLP) in an on-road driving test. There was also no significant next-day impairment on postural balance and verbal memory in elderly subjects. The present study was designed to assess the residual effects of suvorexant on next-day highway driving performance in adults younger than 65 years, after single and repeated doses of 20 and 40 mg (similar exposures to 15 and 30 mg in the elderly subjects).
Methods: This was a double-blind, placebo- and active drug-controlled, 4-period, crossover study in 28 healthy subjects (15 women, 13 men), aged between 23 and 64 years (mean age 45.6 years). Each dose of suvorexant (20 and 40 mg) and placebo was administered for 8 consecutive nights (from Days 1 to 8). Zopiclone 7.5 mg was included as an active control, administered on Day 1 and on Day 8 only. Residual effects were assessed in the mornings of Day 2 and Day 9 of each treatment period, using a one-hour standardized highway driving test at 9 hours postdose, and memory and postural balance tests at 11 hours postdose. The primary dependent variable was SDLP in the driving test, a measure of "weaving". A mean increase in SDLP of 2.4 cm corresponds to effects previously found for alcohol at blood alcohol concentrations (BAC) of 0.5 g/L, the legal limit for BAC while driving in many countries.
Results: Mean increases in SDLP following suvorexant 20 and 40 mg were 1.01 and 1.66 cm on Day 2, and 0.48 and 1.31 on Day 9, respectively. As the 90% CIs of these mean changes in SDLP were all below the pre-specified clinical bound of 2.4 cm, these changes are not considered clinically meaningful. Symmetry analysis of individual changes in SDLP from placebo on Day 2 revealed a statistically greater number of subjects whose SDLP increased more than 2.4 cm (indicating impairment) than those whose SDLP decreased more than 2.4 cm (indicating improvement) following both suvorexant doses. On Day 9 this difference was still significant for the higher dose, but no longer for the lower dose of suvorexant. Four subjects requested that a total of 5 driving tests stop prematurely due to self-reported somnolence: 3 subjects following 40 mg suvorexant on Day 2 and 2 subjects following 20 mg suvorexant, one each on Day 2 and Day 9. There was a statistically significant decrease in number of words recalled following the first dose of 40 mg suvorexant, and a significant increase in body sway area on the morning following the first dose of 20 or 40 mg suvorexant.
Conclusions: As assessed by mean change in SDLP, there was no clinically meaningful residual effect of suvorexant (20 or 40 mg) on driving in healthy subjects less than 65 years old. These results suggest a lack of important effects on next-day driving performance for most subjects. In secondary analyses, some individual subjects had increased SDLP and/or prematurely stopped driving tests due to somnolence, suggesting there may be a small group of individuals more likely to experience next-day effects. Funding: Merck & Co., Inc.
Keywords: suvorexant
Disclosure: A. Vermeeren, **Part 1:** Dr. A. Vermeeren is a fulltime employee of Maastricht University, The Netherlands. Since 2010 Maastricht University was payed for conducting experimental studies in which Dr Vermeeren acted as investigator by: Merck Sharp & Dohme BV, The Netherlands; SGS Life Science Services, Belgium; Transcept Pharmaceuticals Inc., USA, **Part 4:** Dr. A. Vermeeren is a fulltime employee of Maastricht University. Maastricht University was payed for conducting experimental studies in which Dr Vermeeren acted as investigator since 2010 by Merck Sharp & Dohme BV, The Netherlands, SGS Life Science Services, Belgium, Transcept Pharmaceuticals Inc., USA; A. Van Oers, Nothing to Disclose; C. Van Leeuwen, Nothing to Disclose; S. Jongen, Nothing to Disclose; A. Bautmans, **Part 2:** own stock/stock options in Merck, **Part 3:** Merck employee; X. Li, P**art 2:** Work as a

Merck employee; I own stock/options of shares in Merck & Co., Inc., **Part 3:** I am an employee of Merck & Co., Inc.; T. Siringhaus, **Part 2:** I own stock/options of shares in Merck & Co., Inc., **Part 3:** I am an employee of Merck & Co., Inc.; I. Heirman, P**art 2:** Merck employee (stock / stock options), **Part 3:** Merck employee; T. Laethem, **Part 2:** Merck stock/stock options, **Part 3:** Merck employee, **Part 4:** Not applicable; M. Troyer, **Part 2:** Merck stock/stock options, **Part 3:** Merck employee; D. Michelson, **Part 2:** Merck stock/stock options, **Part 3:** Merck employee; H. Sun, P**art 2:** Merck stock / stock options, **Part 3:** Merck employee.

W12. Effects of the Mu-Opioid Receptor Antagonist GSK1521498 on Brain Responses to Food Cues, Hedonic and Consummatory Eating Behaviour and Bodyweight: A Proof of Mechanism Study in Binge Eating Obese Subjects

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Background: The mu opioid receptor system is implicated in the hedonic and motivational processing of food, and in binge-eating, a behaviour strongly linked to obesity. GSK1521498 is a novel mu opioid antagonist being investigated as a candidate treatment for behavioural and substance addictions. It is centrally active and has 14-20 fold greater selectivity for mu versus kappa and delta opioid receptors. In rodents, GSK1521498 suppressed the intake of standard and palatable chow, caused weight loss in diet induced obese rats. It also suppressed food seeking and binge-eating showing superior efficacy to naltrexone. The aim of this study was to evaluate the effects of four-weeks of treatment with the mu-opioid receptor antagonist GSK1521498 on eating behaviour in binge-eating obese subjects.
Methods: Adults with body mass index $\geqslant 30\,kg/m^2$ and binge-eating scale scores $\geqslant$ 19 received one-week single-blind placebo run-in, and were then randomized to 28 days with either 2 mg/day GSK1521498, 5 mg/day GSK1521498, or placebo ($N = 21$ per arm) in a double blind parallel group design. The outcome measures were body weight, fat mass, hedonic and consummatory eating behaviour during inpatient food challenges, safety, and pharmacokinetics. In addition, using fMRI and behavioural measures the effects of GSK1521498 on brain responses to food images and, separately, on motivation to expend energy in order to view comparable images were determined.
Results: The primary analysis was the comparison of change scores in the higher dose treatment group versus placebo, using analysis of covariance, at each relevant time point. GSK1521498 (2 mg and 5 mg) was not different from placebo in its effects on weight, fat mass, and binge-eating scores. However, compared with placebo, GSK1521498 5 mg/day caused a significant reduction in hedonic responses to sweetened dairy products, and reduced calorific intake, particularly of high fat foods during *ad libitum* buffet meals. GSK1521498 5 mg/day also caused a significant reduction in pallidum/putamen responses to high calorie food pictures and a reduction in motivation to view high calorie food images. There were no significant effects of GSK1521498 2 mg/day on eating behaviour or brain responses to food pictures indicating dose-dependency of pharmacodynamics. GSK1521498 was generally well tolerated and no previously unidentified safety signals were identified.
Conclusions: These findings suggest that hedonic and motivation towards high calorie food and their consumption in obese people with binge-eating is sensitive to altered mu opioid function. The attenuation in putamen/pallidal response suggests a direct impact of the drug on the rewarding properties of food stimuli. The findings provide evidence for a link between the opioid system, brain reward pathways and food-related behaviour in binge-eating obese individuals. The potential for these findings to translate into clinically significant effects in the context of binge-eating and weight regain prevention requires further investigation.
Keywords: Mu Opioid receptors, Functional Imaging, Obesity, Eating, Clinical Trial
Disclosure: P. Nathan, **Part 1:** I work for Glaxo Smith Kline Pharmaceuticals, **Part 2:** I work for Glaxo Smith Kline Pharmaceuticals and hold shares in the company, **Part 3:** I work for Glaxo Smith Kline Pharmaceuticals 80% of my time., **Part 4:** I work for Glaxo Smith Kline Pharmaceuticals and receive internal funding for resesarch; H. Ziauddeen, Nothing to Disclose; S. Chamberlain, Nothing to Disclose; V. Cambridge, Nothing to Disclose; M. Bush, **Part 1:** I work for Glaxo Smith Kline Pharmaceuticals, **Part 2:** I work for Glaxo Smith Kline Pharmaceuticals and have shares in the company., **Part 3:** I work for Glaxo Smith Kline Pharmaceuticals, **Part 4:** I work for Glaxo Smith Kline Pharmaceuticals and my researched is funded by GSK.; W. Tao, **Part 1:** I work for Glaxo Smith Kline Pharmaceuticals, **Part 2:** I work for Glaxo Smith Kline Pharmaceuticals and have shares in the company, **Part 3:** I work for Glaxo Smith Kline Pharmaceuticals, **Part 4:** I work for Glaxo Smith Kline Pharmaceuticals; A. Koch, **Part 1:** I work for Glaxo Smith Kline Pharmaceuticals, **Part 2:** I work for Glaxo Smith Kline Pharmaceuticals and have shares in the company, **Part 3:** I work for Glaxo Smith Kline Pharmaceuticals, **Part 4:** I work for Glaxo Smith Kline Pharmaceuticals; C. Dodds, **Part 1:** I work for Glaxo Smith Kline Pharmaceuticals, **Part 2:** I work for Glaxo Smith Kline Pharmaceuticals and have shares in the company, **Part 3:** I work for Glaxo Smith Kline Pharmaceuticals, **Part 4:** I work for Glaxo Smith Kline Pharmaceuticals; K. Maltby, **Part 1:** I work for GlaxoSmith Kline Pharmaceuticals, **Part 2:** I work for Glaxo Smith Kline Pharmaceuticals, **Part 3:** I work for Glaxo Smith Kline Pharmaceuticals, **Part 4:** I work for Glaxo Smith Kline Pharmaceuticals; A. Skeggs, **Part 1:** I work for Glaxo Smith Kline Pharmaceuticals, **Part 2:** I work for GlaxoSmithKline Pharmaceuticals, **Part 3:** I work for Glaxo Smith Kline Pharmaceuticals, **Part 4:** I work for Glaxo Smith Kline Pharmaceuticals; L. Cheke, Nothing to Disclose; S. Farooqi, Nothing to Disclose; S. O'Rahilly, Nothing to Disclose; P. Fletcher, Nothing to Disclose; E. Bullmore, **Part 1:** I work for Glaxo Smith Kline Pharmaceuticals, **Part 2:** I work for Glaxo Smith Kline Pharmaceuticals and hold shares in the company, **Part 3:** I work for Glaxo Smith Kline Pharmaceuticals 50% of my time, **Part 4:** I work for Glaxo Smith Kline Pharmaceuticals.

W13. Mindfulness Training Improves Resilience: Reductions in Adrenocorticotropic Hormone (ACTH) Response to Laboratory Stress

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Background: Mindfulness-Based interventions have greatly increased in popularity, and are being used with patients with anxiety disorders. However, randomized controlled trials are needed to validate preliminary findings and provide additional biological confirmatory evidence of effects on stress and anxiety. We conducted an RCT of Mindfulness-Based Stress Reduction (MBSR), a standardized and manualized mindfulness meditation training, in individuals with generalized anxiety disorder (GAD). To test the effects of the training on anxiety and distress during subsequent stress, we measured stress hormones and ratings of anxiety and distress during a laboratory behavioral stress challenge. We hypothesized that the individuals who participated in the mindfulness meditation group would become more "resilient" to a laboratory stress task than those assigned to the control intervention.

Methods: Participants with Generalized Anxiety Disorder were randomized to either 8 weeks of Mindfulness Based Stress Reduction (MBSR) training or an active control class ("Stress Management Education," (SME)), both of which were conducted in a group format. The SME class incorporated elements of group treatment including attention from instructor, group support, and information about stress, but did not include any meditation training. Subjects underwent the Trier Social Stress Test (TSST), which includes a public speaking task and arithmetic testing, before and after their intervention, and rated state anxiety and distress. Blood samples were collected throughout the procedure (+5. +10, +15. +20, +28, +40, +45, +50, +55, +80 minutes) to measure hypothalamic-pituitary-adrenal axis biomarkers of psychological stress (cortisol and ACTH). Subjects taking SSRI's and benzodiazepines were excluded due to the known interference of medications with TSST response. Area under the Curve (AUC) calculations were made to assess the overall stress response to the TSST, and the changes in AUC from before and after treatment were compared. Anxiety during the stress task was assessed with the state portion of the State-Trait Anxiety Inventory (STAI), and distress with the Subjective Units of Distress Scale (SUDS). Before the TSST, participants completed the Five Factor Mindfulness Questionnaire to assess potential changes in psychological constructs potentially involved in mindfulness mediation training.
Results: Twenty-two subjects completed the SME class (50% women, mean(SD) age = 39(11), 91% white) and 35 completed the MBSR class (43% women, mean(SD) age = 41(15), 77% white) and completed pre-treatment and post-treatment TSSTs. Participants in the MBSR group had a significantly greater drop in their ACTH AUC compared to those in the SME class, for whom there was actually an increase in the ACTH AUC after the intervention (rank sum test, $z = -2.2$, $p = 0.027$). Plasma cortisol AUCs also dropped more in the MBSR group compared to SME, but this difference did not reach significance; however, is worth noting that that ACTH and cortisol were highly correlated ($r = .34$, $p = .009$). The MBSR group also had a greater drop in the STAI state anxiety score over treatment (mean (SD), 53.8 (12.5) to 40.4 (12.2) compared to the SME group (52.2 (10.9) to 45.2 (10.2), comparison of change scores, $t = -2.13$, $p = 0.0365$), and also a greater decrease in the SUDS distress rating (MBSR group mean(SD): 53.2 (24.6) to 28.7 (22.3); SME: 50.5 (23.6) to 39.4 (24), comparison of change scores, $t = -2.29$, $p = 0.025$). Tying these findings together, the ACTH AUC levels were associated with the STAI scores after controlling for age and gender, both of which can affect hormone levels independently. Lastly, the change in ACTH AUC correlated with the mindfulness variable, "Act with Awareness," in the MBSR group ($r = .41$, $p = .02$) but not SME ($r = .04$, $p = .8$).
Conclusions: This RCT of MBSR in GAD found that mindfulness meditation training was associated with an attenuated stress response to a laboratory stress challenge, as measured by plasma stress hormones, raising the possibility that mindfulness may imbue some resilience to stressful psychological challenges. This is further supported by a reduction in patients' self-report ratings of distress and anxiety after the TSST, that were significantly more improved in the MBSR than the SME group, suggesting that the meditation training may have helped participants cope better with subsequent stress. This is important because improved coping appears to be associated with better mental health outcomes: other work demonstrated that worse coping during the TSST was associated with greater depression symptoms in the subsequent year (Aschbacher 2012). Improvements in stress hormones were also associated with the mindfulness variable, "Act with Awareness," which suggests a potential psychological mechanism of this mental training. "Act with Awareness" indicates paying attention to one's current activities and avoiding absent-mindedness and dissociation. Conclusions are limited due to small sample size. In addition, the self-report measures did not universally correlate with the hormonal measurements (e.g. the SUDS). Nonetheless, the findings suggest that mindfulness meditation training may be a helpful strategy to decrease distress and anxiety and improve resilience in patients with GAD.
Keywords: Mindfulness, Adrenocorticotropic Hormone, Generalized Anxiety Disorder
Disclosure: E. Hoge, Nothing to Disclose; T. Bui, Nothing to Disclose; C. Metcalf, Nothing to Disclose; M. Pollack, Nothing to Disclose; N. Simon, Nothing to Disclose.

W14. A Phase III, Double-Blind, Placebo-Controlled, Flexible-Dose Study of Levomilnacipran SR in Patients with Major Depressive Disorder

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Background: Mood dysfunction and functional impairment are disabling features of major depressive disorder (MDD). Levomilnacipran SR (1*S*, 2*R*-milnacipran) is a potent and selective serotonin and norepinephrine reuptake inhibitor (SNRI) in late-stage clinical development for MDD. Levomilnacipran SR has 2-fold greater potency for norepinephrine relative to serotonin reuptake inhibition and over 10-fold higher selectivity for norepinephrine reuptake inhibition compared with duloxetine or venlafaxine; the sustained release formulation allows once-daily dosing. This Phase III study (NCT01034462) evaluated the efficacy, safety, and tolerability of flexibly dosed levomilnacipran SR versus placebo in MDD.
Methods: A multicenter, randomized (1:1), double-blind, placebo-controlled, parallel-group, flexible-dose study compared levomilnacipran SR 40-120 mg/day with placebo. Outpatients from US study centers were 18-80 years of age and met the DSM-IV-TR criteria for MDD with an ongoing depressive episode $\geqslant 4$ weeks' duration, score $\geqslant 30$ on the Montgomery-Asberg Depression Rating Scale, Clinician Rated (MADRS-CR) and $\geqslant 26$ on the MADRS-Self Rated (MADRS-SR). The study consisted of a 1-week single-blind, placebo run-in period followed by an 8-week double-blind treatment period and a 2-week double-blind down-taper period. Patients were randomized by computer-generated schedule; coded medication labels concealed assignment to levomilnacipran SR or placebo. Levomilnacipran SR patients received 20 mg/day for Days 1 and 2, and 40 mg/day beginning on Day 3; dose could be increased from 40 to 80 mg/day (Week 1 or 2), and from 40 to 80 mg/day or 80 to 120 mg/day (Week 4) based on patient response and tolerability. No dosage increase was allowed after Week 4. Primary efficacy endpoint was MADRS-CR total score change from baseline to Week 8; primary analysis was a mixed-effects model for repeated measures (MMRM) using the modified Intent-to-Treat Population (ITT); the modified ITT population was defined as all patients who received at least one dose of study drug and had at least 1 postbaseline assessment of MADRS-CR total score. Sensitivity analyses using the last observation carried forward (LOCF) and pattern-mixture model (PMM) approaches were also conducted. The secondary efficacy parameter was the Sheehan Disability Scale (SDS) total score change from baseline to Week 8. Additional efficacy measures included the 17-item Hamilton Rating Scale for Depression ($HAMD_{17}$), Clinical Global Impressions-Severity (CGI-S) and -Improvement (CGI-I), Motivation and Energy Inventory-Short Form (MEI-SF), and cognitive tests. Safety was evaluated by adverse events (AEs), clinical laboratory tests, vital signs, and physical findings.
Results: Of 442 patients who were randomized and received treatment (Safety Population: placebo = 217; levomilnacipran SR = 217), 79% of placebo and 75% of levomilnacipran SR patients

completed the study. Demographic characteristics were similar between treatment groups. Approximately 44% of patients were up-titrated to receive 120 mg/day as the final dose. The least squares mean difference (LSMD) with 95% confidence interval (CI) for MADRS-CR total score change from baseline to Week 8 was statistically significant for levomilnacipran SR versus placebo (-3.10 [-5.26, -0.94]; $P = .0051$; MMRM). On the MADRS-CR, a statistically significant difference between levomilnacipran SR and placebo was seen at Week 4 and onward. Analyses using LOCF (LSMD [95% CI] = -2.55 [-4.56, -0.55]; $P = .0127$) and PMM approaches supported the primary results. SDS improvement was significant for levomilnacipran SR versus placebo as early as the first assessment (Week 4); LSMD for SDS change at Week 8 was -2.63 (-4.19, -1.07) ($P = .0010$). Significant changes at Week 8 in favor of levomilnacipran SR compared with placebo was also seen on additional efficacy measures including $HAMD_{17}$ total score (-2.15 [-3.60, -0.70]; $P = .0038$), CGI-S score (-0.35 [-0.61, -0.09]; $P = .0083$), and MEI-SF total score (5.05 [0.28, 9.82]; $P = .0382$). AEs led to the discontinuation of 3% of placebo- and 8% of levomilnacipran SR-treated patients; 62% of placebo and 82% of levomilnacipran SR patients had double-blind treatment-emergent AEs. TEAEs that occurred in $\geqslant$10% in either treatment group were nausea, headache, dizziness, dry mouth, and constipation. Serious AEs were reported in 3 placebo patients (noncardiac chest pain in 1 patient; head injury/liver injury/road traffic accident in 1 patient; asthma/chronic obstructive pulmonary disease in 1 patient) and 2 levomilnacipran SR patients (intentional overdose/suicide attempt in 1 patient; back pain/road traffic accident/scratches in 1 patient) during double-blind treatment; suicidal ideation and noncardiac chest pain/hypertension were reported in 1 levomilnacipran SR patient each during down-taper.

Conclusions: After 8 weeks of treatment, there were statistically significant reductions on the MADRS-CR and SDS in favor of levomilnacipran SR over placebo demonstrating improvement in MDD symptoms and patient functioning. Significant differences seen at Week 4 on both the MADRS-CR and SDS were maintained over the remaining weeks of treatment. Levomilnacipran SR was generally well tolerated.

Keywords: levomilnacipran, major depressive disorder, depression, SNRI, serotonin, norepinephrine

Disclosure: A. Sambunaris, **Part 1:** Forest Laboratories, Inc.; A. Bose, **Part 1:** Employee of Forest Research Institute, **Part 2:** Employee of Forest Research Institute, **Part 3:** Employee of Forest Research Institute, **Part 4:** Employee of Forest Research Institute; C. Gommoll, **Part 1:** Employee of Forest Research Institute, **Part 2:** Employee of Forest Research Institute, **Part 3:** Employee of Forest Research Institute, **Part 4:** Employee of Forest Research Institute; C. Chen, **Part 1:** Employee of Forest Research Institute, **Part 2:** Employee of Forest Research Institute, **Part 3:** Employee of Forest Research Institute, **Part 4:** Employee of Forest Research Institute; W. Greenberg, **Part 1:** Employee of Forest Research Institute, **Part 2:** Employee of Forest Research Institute, **Part 3:** Employee of Forest Research Institute, **Part 4:** Employee of Forest Research Institute; S. Zukin, **Part 1:** Employee of Forest Research Institute, **Part 2:** Employee of Forest Research Institute, **Part 3:** Employee of Forest Research Institute, **Part 4:** Employee of Forest Research Institute; D. Sheehan, **Part 1:** Roche, Sagene Pharma, Otsuka, Forest, Novadel, Laboparm-Angelini, Neuronetics, Janssen (JNJ), MAPI, Prime Education, ProPhase, xCenda, Targacept, Pfizer, Eli Lilly, Glaxo, Merck, PharmaNeuroBoost, Quintiles, Hikma, United BioSource, IncResearch, Quadrant HealthCom Inc, eResearch Technology, International Society for CNS Drug Development, **Part 2:** University of South Florida College of Medicine, Labopharm – Angelini, Pfizer, Eli Lilly, Sagene Pharma, MAPI, **Part 4:** Astra-Zeneca, CeNeRx BioPharma, Otsuka, Takeda Global Research, Repligen, Eli Lilly, Dainippon Sumitomo Pharma-America. (All these grants were indirectly through the University of South Florida College of Medicine).

W15. Relapse Risk after Discontinuation of Risperidone in Alzheimer's Disease

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Background: In patients with Alzheimer's disease (AD) who respond to treatment with antipsychotic medication for psychosis or agitation/aggression, the risk of recurrent symptoms after discontinuation is not established.

Methods: AD patients with psychosis or agitation/aggression received 16 weeks of open treatment with risperidone. Responders were then randomized, double-blind, to one of three arms: (1) continuation risperidone for 32 weeks, (2) risperidone for 16 weeks followed by placebo for 16 weeks, (3) placebo for 32 weeks. The primary outcome was time to relapse of psychosis/agitation.

Results: 180 patients received open-label risperidone (mean 0.97 mg daily). Psychosis and agitation improved with mild increase in extrapyramidal signs; 112 patients met criteria for response to treatment, and 110 responders were randomized. In the first 16 weeks after randomization, discontinuation to placebo (Arm 3) showed greater relapse than continuation risperidone (Arms 1 and 2) with hazard ratio 1.94, 95% CI 1.09-3.45, $p = 0.022$. On placebo, 60% (24/40) relapsed compared to 32.9% (23/70) on risperidone ($P = 0.004$). During the next 16 weeks, relapse was greater with discontinuation to placebo (Arm 2) compared to continuation risperidone (Arm 1): hazard ratio 4.88, 95% CI 1.08-21.98, $p = 0.023$. On placebo, 48.1% (13/27) relapsed compared to 15.4% (2/13) on risperidone ($P = 0.017$). Post-randomization, adverse events and deaths did not differ significantly although comparisons were based on small numbers of patients, especially during the final 16 weeks.

Conclusions: In AD patients with psychosis or agitation who maintained response to risperidone for 4 to 8 months, risperidone discontinuation was associated with increased risk of relapse. These findings suggest that existing Federal regulations requiring early discontinuation of antipsychotics in nursing homes need reconsideration.

Keywords: Alzheimer, psychosis, agitation, antipsychotic, discontinuation

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W16. Predictors of Middle-of-the-Night Dosing in Primary Insomnia Subjects (Sleep Maintenance Type) Participating in a 4-Week Outpatient Clinical Trial of 3.5 mg Sublingual Zolpidem Tartrate versus Placebo

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Background: Frequent middle-of-the-night (MOTN) awakenings with difficulty retuning to sleep is a common insomnia phenotype. However, given the absence until recently of any drugs approved for this indication, there has been little systematic research on the pattern and predictors of MOTN awakenings or their treatment. A 4-week, double-blind, outpatient clinical trial in insomnia characterized by MOTN awakenings provides data to evaluate various factors potentially associated with MOTN medication use, including sex, age, and night of the week.
Methods: The study evaluated the efficacy of sublingual zolpidem tartrate (ZST) 3.5 mg tablets vs. placebo (PBO) in female and male patients ages 18–64, inclusive, with a diagnosis of DSM-IV-TR primary insomnia and a history of MOTN awakenings. (While all subjects randomized to active treatment received 3.5 mg ZST, the FDA-approved dose of ZST (Intermezzo) for adult women is 1.75 mg.) Subjects were required to report (1) $\geqslant$ 3-month history of prolonged MOTN awakenings characterized by $\geqslant$ 3 awakenings/week as proposed in DSM V; (2) an average total sleep time $\leqslant$ 6.5 hours; (3) usual time in bed of 7 – 9 hours; and (4) usual bedtime 2100 - 2400, not varying by $\geqslant$ 2 hours on 5/7 days. After meeting preliminary inclusion/exclusion criteria, subjects participated in a 2-week, single-blind, placebo run-in screening period (baseline) prior to the 4 week treatment period. Subjects called an Interactive Voice Response System (IVRS) after a MOTN awakening $\geqslant$ 10 min to confirm they had 4 hours remaining in bed and to receive instructions to dose (placebo only). Subjects also called the IVRS every morning, whether or not study medication was taken, to answer questions about the previous night's sleep. At the end of screening, 295 subjects were randomized to 4 weeks of double-blind treatment based on IVRS records of $\geqslant$ 2 MOTN awakenings $>$30 min and $\geqslant$ 1 MOTN awakening $>$ 60 min during each of the 2 weeks. Subjects continued to use the IVRS system throughout the double-blind period to record the time of awakening, to receive permission to dose, and in the morning, to complete post-sleep questions including level of morning sleepiness/alertness. To assess the effects of treatment and time (study week) on average number of doses a mixed model for repeated measures (MMRM) ANCOVA with treatment and treatment*week as fixed effects, baseline total number of doses as covariate and compound symmetry covariance structure was used. For assessment of sex, p-values were obtained from an MMRM ANCOVA with treatment, treatment*week, sex, treatment*week*sex as fixed effects, baseline total number of doses as a covariate, and compound symmetry covariance structure. The distribution of number of dosing nights was analyzed by Cochran–Mantel–Haenszel tests, adjusting for week or for week and sex, depending on the analysis.
Results: The efficacy and safety results have been published and are summarized here. ZST significantly ($p<.0001$) decreased self-reported latency to sleep onset across all 4 weeks (LS means are: ZST baseline 68.1 min; ZST DB treatment 38.2 min; PBO baseline 69.4 min; PBO DB treatment 56.4 min). Sleep quality and morning sleepiness/alertness also significantly improved with ZST. ZST was well tolerated; adverse events were generally mild and occurred at the same rate (19.3%) as placebo. There were no treatment-related SAEs. Across the 4-week double-blind period, 5142 awakenings (96% of calls to the IVRS system) were eligible for dosing. Across groups, there was a significant decrease in the mean number of doses taken over treatment week ($p<0.001$), from 4.9/wk in both groups during Week 1 to 4.0/wk for ZST and 4.1/wk for PBO during Week 4. There was no treatment effect on the frequency of dosing. Across both groups, there was a statistically significant difference between the female and male subjects in mean number of doses taken ($p<0.02$), with a greater decline seen in females (ZST: 4.9/Wk 1; 3.8/Wk 4; PBO: 4.7/Wk 1; 3.9/Wk 4) than in males (ZST: 4.8/Wk 1; 4.4/Wk 4; PBO: 5.1/Wk 1; 4.6/Wk 4). When subjects who took $\geqslant$ 6 doses/wk were excluded from the analyses, this sex difference remained the same. There was no statistically significant influence of age or age*sex interaction on total number of dosing nights, across the treatment period, based on an ANCOVA model with age or age*sex as effects. Across the 4 weeks, the majority of subjects took between 5 – 7 doses/wk in both groups (ZST: 50.6%; PBO: 59.0%). The number of subjects taking $\leqslant$ 3 doses/wk was 18.0% in the ZST group and 13.2% in the PBO group. This result is important, as subjects needed to have at least 3 MOTN awakenings per week to qualify for the study. However, there were no significant differences in the overall distribution between treatment groups. Interestingly, the rate of taking medication was essentially the same on all 7 nights of the week in both treatment groups.
Conclusions: These analyses are the first description of dosing for MOTN awakenings in this patient population. The results show that the use of MOTN prn medication did not increase over time; in fact, the frequency significantly decreased. The frequency of use also differs by gender but not by age or day of the week. More research is required to determine additional aspects of MOTN hypnotic use such as daytime factors and sleep on the previous night.
Keywords: insomnia, zolpidem, prn hypnotics, middle-of-the-night, self-administration
Disclosure: T. Roth, **Part 1:** Abbott, GSK, Impax, Intec, Jazz, Merck, Neurocrine, Novartis, Proctor and Gamble, Pfizer, Purdue, Shire, Somaxon, Transcept, **Part 2:** Novartis, Transcept, **Part 4:** Apnex Impax, Merck; W. Mendelson, **Part 1:** Speaker bureau: Purdue Pharma LP, Consulting: Merck, Allergan, GSK, **Part 2:** Psychiatrist Remuda Branch Program for Eating Disorders, **Part 3:** Consultant: Allergan, GSK; N. Singh, **Part 1:** I am an employee of Transcept Pharmaceuticals, **Part 2:** My fair value compensation from Transcept in the form of salary and equity exceeds $10,000, **Part 3:** My compensation from Trascept is more than 5% of my personal income; F. Steinberg, **Part 1:** I am Chief Medical Consultant for Transcept Pharmaceuticals, **Part 2:** Transcept Pharmaceuticals, **Part 3:** Transcept Pharmaceuticals; M. Moline, **Part 1:** I am currently employed by Purdue Pharma LP. From 2010 - October 2011, I was employed by Eisai, Inc., **Part 2:** I receive salary from Purdue Pharma LP from 2010 - October 2011, I was employed by Eisai, Inc.

W17. Partial Adherence to Antipsychotic Treatment and Return of Positive Symptoms in First-episode Schizophrenia Patients

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Background: Antipsychotic maintenance treatment is critical to prevent the re-emergence of psychotic symptoms after the successful treatment of a first episode of schizophrenia. What level of adherence (and therefore actual dose ingested) is required to prevent the return of symptoms? We tested the hypothesis that patients who are partially adherent compared to those who were fully adherent to maintenance antipsychotic treatment would have greater levels of positive symptoms and also shorter time to first recurrence of positive symptoms.

Methods: The sample consisted of 47 first-episode schizophrenia-spectrum disorder patients who fulfilled stringent response criteria (a rating of mild or less on the positive symptom items on the Schedule for Affective Disorders and Schizophrenia Change version with psychosis and disorganization items [SADS C + PD] for two consecutive visits) within 16 weeks of starting randomized, controlled treatment with flexible-dosed olanzapine or risperidone. Subjects were assessed weekly, then biweekly and finally monthly for 3 years. For this analysis, follow-up data were censored at the time that subjects left their randomly assigned treatment for any reason. Adherence was determined based on data obtained from patients, family members and clinicians treating subjects. We defined the adherence reference dose as the antipsychotic dose at the time subjects first achieved response criteria. A mean adherence level was determined for each subject based on all weekly adherence ratings; this was converted to a percentage of the adherence reference dose. Based on mean adherence levels, subjects were classified as being fully adherent (>80% adherence reference dose), partially adherent (20-80%) or non-adherent (<20%). Survival analysis compared time to re-emergence of positive symptoms (i.e. a rating of moderate or greater on one or more SADS C + PD psychosis items) between groups. Mixed model analyses were conducted to determine the longitudinal effect of partial adherence on repeated measures of positive symptoms, using a composite score of seven positive symptoms items (severity of hallucinations, severity of delusions, impaired understandability, derailment, illogical thinking, bizarre behavior and grandiosity) from the SADS C +PD scale.
Results: The subjects were young (mean age of 22.7 years (SD = 4.4)) and mostly male (n = 32, 68%). Twenty (42.6%) patients had responded to olanzapine and 27 (57.4%) to risperidone. Mean dose at the time of response was 7.9 mg (SD: 3.7) with olanzapine and) and 2.9 mg (SD: 1.2) with risperidone. Analysis by adherence groups showed that 15 patients were in the 20-80% category and 32 patients were in the >80% category. No subjects were in the <20% category. Overall, 25 (53.2%) patients experienced a re-emergence of positive symptoms while on their original assigned antipsychotic. Fifteen of 31 (48.4%) fully adherent subjects and 10 of 16 (62.5%) partially adherent subjects experienced a recurrence of positive symptoms. Time to recurrence of positive symptoms did not differ between fully adherent and partially adherent groups (log rank test, $\mathbf{x}^2 = 0.44$, $p = 0.5$). However, the mixed model analysis revealed a significant ($P = 0.0046$) increase in positive symptom scores over time in those subjects who were partially adherent to treatment, contrary to the effect observed in fully adherent subjects, in whom positive symptom scores decreased or did not change over time.
Conclusions: We found that first-episode schizophrenia spectrum disorder patients who were partially adherent to their maintenance antipsychotic medication had greater levels of positive symptoms over time compared to patients who are fully adherent to their maintenance medication. This is consistent with a prior study (Subotnik et al., 2011) that also examined the effect of partial adherence in a first episode schizophrenia sample. Our study design employed a low dose strategy for initial treatment. Our data suggest that further dose reduction during maintenance treatment is not advisable.
Keywords: first-episode, schizophrenia, adherence, response, positive symptoms
Disclosure: J. Gallego, Nothing to Disclose; D. Robinson, **Part 1:** Consultant: Asubio Pharmaceuticals, **Part 4:** Grant Support: Bristol Myers Squibb; Janssen; M. John, Nothing to Disclose; P. Guveneck-Cokol, Nothing to Disclose; J. Greenberg, Nothing to Disclose; J. Kane, **Part 1:** Organon, Eli Lilly, BMS, Intracellular Therapeutics, Boehringer , Rules Based Medicine, Astra Zeneca, Otsuka, Novartis, Merck, Myriad, Esai, Pfizer, Lundbeck, J & J, Targacept, Shire, Amgen, Sunovion, Pierre Fabre, Janssen, Alkermes, Jazz, Forest Labs, **Part 2:** BMS, Otsuka, Merck, Novartis, Lilly, MedAvante.

W18. ALKS 5461, a Novel Opioid Receptor Modulator, Reduces the Subjective Effects of Cocaine and was Safe and Well Tolerated during Concurrent Cocaine Administration

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Background: There are no currently approved therapies for the treatment of cocaine abuse/dependence. Recent clinical studies have demonstrated a significant reduction in cocaine-positive urine samples in patients receiving buprenorphine (BUP), a partial opioid agonist, in combination with naltrexone, an opioid antagonist, compared to controls. It is hypothesized that pharmacologic activity at μ and/or κ opioid receptors may be beneficial in the treatment of cocaine abuse. However, co-formulation of BUP and naltrexone is impractical due to pharmacokinetic, and physiochemical limitations. ALKS 5461 is a combination therapy of ALKS 33, a novel opioid receptor antagonist, and BUP co-formulated for sublingual (SL) administration. In a previous clinical study, a 1:1 dose ratio of ALKS 33:BUP blocked μ-opioid agonism of BUP as demonstrated by pupilometry and subjective responses. The purpose of the current DDI study was to determine the safety, tolerability and pharmacokinetics (PK) of ALKS 5461 and ALKS 33 during concurrent cocaine administration. Pharmacodynamic (PD) measures of subjective response to cocaine were also collected.
Methods: A single-center, randomized, double-blind, PBO-controlled, multiple dose, parallel group study was conducted in 33 opioid-experienced non-treatment seeking cocaine users over a 14 Day (D) in-patient period. Subjects that tolerated baseline cocaine infusions (20 mg, D1; 40 mg D2) were randomized to ALKS 33 (8 mg), ALKS 5461 (8 mg ALKS 33 + 8 mg BUP, co-formulated), or PBO. Study drug was administered sublingually on D3-12 (AM); concurrent cocaine infusions (2 min) occurred at steady state of study drug on D11 (20 mg) and D12 (40 mg). Safety assessments included cardiovascular changes (HR, BP) and adverse event (AE) reporting. PK samples were collected on D1, D2, D11, and D12 for cocaine assay and D3-12 for study drug assay by validated LC/MS/MS methods. PD endpoints following cocaine infusion included BSCS, VAS measures. Statistical comparisons were made across study days and treatment groups.
Results: The mean age of all subjects was 38.1 years (range: 22-49); 73% were male; age, sex and race were generally balanced across treatment groups. 24 subjects completed all study assessments (ALKS 5461, n = 9; ALKS 33, n = 6; PBO, n = 9). There were no differences in HR or BP changes following cocaine infusion across treatment groups. Study drug related AEs were reported in 90%, 77%, and 10% of subjects in the ALKS 5461, ALKS 33 and PBO groups, respectively. Most common AEs included vomiting, nausea, and sedation, were moderate in severity and were generally equal across ALKS 5461 and ALKS 33 groups. BUP did not affect ALKS 33 PK and cocaine PK was not affected by study drug. ALKS 5461 reduced VAS measures of High, Drug Liking, Desire for Cocaine, and Overstimulation during cocaine infusion (40 mg) on D12; BSCS score for intensity of cocaine craving was significantly lower for ALKS 5461 vs. PBO ($p < 0.05$) on D12.
Conclusions: Consistent with previous study results, administration of ALKS 5461 and ALKS 33 resulted in an acceptable safety and tolerability profile. SL administration of ALKS 5461 resulted in a reliable PK profile for both ALKS 33 and BUP. PD endpoints were suggestive of a treatment effect for ALKS 5461 > ALKS 33 > PBO. These results warrant further investigation of ALKS 5461 and ALKS 33 in a clinical study of cocaine abstinence and/or reduction.
Keywords: Buprenorphine, Cocaine, pharmacokinetics, treatment, opioid

Disclosure: R. Turncliff, Nothing to Disclose; B. Silverman, **Part 1:** Employee of Alkermes, Inc.; Y. Du, **Part 1:** Employee of Alkermes, Inc.; B. Vince, **Part 1:** Consultant to Alkermes, Inc.; E. Sellers, **Part 1:** Dr. Ed Sellers is a Principal in DL Global Partners, a consulting firm that provides consultation to pharmaceutical and device companies. Alkermes Inc has been a client of DL Global Partners; N. Chen, Nothing to Disclose; M. Shram, Nothing to Disclose; M. Todtenkopf, **Part 1:** Employee of Alkermes, Inc.; E. Ehrich, **Part 1:** Employee of Alkermes, Inc.

W19 The Failed CNS Studies Phenomenon: Is the Final Factor Looking Us Right in the Eye?

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Background: The ever-increasing incidence and prevalence of failed clinical trials within the CNS arena is well-documented and, at times, believed to be unstoppable – as evidenced by the number of pharmaceutical companies reducing their commitment to, and in some cases altogether exiting from, the neuroscience area$_{(1)}$. As numerous retrospective analyses have led to increasingly complex designs for current and immediately forthcoming studies, we reviewed more than 100 scientific publications, including several now in press, pertaining to the reported causes and potential remedies to the failed trials phenomenon.
Methods: When reviewing the pertinent publications, we categorized the cited factors leading toward failed trials as being primarily Study Design-Oriented, Clinician-Oriented, or Patient-Oriented – recognizing that all three categories are contextually integrated. Our primary objective was to analyze the reported findings looking for repeatedly identified and/or validated predictors of success in combating this problem. In tandem, our secondary objective was to investigate the possibility that a key (potentially) over-looked variable further contributing to the failed studies epidemic could be identified and/or further investigated and evaluated.
Results: (1) The degree to which Study Design issues have been reported as contributing toward the problem of failed CNS clinical trials was rarely cited; however, recently published reports of the degree to which enrichment designs may reduce placebo response, and thereby decrease the probability of a failed trial, have been gaining attention$_{(2)}$. (2) The most frequently cited contributing factors within the literature pertained to Clinician-Oriented variables – almost exclusively focusing on primary efficacy raters: poor inter-rater reliability, interview quality and rater bias. However, the resultant solutions, including but not limited to – scrutinized rater selection, centralized rater involvement, enhanced rater training and monitoring, more standardized assessment practices and even calls for 'improved rating scales,' have not resulted in a decreasing percentage of failed trials – hence the exit strategy by some companies. (3) The Patient-Oriented variables have not been frequently cited as contributing factors, except within the context of rater-related concerns allegedly allowing inappropriate subjects into a trial and/or increasingly restrictive inclusionary and exclusionary criteria seemingly prohibiting otherwise good (e.g., appropriate) candidates from entry into a trial. However, one pervasive and operationally over-looked variable is that of the "imposter subject," a.k.a. "professional patient." One paper (now in press) indicated that four percent of the initially screened subjects were simultaneously participating in other CNS studies; some "off-the-record," e.g., unpublished reports from study sponsors have indicated significantly higher percentages.
Conclusions: The recent and ongoing emphasis on rater-related concerns and, to a much lesser degree, study design refinements can all too easily be rendered totally ineffective by the inclusion of skillfully dishonest, fraudulent research subjects. We will present data from three websites empowering and enabling these imposter/professional patients. In tandem, we will present data from three websites as to how to combat the inclusion of research subjects who are intent on fraudulently participating. Estimating the number of clinical studies categorized as "failed" and/or the number of promising CNS compounds discontinued from development, as a result of Type-II error, vis-à-vis research subject fraud, is too speculative. Nonetheless, as an industry, we can no longer turn a blind-eye or deaf-ear to this known problem; indeed, we will share additional information indicating that the final key factor contributing to the failed studies phenomenon may be looking us right in the eye. References:
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2. Chen Y, Yang Y, et al. Evaluation of performance of some enrichment designs dealing with high placebo response in psychiatric clinical trials. Contemp Clin Trials. 2011: 32 592-604.
Keywords: failed trials, subjects, imposters, fraud
Disclosure: C. Wilcox, Nothing to Disclose; J. Morrissey, Nothing to Disclose; N. Oskooilar, Nothing to Disclose; M. Henry, Nothing to Disclose; D. Grosz, Nothing to Disclose; M. Tong, Nothing to Disclose; D. De Francisco, Nothing to Disclose.

W20. GLYX-13, an NMDA Receptor Functional Partial Agonist, Reduced Depression Scores without Psychotomimetic Effects in Subjects with Major Depressive Disorder Who had Failed Another Antidepressant Agent during the Current Episode

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Background: GLYX-13 (ThrProProThr-amide) is an NMDA (N-methyl-D-aspartate) receptor glycine site functional partial agonist with about 25% of the agonist activity of glycine or D-serine. Plasma half-life of GLYX-13 is approximately 5 minutes in animals and humans. A single intravenous (IV) dose of GLYX-13 produces long-term efficacy in the Porsolt test and other animal models relevant to major depressive disorder without causing effects that predict psychotomimetic effects in humans.
Methods: Subjects with HDRS-17 (Hamilton Depression Rating Scale - 17) scores of at least 21 were enrolled in the study and any antidepressant agent being taken was stopped for at least two weeks prior to randomization. A single IV (intravenous) dose of GLYX-13 (1, 5, 10, or 30 mg/kg) or placebo was infused in 48 male and 68 female subjects, aged 18-65 years (17-25 subjects per group of similar mean age and sex ratio) who had reported less than 25% response to at least one adequate trial of an antidepressant agent during the current depressive episode. HDRS-17 and BPRS + (brief psychiatric rating scale positive score) as well as other adverse events were assessed for at least 14 days.
Results: In the complete analysis population, GLYX-13 reduced depression scores with a U-shaped dose-response (as it does in animal pharmacodynamic models and *in vitro*) with maximum reduction in HDRS-17 of -2.9, -3.5, -4.9, or -1.1 units, (1, 5, 10, or 30 mg/kg) compared to placebo at the same time. GLYX-13, 10 mg/kg, produced a statistically significant ($P < 0.05$) reduction in HDRS-17 (-3.9 units) at 24 hours and at Day 7 (-4.9 units) following a single dose. At Day 14, the difference from placebo (-0.37 units) was not statistically different. GLYX-13 did not cause psychotomimetic side effects at any dose studied. At baseline, BPRS + was 4.2, 4.3, 4.2, 4.3 and 4.1 in the 1, 5, 10, and 30 mg/kg and placebo groups, respectively. When assessed at 30, 45, 60, and 90 minutes, and 2, 4, 8, 12, and 24 hours following dosing, BPRS + scores were reduced 0.2–0.3 units from baseline in all groups at all times. GLYX-13

administration was not associated with any serious adverse events; all treatment emergent adverse events were mild or moderate and were largely constitutional in nature (headache, fatigue, dizziness, gastrointestinal disturbances) and were of similar incidence in each dose group and in the placebo group.
Conclusions: Based on previous studies, ketamine and other full antagonists of the NMDA receptor rapidly reduce depression scores for several days following a single dose, but are associated with psychotomimetic effects. The current study demonstrates that GLYX-13, an NMDA receptor glycine site functional partial agonist, reduces depression scores in a manner similar to full antagonists but without eliciting psychotomimetic effects at therapeutic doses. The enhanced therapeutic window for GLYX-13 may be a consequence of its incomplete blockade of the NMDA receptor. This trial was registered with clinicaltrials.gov NCT01234558.
Keywords: GLYX-13, major depressive disorder, dissociative effects, psychotomimetic effects
Disclosure: S. Preskorn, **Part 1:** Abbott, Biovail, Boehringer-Ingelheim, Bristol-Myers Squibb, Cyberonics, Dey Pharma, Eisai, Johnson & Johnson, Lundbeck, Merck, Naurex, Orexigen, Pierre Fabre, Pfizer, Stanley Med. Res. Inst., Sunovion, **Part 4:** Abbott, Cyberonics, Lundbeck, Naurex, Pfizer, Stanley Med. Res. Inst.; M. Macaluso, **Part 1:** Abbott, Envivo, Evotec, Jannsen, Lilly, Naurex, Pfizer/Wyeth, Targacept, **Part 4:** Abbott, Envivo, Evotec, Jannsen, Lilly, Naurex, Pfizer/Wyeth, Targacept; B. Kurian, **Part 1:** Targacept, Pfizer, Johnson & Johnson, Evotec, Rexahn, Naurex, Forest, **Part 4:** Targacept, Pfizer, Johnson & Johnson, Evotec, Rexahn, Naurex, Forest; R. Manning, **Part 1:** Naurex Inc - grant, **Part 4:** Naurex Inc - grant; V. Mehra, **Part 1:** Naurex Inc - consultant, **Part 4:** Naurex Inc - grant; G. Zammit, **Part 1:** Naurex Inc - grant, **Part 4:** Naurex Inc - grant; J. Moskal, **Part 1:** Naurex Inc - consultant, **Part 2:** Naurex Inc - consultant, **Part 3:** Naurex Inc - consultant, **Part 4:** Naurex Inc - consultant and grant; J. Burgdorf, **Part 1:** Naurex, Inc - consultant, **Part 2:** Falk Institute of Molecular Therapeutics, Northwestern University, **Part 3:** Naurex, Inc - consultant, **Part 4:** Naurex, Inc - consultant and grant recipient; R. Burch, **Part 1:** Naurex, Incorporated - employee, **Part 2:** Naurex, Incorporated - employee, **Part 3:** Naurex, Incorporated - employee.

W21. Attrition and Retention among African Americans in a Pharmacological Treatment Study of Depression: Insights from the STAR*D Study

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Background: Disparities in depression treatment completion persist amongst African-Americans for whom low retention in clinical trials remains a major hurdle to achieving remission. This study examined reasons for attrition among African Americans enrolled in a pharmacologic depression treatment study, and to distinguish those who withdrew early from those who remained in treatment, on a range of social, clinical and attitudinal factors.
Methods: Sample consisted of non-Hispanic African-American participants ($n = 693$) in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study. Principal components analyses were used to investigate potential underlying constructs among top reasons cited for study exit. ANOVAs and Chi-square tests were used to investigate social, clinical, and attitudinal differences between participants who withdrew and those who remained in treatment, and between early and late withdrawers.
Results: No group differences were detected in baseline attitudes towards professional help-seeking or perceived support by friends and family. Participants who dropped out of treatment were generally younger, less educated, reported greater baseline depression and symptom severity (but lower perceived impairment), and reported less satisfaction with clinicians and treatment. Early dropouts had more family history of depression and alcohol abuse, and greater perceived quality of life and physical functioning than late dropouts.
Conclusions: Early attrition among African-Americans in this depression treatment clinical trial stemmed from a general disengagement with treatment, rather than lack of efficacy or negative attitudes towards pharmacological treatment of depression. Future clinical trials that include African-American participants should consider implementing psychosocial strategies to prevent early dropouts.
Keywords: Clinical trials, Depression, African-Americans, Attrition
Disclosure: E. Murphy, Nothing to Disclose; L. Kassem, Nothing to Disclose; A. Rush, **Part 1:** Dr. Rush has served as an advisor, consultant, or speaker for or received research support from Advanced Neuromodulation Systems, Inc.; AstraZenica; Best Practice Project Management, Inc.; Bristol-Meyers Squibb Company; Cyberonics Inc.; Eli Lilly & Company; Forest Pharmaceuticals Inc.; Gerson Lehman Group; Glaxo Smith Kline; Healthcare Technology Systems Inc.; Jazz Pharmaceuticals; Magellan Health Services; Merck & Co. Inc.; the National Institute of Mental Health; Neuronetics; Ono Pharmaceutical; Organon USA Inc.; Otsuka; Pamlab; Personality Disorder Research Corporation; Pfizer Inc.; the Robert Wood Johnson Foundation; the Stanley Medical Research Institute; the Urban Institute; and Wyeth-Ayerst Laboratories Inc., **Part 2:** Dr. Rush has equity holdings in Pfizer Inc., and receives royalty/patent income from Guilford Publications and Healthcare Technology Systems Inc., and UT Southwestern Medical Center; G. Laje, Nothing to Disclose; F. McMahon, Nothing to Disclose.

W22. Assessment of Safety, Cardiovascular and Subjective Effects After Intravenous Cocaine and Lofexidine

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Background: Genetic and pharmacological evidence implicate noradrenergic mechanisms in mediating the effects produced by cocaine and other stimulants. Lofexidine is an $\alpha 2$ receptor agonist that decreases central norepinephrine (NE) release and has shown promise as a potential pharmacotherapy for cocaine dependence in animal models. The primary objective of this study was to determine the safety of daily oral lofexidine alone and concurrent with intravenous cocaine infusions in non-treatment seeking cocaine-dependent or cocaine-abusing participants.
Methods: Safety outcome measures included cardiovascular responses (heart rate [HR], blood pressure [BP] and electrocardiogram [ECG]), adverse events (AEs), and clinical laboratory analyses. Secondary objectives were to evaluate whether administration of lofexidine alters the subjective effects produced by cocaine. Subjective measures included a 10-item visual analog scale (VAS) and brief substance craving scale. After screening, eligible participants were housed in an inpatient unit for 9 days. Participants received double-blind, randomized baseline infusions of saline and 20 mg of cocaine on Day 1, and saline and 40 mg of cocaine on Day 2. Cardiovascular responses during infusion sessions on Days 1 and 2 were used as baseline data to compare responses to cocaine after lofexidine administration. Subjects were randomized and started receiving daily administration of lofexidine (0.8 mg QID - N = 4; total daily dose – 3.2 mg or 0.2 mg QID - N = 11; total daily dose - 0.8 mg) or matched placebo control (N = 4) on Day 3 and continued on this schedule until Day 7. On Days 6 and 7, subjects received double-blind infusions of saline and 20 mg of cocaine on Day 6, and saline and 40 mg of cocaine on Day 7. Clinic discharge occurred on Day 9, approximately 48 hours

after the last dose of lofexidine/placebo. Subjects were asked to return for follow-up visit approximately 7 days after clinic discharge.

Results: The data reveal a notable incidence of cardiovascular-related AEs over the course of the study. Two (67%) of the three patients at the 0.8 mg dose level discontinued, and five (45%) of 11 patients at the 0.2 mg dose level were withdrawn (or voluntarily discontinued) after cardiovascular AEs. ECG measures indicated that lofexidine had statistically significant effects on the average post-infusion ventricular rate, minimum maximum post-infusion QTcF interval, RR interval, and PR interval. Subjective effects data were analyzed only from those who completed the full protocol (6 received lofexidine - 0.2 mg QID and 4 received placebo). Cocaine significantly increased all VAS ratings with the exception of "Depressed". Importantly, lofexidine decreased VAS ratings for "Any Drug Effect", "High", and "Good Effects" (all p's < 0.05).

Conclusions: Although lofexidine significantly reduced several positive subjective effects associated with acute cocaine exposure in the laboratory, cardiovascular AEs may limit future utility of lofexidine as a treatment for this population. It is important to note that lofexidine is also an imidazoline agonist, and this action likely accounts for its propensity to produce hypotension. Other NE $\alpha 2$ agonists that do not bind imidazoline receptors may be superior to lofexidine (e.g., guanfacine).

Keywords: cocaine, treatment, addiction, lofexidine, norepinephrine, α-2 agonist

Disclosure: R. De La Garza, Nothing to Disclose; G. Galloway, Nothing to Disclose; T. Newton, Nothing to Disclose; J. Mendelson, Nothing to Disclose; C. Haile, Nothing to Disclose; E. Dib, Nothing to Disclose; R. Hawkins, Nothing to Disclose; C. Chen, Nothing to Disclose; J. Mahoney, Nothing to Disclose; J. Mojsiak, Nothing to Disclose; G. Lao, Nothing to Disclose; A. Anderson, Nothing to Disclose; R. Kahn, Nothing to Disclose.

W23. In a 2-Year Placebo-controlled Randomized Trial, Galantamine-treated Patients had Lower Mortality Rates and Slower Decline in Cognition and Activities of Daily Living

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Background: Galantamine (GAL) is approved for treatment of mild to moderately severe dementia of the Alzheimer type (in some countries outside of the US, GAL is also indicated for Alzheimer's dementia with cerebrovascular disease). The efficacy of GAL in the treatment of mild to moderately severe dementia of the Alzheimer type has been demonstrated in several Phase 3, double-blind, placebo-controlled studies lasting up to 6 months. This study was conducted to assess the risk-benefit profile following 2 years of GAL dosing in patients with AD.

Methods: We conducted a multicenter, randomized, double-blind, placebo-controlled, parallel group study to evaluate GAL's long term (2-year) efficacy and safety profile in the treatment of patients with mild to moderately severe Alzheimer's disease (AD). GAL was titrated to a dose of 16-24 mg/day. The primary efficacy endpoint was change from baseline to month 24 in Mini-Mental State Examination (MMSE) score. An intent-to-treat analysis with last observation carried forward approach, and analysis of covariance model, was used for the primary efficacy analysis. Secondary efficacy endpoints included change from baseline to month 6 in MMSE score and change from baseline to months 12 and 24 in activities of daily living as measured by the Disability Assessment in Dementia (DAD). The primary safety endpoint was the mortality rate between patients randomly assigned to receive GAL or matching placebo over the course of 2 years. Mortality data were analyzed by the time-to-event (death) method using the Cox-regression model. Treatment-emergent adverse events (TEAEs) were also compared among treatment groups. A company-commissioned external Data Safety Monitoring Board (DSMB) monitored the study's progress and provided oversight to ensure that the safety of patients was not compromised.

Results: At the final interim mortality analysis (conducted when the study reached the prespecified milestone of 80 deaths), the DSMB recommended early termination of the study due to an imbalance of deaths between the treatment groups. Subsequent unblinding of the data indicated that the mortality rate was significantly lower (odds ratio [95% CI]: 0.56 [0.35-0.88]; $p = 0.021$) in GAL-treated patients compared with patients treated with placebo.

Two thousand fifty one (2051) patients in 127 sites and 13 countries were randomized in the study: 1023 patients to the placebo group, 1028 to the GAL group. Most patients were women (65%) and white (99.9%); mean age was approximately 73 years and mean baseline MMSE score was 19 (range: 10-26). There were no notable demographic differences between groups. Due to the early termination of the study, the mean duration of treatment was approximately 16 months. Over 700 patients (GAL, $n = 377$; placebo, $n = 345$) received more than 24 months of treatment. There was a total of 89 deaths; the death rate was significantly higher in patients treated with placebo (56 deaths; 5.5%) than in patients treated with GAL (33 deaths; 3.2%): odds ratio (95% CI) of 0.58 (0.37 – 0.89); $p = 0.011$ vs. placebo. This was consistent with the findings from the final interim mortality analysis. GAL-treated patients reported numerically more TEAEs, most notably in the gastrointestinal disorders body system category. The incidence and type of serious AEs were similar in both groups. Patients treated with placebo had significantly greater cognitive impairment compared with GAL-treated patients, based on mean change from baseline in MMSE scores at 6 months (-0.28 for placebo; 0.15 for GAL; difference = 0.43; $p < 0.001$) and 24 months (-2.14 for placebo; -1.41 for GAL; difference = 0.73; $p < 0.001$). The mean DAD score at baseline was 61.04 for placebo-treated patients and 61.22 for GAL-treated patients. The change from baseline to month 12 was significantly worse in the placebo group compared with the GAL group (-6.50 vs -4.55; difference = 1.95; $p = 0.009$). The change from baseline to month 24 was also significantly worse in the placebo group compared with the GAL group (-10.81 vs -8.16; difference = 2.65; $p = 0.002$).

Conclusions: This 2-year study is the longest placebo-controlled study of GAL in patients with mild to moderately severe AD conducted to date. In this study, GAL was associated with a significantly lower mortality rate and a significantly slower decline in cognition and activities of daily living.

Keywords: Alzheimer disease, galantamine, long-term treatment, mortality

Disclosure: K. Hager, **Part 1:** I have served as an investigator on clinical trials for Janssen Research & Development, as well as for other pharmaceutical companies, **Part 2:** Salaried employee of Center for Medicine of the Elderly (Klinik für Geriatrie u. Medizinische Rehabilitation); A. Baseman, **Part 1:** I am employed by Janssen Research and Development, who was the sponsor of this trial, **Part 2:** Janssen Research and Development, **Part 3:** employee of Janssen Research and Development; J. Han, **Part 1:** I am employed by Janssen Research and Development, who was the sponsor of this trial, **Part 2:** Janssen Research and Development, **Part 3:** employed by Janssen Research and Development; M. Sano, **Part 1:** Name of Commercial Interest Nature of Relationship for all, Medivation, Novartis, Pfizer, Consultant / Advisor, Bristol-Myers Squibb, Esai Pharmaceutical, Eli Lilly, Takeda, Sanofi-Aventis, Bayer, and, Medpace, **Part 2:** Mount Sinai Medical Center, NY, NY, James J Peter VA Medical Center, Bronx, NU; H. Richards, **Part 1:** I am employed by Janssen Research and Development, who was the sponsor of this trial, **Part 2:** employed by Janssen Research and Development, **Part 3:** Janssen Research and Development.

W24. Keeping it Real: Dissemination of Clinical Trial Results Using Clinician-friendly Effect Size Measures

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Background: Although great effort is made in clinical trials to demonstrate statistical superiority of one intervention vs. another, insufficient attention is paid regarding the clinical relevance or clinical significance of the outcomes. Effect sizes are not always reported. Available absolute effect size measures include Cohen's d, area under the curve, success rate difference, attributable risk, and number needed to treat (NNT). Of all of these measures, NNT is perhaps the most clinically intuitive and helps relate the effect size difference back to the realities of clinical practice.
Methods: Three examples of effect size analyses for different psychotropic agents are presented, each using NNT to describe clinically relevant differences between interventions. In the first analysis, pooled data from six 6-week studies of lurasidone for the treatment of acute episodes of schizophrenia are used to determine the NNT for antipsychotic response as defined by a reduction of $\geqslant$20, 30, 40 or 50% from baseline on the Positive and Negative Syndrome Scale (PANSS) total score. Number need to harm (NNH) is also calculated for the most commonly encountered spontaneously reported adverse events (AE). Likelihood to be helped or harmed (LHH) is also calculated taking the ratio of NNH to NNT. The second analysis targets the potential utility of vilazodone by pooling the results of two 8-week clinical trials for the treatment of major depressive disorder (MDD). Response is defined as a $\geqslant$50% reduction from baseline on the Montgomery Asberg Depression Rating Scale (MADRS) and remission is defined as achieving a MADRS total score less than 10 at endpoint. NNH for the commonly encountered AEs, as well as any AE related to sexual dysfunction, and the relevant LHH estimates are also determined. The third example outlines the time course of response in the use of inhaled loxapine 5 or 10 mg for the treatment of acute agitation associated with schizophrenia or bipolar mania. The NNT for response is defined by a $\geqslant$40% reduction from baseline on the PANSS Excited Component (PEC), and is calculated at 10, 20, 30, 45, 60, 90 and 120 minutes following drug administration.
Results: In the analysis of lurasidone for the treatment of schizophrenia, responder rates decreased as the threshold for response increased from 20 to 50%. For the threshold of a 30% decrease in the PANSS total score, NNT vs. placebo were 6, 6, 7 and 4 for lurasidone doses of 40, 80, 120 and 160 mg/d, respectively. The 5 most consistently encountered adverse events attributable to lurasidone were akathisia, nausea, sedation, somnolence and parkinsonism, with NNH vs. placebo for lurasidone 40–120 mg/d ranging from 6 (akathisia with 120 mg/d) to 30 (parkinsonism with 80 mg/d). Lurasidone 160 mg/d appeared better tolerated than doses of 40, 80 or 120 mg/d for akathisia, nausea, sedation or somnolence, with no NNH values for these adverse events for 160 mg/d vs. placebo being statistically significant. A LHH of 5.0 for lurasidone 160 mg/d for response vs. parkinsonism can be interpreted that "lurasidone treatment at 160 mg/d is 5 times more likely to help the patient ($\geqslant$30% decrease in PANSS) than harm the patient (parkinsonism)." Regarding vilazodone for the treatment of MDD, NNT for response vs. placebo was 8 and for remission was 14. The most commonly encountered AEs were diarrhea, nausea, vomiting and insomnia, with NNH values vs. placebo of 6, 6, 30 and 26, respectively. NNH vs. placebo for any sexual AE was 12. One potentially relevant example of LHH is for the outcome of achieving response vs. encountering nausea, LHH = 68 = 0.75. This means that the likelihood of achieving a response is actually less than the likelihood of encountering nausea. This may not be relevant if the nausea is time-limited and easily managed. Regarding inhaled loxapine for the treatment of agitation in patients with schizophrenia or bipolar mania, when plotting the PEC responders over time, NNT vs. placebo appears more robust as time after dosing elapses. The 10 mg dose appears to perform better, reaching in 20 minutes a NNT of 4 in subjects with schizophrenia and a NNT of 3 in subjects with bipolar mania.
Conclusions: NNT and NNH can be used to illustrate clinically relevant outcomes in clinical trials. LHH can explicitly quantify the trade-offs that are at the core of medical decision-making. A major limitation of NNT and NNH is that these metrics are limited to dichotomous outcomes. Other effect size measures are necessary when describing continuous outcomes, such as mean changes in PANSS scores. However, NNT and NNH, measured in "patient units" are more clinically intuitive than effect sizes such as Cohen's d which requires an understanding of standard deviation units when describing differences between interventions. In the case of lurasidone, illustrated is the importance of selecting appropriate thresholds for assessing antipsychotic response. The analysis of vilazodone illustrates one of the difficulties when selecting the appropriate outcomes for the determination of LHH – transient nausea, although frequently encountered cannot be reasonably equated with achieving response, unless discontinuation because of this AE is relevant for that particular patient. The final example using inhaled loxapine for agitation demonstrates the importance of time when considering effect sizes and when calculating NNT.
Keywords: Clinical trials, effect sizes, NNT, antipsychotic, antidepressant
Disclosure: L. Citrome, **Part 1:** In the past 24 months Leslie Citrome has engaged in collaborative research with, or received consulting or speaking fees, from: Alexza, Alkermes, AstraZeneca, Avanir, Bristol-Myers Squibb, Eli Lilly, Forest, Genentech, Janssen, Lundbeck, Merck, Novartis, Noven, Otsuka, Pfizer, Shire, Sunovion and Valeant, **Part 2:** Private practice of psychiatry, Collaborative research with, or received consulting or speaking fees $10,000 or greater per year: Alkermes, AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Janssen, Merck, Novartis, Otsuka, Pfizer, Sunovion, **Part 3:** AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Janssen, Merck, Novartis, Otsuka, Pfizer, Sunovion, **Part 4:** Grants/contracts to institution to November 2010: Pfizer, Sunovion, AstraZeneca.

W25. GIRK Channel Inhibitors Decreased Preference in Mice and Relapse Risk Scores in Alcoholics

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Background: The effects of G protein-activated inwardly rectifying potassium (GIRK) channels in the rewarding effects of addictive substances have attracted much attention. GIRK channel opening hyperpolarizes the cell membrane, and modulates neuronal excitability. Ethanol opens GIRK channels directly (Kobayashi et al., 1999). A genetic polymorphism in GIRK channels was shown to be a heritable factor related to alcohol sensitivity in mice (Ikeda et al., 2002; Kobayashi et al., 1999). In addition, we have shown that fluoxetine, paroxetine and ifenprodil, but not fluvoxamine, inhibit GIRK channels (Kobayashi et al., 2003; 2004; 2006). In order to investigate the effects of GIRK channel inhibitors on aspects of substance dependence, we report here on [Study 1] basic research in mice investigating the effects of the selective serotonin inhibitors paroxetine and fluvoxamine, that have differential effects on GIRK channel inhibition, on methamphetamine (METH) conditioned place preference (CPP), [Study 2] a retrospective study on the influence of GIRK channel inhibition on relapse risk in alcohol-dependent inpatients, and [Study 3] a prospective

randomized controlled study investigating the effects of the GIRK channel inhibitor (ifenprodil) on relapse prevention in patients with alcohol dependence.
Methods: [Study 1]: Male C57BL/6J mice (8-10 weeks old) were used. The CPP test was performed. Conditioning sessions were conducted once daily for 4 consecutive days. For the first day of conditioning, mice were intraperitoneally (i.p.) injected with saline, 20 mg/kg paroxetine, or 100 mg/kg fluvoxamine 60 min before injection with METH (2 mg/kg, i.p.). Immediately after METH administration, mice were confined to the black or white compartment of the apparatus for 50 min. On the second day, the mice were pretreated with the same solution (saline, paroxetine, or fluvoxamine) 60 min before a saline injection. Immediately after the saline injection, mice were confined to the opposite compartment for 50 min. On the third and fourth days, the same conditioning as the first and second days was repeated. [Study 2]: The participants included 11 patients who received GIRK inhibition treatment (i.e., paroxetine, sertraline, chlorpromazine, trazodone, and levomepromazine) and 39 patients who did not receive GIRK inhibition treatment. The participants answered a questionnaire, including the Alcohol Relapse Risk Scale (ARRS, 5 subscales: stimulus-induced vulnerability, emotionality problems, compulsivity for alcohol, lack of negative expectancy for alcohol, and positive expectancy for alcohol) and items about their experiences of stressful events 2 weeks after hospitalization (Time 1) and completed follow-up questionnaires 45-60 days (Time 2). [Study 3]: Participants of the present study were 21 outpatients with alcohol dependence who were treated in the Tokyo Metropolitan Matsuzawa Hospital. Patients were randomly divided into two groups: 1) Prior administered group: 10 patients administered ifenprodil (60 mg/day) for 3 months prior to administration of a control drug (ascorbic acid, calcium pantothenate, 600 mg/day) for 3 months, 2) Latter administered group: 11 patients administered ifenprodil for 3 months after control drug for 3 months. Participants completed the questionnaire containing an item about craving assessed by a visual analogue scale and the ARRS before the first medication administration period (Time 1), at which time the patients were switched to the other drug (Time 2), and also after the second administration period (Time 3).
Results: [Study 1]: In the CPP test, pretreatment with paroxetine abolished the CPP for METH, whereas pretreatment with fluvoxamine prior to administration of METH did not inhibit METH CPP. [Study 2]: A significant interaction was found between *Group* and *Time* on positive expectancy for alcohol scores on the ARRS. The scores at *Time 2* were lower than that at *Time 1* only in the GIRK inhibition treatment group but not inthe non-GIRK inhibition treatment group. [Study 3]: There was a significant interaction between *Group* and *Time* in the stimulus-induced vulnerability score of the ARRS. A simple effect test showed that the score at *Time 2* was lower than at *Time 1* in the group that received the active drug first, and that the score at *Time 3* was lower than at *Times 1* and *2* in the group that received the active drug treatment as the second treatment.
Conclusions: The results from Study 1 suggest that paroxetine may be a useful tool for treating METH dependence. Further, these data suggest that molecules other than the serotonin transporter, such as GIRK channels, whose activities are modulated by paroxetine, but not by fluvoxamine, are involved in reducing METH CPP by paroxetine. The results of Study 2 suggest that GIRK inhibition treatment may decrease the positive expectancy for alcohol, a component of relapse risk. Study 3 suggested that ifenprodil decreased stimulus-induced vulnerability as a component of relapse risk. Taken together, the results from Studies 1-3 suggest that GIRK channel inhibition may contribute to effective treatment of substance dependence on drugs, such as methamphetamine and alcohol.
Keywords: GIRK channel inhibitor, addiction, conditioned place preference, relapse risk

Disclosure: N. Sugaya, Nothing to Disclose; Y. Ogai, Nothing to Disclose; Y. Aikawa, Nothing to Disclose; M. Umeno, Nothing to Disclose; Y. Yumoto, Nothing to Disclose; M. Takahama, Nothing to Disclose; M. Tanaka, Nothing to Disclose; Y. Kakibuchi, Nothing to Disclose; E. Senoo, Nothing to Disclose; Y. Takamatsu, Nothing to Disclose; H. Yamamoto, Nothing to Disclose; Y. Hagino, Nothing to Disclose; A. Markou, Nothing to Disclose; K. Ikeda, Nothing to Disclose.

W26. A Randomized Controlled Trial of Cognitive-behavioral Therapy Versus Risperidone for Augmenting Serotonin Reuptake Inhibitors in Obsessive-compulsive Disorder

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Background: Serotonin reuptake inhibitors (SRIs, i.e., clomipramine and the selective SRIs) are approved by the Food and Drug Administration to treat obsessive-compulsive disorder (OCD). Although many patients respond, few achieve remission from an SRI alone. To augment SRIs response, two strategies are recommended: adding antipsychotic medication or cognitive-behavioral therapy (CBT) consisting of exposure and ritual prevention (EX/RP). Here, we report results from the first trial to compare these two SRI augmentation strategies directly.
Methods: A randomized, controlled trial was conducted at two academic outpatient clinics to compare the effects of augmenting SRIs with risperidone and EX/RP. Participants were 100 adults with OCD and a Yale-Brown Obsessive Compulsive Scale (Y-BOCS) score of 16 or above despite a therapeutic SRI dose for at least 12 weeks prior to entry. Participants continued their SRI and were randomized to 8 weeks of risperidone ($n = 40$), EX/RP ($n = 40$), or pill placebo ($n = 20$). Assessments were conducted every four weeks.
Results: Patients receiving EX/RP had significantly greater reduction in Y-BOCS scores at Week 8 than those receiving risperidone or placebo based on mixed effects models (versus risperidone: -9.72 [SE = 1.38], $z = -7.02$ $p < 0.0001$; versus placebo: -10.10 [SE = 1.68], $z = -5.99$, $p < 0.0001$). Patients randomized to risperidone did not significantly differ from placebo (-0.38 [SE = 1.72], $z = -0.22$, $p = 0.825$). Adding EX/RP to SRIs was also superior to placebo and to risperidone in improving insight, functioning, and quality of life. Significantly more patients receiving EX/RP than patients receiving risperidone or placebo responded to treatment (Y-BOCS decrease of at least 25%: 32/40 [80%] versus 9/40 [22.5%] versus 3/20 [15%]; $\chi^2 = 35.37$, $df = 2$, $p < 0.0001$); significantly more patients receiving EX/RP also achieved remission (Y-BOCS of 12 or less: 17/40 [42.5%] versus 5/40 [12.5%] versus 1/20 [5%]; $\chi^2 = 14.74$, $df = 2$, $p = 0.001$).
Conclusions: This is the first RCT to directly compare two empirically supported SRI augmentation strategies for patients with OCD. Adding EX/RP to SRIs was superior to both risperidone and placebo in reducing OCD symptoms and improving insight, functioning, and quality of life. Risperidone was numerically but not statistically superior to placebo on all outcome measures. These data have are two important clinical implications. First, OCD patients on SRIs should be offered EX/RP before antipsychotics given its superior efficacy and lower rate of side effects. Second, if risperidone is tried, given that it is only likely to help a small subset, it should be discontinued if there is no obvious benefit to minimize risk.
Keywords: OCD, risperidone, cognitive-behavioral therapy (CBT)
Disclosure: H. Simpson, **Part 1:** This randomized controlled trial was funded by the National Institutes of Mental Health. Risperidone and matching placebo was provided at no-cost by Janssen Pharmaceuticals. During the course of this study, in addition to the medication at no-cost from Janssen Pharmaceuticals, Dr. Simpson received research funds from Transcept

Pharmaceuticals (2011-present) and Neuropharm, Ltd (2009), served on a Scientific Advisory Board for Pfizer (about Lyrica, 2009-2010) and for Jazz Pharmaceuticals (about Luvox CR, 2007-2008), and received royalties from Cambridge University Press and Up To Date, Inc., **Part 4:** Risperidone and matching placebo was provided at no-cost by Janssen Pharmaceuticals. During the course of this study, in addition to the medication at no-cost from Janssen Pharmaceuticals, Dr. Simpson received research funds from Transcept Pharmaceuticals (2011-present) and Neuropharm, Ltd (2009), served on a Scientific Advisory Board for Pfizer (about Lyrica, 2009-2010) and for Jazz Pharmaceuticals (about Luvox CR, 2007-2008), and received royalties from Cambridge University Press and Up To Date, Inc; E. Foa, **Part 1:** This study was funded by NIMH. Janssen Pharmaceuticals provided risperidone and matching placebo. During the course of this study (07/06-07/12), in addition to the medication at no-cost from Janssen Pharmaceuticals, Dr. Foa has been a consultant for the VA National Center for PTSD (2006-present), U.S. Army (2009-present), City of Philadelphia (2011-present), Los Angeles Department of Mental Health (2011-present), Canada VA (2011-present), Florida VA 2011-present), Philadelphia VA (2010-present), Pennsylvania VA VISN 4 (2010-present), California Institute of Mental Health, Ventura County (2011-present) and Jewish Family Services of Atlantic and Cap May Counties (2011-present). She receives royalties from Bantam and Oxford University Press for book sales, including a manual of cognitive behavioral therapy for OCD, **Part 4:** This study was funded by NIMH. Janssen Pharmaceuticals provided risperidone and matching placebo. During the course of this study (07/06-07/12), in addition to the medication at no-cost from Janssen Pharmaceuticals, Dr. Foa has been a consultant for the VA National Center for PTSD (2006-present), U.S. Army (2009-present), City of Philadelphia (2011-present), Los Angeles Department of Mental Health (2011-present), Canada VA (2011-present), Florida VA (2011-present), Philadelphia VA (2010-present), Pennsylvania VA VISN 4 (2010-present), California Institute of Mental Health, Ventura County (2011-present) and Jewish Family Services of Atlantic and Cap May Counties (2011-present). She receives royalties from Bantam and Oxford University Press for book sales, including a manual of cognitive behavioral therapy for OCD.

W27. Empirical Development of Depression Subtypes Using Factor Analysis of Subject Self-Reports Across Symptom Domains

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Background: Relatively low rates of remission with antidepressant treatments demand methods of improving treatment matching. Personalized care for Major Depressive Disorder (MDD) will involve identification of traits or symptom patterns defining clinical subtypes that can be used in treatment algorithms. Traditional methods of subtyping patients have looked at patient features singly or, at most, within single rating scales because of the difficulty in statistical assessment of many variables at once. However, no system using one clinical or biological marker has had the specificity for clinical application and it has become clear that high-dimension data sets and more complex definition of subtypes will be necessary to meaningfully capture patient presentation. Thus methods reducing data complexity may prove valuable in developing patient subtypes. In this analysis we present a novel method of empirical generation of patient subtypes using a large number of clinical variables simultaneously.
Methods: The COmbining Medications to Enhance Depression Outcomes study enrolled adults with chronic or recurrent MDD and compared antidepressant monotherapy (escitalopram + placebo) to two combination treatment arms (bupropion + escitalopram and venlafaxine + mirtazapine) over a 12 week acute treatment phase. N = 665 subjects completed 15 comprehensive diagnostic, symptom, and functional self-reported assessments at baseline. We performed a factor analysis on the 383 individual items from these assessments, considering both the reported presence and absence of each item for dichotomous items and the numerical score of rated items. We then used the factors in a hierarchical cluster analysis to define patient subgroups and used Fisher's exact test to compare remission rates among them in the N = 646 subjects with sufficient post baseline data to determine outcome.
Results: We derived a six-factor model covering a wide domain of symptoms. The first factor primarily included items rating physiological anxiety and activation symptoms, and lack of life satisfaction. Factor two included presence of intrusive trauma, manic symptoms and lack of many core MDD symptoms. Factor three included somatic symptoms and lack of suicidal ideation. Factor 4 features lack of eating and appetite symptoms. Factor 5 included lack of trauma history and factor 6 indicated lack of impaired social functioning. Cluster analysis of these six factors resulted in three subgroups. Roughly, group I contained subjects with prominent factor 1 and 2. In group II, factor scores were more evenly distributed, with some prominence of factor 1. Subjects in group III had prominent factor 6 with low factor 1. Fisher's exact test showed significantly different rates of remission across the three treatment arms ($p < 0.01$).
Conclusions: Our results demonstrate the empirical development of depression subtypes with differing outcomes. It appears that within this sample of depressed subjects, anxiety, manic symptoms, trauma and social functioning were important areas differentiating the outcome groups, while core depression symptoms were less discriminating, presumably because these symptoms were prevalent across all patients in the sample based upon the study's eligibility criteria. Further consideration of the items in each factor and composition of each cluster may be useful in generating hypotheses for future studies of patient subtyping. In addition, our methods may be useful in analyzing data sets that include biomarker and/or genetic data as well as clinical features in large patient samples.
Keywords: Major Depressive Disorder, Clinical Subtypes, Antidepressant Treatment
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W28. Varenicline Attenuates Methamphetamine-induced Subjective Effects in Methamphetamine-dependent Volunteers

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Background: Amphetamine-type stimulants are abused by more people globally than opiates and cocaine combined. In the US,

2010 estimates suggest there are 353,000 current and 105,000 new users per year. However, treatments are limited to behavioral interventions, as there are no FDA-approved medications for methamphetamine (METH) dependence. Preclinical and clinical studies suggest that METH users may benefit from treatments that enhance cholinergic neurotransmission. Preclinical data indicates that varenicline (VAR), a partial agonist at $\alpha4\beta2$, and a full agonist at $\alpha7$, nicotinic acetylcholine receptors, increases mesolimbic dopamine levels, and this is thought to underlie its efficacy as a nicotine dependence treatment. Thus, we hypothesized VAR would attenuate METH-induced subjective effects.

Methods: We conducted a double-blind, placebo-controlled, human laboratory-based study using a within-subjects design. Non-treatment-seeking volunteers who met DSM criteria for METH-dependence were randomized to receive placebo (0 mg) or VAR (1 or 2 mg) each day during three separate, 7-day inpatient phases. During each phase, participants received placebo or VAR on days 1-7. On day 6, participants smoked METH (0, 10, and 30 mg) during three separate sessions. Subjective effects, measured on a visual analog scale (VAS) digitized from 0 to 100 (strongest), were assessed prior to and 5, 15, 30, 45, and 60 min after METH. Safety was measured by summing the frequencies of each adverse event (AE) reported under each VAR condition. Cardiovascular and self-administration data were collected but will be presented elsewhere. To account for baseline differences, data are presented as change from baseline. Two participants did not respond to METH and were excluded. We used three-way ANOVAs (VAR dose, METH dose, and time) to determine effects of VAR on subjective effect ratings. Safety was analyzed by one-way ANOVAs. Significant findings were followed by the Holm-Sidak *post hoc* method of pairwise multiple comparisons.

Results: The 15 eligible subjects who completed all 3 phases averaged 13 years of education, and were 36 years old, Caucasian (66%), male (73%), cigarette smokers (87%). Significant VAR, METH, and time effects, and a VAR × METH interaction were revealed on "Any Drug Effect". The VAR dose effect was due to differences between 0 vs. 2 mg ($t = 2.492$; $p = 0.038$) and the interaction was due to differences between 0 vs. 2 ($t = 3.960$; $p < 0.001$) and 1 vs. 2 mg ($t = 2.627$; $p = 0.018$) from the 30 mg METH dose. Significant VAR, METH, and time effects, and a VAR × METH interaction were revealed on "Good Effects". The VAR dose effect was due to differences between 0 vs. 1 ($t = 2.955$; $p = 0.010$) and 0 vs. 2 mg ($t = 2.950$; $p = 0.007$) and the interaction was due to differences between 0 vs. 2 ($t = 5.711$; $p < 0.001$) and 0 vs. 1 mg ($t = 3.825$; $p < 0.001$) from the 30 mg METH dose. Significant VAR, and METH effects, and a VAR × METH interaction were revealed on "Stimulated". The VAR dose effect was due to differences between 0 vs. 2 mg ($t = 2.655$; $p = 0.024$) and the interaction was due to differences between 0 vs. 2 ($t = 4.507$; $p < 0.001$) and 1 vs. 2 mg ($t = 3.314$; $p = 0.002$) from the 30 mg METH dose. There were significant METH, and time effects, and a VAR × METH interaction on "High". The interaction was due to differences between 0 vs. 2 ($t = 3.621$; $p < 0.001$) and 1 vs. 2 mg ($t = 3.166$; $p = 0.003$) from the 30 mg METH dose. There were significant METH, and time effects, and a VAR × METH interaction on "Drug Liking". The interaction was due to differences between 0 vs. 2 ($t = 2.484$; $p = 0.026$) and 1 vs. 2 mg ($t = 2.672$; $p = 0.023$) from the 10 mg, and 0 vs. 2 ($t = 5.634$; $p < 0.001$) and 0 vs. 1 mg ($t = 3.946$; $p < 0.001$) from the 30 mg, METH doses. There was a significant METH effect, and a VAR × METH interaction on "Likely to Use". The interaction was due to differences between 0 vs. 2 ($t = 2.570$; $p = 0.021$) and 1 vs. 2 mg ($t = 3.170$; $p = 0.005$) from the 30 mg METH dose. There were no significant differences between VAR and placebo on AEs or neuropsychiatric sequelae during either VAR titration or following METH administration.

Conclusions: VAR dose-dependently and significantly attenuated several positive subjective ratings typically produced by smoked METH in dependent volunteers. Similar to Zorick et al. (2009), we found no differences, compared to placebo, on AEs or neuropsychiatric sequelae. The ability of VAR to attenuate METH-induced subjective effects, the lack of VAR-induced neuropsychiatric AEs seen in METH-dependent participants, along with the overall safety and tolerability of co-administering VAR with smoked METH, collectively suggests that VAR has potential therapeutic efficacy as a treatment for METH dependence. Our conclusions are supported by a recently completed outpatient clinical trial by Shoptaw and colleagues (presented at CPDD, 2011), which indicated treatment with VAR (2 mg/d for 8 weeks) enhanced retention rates and reduced METH use in METH-dependent volunteers. Lastly, the current finding that a lower dose of VAR (1 mg/d) significantly decreased some METH-induced subjective effects suggests that a lower dose may also be equally effective in increasing abstinence.

Keywords: Substance-related Disorders, Methamphetamine, Varenicline, Pharmacotherapy, Human

Disclosure: C. Verrico, Nothing to Disclose; J. Mahoney, Nothing to Disclose; R. Bennett, Nothing to Disclose; T. Newton, Nothing to Disclose; R. De La Garza, **Part 1:** I served as an expert witness for Pfizer (the pharmaceutical company that makes varenicline) in the Chantix litigation, I was paid on an hourly basis to write an expert report and opinions on published articles by other scientists with regard to the safety of Chantix administration in humans, The potential interest that could be affected with regard to this specific project is that we have collected safety data (i.e., adverse events) in this trial, which will be analyzed and presented at this conference, **Part 2:** DLA Piper (law firm representing Pfizer), **Part 3:** I served as an expert witness for Pfizer (the pharmaceutical company that makes varenicline) in the Chantix litigation, I was paid on an hourly basis to write an expert report and opinions on published articles by other scientists with regard to the safety of Chantix administration in humans, The potential interest that could be affected with regard to this specific project is that we have collected safety data (i.e., adverse events) in this trial, which will be analyzed and presented at this conference.

W29. A Double-blind, Placebo-controlled, Multicenter Trial of Adjunctive Armodafinil in Adults with Major Depression Associated with Bipolar I Disorder

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Background: Treatment for the depressive phase of bipolar disorder continues to be an area of unmet need, with only a limited number of effective therapies that are often associated with undesirable side effects. The objective of this study was to evaluate the efficacy and safety of armodafinil as an adjunctive therapy for major depression associated with bipolar I disorder.

Methods: Patients 18-65 years of age with a diagnosis of bipolar I disorder currently experiencing a major depressive episode (DSM-IV-TR) for 4 to 52 weeks, with a baseline score $\geqslant 13$ on the 16-item Quick Inventory of Depression Symptomatology-Clinician-rated (QIDS-C16) and who were prospectively documented as being refractory to treatment with a mood stabilizer, were randomized to receive armodafinil 150 mg, 200 mg, or placebo. Patients continued their current mood stabilizing regimen throughout the study, consisting of 1 or 2 of the following: lithium, valproic acid, lamotrigine, risperidone, aripiprazole, olanzapine, or ziprasidone (only in combination with lithium or valproic acid). The primary outcome was the mean change from baseline to week 8 in the 30-Item Inventory of Depressive Symptomatology-Clinician-rated (IDS-C30) total score. Secondary outcomes included mean change at week 8 on IDS-C30 individual items, IDS-C30 response rate (percentage of participants with $\geqslant 50\%$ decrease from baseline on

IDS-C30), Clinical Global Impression of Severity (CGI-S) response rate (percentage of participants with ⩾2 point decrease from baseline), and mean change at week 8 on the Global Assessment of Function (GAF). Safety assessments included adverse events (AEs), Young Mania Rating Scale (YMRS), Columbia Suicidality Rating Scale, Hamilton Anxiety Scale (HAM-A), and Insomnia Severity Index (ISI). The change from baseline in the IDS-C30 was analyzed using mixed-model repeated measures and secondary outcomes were assessed with analysis of variance or Cochran-Mantel-Haenszel test. Final visit data is from the last post-baseline assessment.

Results: Of 786 patients screened, 433 were randomized (n = 199 placebo, n = 201 armodafinil 150 mg, n = 33 armodafinil 200 mg). The 200-mg armodafinil group was discontinued based on previous findings of a lack of differential dose response between the 150- and 200-mg groups, and these patients were assessed for safety only. Baseline demographics and disease characteristics were comparable between the armodafinil 150-mg group and placebo group. Mean (SD) time from first depressive episode was 15 (11) years and all patients in the study reported receiving prior medication for their current depressive episode. There was a significantly greater decrease at week 8 for the armodafinil 150-mg group compared with placebo for mean IDS-C30 total score (−23.3 vs −19.8; p = 0.0092), and at final visit for five IDS-C30 individual items: panic/phobic symptoms (p = 0.0440), increased appetite (p = 0.0096), concentration/decisions (p = 0.014), energy/fatigability (p = 0.0375), and leaden paralysis/physical energy (p < 0.001). Furthermore, the percentages of IDS-C30 responders were significantly greater in the armodafinil 150 mg group vs. placebo at week 8 (55% vs. 39%; p = 0.0084) and final visit (46% vs. 34%; p = 0.0147). However, the percentage of CGI-S responders and change in GAF were not significantly different between armodafinil 150 mg and placebo at final visit. Discontinuations due to AEs were 4% for placebo, 6% for armodafinil 150 mg, and 3% for armodafinil 200 mg. The most common AEs were headache (10% vs. 10%), diarrhea (9% vs. 7%), and nausea (6% vs. 5%) for the armodafinil 150-mg and placebo groups, respectively. Headache (23%), insomnia (13%), and nausea (10%) were the most common AEs for the armodafinil 200-mg group. YMRS, HAM-A, and ISI scores decreased from baseline to final visit in all groups, although mean scores for these measures were greater in the armodafinil 200-mg group compared with the placebo and armodafinil 150-mg groups. There was 1 suicide attempt in the placebo group and 2 reports of suicidal ideation in the armodafinil 150-mg group. Among patients with weight reported at final visit, 5.0% (8/183) in the placebo group, 1.6% (3/186) in the 150-mg group, and 3.6% (1/28) in the 200-mg group had ⩾7% weight gain from baseline. Based on IDS-C30 responder rate, the number needed to treat for armodafinil 150 mg vs. placebo in this study was 9. Number needed to harm with regards to AE discontinuation for armodafinil 150 mg vs. placebo was 100.

Conclusions: Armodafinil 150 mg significantly improved depressive symptoms compared with placebo in patients with bipolar I disorder when given as adjunctive treatment to mood stabilizers. Adjunctive armodafinil 150 mg compared with placebo was well tolerated, with no evidence for worsening symptoms of mania, suicidality, anxiety, insomnia, clinically significant weight gain, or other adverse events. This study was funded by Teva Pharmaceuticals.

Keywords: armodafinil, bipolar disorder, depression

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W30. Efficacy and Safety of Lisdexamfetamine Dimesylate in Treatment of Adults with Binge Eating Disorder: A Randomized, Double-Blind, Placebo-Controlled Trial

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Background: Effective treatments for binge eating disorder (BED) are needed. This study examined the efficacy and safety of lisdexamfetamine dimesylate (LDX), a d-amphetamine prodrug, to treat moderate to severe BED.

Methods: This was a multicenter, 11-week (wk), randomized, double-blind, parallel-group, forced-dose titration, placebo-controlled trial. Adults (18-55 years) meeting DSM-IV-TR criteria for BED were randomized to LDX (30, 50, or 70 mg/d) or placebo. LDX dose was initiated at 30 mg/d, titrated over 3 wk to assigned dose, which was maintained for an additional 8 wk. The primary efficacy objective was assessed using binge days per wk. Data analysis used mixed effects model for repeated measures on change from baseline for the transformed scale of log (binge days/wk +1); primary comparisons were performed at wk 11. Secondary measures included binge episodes per wk; Three-Factor Eating Questionnaire (TFEQ); Clinical Global Impressions-Improvement (CGI-I, dichotomized as improved [very much and much improved ratings] or not improved [all other ratings]); and Yale-Brown Obsessive Compulsive Scale for Binge Eating (YBOCS-BE). Safety assessments included treatment-emergent adverse events

(TEAEs), Columbia-Suicide Severity Rating Scale, vital signs, electrocardiogram, weight, and laboratory tests.
Results: Of 271 randomized participants, 270 were included in safety analyses and 266 (placebo, n = 65; LDX 30 mg/d, n = 68; LDX 50 mg/d, n = 67; LDX 70 mg/d, n = 66) in efficacy analyses. 58 participants (placebo, n = 17; LDX 30 mg/d, n = 15; LDX 50 mg/d, n = 13; LDX 70 mg/d, n = 13) did not complete the study; 7 withdrew due to AEs (all receiving LDX); none withdrew due to lack of efficacy. Of 270 participants, 220 (81.5%) were female, 137 (50.7%) were Mean (SD) weekly binge days at baseline for placebo and LDX 30, 50, and 70 mg/d were 4.3 (1.35), 4.6 (1.45), 4.6 (1.27), and 4.5 (1.26), respectively. Mean (SD) change from baseline to wk 11/ET in weekly binge days for placebo and LDX 30, 50 and 70 mg/d was -3.12 (2.093), -3.56 (1.970), -4.17 (1.512), and -4.06 (1.548), respectively. Significant differences for LDX vs placebo in mean log-transformed change from baseline in weekly binge days at wk 11 were found for LDX 50 mg/d ($P < .001$) and 70 mg/d ($P < .001$) but not 30 mg/d ($P = .35$). At wk 11/ET, significantly greater proportions ($P < .003$ for all) were rated as improved on the CGI-I for LDX 30 mg/d (85.1%), 50 mg/d (91.0%), and 70 mg/d (93.9%) vs placebo (61.5%). For TFEQ cognitive restraint, disinhibition, and hunger scores, significant differences in mean change at wk 11 were found for all LDX dose groups vs placebo ($P <= .034$ for all). Mean (SD) baseline for YBOCS-BE total score for placebo, LDX 30, 50, and 70 mg/d was 20.9 (4.59), 20.6 (4.80), 19.5 (5.14), and 19.9 (5.39), respectively; LS mean (SE) change from baseline to wk 11 was -11.4 (0.85), -15.2 (0.83), -15.5 (0.81), and -17.1 (0.81), respectively. For YBOCS-BE total score, significant differences in mean change at wk 11 for LDX vs placebo were found for all LDX dose groups ($P < .002$ for all). In the placebo group, 38/66 (57.6%) experienced TEAEs, and no participants died, had serious TEAEs, or were discontinued due to TEAEs. For all LDX dose groups, 168/204 (82.4%) experienced TEAEs, 3/204 (1.5%) had serious TEAEs, and 6/204 (2.9%) were discontinued due to TEAEs. One participant (LDX 70 mg/d group) died due to drug toxicity (verbatim: methamphetamine and amphetamine) that the investigator and sponsor considered unrelated to study drug; 2 participants (both LDX 30 mg/d) experienced unrelated serious TEAEs (acute pancreatitis and appendicitis). TEAEs with incidence $\geqslant$5% for the placebo group were decreased appetite, dry mouth, headache, irritability, and upper respiratory tract infection; for LDX all-dose group was constipation, decreased appetite, dry mouth, headache, insomnia, irritability, nasopharyngitis, nausea, and weight decrease. For placebo and LDX (all doses) respectively, mean (SD) change from wk 0 to 11/ET in systolic blood pressure -2.1 (8.77) and 0.2 (9.83) mmHg; -1.0 (7.03) and -0.8 (7.41) mmHg for diastolic blood pressure, and 1.1 (7.94) to 3.7 (11.44) bpm for pulse. Mean (SD) change in body weight was -0.01 (6.704), -7.26 (8.394), -10.87 (9.602), and -11.03 (8.618) lb for placebo and LDX 30, 50 and 70 mg/d, respectively.
Conclusions: After 11 wk, LDX (50 and 70 mg/d) demonstrated efficacy vs placebo in decreased binge days (primary endpoint: log-transformed binge days), increased proportion achieving 4-wk cessation, had superior response status, and increased proportion rated with global improvement in severity by CGI-I. LDX safety profile was consistent with the known safety profile in adults. Additional large, randomized, placebo-controlled trials are warranted to confirm the efficacy and safety profile of LDX in treatment of adults with BED. Clinical research was funded by the sponsor, Shire Development LLC.
Keywords: Binge eating disorder, lisdexamfetamine dimesylate, Eating Questionnaire, Obsessive Compulsive Scale
Disclosure: S. McElroy, **Part 1:** Alkermes, AstraZeneca, Corcept, Eli Lilly, MedAvante, Schering Plough, Shire, Teva, Bristol Myers Squibb, Pamlab, Sepracor (Spouse), **Part 4:** Abbott, Alkermes, AstraZeneca, Bristol Myers Squibb, Cephalon, Eli Lilly, Forest, Glaxo Smith Kline, Jazz, Orexigen, Pizer, Shire, Takeda, Transcept; J. Mitchell, Nothing to Disclose; D. Wilfley, **Part 2:** Salary, Washington Univeristy School of Medicine (2010-Present), United Health Group, for Training workshop presented to United Health Group YMCA JOIN (2011), **Part 4:** Shire Development Inc. grant funds; M. Gasior, **Part 1:** I am full time Shire employee. I have company options and stocks; Full Salary from Shire, **Part 3:** See Above; M. Ferreira-Cornwell, **Part 1:** I am a Shire employee and hold stocks or/and stcok options in Shire; J. Gao, **Part 1:** I am an employee of Shire and holds stock and/or stock options in Shire; J. Wang, **Part 1:** I am working for Shire Pharmaceuticals; S. Stephen, **Part 1:** Consulting and speaking: Amer Assoc Child Adol Pyschiatry, CME Outfitters, Adamed, Univeristy of Utah, Johns Hopkins University, Univeristy of Nebraska, **Part 4:** Research Support to the UC Academic Health Center: Eli Lily, Janssen, AstraZeneca, Martek, Nutrition 21, Repligen, Sumatomo, NIDA, NIAAA, NIMH, NARSAD; J. Hudson, **Part 1:** Alkermes, Genetech, Healthcore, Otsuka, Pfizer, Roche, Shire, **Part 2:** Pfizer (2010), P**art 4:** Lil, Otsuka, Shire.

W31. Kynurenic Acid Correlates with Neopterin in Hepatitis C Virus Patients: Implications for the Efficacy and Psychological Side-effects of Interferon-alpha Treatment

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Background: Pro-inflammatory Th-1 type cytokine, interferon-gamma (IFNG), transcriptionally induces rate-limiting enzymes ofkynurenine (KYN) formation from tryptophan (TRP) and of production of neopterin (by-product of biosynthesis of BH_4, an obligatory cofactor of nitric oxidesynthase) from guanosine triphosphate (GTP). Elevation of KYN and neopterin inbiological fluids was reported in depression and schizophrenia, diseasesassociated with chronic inflammation. Depression and psychoses are oftenside-effects of interferon-alpha treatment of patients with hepatitis C virus (HCV), melanoma and multiple sclerosis. The positive correlation betweenincreased levels of KYN and neopterin was reported in healthy subjects. KYN is an immediate precursor of kynurenic acid (KYNA). We present the preliminaryresults of the ongoing investigation of TRP – KYN pathway and neopterin in HCV patients.
Methods: We evaluated KYNA, KYN, TRP (HPLC-UV-fluorometricmethod) and neopterin (ELISA, American Research Products, Inc., Belmont, MA) inblood samples of 41 hepatitis C virus patients treated in the previous 3 yearswith interferon-alpha. Study was approved by IRB of the Tufts Medical Center.
Results: *TRP – KYNpathway*: we found highly significant correlations of KYNwith TRP ($r = 0.52$, $p = 0.0005$) and KYN with KYNA ($r = 0.51$, $p = 0.0006$) levels. *Neopterin and TRP – KYN pathway*: there was strong and highly significant correlation between neopterin and KYNlevels ($r = 0.76$, $p = 0.0001$). Neopterin correlated moderately with KYNA ($r = 0.36$, $p = 0.02$) and TRP ($r = 0.33$, $p = 0.03$).
Conclusions: The strong correlation between TRP and KYN and between KYN and KYNA might reflect the activity of indoleamine 2,3-dioxygenase (IDO), the rate-limiting enzyme of TRP conversion into KYN, and of kynurenine aminotransferase (KAT), catalyzing the production of KYNA from KYN. The very strong ($r = 0.76$) correlation between neopterin and KYN reflects, most likely, IFNG-induced concurrent activation of IDO and rate-limiting enzyme of neopterin production, GTP cyclohydrolase I (GTPCH). While KYN/TRP ratio is widely used in clinical settings for the assessment of IFNG-induced IDO activation, our data suggest that neopterin is a reliable indirect marker of IFNG-induced activation of IDO (in addition to neopterin role as a marker of GTPCH activity). Our study revealed the positive correlation between blood concentrations of KYNA and neopterin. We have previously reported that neopterin correlates with

anti-viral efficacy, and IFNG gene polymorphisms correlates with psychiatric side-effects of interferon-alpha treatment. The relationship between KYNA and neopterin might be considered in the future studies of the mechanisms of the incidents of depression and psychoses during treatment with interferon-alpha. Supported by MH083225.
Keywords: kynurenic acid, neopterin, interferon-alpha, hepatitis C virus
Disclosure: W. Turski, Nothing to Disclose; W. Zgrajka, Nothing to Disclose; G. Oxenkrug, Nothing to Disclose.

W32. Functional Connectivity Following GABAergic Challenge: Neural Correlates of Sedation and Intoxication

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Background: Networks of brain regions having coherent fluctuations of the blood oxygen level-dependent (BOLD) time-series at rest, or "resting state networks" (RSNs), contain information about the functional organization of the brain. RSNs are topographically consistent with activity-related networks, suggesting that studying their spontaneous fluctuations following a pharmacological challenge may reveal information about how neurotransmitter systems influence brain activity at the network level to give rise to behavioral output.
Methods: This within-subject, double-blind, placebo-controlled study investigated how GABA-mediated inhibition influences behavior at the network level using acute administration of the GABA-A receptor modulator zolpidem (Ambien) as a tool to probe functional connectivity (FC) in relation to observable drug effects. Healthy participants ($n = 12$) underwent functional magnetic resonance imaging 45 min after zolpidem (0, 5, 10, or 20 mg, p.o.), and BOLD signals were measured while participants gazed at a static fixation point (i.e., at rest). Data were analyzed using group independent component analysis with dual regression.
Results: Our exploratory analysis indicated that compared to placebo, the highest dose of zolpidem increased FC within a number of sensory, motor, and limbic RSNs. The extensive increases in resting BOLD signal coherence were consistent with those reported following administration of other sedating drugs acting at GABA-A receptors, and we speculate that a GABA-facilitated enhancement of RSN synchrony may reflect an aberrant state of neuronal rigidity that prevents efficient communication, thus giving rise to the behavioral manifestation of sedation. A more detailed analysis focused on limbic effects and examined the relationship between FC in amygdala-containing RSNs and the self-reported subjective state of intoxication associated with the 20 mg dose of zolpidem. Three amygdala networks were identified, all of which exhibited reduced amplitude in response to zolpidem; one was comprised of deep nuclei that were connected to regions contributing to "salience integration", the second was comprised of superficial nuclei that were connected to regions important for mediating "motivational state", and the third was the entire bilateral amygdala that was connected to previously reported "salience processing" regions. Specifically with respect to zolpidem's subjective effects, drug-induced increases in self-reported ratings of "like" were related to increased FC in the first network, increased "high" was related to increased FC in the second network, and a measure of general intoxication was related to all three networks. Our data were consistent with the idea that intoxication is likely a general term encompassing a number of nuanced feelings in the drugged state including both "like" and "high". The networks involved were in agreement with those areas shown previously to undergo hemodynamic or metabolic alterations in association with the subjective states of intoxication following administration of cocaine, alcohol, and hydromorphone, and they speak to a body of literature implicating limbic, paralimbic, and mesocortical regions in mediating the actions of psychotropic drugs.
Conclusions: These results suggest that investigating pharmacological effects on RSNs may identify the neural correlates of drug action and behavior, thereby revealing the functional significance of GABAergic modulation on intrinsic brain activity.
Keywords: fMRI, resting state, GABA, zolpidem, subjective
Disclosure: S. Licata, Nothing to Disclose; L. Nickerson, Nothing to Disclose; A. Janes, Nothing to Disclose; S. Lowen, Nothing to Disclose; G. Trksak, Nothing to Disclose; S. Lukas, Nothing to Disclose.

W33. Genetic Risk of Suicidal Behavior in Bipolar-spectrum Disorder: Analysis of 737 Pedigrees

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Background: The risk of suicidal behavior is significantly higher in individuals with major affective disorders (MAD) than in the general population. Both suicidal behavior and MAD have a genetic diathesis and aggregate in families. However, the transmission of suicidal behavior is partially independent from the transmission of MAD. In this study, we analyzed the lifetime prevalence of completed and attempted suicides in a large sample of families with bipolar disorder (BD), and its relation to family history of MAD and BD. In addition, we evaluated the contribution of clinical and treatment factors to the risk of suicidal behavior in probands and first-degree relatives.
Methods: The lifetime prevalence of completed and attempted suicides was analyzed in 737 families of probands with BD with 4,919 first-degree relatives (of whom 818 were affected with MAD, 3,948 unaffected and information was not available for 153 subjects). Cox proportional hazard regression and logistic regression models were used to investigate the role of specific covariates [sex, diagnosis, age at onset, illness duration, proband's diagnosis and the history of suicidal behavior, family history of BD and MAD in first-degree relatives, type of relationship to the proband, response to lithium treatment (codified as poor, partial and full response) and family history of suicide in first-, second- and third-degree] on the risk of suicidal behavior, and on the prevalence of MAD and BD.
Results: The lifetime prevalence of suicidal behavior (attempted and completed suicides) adjusted for the duration of illness was at $38.4 \pm 3.0\%$ in 737 probands. Family history of suicidal behavior in first-degree relatives and early illness onset were associated with an increased risk of suicidal behavior in probands ($p = 0.004$ and $p = 0.002$, respectively). Conversely, probands treated with lithium had a lower risk of suicide, in part irrespective of the clinical response (partial response: $p = 0.03$; and full response: $p = 0.0009$). The significant contribution of treatment with lithium to the decreased risk of suicide remained even when we included poor responders in the analysis dichotomizing the outcome as presence/absence of treatment ($p = 0.007$). Further, treatment with lithium, irrespective of the degree of clinical response, was associated with a higher median of survival (73 versus 65 years; log-rank test $p = 0.004$). In first-degree relatives, family history of suicidal behavior contributed significantly to the joint risk of MAD and suicidal behavior ($p = 0.0006$), while the proband suicide status was a significant risk factor for MAD ($p = 0.03$) and BD ($p = 0.03$).
Conclusions: The liability to suicidal behavior appears to be determined by genetic risk for suicidal behavior and MAD as well. An early age of illness onset and short duration of illness increase significantly the risk of suicide. Even in the presence of high

genetic risk for suicidal behavior, lithium treatment decreases suicide rates significantly. This antisuicidal effect was at least in part irrespective of the mood stabilizing action of lithium.
Keywords: bipolar disorder, suicidal behavior, family study, lithium response, genetic risk
Disclosure: M. Manchia, Nothing to Disclose; T. Hajek, Nothing to Disclose; C. O'Donovan, Nothing to Disclose; V. Deiana, Nothing to Disclose; C. Chillotti, Nothing to Disclose; M. Ruzickova, Nothing to Disclose; M. Del Zompo, Nothing to Disclose; M. Alda, Nothing to Disclose.

W34. Effect of Chronic Haloperidol on Glutamate Metabolism in Rat Cortex

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Background: Haloperidol is a widely utilized antipsychotic which strongly antagonizes the dopamine D2receptor. Chronic exposure to oral haloperidol in macaque monkeys reducedastrocyte number in the parietal cortex (Konopaske *et al. Biol Psych*, 2008). Given the central role of astrocytes in glutamate metabolism, this study soughtto elucidate the effects of chronic haloperidol on cortical glutamatemetabolism.
Methods: Adult, male, rats were given daily i.p. injections of haloperidol or saline for 28days. Twenty-four hours after the last injection, metabolic fluxes of glutamateand GABA were assessed using intravenous infusions of [1-^{13}C]glucose for different time periods, or [2-^{13}C]acetate for 2 hours (steadystate). Total amino acid levels and ^{13}C enrichments were measured *ex vivo* in frontoparietal cortex tissueextracts using HPLC and ^{13}C magnetic resonance spectroscopyrespectively. A three compartment model (glutamatergic neurons, GABAergicneurons, and astrocytes) was used to estimate metabolic fluxes by fitting the ^{13}C-enrichmenttime courses from [1-^{13}C]glucose. The best fits were constrainedusing ratios of glutamate and GABA cycling (V_{cyc}) to TCA cycle flux(V_{TCA}).
Results: Relative to the control rats, haloperidol-exposed rats had no changes in totalglutamate, glutamine, GABA, or aspartate levels. However, percent enrichment of C4-glutamine was significantly increased in the haloperidol group (15.4 ± 2.7 vs.9.4 ± 3.3, $p < 0.01$). Estimates of V_{cyc} for glutamate/glutamine and GABA, of $V_{TCA}$for glutamate neurons, GABAergic neurons and astrocytes, and of otherparameters related to glutamate metabolism (e.g., V_{Gln} whichestimates the rate of glutamine synthesis) will be presented in detail.
Conclusions: These data suggest that haloperidol significantly affects astrocytic function and glutamate metabolism. The estimates, derived from the metabolic model, will help elucidate the mechanisms by which haloperidol exerts its effect on astrocytic function and glutamate metabolism.
Keywords: haloperidol, 13C magnetic resonance spectroscopy, glutamate, astrocyte, cortex, rat
Disclosure: G. Konopaske, Nothing to Disclose; A. Basu, Nothing to Disclose; J. Coyle, **Part 1:** Consulting fees from Abbott, Janssen, Lilly, PureTech, EnVivo, Sage, and Synaptec.

W35. Synaptic and Mitochondrial Changes in the Anterior Cingulate Cortex in Schizophrenia

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Background: Schizophrenia (SZ) is a mental illness that manifests itself with psychotic symptoms, negative symptoms, and cognitive deficits. The anterior cingulate cortex (ACC) is one of several brain regions that are abnormal in SZ. Many studies show impairments in ACC function, blood flow, glutamtergic axons, pyramidal cell density and mitochondrial function. The purpose of the present study is to compare the synaptic organization and mitochondrial morphology in SZ and control postmortem human ACC.
Methods: Postmortem human brain tissue was obtained from the Maryland and Alabama Brain Collections. The demographics of the NCs and SZs were, respectively: 1) age, 51.0 ± 24.6y and 54.5 ± 8.5y; 2) race, 2C&2AA and 1C&3AA; 3) sex, 2F&2M and 1F&3 M, and 4) PMI, 7.4 ± 0.48 h and 5.6 ± 1.49 h. Total synaptic densities, various synaptic features, number of mitochondria (MT) per terminal and MT morphology were measured in layers III and V-VI of the ACC.
Results: The proportions of asymmetric (glutamatergic) to symmetric (inhibitory) synapses in both layers were similar in NCs and SZs. In NCs, 86% of asymmetric synapses were axospinous and 14% were axodendritic. In SZs (both layers), there was a significant ($p < 0.05$) shift in proportion of synapses formed with spines vs. dendrites compared to NCs: 77% were axospinous and 22% were axodendritic. Throughout, there was an equivalent decrease in total synaptic density of about 20% in the SZ vs. the NCs, consistent with the reduced neuropil hypothesis. Proportion of axospinous synapses was equivalently decreased by about 30%, while axodendritic synapses were equal to or increased in proportion in the SZ vs. the NCs. The proportion of axon terminals containing at least one mitochondrion was 32% in NCs and 28% in SZs, for layers combined. The percentage of asymmetric axospinous terminals in layer III in SZ that contained MT was reduced to 76% of that of NCs ($p < 0.05$). The percentage of symmetric axospinous synapses that contained at least one MT was 70% of that of NCs ($p < 0.03$). This change was confined to layers V-VI where only 45% symmetric axospinous synapses contained at least one MT. Furthermore, MT size was increased in both layers in SZ subjects, indicating swelling and reduced function. MT optical density, an overall readout of MT health, was reduced in layer V-VI in SZ but elevated in layer III in SZ.
Conclusions: Thus, the data concerning synaptic proportions and MT morphology suggest alterations in multiple cortical connections and an overall decrease in cortical synaptic efficiency in SZ.
Keywords: ultrastructure, postmortem, psychosis
Disclosure: K. Barksdale, Nothing to Disclose; J. Roche, Nothing to Disclose; R. Roberts, Nothing to Disclose; A. Lahti, Nothing to Disclose.

W36. Persistently Increased Danger Signaling in the Adult Prefrontal Cortex Following Adolescent Intermittent Ethanol is Associated with Reversal Learning Deficits

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Background: Adolescence is a developmental period of prefrontal refinement, neuroplasticity, and increased risk-taking and sensation seeking that promotes the acquisition of skills necessary for adult independence. Human adolescence is also a period of increased levels of binge alcohol drinking that might impart long-term effects on adult neurocognitive functioning due to the heightened frontal cortical neuroplasticity associated with adolescent brain maturation. Our laboratory recently linked alcohol-induced neuroinflammation to neurodegeneration through the upregulation of high-mobility group box 1 (HMGB1) signaling to Toll-like receptors (TLRs). HMGB1/TLR 'danger signaling' induces multiple brain innate immune genes that could alter brain function. Interest in another danger signaling receptor, the receptor for advanced glycation end-products (RAGE), has begun given its role in neuroinflammation and cognitive dysfunction associated with Alzheimer's disease. Since adolescent binge

drinking is common in humans, the persistent effects of adolescent intermittent ethanol (AIE) exposure on danger signal expression was assessed in the prefrontal cortex of adolescent and adult rats. Furthermore, the effect of AIE on spatial and reversal learning was assessed on the Barnes maze in adult rats.

Methods: To determine whether adolescent binge drinking persistently increases innate immune gene expression in the prefrontal cortex, male Wistar rats were exposed to AIE (5.0 g/kg, i.g., 2-day on/2-day off) from postnatal day (P)25 to P55. On P56, HMGB1/TLR/RAGE danger signaling was assessed using immunohistochemistry. In a separate group of rats, spatial and reversal learning was assessed on the Barnes maze in early adulthood (P64 to P75). On P80, HMGB1/TLR/RAGE danger signaling was assessed using immunohistochemistry and RT-PCR in adulthood. In addition, expression of danger signals was measured in the orbitofrontal cortex from human alcoholic post-mortem samples, and was compared to reported age of drinking onset.

Results: Immunohistochemical assessment at P56 revealed increased frontal cortical expression of HMGB1, TLR4, TLR3, and RAGE in the AIE-treated rats. Adolescent intermittent ethanol treatment did not alter adult spatial learning on the Barnes maze, but did cause reversal learning deficits and increased perseverative behavior. Immunohistochemistry and/or RT-PCR revealed that adult rats exposed to AIE also had increased frontal cortical HMGB1, TLR4, TLR3, and RAGE expression in adulthood. Furthermore, we found persistently upregulated proinflammatory cytokines and oxidases in the frontal cortex of adult rats (P80) exposed to AIE. Long-term deficits on the reversal learning component of the Barnes maze was associated with elevated levels of danger signal receptor expression in the prefrontal cortex. In human alcoholics, we found significantly increased expression of HMGB1, TLR4, TLR3, TLR2, and RAGE expression in the post-mortem orbitofrontal cortex, which was correlated with age of drinking onset.

Conclusions: These findings provide evidence that adolescent binge drinking increases the expression of HMGB1/TLR/RAGE innate immune danger signaling in the adolescent prefrontal cortex that persists into adulthood. Furthermore, AIE leads to impaired behavioral flexibility as assessed on the reversal learning component of the Barnes maze, which was correlated with expression of danger signal receptors. Finally, we found that age of drinking onset in humans is predictive of HMGB1/TLR/RAGE innate immune danger signal expression in the post-mortem orbitofrontal cortex. Taken together, the human and animal data support the hypothesis that an earlier age of drinking onset sets the stage for enduring danger signaling in the prefrontal cortex.

Keywords: binge drinking, alcohol, innate immunity, age of drinking onset

Disclosure: R. Vetreno, Nothing to Disclose; L. Qin, Nothing to Disclose; F. Crews, Nothing to Disclose.

W37. Association of Anticipatory Connectivity in Insula with the Clinical Course of Major Depression: a Follow-up fMRI Study

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Background: Major depressive disorder (MDD) is common (i.e., 12 month prevalence rates are 5.3% and 13.2% for men and women respectively), recurrent (i.e., individuals with MDD experience a mean of 4.7 lifetime episodes), and disabling (i.e., it affects most areas of psychosocial functioning). While the neurosubstrates of MDD have been examined cross-sectionally, little is known about the mechanism of MDD symptom evolution over time. Studies that examined functional and structural correlates of the effects of pharmacological and non-pharmacological interventions in MDD provided vital information about potential neural biomarkers of treatment response in this disorder. Although extremely valuable these studies could not separate the brain effect of treatment from that of improvement, making it unclear whether treatment effects are due to improvement through naturalistic fluctuations or to therapeutic intervention. Naturalistic longitudinal observation provides a unique opportunity to examine brain changes over time that are not directly linked to a treatment course but are more related to waxing and waning of symptoms that is characteristic to this disorder. The purpose of this study was to use functional magnetic resonance imaging (fMRI) together with a validated thermal pain anticipation task at baseline and after naturalistic follow-up to investigate whether change in anticipatory brain activation related to changes in MDD symptoms severity over time.

Methods: Nineteen individuals (7F, 12M; age: 26.7 ± 7.6; education: 14.3 ± 1.5) performed experimental pain anticipation task during two fMRI sessions, once at baseline and a second time after approximately a year of naturalistic follow-up. Current and past DSM-IV Axis I disorders were determined using the structured clinical interview and current depressive symptom severity was assessed using the Beck Depression Inventory 2 (BDI-2). fMRI data were collected during an event-related pain anticipation paradigm, during which subjects were cued to anticipate painful stimuli of high or low intensity. All temperature stimuli were applied to each subject's left forearm using an MR-compatible thermode. All subjects perceived temperature stimuli as mildly (low pain intensity stimulus) or moderately (high pain intensity stimulus) painful.

Results: At the time of the initial testing all 19 subjects were experiencing Major Depressive Episode (MDE) with moderate to severe depressive symptoms (Mean ± SD BDI-2: 26.2 ± 8.4). Patients were naturalistically treated: five of them with antidepressant drugs, one with behavior therapy and thirteen patients had not received any treatment. At the follow-up evaluation 9 (4F, 5M) of 19 subjects showed significant clinical improvement (i.e., they had significant reduction in their baseline BDI-2 scores and they no longer met criteria for current MDD) (BDI-2 at follow-up: 5.6 ± 6.1) and 10 (3F, 7M) of 19 subjects did not show clinical improvement and still met criteria for current MDD at follow-up (BDI-2 at follow-up: 25.1 ± 8.5). At the time of the initial testing, subjects who improved did not differ significantly in their depressive symptom severity from those who did not improve and, in our sample, improvement in depressive symptoms severity had no relation to treatment history ($r = 0.03$; $p = 0.88$) or to the time of the follow-up ($r = 0.28$; $p = 0.25$).

At the time of the initial testing, all subjects showed increased activation within bilateral anterior insula (AI), anterior cingulate and several regions within parietal and temporal cortices during anticipation of high compared to anticipation of low painful heat stimulus. Furthermore, we found that the right AI (X/Y/Z: 40/14/9) was the only task-related region that showed significant time by BDI-2 scores relationship whereby those subjects who showed clinical improvement showed decreased activation within this region over time. In addition, over time, those subjects who showed clinical improvement showed increased functional connections between right AI and the fronto-parietal control network, namely bilateral dorsolateral prefrontal cortices (dlPFC) and left Inferior Parietal Lobule (IPL). Finally, the change in functional connection between right AI and left dlPFC and left IPL showed highly significant correlations with the change in BDI-2 scores over time in our subjects ($r's > 0.6$, $p' < 0.05$).

Conclusions: Our results show that naturalistic healing in MDD may be driven by both decreased "bottom-up" processing of negative information via decreased activation within the right anterior insula but also with increased "top-down" processing via increased functional connection between this region and the fronto-parietal control network. In addition, these results indicate that dysfunction in the interconnections between anterior insula and the fronto-parietal control network involved in emotion regulation is a neural biomarker of MDD. Furthermore, this work

supports and extends the uniqe role the anteiror insula plays in mood disorders and suggests that naturalistic follow-up imaging studies provide an opportunity to map out the neural networks of waxing and waning of symptoms in depression. If replicated in larger samples, these findings may have important implications for early intervention and treatment of individuals with MDD.

Keywords: pain, anticipation, insula, connectivity, longitudinal, fronto-parietal, imaging, fMRI, naturalistic

Disclosure: I. Strigo, **Part 4:** NIMH (MH8003), Veterans Administration Center of Excellence for Stress and Mental Health; E. Kosheleva, Nothing to Disclose; A. Simmons, **Part 4:** Veterans Administration (1I01CX000292), Veterans Administration Center of Excellence for Stress and Mental Health.

W38. Exercise Reduces Cocaine Abuse and Enhances Pharmacotherapy: Sex Differences

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Background: Cocaine seeking modeled by bingeing and relapse in rats has been resistant to pharmacological treatments, but recent data show promising results with the use of behavioral approaches, such as exercise, and treatment success is even greater when opportunity for exercise is combined with pharmacological interventions such as progesterone. Exercise has previously been shown in our lab and others to reduce maintenance, escalation, and reinstatement of cocaine-seeking behavior. Previous work in our lab has also indicated progesterone reduces cocaine intake under bingeing conditions and suppresses cocaine-primed reinstatement. The purpose of this research was to investigate the individual and combined effects of concurrent wheel running and progesterone pretreatment on cocaine-, stress (yohimbine)-, and cue-induced reinstatement of cocaine seeking in male and female rats using an animal model of human relapse. There have been very few studies of combined treatment effects for drug abuse, but initial results suggest that this is a powerful treatment combination, especially when using novel behavioral and pharmacological approaches.

Methods: All rats were briefly exposed to a running wheel (3 days) to establish running, and then different groups were trained to self-administer iv cocaine in an operant chamber that either had an adjoining running wheel that allowed the animal to run or an attached wheel that was locked and allowed entry but not running. After a maintenance period of 6-h sessions of access to cocaine (0.4 mg/kg) self-administration for 10 days, cocaine self-administration was subsequently extinguished by substituting saline for cocaine for 14 daily 6-h sessions. Separate groups had access to a running wheel or locked wheel during this extinction period to determine whether exercise during cocaine extinction would carry over to the reinstatement period and suppress cocaine seeking after priming conditions. During a subsequent 23-day reinstatement period, rats received priming conditions of cocaine (COC) injections (ip), stress (ip yohimbine - YOH), cues previously associated with cocaine infusions, cues + COC, or cues + YOH, interspersed with days when saline priming injections were given as a control condition. The treatment conditions given during the reinstatement phase were: wheel (W) access or locked wheel (LW) access, progesterone (P) or vehicle control (C) injections, or the combination, W + P. Thus, there were 4 treatment conditions LW + C, LW + P, W + C, and W + P. The P or C injections were given 30 min before the 6-h reinstatement sessions, and the priming dose for reinstatement was 10 mg/kg. It was hypothesized that W + P (Wheel access + Progesterone) would produce the greatest suppression of cocaine seeking during reinstatement.

Results: During the maintenance phase, females and males both escalated their cocaine intake over 10 days, and females self-administered significantly more than males. During the 10 days of extinction, wheel running attenuated extinction responding in females but not in males. During the reinstatement phase, wheel running and the combination of (W + P) produced maximal suppression of reinstatement in females. In males the wheel-running effect was less than in females, and P had little effect, but the W + P treatment produced greater suppression of cocaine seeking than W or P alone. In both males and females W and P reduced cue-primed reinstatement. The present results indicate that females had more reduction in cocaine seeking with wheel running than males during extinction and COC-primed reinstatement; however, there were no sex differences in reinstatement primed by YOH, cues, YOH + cues, or COC + cues. Cocaine-paired cues enhanced responding following both YOH and COC priming injections, and this enhancement was attenuated by W and P treatment, separately and in combination.

Conclusions: These results confirm previous findings that female rats showed greater cocaine intake, escalation of intake, and greater resistance to extinction than male rats. Also, access to a running wheel reduced extinction in female rats, and females showed more cocaine- and stress-induced reinstatement responding than male rats. The present results also indicate that combining the behavioral treatment (e.g., wheel running) with a pharmacological treatment (e.g., progesterone) was more effective than either treatment alone at preventing relapse to cocaine seeking under the most challenging priming conditions (COC, YOH, cues), and this combined effect was stronger in females than males. These results concurred with earlier findings that while females are more avid drug seekers than males, females also respond better to behavioral and pharmacological treatments to suppress cocaine seeking than males. However, the present results showed that combining wheel running and progesterone produced a dramatic reduction in cocaine-seeking behavior in both males and females. Further work with combined therapies is encouraged.

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Keywords: treatment, exercise, progesterone, cocaine abuse, combined treatments, relapse, sex differences

Disclosure: M. Carroll, Nothing to Disclose; N. Zlebnik, Nothing to Disclose; A. Saykao, Nothing to Disclose.

W39. *In Vivo* Binding of the Dopamine-1 Receptor PET Tracers [11C]NNC112 and [11C]SCH23390: A Comparison Study in Individuals with Schizophrenia

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Background: A deficit in dopamine-1 (D_1) receptor function in the prefrontal cortex (PFC) is suggested to play a role in the cognitive dysfunction observed in patients with schizophrenia. However, the results from positron emission tomography (PET) imaging studies of D_1 receptor levels in individuals with schizophrenia are mixed. The aim of this study is to determine whether the *in vivo* characteristics of the different D1 receptor tracers used in these studies, [^{11}C]SCH23390 and [^{11}C]NNC112, may contribute to these discrepancies reported in the literature.

Methods: Seven patients with schizophrenia and 11 healthy control subjects were scanned with both [^{11}C]SCH23390 and [^{11}C]NNC112. This sample was a subset of subjects included in previous PET studies using [11C]NNC112 in schizophrenia.

Results: We calculated the magnitude of [^{11}C]SCH23390 to [^{11}C]NNC112 binding between patients and control subjects and observed no difference in any region. To determine whether drug status might influence binding potential of [^{11}C]SCH23390 and [^{11}C]NNC112 in dorsolateral prefrontal cortex (DLPFC), we performed group-wise analyses in drug naïve (DN, n = 4) and drug free (DF, n = 3) patients separately. Binding potential was

greater in DN patients than in control subjects using both ligands. Although these results were not significant, likely due to limited sample sizes, the effect sizes were large ([^{11}C]SCH23390 = 1.05; [^{11}C]NNC112 = 0.99).

Conclusions: The results of this study suggest that differences in the binding of [^{11}C]SCH23390 and [^{11}C]NNC112 observed in previous studies are not due to differences in the *in vivo* behavior of these tracers.

Keywords: D1 receptor, dorsolateral prefrontal cortex, PET, schizophrenia, NNC112, SCH23390

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W40. Aripiprazole Once-monthly for the Treatment of Schizophrenia: a Double-blind, Randomized, Non-inferiority Study vs. Oral Aripiprazole

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Background: To evaluate the efficacy of aripiprazole once-monthly (ARI-OM) compared with oral aripiprazole for thetreatment of schizophrenia in a double-blind, randomized study.

Methods: Subjects with schizophrenia requiring chronic treatment with an antipsychotic were eligible. Subjects not receiving oral aripiprazole were cross-titrated to oral aripiprazole monotherapy during a 4–6-week oral conversion phase (Phase 1). All subjects then entered an 8–28-week stabilization phase (Phase 2) with 10–30 mg/day of oral aripiprazole. Patients already receiving oral aripiprazole entered the study in Phase 2. Subjects meeting stability criteria for 8 consecutive weeks were randomized (2:2:1) to a 38-week, double-blind maintenance phase (Phase 3) to receive either ARI-OM 400 mg (ARI-OM-400, option to decrease to 300 mg permitted), oral aripiprazole (10–30 mg/day), or ARI-OM 50 mg (ARI-OM-50; a sub-threshold therapeutic dose for assay sensitivity; option to decrease to 25 mg permitted). All subjects received concomitant oral aripiprazole for 2 weeks from the date of randomization. The primary endpoint was to assess the proportion of patients meeting criteria for exacerbation of psychotic symptoms/impending relapse by Week 26. The objective of the primary analysis was to demonstrate non-inferiority in the efficacy of ARI-OM-400 compared to oral aripiprazole. Safety and tolerability were also assessed.

Results: Seven hundred and nine patients were enrolled in Phase 1; 842 entered Phase 2, of which 133 had already received oral aripiprazole before entering the study. Six hundred and sixty two patients were randomized to double-blind treatment in Phase 3. The estimated relapse rates by Week 26 were 7.1% for ARI-OM-400 and 7.8% for oral aripiprazole based on Kaplan-Meier curve for time-to-relapse. The difference of estimated relapse rate by week 26 between ARI-OM-400 and oral aripiprazole was –0.6% at the 95% confidence interval ([CI]: –6.3, 4.0), which excluded the pre-defined non-inferiority margin of 11.5%. The estimated relapse rate by Week 26 for ARI-OM and oral aripiprazole were superior to ARI-OM-50 (21.8%; $p < 0.001$ from z-statistics). Time to impending relapse was also significantly delayed in ARI-OM-400 ($n = 265$) compared with ARI-OM-50 ($n = 131$; hazard ratio [HR] = 3.2, 95% CI: 1.8, 5.5; log-rank test $p < 0.0001$), but was similar between ARI-OM-400 and oral aripiprazole ($n = 266$; HR = 1.0, 95% CI: 0.6, 1.8; log-rank test $p = 0.99$). The most common treatment-emergent adverse events ($\geq 10\%$ in any group for ARI-OM-400, oral aripiprazole, and ARI-OM-50, respectively) were insomnia (11.7% vs. 13.9% vs. 13.7%), akathisia (10.6% vs. 6.8% vs. 8.4%), headache (9.8% vs. 11.3% vs. 5.3%), weight increase (9.1% vs. 13.2% vs. 5.3%), and back pain (3.8% vs. 5.3% vs. 11.5%). There was a statistically significant change in body weight from baseline to endpoint between ARI-OM-50 (–1.6 kg) and ARI-OM-400 (+0.1 kg; $p < 0.05$). Patients on oral aripiprazole gained +1.0 kg. There were no clinically relevant changes on objective measures of extrapyramidal symptoms.

Conclusions: ARI-OM-400 was non-inferior to oral aripiprazole, and significantly delayed time to exacerbation of psychotic symptoms/impending relapse compared with ARI-OM-50. These results expand on recent evidence supporting the efficacy and tolerability of ARI-OM for the treatment of schizophrenia. In a randomized, placebo-controlled study, the relapse rate for ARI-OM-400 was 10% vs. 40% with placebo (Kane et al., 2012), and the reported safety and tolerability for ARI-OM-400 was similar to existing evidence for oral aripiprazole. The investigational drug ARI-OM appears to provide a new treatment option for schizophrenia, with a different risk-benefit profile than currently approved agents.

Reference: Kane J. et al. J Clin Psych. 2012;73:317–624. Supported by Otsuka Pharmaceutical Development and Commercialization, Inc. and H. Lundbeck A/S.

Keywords: Long-acting injection, schizophrenia, efficacy, non-inferiority, aripiprazole

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W41. Inflammatory Genes Expression as Biomarkers for Personalised Treatment in Psychiatry

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Background: To improve the "personalized-medicine" approach to the treatment of psychiatric patients, we need to identify biomarkers that predict future response to treatment or that correlate to brain functions that are relevant to the pathogenesis of the disorders. Moreover, we need to understand the molecular mechanisms underlying the role of these biomarkers in the pathogenesis of mental disorders.

Methods: We present converging evidence from our Laboratory using both clinical samples (depressed patients from the European-based GENDEP study; patients with a first episode psychosis from the South London and Maudsley Hospital in London; and patients with chronic HCV infection taking interferon-alpha from King's College Hospital in London), as well as our *in vitro* human embryonic neuronal precursors model. In all these models, we have examined gene expression of inflammatory genes from blood mRNA (via PaxGene tubes) or from neuronal precursors mRNA and supernatant.
Results: In the GENDEP sample, non-responders to 8 weeks of treatment with escitalopram or nortriptyline had higher baseline mRNA levels of IL-1β, MIF and TNF-α. Using a linear regression model, the levels of these three genes predicted 46% of the variance in treatment response. Moreover, antidepressant treatment reduced levels of IL-1β and MIF in all patients, and of IL-6 in responders only. In patients with first-episode psychosis, m-RNA levels of IL-1α, IL-6 and TNF-α were all significantly higher compared with controls. Moreover, levels of IL-6 were significantly and negatively correlated with the size of the left hippocampus volume, measured using MRI ($r = -0.45$, $P = 0.04$). Using a linear regression model, the mRNA levels of BDNF and IL-6, together with diurnal cortisol levels, accounted for 71% of the variance in left hippocampal volume. In patients with chronic HCV infection, baseline mRNA levels of PLA2 were significantly higher in patients who subsequently developed IFN-α-induced depression; these same patients also had lower levels of the PUFA, DHA, which is a target of the PLA gene. Finally, in our human embryonic neuronal precursors model, we found that IL-1β reduced neurogenesis, and that the antidepressant, venlafaxine, as well as the PUFA, DHA, attenuated the levels of IL-6 induced by IL-1β.
Conclusions: Both in clinical and experimental models, inflammatory genes expression is linked to mechanism relevant to brain function and treatment response, and is regulated by psychotropic medications. We claim that measuring inflammatory biomarkers is both clinically and mechanistically relevant in psychiatry.
Keywords: antidepressant, depression, inflammation, neuroimmunology, cytokines, psychosis
Disclosure: A. Cattaneo, Nothing to Disclose; C. Anacker, Nothing to Disclose; N. Hepgul, Nothing to Disclose; M. Horowitz, Nothing to Disclose; V. Mondelli, Nothing to Disclose; K. Musaelyan, Nothing to Disclose; P. Zunszain, Nothing to Disclose; C. Pariante, **Part 1:** Dr. Pariante has received speakers fees from company interested in the development of antidepressants, such as Lilly and Servier, **Part 4:** Dr. Pariante is collaborating in a research project with Janssen, a pharmaceutical company interested in the development of antidepressants based on the inflammation theory of depression.

W42. "Nonlinear Techniques as an Approach to Understand Mood Regulation in Bipolar Disorder"

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Background: Mood regulation is a complex and poorly understood process. Most of the studies in mood disorders have focused on cross-sectional correlations, rather than longitudinal dynamics, having as a result a reduced understanding of the co-variation of anxiety and mood ratings over time. Moreover, and despite the apparently well-established features of mood dysregulation in mood disorders, there has been little phenomenological research comparing mood regulation in non-affected and affected subjects. Nonlinear techniques offer new tools with which to quantify, model, and attempt to predict the behavior of complex biological systems. Our goal for this study was to analyze mood regulation in healthy controls and bipolar disorder patients using nonlinear analyses.
Methods: Sixty participants were included in the study: in the first group, thirty healthy controls (15 women and 15 men), between 18-70 years were recruited. The absence of any current or past psychiatric history was corroborated by the Schedule for Affective Disorders and Schizophrenia, Lifetime version (SADS-L). Family history of major psychiatric disorders in any first-degree relatives was an exclusion criteria. In the second group, thirty subjects with diagnosis of bipolar I / II disorder (age- and sex-matched) according to DSM-IV criteria were included. Participants in this group were euthymic for at least three months, based on a score of £ 5 on the Young Mania Rating Scale and £7 on the Hamilton Depression Rating Scale. All participants rated their mood, anxiety, energy levels and sleep daily, twice a day, over a three month period, via a paper-based visual analog scale, which are particularly sensitive instruments for identifying changes in mood state over time. In order to obtain related information that could account for mood changes, we systematically recorded life events experiences through the Interview for Recent Life Events. We analyzed the data using nonlinear techniques: time series analysis and complexity measures. Several complexity measures exist, however, entropy measures are widely use in practical applications. Entropy is a measure of the amount of noise: it identifies the existence and degree of order and regularity in what otherwise may be viewed as random or disordered serial data. Larger values corresponding to greater apparent randomness (serial irregularity), and smaller values corresponding to more instances of recognizable features or patterns in the data. Because entropy-based measures grow with the degree of randomness, these measures may assign the highest values to uncorrelated random signals, which are highly unpredictable but not structuraly complex, and may be misleading. For this reason, the multiscale entropy measure, which does not assume any particular mechanism (i.e., deterministic or stochastic), was used in the study. Autoregressive models were used to explain the variation in the series. We controlled for seasonal effects by using frequency determined filter procedures. All analyses were performed using MATLAB.
Results: (1) Demographics: A total of 5400 data points were collected in each group. The HC group was younger (42.2 ± 12.3 years) and more educated (17.3 ± 2.7 years of education) than the BD group (44.7 ± 11.9 years; 15.4 ± 2.7 years of education), but these differences were not statistically significant ($p = 0.6$). In contrast, 88.3% of HC were employed, compared to 47.4% in the BD group ($p < 0.001$). Participants with bipolar disorder who did not complete the study ($n = 11$) were younger and less educated that those that completed it. These differences were not statistically significant. In terms of treatment, 73.3% were on combination treatment with mood stabilizers and antipsychotics/antidepressants; 26.7% were on lithium monotherapy. (2) Time-series analysis: HC showed low fluctuations (high variability) in their mood, anxiety, and energy levels. In particular, the autocorrelation analysis for mood showed a strong weekly periodicity in 70% of the sample. In contrast, BD patients showed less variability in their mood, anxiety and energy levels. There was a negative cross-correlation between anxiety and mood in both samples. The differences between morning and evening ratings were not statistically different ($D = 1.0$, $p > 0.05$) in any of the groups; however, BD patients showed higher anxiety levels in the evening. (3) Complexity measures: All different entropy levels were significantly higher in the HC group [mean ± SD]: (0.6 ± 0.3; 0.9 ± 0.4; 1.2 ± 0.5; 1.4 ± 0.6; 1.5 ± 0.6; 1.5 ± 0.6) compared to BD patients (0.3 ± 0.3; 0.5 ± 0.5; 0.7 ± 0.6; 0.9 ± 0.7; 1.0 ± 0.7; 1.1 ± 0.8) (all $p < 0.01$).
Conclusions: Mood fluctuates even in the absence of stimuli in healthy subjects, resulting in higher entropy levels. This is in keeping with the notion that greater regularity, as shown in the BD group, is associated with compromised physical status. Our results suggest that the mechanisms of mood regulation in HC and BD patients may be essentially different. This understanding is a prerequisite to the development of protocols for episode prediction.
Keywords: Bipolar disorder, mood regulation, nonlinear techniques

Disclosure: A. Ortiz, Nothing to Disclose; K. Bradler, Nothing to Disclose; J. Garnham, Nothing to Disclose; C. Slaney, Nothing to Disclose; M. Alda, Nothing to Disclose.

W43. A Re-Analysis Using a Population-Enrichment Strategy of a Double-Blind, Placebo-Controlled Study of Chromium Picolinate in Atypical Depression

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Background: Following the publication of a positive small pilot, placebo-controlled trial of chromium picolinate in patients with atypical depression, a double-blind, multicenter, 8-week study randomized 110 adult outpatients (mean age: 46 years, 69% female, 81% Caucasian) with atypical depression (with a 2:1 ratio) to receive 600 μg/day of elemental chromium, as provided by chromium picolinate (CrPic), or placebo. There was no significant difference between the CrPic and placebo groups in both the ITT and evaluable populations on the primary efficacy measures. A novel methodology, called band-pass filtering, based on the signal detection theory has been recently proposed for assessing the signal of antidepressant drugs' efficacy by controlling the excessively high/low level of placebo response. The primary objective of this re-analysis is to reassess the outcomes of the CrPic clinical trial using the band-pass filtering approach.
Methods: The total HAMD-21 and HAMD-29 observed case scores were analyzed using a linear mixed-effects modeling approach for repeated measures (MMRM) to detect differences in CrPic versus placebo. The analysis was performed on both the complete dataset (No band-pass) and on the dataset remaining after the application of the band-pass filter for noise control. The following criteria for the band-pass filter has been applied: HAMD-21 (Change from baseline at week 6: 11pts; Percentage change from baseline at week 6: $<10\%$ and $>45\%$) and HAMD-29 (Change from baseline at week 6: 20 pts; Percentage change from baseline at week 6: $<10\%$ and $>45\%$). The centers with a mean placebo response falling outside the cutoff boundaries were excluded from the analysis. In the MMRM analyses the random effect model was used on the change from baseline value, using unstructured covariance matrix, time as a classification variable, and baseline measurement as covariate, baseline $\times$ time interaction, and treatment $\times$ time interaction. A significance level of $\alpha = 0.05$ was used to establish the significance of treatment effect.
Results: The results of the analysis indicated that there is a substantial improvement in the treatment effect when the band-pass filter is applied. However, all the analyses conducted based on the application of the band-pass filter were unable to reach statistical significance. The responders' analysis results are shown in the Table 1. Responders have been defined by a drop = or $>$ 50% on the HAMD score at week 6 with respect to baseline.
Table 1

	HAMD-21		HAMD-29	
	Placebo	**CrPic**	**Placebo**	**CrPic**
No band-pass	47.4%	49.2%	52.6%	56.9%
Filter on change from baseline	42.3%	53.3%	42.3%	53.3%
Filter on % change from baseline	31.2%	48.0%	31.3%	48.0%

Conclusions: Contrary to the findings of the analyses conducted on the ITT sample, this band-pass filter analysis suggests that CrPic may actually have antidepressant effects in patients with atypical depression. However, the relatively small sample size prevented the analyses from achieving statistical significance. Our results warrant further studies of this compound.
Keywords: chromium picolinate, clinical trial, placebo, band-pass filter, depression
Disclosure: M. Fava, **Part 1:** Advisory/Consulting/ Lifetime, Abbott Laboratories; Affectis Pharmaceuticals AG; Alkermes, Inc.; Amarin Pharma Inc.; Aspect Medical Systems; AstraZeneca; Auspex Pharmaceuticals; Bayer AG; Best Practice Project Management, Inc.; BioMarin Pharmaceuticals, Inc.; Biovail Corporation; Brain Cells Inc; Bristol-Myers Squibb; CeNeRx BioPharma; Cephalon, Inc.; Clinical Trials Solutions, LLC; CNS Response, Inc.; Compellis Pharmaceuticals; Cypress Pharmaceutical, Inc.; DiagnoSearch Life Sciences (P) Ltd.; Dinippon Sumitomo Pharma Co. Inc.; Dov Pharmaceuticals, Inc.; Edgemont Pharmaceuticals, Inc.; Eisai Inc.; Eli Lilly and Company; EnVivo Pharmaceuticals, Inc.; ePharma-Solutions; EPIX Pharmaceuticals, Inc.; Euthymics Bioscience, Inc.; Fabre-Kramer Pharmaceuticals, Inc.; Forest Pharmaceuticals, Inc.; GenOmind, LLC; Glaxo Smith Kline; Grunenthal GmbH; i3 Innovus/Ingenis; Janssen Pharmaceutica; Jazz Pharmaceuticals, Inc.; Johnson & Johnson Pharmaceutical Research & Development, LLC; Knoll Pharmaceuticals Corp.; Labopharm Inc.; Lorex Pharmaceuticals; Lundbeck Inc.; MedAvante, Inc.; Merck & Co., Inc.; MSI Methylation Sciences, Inc.; Naurex, Inc.; Neuronetics, Inc.; NextWave Pharmaceuticals; Novartis AG; Nutrition 21; Orexigen Therapeutics, Inc.; Organon Pharmaceuticals; Otsuka Pharmaceuticals; PamLab, LLC.; Pfizer Inc.; PharmaStar; Pharmavite LLC.; PharmoRx Therapeutics; Precision Human Biolaboratory; Prexa Pharmaceuticals, Inc.; Puretech Ventures; PsychoGenics; Psylin Neurosciences, Inc.; Rexahn Pharmaceuticals, Inc.; Ridge Diagnostics, Inc.; Roche; RCT Logic, LLC; Sanofi-Aventis US LLC.; Sepracor Inc.; Servier Laboratories; Schering-Plough Corporation; Solvay Pharmaceuticals, Inc.; Somaxon Pharmaceuticals, Inc.; Somerset Pharmaceuticals, Inc.; Sunovion Pharmaceuticals; Supernus Pharmaceuticals, Inc.; Synthelabo; Takeda Pharmaceutical Company Limited; Tal Medical, Inc.; Tetragenex Pharmaceuticals, Inc.; TransForm Pharmaceuticals, Inc.; Transcept Pharmaceuticals, Inc.; Vanda Pharmaceuticals, Inc., Speaking/Publishing/Lifetime:, Adamed, Co; Advanced Meeting Partners; American Psychiatric Association; American Society of Clinical Psychopharmacology; AstraZeneca; Belvoir Media Group; Boehringer Ingelheim GmbH; Bristol-Myers Squibb; Cephalon, Inc.; CME Institute/Physicians Postgraduate Press, Inc.; Eli Lilly and Company; Forest Pharmaceuticals, Inc.; Glaxo Smith Kline; Imedex, LLC; MGH Psychiatry Academy/Primedia; MGH Psychiatry Academy/Reed Elsevier; Novartis AG; Organon Pharmaceuticals; Pfizer Inc.; Pharma Star; United BioSource, Corp.; Wyeth-Ayerst Laboratories, Equity Holdings: Compellis, Royalty/patent, other income, Patent for Sequential Parallel Comparison Design (SPCD) and patent application for a combination of azapirones and bupropion in Major Depressive Disorder (MDD); for research and licensing of SPCD with RCT Logic, Copyright for the MGH Cognitive & Physical Functioning Questionnaire (CPFQ), Sexual Functioning Inventory (SFI), Antidepressant Treatment Response Questionnaire (ATRQ), Discontinuation-Emergent Signs & Symptoms (DESS), and SAFER; Lippincott, Williams & Wilkins; Wolkers Kluwer; World Scientific Publishing Co. Pte. Ltd., **Part 2:** Belvoir Media Group for editing medical newsletter, **Part 4:** Research Support/Lifetime, Abbot Laboratories; Alkermes, Inc.;Aspect Medical Systems; AstraZeneca; BioResearch; BrainCells Inc.; Bristol-Myers Squibb; CeNeRx BioPharma; Cephalon; Clinical Trials Solutions, LLC; Clintara, LLC; Covance; Covidien; Eli Lilly and Company; ElMindA, Ltd.; EnVivo Pharmaceuticals, Inc.; Euthymics Bioscience, Inc.; Forest Pharmaceuticals, Inc.; Ganeden Biotech, Inc.; Glaxo Smith Kline;

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W44. Multi-site Validation of Touch Screen-based Translational Assays of Cognition and Their Pharmacological Sensitivity

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Background: Effective treatments for the cognitive symptoms of neurodegenerative and neuropsychiatric disorders are currently unavailable and the development of preclinical methods for the screening of putative cognition enhancers remains challenging. A particular focus in recent years has been on touch screen technology for rodents. This technology is a computer-automated behavioral testing method that provides objective assessment and can easily be translated to other species, including humans. In collaboration with partners from the Innovative Medicines Initiative (IMI), a European coordinated public and private partnership between the European Commission and the European Federation of Pharmaceutical Industries and Associations (EFPIA), we aim to identify the most relevant and effective tasks and experimental manipulations in touch screen-based animal models and to implement measures that will increase confidence in the translatability of our preclinical measures of cognition.
Methods: For this aim, seven independent sites in Europe (Lilly, Lundbeck, Orion, Roche, and Janssen) and the US (Abbott and Pfizer) agreed to conduct an across-site study in which a common protocol for the Visual Discrimination (VD) task was run using animals of the same strains, gender and age. Testing equipment, animal suppliers and general husbandry parameters were allowed to vary between sites. Adult male Lister Hooded rats were maintained via food restriction at approximately 85% of body weight. Operant chambers were equipped with a touch-sensitive screen fronted by a mask with two windows (10×10 cm), providing two response areas for displaying stimuli. The plane/spider stimuli used (5.5×5.5 cm) had previously been shown to be equally salient. The daily VD acquisition sessions was comprised of 60 trials or 45 minutes, with trial initiation required. The inter-trial interval was 20 seconds, and an incorrect response initiated a 5 second timeout, with correction trials used until the acquisition criteria was met (regression curve indicating $<5\%$ change in maximum % correct from previous day and an SE of maximum % correct <5). Animals then began the testing phase, which was identical to the acquisition phase without correction trials. The effect of compounds known to influence cognition, including the NMDA antagonists phencyclidine (0.25, 0.5, 1 and 2 mg/kg) and ketamine (1, 2.5, 5 and 10 mg/kg), the indirect dopamine agonist amphetamine (0.25, 0.5, 1 and 2 mg/kg) and the muscarinic antagonist scopolamine (0.01, 0.025, 0.05 and 0.1 mg/kg) were tested. The experimenter was blinded to the drug treatment, and a crossover design was used (5 groups, vehicle + 4 doses for each drug). All drugs were administered s.c., with a pretreatment time of -30 min and 0.9% saline as vehicle. Brain and plasma samples were taken to confirm appropriate drug exposure.
Results: All cohorts were completing all 60 trials and had acquired the task with a % correct response of $>$ 85% upon reaching the standardised acquisition criteria. A differential effect of the pharmacological classes on animal performance was observed. The potential similarity/divergence between the 7 research centres is currently under investigation.
Conclusions: This collaborative effort represents a unique opportunity to validate and standardize assays within and between laboratories and will ultimately increase our confidence in the value of preclinical cognitive assay testing.
Keywords: Animal model, Touch screen, Cognition, NMDA antagonists, Scoplamine, Amphetamine
Disclosure: R. Kozak, **Part 1:** I am an employee at Pfizer Inc., **Part 2:** I am an employee at Pfizer Inc., **Part 3:** I am an employee at Pfizer Inc., **Part 4:** I am an employee at Pfizer Inc.; L. Mulryan, **Part 1:** I am an employee at Eli Lilly & Co., **Part 2:** I am an employee at Eli Lilly & Co., **Part 3:** I am an employee at Eli Lilly & Co., **Part 4:** I am an employee at Eli Lilly & Co.; B. Eastwood, **Part 1:** I am an employee at Eli Lilly & Co., **Part 2:** I am an employee at Eli Lilly & Co., **Part 3:** I am an employee at Eli Lilly & Co., **Part 4:** I am an employee at Eli Lilly & Co.; D. Chapin, **Part 1:** I am an employee at Pfizer Inc., **Part 2:** I am an employee at Pfizer Inc., **Part 3:** I am an employee at Pfizer Inc., **Part 4:** I am an employee at Pfizer Inc.; T. Ballard, **Part 1:** I am an employee at F. Hoffmann-La Roche Ltd., **Part 2:** I am an employee at F. Hoffmann-La Roche Ltd., **Part 3:** I am an employee at F. Hoffmann-La Roche Ltd., **Part 4:** I am an employee at F. Hoffmann-La Roche Ltd.; G. Gilmour, **Part 1:** I am an employee at Eli Lilly & Co., **Part 2:** I am an employee at Eli Lilly & Co., **Part 3:** I am an employee at Eli Lilly & Co., **Part 4:** I am an employee at Eli Lilly & Co.; F. Gastambide, **Part 1:** I am an employee at Eli Lilly & Co., **Part 2:** I am an employee at Eli Lilly & Co., **Part 3:** I am an employee at Eli Lilly & Co., **Part 4:** I am an employee at Eli Lilly & Co.; S. Dix, **Part 1:** I am an employee at Eli Lilly & Co., **Part 2:** I am an employee at Eli Lilly & Co., **Part 3:** I am an employee at Eli Lilly & Co., **Part 4:** I am an employee at Eli Lilly & Co.; S. Janhunen, **Part 1:** I am an employee at Orion Corp., **Part 2:** I am an employee at Orion Corp., **Part 3:** I am an employee at Orion Corp., **Part 4:** I am an employee at Orion Corp.; N. Plath, **Part 1:** I am an employee at H. Lundbeck A/S., **Part 2:** I am an employee at H. Lundbeck A/S., **Part 3:** I am an employee at H. Lundbeck A/S., **Part 4:** I am an employee at H. Lundbeck A/S. Talpos, **Part 1:** I am an employee at Janssen Research & Development., **Part 2:** I am an employee at Janssen Research & Development., **Part 3:** I am an employee at Janssen Research & Development., **Part 4:** I am an employee at Janssen Research & Development; L. Fellini, **Part 1:** I am an employee at Janssen Research & Development., **Part 2:** I am an employee at Janssen Research & Development., **Part 3:** I am an employee at Janssen Research & Development., **Part 4:** I am an employee at Janssen Research & Development.; L. Lerdrup, **Part 1:** I am an employee at H. Lundbeck A/S., **Part 2:** I am an employee at

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W45. Targeting Cortical Oscillations with Non-invasive Brain Stimulation in Computer Simulations and Humans

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Background: Psychiatric disorders such as schizophrenia are network disorders, in which aberrant temporal patterning of the electrical signaling in cortex mediates symptoms. Interventions at the network level by non-invasive transcranial current stimulation may provide an effective treatment modality. Direct current stimulation (tDCs) has been shown to globally enhance or suppress neural activity. Transcranial alternating current stimulation (tACs) may more specifically modulate cortical network activity by directly targeting its temporal structure. Yet, little is known about the interaction between externally applied, weak stimulation waveforms and endogenous cortical oscillations. Here, we bring together computer simulations and safety and feasibility data in healthy human subjects to elucidate the mechanism of tACs.

Methods: Simulated networks consisted of two 2D layers of pyramidal cells (160,000 PYs) and inhibitory interneurons (40,000 INs). Model neurons exhibited physiologically plausible dynamics and were coupled with conductance-based synapses. PYs provided recurrent excitation to each other through local connections and also excited INs through random global connections. INs provided feedback inhibition to the PYs through global random connections. Transcranial current stimulation was modeled with a small current injection into all PYs. Sixteen healthy subjects (ages 18-26) participated in three sessions of tACs (sham stimulation, 0.75 Hz, 40 Hz). Stimulation with peak to peak amplitude of 750 μA was delivered via two electrodes (NeuroConn Ltd) placed anterior and posterior on the right hemisphere. Each session consisted of five periods of 5 minutes stimulation, separated by one minute of whole-head EEG recording. During stimulation and EEG recording, subjects were seated comfortably in a recliner and asked to watch a relaxing movie. EEG data was re-referenced to averaged A1 and A2 for subsequent processing using EEGLAB and custom written scripts in Matlab. EEG data were divided into one second epochs, and those with activity exceeding +/-75 μV were excluded. To analyze alpha (8-12 Hz) and gamma (25-50) frequencies, ICA components accounting for muscle activity were regressed out. Spectra were computed using the Morlet wavelet transform. Statistical significance was assessed with the Wilcoxon rank sum test.

Results: We found that sine-wave stimulation was more effective at enhancing spontaneous rhythmic activity in our computer simulations (total power in 0.5-10 Hz for tDCs: 3.05 vs. tACs: 6.93, a.u.; smaller increase in overall firing rate for tDCs: 20 Hz vs. tACs: 22 Hz). Matching the stimulation frequency to the intrinsic frequency caused the largest stimulation effect due to resonance (oscillation power at stimulation frequency: matched tACs at 3 Hz: 3.97 versus mismatched tACs at 4 Hz: 0.82 a.u.). In agreement with occurrence of resonance, stimulation at twice the intrinsic frequency (harmonic frequency) had an almost equally pronounced effect (tACs at 6 Hz: 3.94). tACs further increased the number of spontaneous initiation sites of spatially localized activity that then spread through the network and enhanced overall synchrony (number of initiation sites, tDCs: 2.42 vs. tACs: 3.51). Together, these results illustrate the importance of matching stimulation waveforms to the temporal structure of ongoing cortical network activity. Furthermore, tACs appears to be a more effective stimulation modality than tDCs. To translate these findings, we performed a safety and feasibility study with healthy human subjects to probe the EEG-level response to tACs. We found that the sham condition was successful at blinding the subject with regards to presence of 0.75 Hz tACs but not for 40 Hz (for sham: 10/16 indicated receiving stimulation, $p = 0.31$; for 0.75 Hz: 7/16, $p = 0.61$; for 40 Hz: 15/16, $p < 0.001$). In addition, tACs at 40 Hz induced phosphenes reported by 11/16 subjects. All stimulation sessions were well tolerated with no significant differences in side-effect scores between sham, 0.75 Hz, and 40 Hz tACs. We analyzed changes in alpha (8-12 Hz) and gamma (25-50 Hz) frequency range since the relationship between these two frequency bands has emerged as a promising marker of overall physiological/pathological brain state. We found significant changes in the alpha band of cortical activity measured by scalp EEG. In baseline before stimulation, the alpha power was not significantly different between the left and right occipital electrodes (ratio: 0.95, s.e.m. 0.0442, $p > 0.05$, $N = 16$). However, in response to unilateral stimulation of the right hemisphere with 40 Hz tACs, we found a significant shift in power to the unstimulated occipital region in the alpha band (ratio: 1.08, s.e.m. 0.038, $p = 0.0295$, $N = 16$). To exclude non-specific effects, we repeated the same analysis for the sham condition and found no significant asymmetry (ratio: 0.99, s.e.m. 0.041, $p = 0.98$, $N = 16$). These results suggest that 40 Hz tACs causes lateralization in the occipital alpha band but not in the frontal region ($p > 0.05$). At the stimulation electrodes, 40 Hz tACs enhanced gamma activity relative to sham but failed to reach significance ($p > 0.05$).

Conclusions: We show that computational simulations are a powerful tool to predict the network-wide effects of different non-invasive brain stimulation paradigms and to elucidate the underlying mechanisms. The safety and feasibility study in humans indicates that the application of tACs is safe and may modulate network activity and exhibit cross-frequency interaction. Larger trials will be necessary to fully understand how tACs affects different brain areas and activity signatures. Our results support tACs as a promising future neurotherapeutic for network disorders such as schizophrenia. Support from the University of North Carolina Chapel Hill, the Foundation of Hope, and the National Center for Research Resources (UL1RR025747, NCTraCS # 550KR11111) is gratefully acknowledged. We thank the UNC Scientific Computing group and the Clinical Neurophysiology Laboratory at UNC for support and resources.

Keywords: brain stimulation, tDCs, tACs, cortex, computer simulations, computational neuroscience, EEG

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W46. Mapping Brain Metabolic Connectivity in Awake Rats with MicroPET and Optogenetic Stimulation

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Background: Optogenetics allows researchers to map neuronal circuit function in the rodent brain *in vivo* (Zhang et al., 2010; Lee and Deisseroth, 2012). The combined use of optogenetics and functional magnetic resonance imaging (fMRI) has been used to investigate functional connectivity in the rodent brain (Lee et al., 2010; Lee 2012; Lee and Deisseroth, 2012); however, these are limited by the use of anesthesia, which affects neuronal activity (Qiu et al., 2008; Tsurugizawa et al., 2010). Positron emission tomography (PET) using [^{18}F] 2-fluoro-2-deoxy-D-glucose (FDG), however, allows researchers to non-invasively measure regional brain glucose metabolism (BGluM), a marker of brain activity, in the awake rodent. The present study used mPET with FDG to measure optogenetic stimulation (OGS) of the nucleus accumbens (NAc). We tested the hypothesis that excitation of the NAc by OGS would increase metabolism in the NAc and in its downstream projection regions. In parallel, we mapped c-Fos expression to corroborate regional activation by OGS.
Methods: Male Sprague Dawley rats (8-10 weeks) were anesthetized and Adeno-associated virus serotype 2 (AAV2)-hsyn-ChR2-EYFP ($n = 8$/group) or AAV2-GFP control virus ($n = 9$/group) was infused into the right NAc core (AP +1.7, ML +1.5, DV -6.5 from bregma) through a 20 gauge cannula. Rats recovered for a minimum of two weeks while waiting for optimal AAV expression. The experiment was conducted in accordance with the Guide for the Care and Use of Laboratory Animals (1996) and approved by the BNL Institutional Animal Care and Use Committee (IACUC). Each rat was scanned twice using FDG-mPET, one week apart (counterbalanced design): once at baseline (optical fiber attached but no stimulation applied) and once following OGS. Rats were placed in a small plexiglass cage to restrict movement and minimize activation from motor behavior. Blue (473 nm) light stimulation, pulsed at 10 Hz, was applied through the optical fiber at 30 second intervals for five minutes (light turned off for the baseline scan). Rats were injected intraperitoneally with ~0.5 mCi of FDG (30 minute awake uptake), during which time blue light stimulation was continued, and locomotor activity was measured. After the uptake period, rats were anesthetized and scanned on an R4 mPET tomograph for 30 minutes. Statistical Parametric Mapping (SPM) analysis was performed using paired t-tests for each group (GFP and ChR2) comparing regional brain glucose metabolism between the baseline and the stimulation scans [threshold: $p < 0.005$, $K_e > 100$, $T > 5.7$]. A region of interest (ROI) was manually drawn in the NAc cluster that was significantly activated in the ChR2 group, and activity was measured for the baseline and stimulation condition for the GFP and ChR2 rats. Rats (GFP: $n = 4$; ChR2: $n = 6$) were again stimulated with blue light for ten minutes, and 90 minutes later, rats were anesthetized, perfused, and brain harvested to assess c-Fos immunofluorescence in the NAc.
Results: Brain metabolic differences between baseline and OGS stimulation of the NAc were determined both for activation (stimulation > baseline) and inhibition (stimulation < baseline). OGS in the ChR2 group resulted in five activated and two inhibited clusters. Activation was seen in the NAc, dorsal hippocampus and stria terminalis; secondary somatosensory cortex and caudate/putamen; globus pallidus, ventral pallidum, and amygdala; and periaqueductal gray. Inhibition was seen in the retrosplenial cortex, anterior cingulate gyrus and secondary motor cortex. The ROI analysis determined that the NAc of each rat in the ChR2 group was activated between the baseline and stimulation scans. Only ChR2 rats showed a significant increase (16% ±3) in BGluM in NAc ROI from baseline to stimulation scans ($p < 0.01$; group-intervention [$F(1,15) = 9.332$, $p < 0.01$]). Locomotor measures determined only a significant main effect of time [$F(4,56) = 5.188$, $p = 0.001$]; as expected, rats were more active during the habituation sessions compared to the mPET sessions. Analysis of c-Fos expression in the NAc following OGS found that c-Fos expression was greater in ChR2 rats compared to GFP rats [$F(1,8) = 20.392$; $p < 0.01$], and changes in brain glucose metabolism in the NAc (baseline vs. stimulation) and c-Fos expression were significantly correlated ($R = 0.77$, $p < 0.01$).
Conclusions: OGS of the NAc increased c-Fos expression and BGluM in the region of stimulation, and these measures were correlated. This is consistent with fMRI results reporting BOLD increases in the area of stimulation (Lee and Deisseroth, 2012). We also observed increased metabolism in regions connected to the NAc including the basal ganglia (caudate, putamen, globus pallidus, and ventral pallidum) and limbic regions (amygdala, hippocampus). Interestingly, we showed decreased metabolic activity in the restrosplenial cortex (posterior cingulate gyrus) and anterior cingulate gyrus, which are regions that form part of the default mode network (DMN), which in conjunction with brain imaging findings in humans (Tomasi et al., 2009; Dang et al., 2012), suggests that activation of the NAc may facilitate DMN inhibition. These results demonstrate the feasibility of using mPET with FDG in conjunction with OGS to map connectivity in the awake rat brain.
Keywords: FDG, dopamine, nucleus accumbens, default mode network
Disclosure: P. Thanos, Nothing to Disclose; L. Robison, Nothing to Disclose; E. Nestler, Nothing to Disclose; R. Kim, Nothing to Disclose; M. Michaelides, Nothing to Disclose; M. Lobo, Nothing to Disclose; N. Volkow, Nothing to Disclose.

W47. A Brief Monetary Progressive Ratio Task Predicts Clinical Amotivation and Ventral Striatum Activation in Schizophrenia

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Background: Motivational deficits play a central role in disability due to negative symptoms of schizophrenia, which constitute a major unmet therapeutic need in psychiatry. Despite this importance, amotivation in schizophrenia has been understudied and its pathophysiology remains largely unknown. Negative symptoms of schizophrenia have previously been linked to hypofunction in ventral striatum (VS), a crucial component of the mesolimbic dopamine motivation circuitry. However, further work is needed to determine whether specific negative symptoms such as amotivation drive this relationship. This effort can be facilitated by new interview-based assessments like the Clinical Assessment Interview for Negative Symptoms (CAINS), which distinguishes amotivation from related negative symptoms such as anhedonia and asociality by emphasizing both subjective experience and objective behaviors. In addition, improved reliability, validity and translatability to animal models will require applying neurobehavioral measures of amotivation in the laboratory. Here we report initial validation of a brief, computerized progressive ratio task (PRT) that quantifies effort exerted in pursuit of monetary reward. We show that motivation assessed dimensionally with this PRT predicts both clinical amotivation on the CAINS and VS fMRI responses to monetary reward.
Methods: 41 patients with schizophrenia (SCH, stable/medicated) and 37 group-matched controls (CTR) performed a brief

computerized PRT to earn money. The PRT required repetition of easy but attention-requiring trials (choosing which of 2 numbers was larger). Within each of three runs, an increasing number of repetitions were required to obtain the monetary reward. Across the three runs, the amount of reward progressively decreased (50 cents, 25 cents, 10 cents). A run ended when the subject chose not to attempt or complete the required number of repetitions. This "breakpoint" was used to quantify motivation, and was defined here as the ratio of effort (maximum number of performed trials) to monetary value, averaged across runs. Prior to the PRT, subjects performed BOLD fMRI at 3T including a monetary guessing paradigm that robustly activates VS. VS activation measures (win > lose) were extracted and correlated with PRT breakpoints. Psychopathology was evaluated with self-report and interview scales; the CAINS provided the primary measure of clinical amotivation.

Results: Total PRT duration averaged 16 min (+/-14), without group differences. PRT breakpoints ranged widely in both groups, from ~0.1 trials per cent (tpc) up to ~10 tpc. As expected, average PRT motivation was reduced in patients [SCH 2.3 tpc (+/-2.8), CTR 4.3 tpc (+/-3.7), 1-tail $p = 0.03$]. In SCH, the predicted inverse correlation of PRT with CAINS amotivation was significant ($r = -0.40$, 1-tail $p = 0.005$). The same relationship was found in CTR ($r = -0.29$, 1-tail $p = 0.04$). When the relationship of PRT breakpoint to both diagnosis and CAINS amotivation were tested in a multiple regression, the effect of CAINS was significant (2 tail $p = 0.002$) but not diagnosis ($p = 0.75$), indicating that the group difference in PRT was attributable to individual differences in motivation as assessed with the CAINS, rather than to a simple categorical effect of diagnosis. Correlations between PRT and other negative symptom domains were also negative, but less robust. Potential confounds including socioeconomic status, cognition, reaction time, smoking, depression, and positive symptoms did not explain the relationship between PRT breakpoint and CAINS amotivation. In SCH, lower PRT motivation also predicted reduced VS activation to monetary reward ($r = 0.36$, 2-tail $p = 0.03$).

Conclusions: We report one of the first applications of PRT in schizophrenia, and provide initial evidence of its construct validity in relationship to clinical motivation and an fMRI measure of motivation circuit function. It is striking that a brief laboratory measure of motivation shows even these moderate correlations with a clinical measure that is inevitably impacted by various life circumstances operative outside, but not necessarily inside, the laboratory. The brief computerized PRT described here has advantages over clinical measures of motivation, including translatability to non-human models, greater objectivity, and potentially greater specificity. The observed correlation with VS activation supports further use of the PRT in studies aiming to identify neural circuit, molecular-genetic, and psychiatric symptom correlates of motivation, and for assessing and predicting response to novel therapeutic interventions.

Keywords: schizophrenia, motivation, negative symptoms, fMRI, ventral striatum

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W48. The Relationship between Early Life Stress and Brain Volume in Treatment-seeking Alcoholics

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Background: Early life stress (ELS) is one of the most robust predictors of alcohol use disorders in adulthood, but the mechanisms underlying this association are unclear. ELS has been associated with reduction in brain structures such as hippocampus. Reductions in brain volume are also found in individuals with alcohol dependence, most commonly in the overall gray and white matter. Despite the association between ELS and alcohol dependence, and that both factors affect brain volume, there is very little research that explores the influence of ELS on brain volume in individuals with alcohol dependence. Thus, the goal of this study is to examine the impact of ELS on brain volume in a sample of treatment-seeking alcoholics.

Methods: Participants included 245 alcoholics undergoing inpatient treatment at the National Institutes of Health (NIH) Clinical Center in Bethesda, MD. Individuals were all diagnosed with alcohol dependence according to the Structured Clinical Interview for DSM-IV (SCID) and stayed at NIH for approximately four weeks. They ranged in age from 19 to 62 years ($M = 40.40$, $SD = 10.01$); 64.5% were male and 60.4% were Caucasian. Exposure to early life stress was assessed using the Childhood Trauma Questionnaire (CTQ), a 28-item self-report measure that yields a score for overall trauma severity (CTQTotal), total number of traumatic events experienced (CTQNumeric), and severity scores for five subtypes of trauma: physical abuse, sexual abuse, emotional abuse, physical neglect, and emotional neglect. Alcohol dependence severity was assessed using the Alcohol Dependence Scale. During the fourth week of their stay, participants underwent structural magnetic resonance imaging (MRI) scans on a 3T General Electric MRI scanner and a standard head coil. Whole-brain high-resolution coronal structural scans were collected using a T1-weighted magnetization-prepared rapid gradient echo (MPRAGE) pulse sequence with matrix $256 \times 256 \times 124$, repetition time (TR) = 100 ms, echo time (TE) = 12 ms, field of view (FOV) = 24 cm, and voxel size of $(0.9375 \times 0.9375 \times 2.0)$ mm^3. Structural data was analyzed with FSL-FIRST, an integrated registration and segmentation software. Volume measurements were obtained using an FSL Utility, which obtained the number of voxels in each subcortical mask for individual subjects. The subcortical regions of interest included: right and left accumbens, amygdala, caudate, hippocampus, pallidum, putamen, and thalamus. Linear regression models were used to explore the relationships between CTQ measures and brain volume.

Results: We first tested whether ELS predicted total brain volume, intracranial volume (ICV), and brain shrinkage (brain volume/intracranial volume). There was a trend for significance of physical abuse severity score predicting lower ICV, $b = -0.094$, $p = 0.09$, after controlling for age and gender. In the same model, gender significantly predicted ICV, $b = 0.508$, $p = 0.000$ (men had larger ICV than women), and there was a trend for age predicting ICV, $b = -0.092$, $p = 0.09$. CTQTotal, CTQNumeric, and the other trauma subtypes did not significantly predict total brain volume, ICV, or brain shrinkage. We then tested the effect of CTQTotal and CTQNumeric on the various subcortical regions of interest, controlling for total brain volume, age, gender, and alcohol dependence severity. There was a trend for significance of CTQTotal score predicting lower left amygdala volume, $b = -0.11$, $p = 0.07$. CTQTotal did not significantly predict any other subcortical regions. CTQNumeric significantly predicted lower right thalamus volume, $b = -0.073$, $p = 0.05$, and there was a trend for prediction of lower left thalamus volume, $b = -0.064$, $p = 0.10$. We next tested the effect of specific trauma subtypes on the subcortical structures. Physical neglect severity score significantly predicted lower right thalamus volume, $b = -0.077$, $p = 0.03$, and there was a trend for physical neglect prediction of lower left thalamus volume, $b = -0.061$, $p = 0.10$ and lower left pallidum volume, $b = -0.095$, $p = 0.07$. There were also trends for sexual abuse severity score predicting higher left amygdala volume, $b = 0.112$, $p = 0.06$; emotional abuse severity score predicting higher left accumbens, $b = 0.101$, $p = 0.10$, and higher right amygdala volume, $b = 0.117$, $p = 0.06$; and emotional neglect predicting higher left amygdala volume, $b = 0.097$, $p = 0.08$, and higher left caudate volume, $b = 0.096$, $p = 0.09$.

Conclusions: These results comprise the first analysis of the effects of early life stress on brain volume among alcohol dependent individuals. Greater childhood trauma (number of traumatic events, physical neglect severity) was associated with smaller thalamus volume, while sexual and emotional abuse showed trends for association with larger amygdalar and accumbens volumes. Given the robust links between ELS and risk for alcohol dependence, these findings may elucidate the mechanisms underlying this association. Our findings suggest that certain brain regions associated with reward function and emotional processing may be affected by exposure to ELS. Moreover, these changes in structure may be linked to changes in function. Further studies with larger samples are needed to replicate and extend these findings.

Keywords: alcohol dependence, brain volume, early life stress

Disclosure: L. Kwako, Nothing to Disclose; M. Schwandt, Nothing to Disclose; V. Brown, Nothing to Disclose; E. Grodin, Nothing to Disclose; M. Heilig, Nothing to Disclose; D. Hommer, Nothing to Disclose; V. Ramchandani, Nothing to Disclose.

W49. Chronic Naltrexone Modulates Marijuana's Reinforcing, Subjective and Cardiovascular Effects

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Background: Acute pretreatment with the opioid receptor antagonist, naltrexone (NTX: 12, 25, 50, 100 mg), increases the intoxicating effects of marijuana in daily marijuana smokers (Cooper and Haney, 2010). Given that chronic antagonist administration can produce different effects on drug intoxication than acute antagonist administration (e.g., Huestis et al., 2001; Haney and Spealman, 2008), this placebo-controlled, human laboratory study assessed the effects of active and inactive marijuana before, during and after chronic NTX administration.

Methods: Non-treatment-seeking, healthy marijuana smokers were randomized to receive NTX (50 mg) or placebo (0 mg) for 16 consecutive days. Each participant completed 10 laboratory sessions over 3-4 weeks: before NTX administration, after a single NTX administration, after 1 and 2 weeks of daily NTX administration, and 1 week after termination of NTX administration. At each timepoint, the reinforcing, subjective, psychomotor, and cardiovascular effects of active (5.5% THC) and inactive (0.0%) marijuana were assessed. Medication compliance was ensured by: observed capsule administration $\geqslant$ 4 times/week, plasma naltrexone measurement, and urine riboflavin levels. Marijuana's reinforcing effects were measured by offering participants the choice to pay $1.00 for individual puffs of marijuana (0-3 puffs/session) using their study earnings or to receive this money upon study conclusion.

Results: Fifty-one participants, receiving either placebo (n = 26M; 2F) or NTX (n = 18M; 5F), completed the study. Demographic variables were comparable across the two groups, with participants reporting to smoke an average of 6 marijuana cigarettes/day, 6 days/week. The number of participants who failed to complete the study, primarily due to unreliability, was also comparable across the 2 groups (placebo: n = 8; NTX: n = 9). In terms of outcome, relative to baseline (pre-NTX), NTX administration for 1 and 2 weeks significantly reduced marijuana self-administration and ratings of marijuana craving ($p < 0.05$). NTX also significantly decreased ratings of marijuana's 'Good Effect' and 'Liking' and heart rate at the 2-week timepoint ($p < 0.05$). Self-reported marijuana use outside of the laboratory, assessed using timeline followback procedures, was significantly increased in the second week of NTX administration ($p < 0.05$). By contrast, participants receiving placebo capsules showed no change in marijuana self-administration, subjective-effects ratings, heart rate, or marijuana use in the natural ecology over the 2-week course of capsule administration compared to baseline. One week after termination of capsule administration, participants in the NTX group persisted in self-administering less active marijuana, and had lower ratings of marijuana craving, liking, and good drug effect compared to baseline, whereas heart rate and outpatient marijuana use returned to baseline levels. In the placebo group, participants self-administered less marijuana one week after capsule termination compared to baseline.

Conclusions: These results show that chronic but not acute naltrexone administration decreased active marijuana's reinforcing, subjective and cardiovascular effects relative to pretreatment. These nontreatment-seeking marijuana smokers also reported increased marijuana use in the natural ecology, suggesting that they experienced less effect from marijuana and therefore smoked more to overcome this attenuation (in the laboratory, only 3 puffs of marijuana were available for self-administration, which may not have been enough to overcome the attenuated effect). These data suggest that clinical studies among patients motivated to reduce their marijuana use are warranted to determine if NTX may have use for the treatment of marijuana dependence, in a manner similar to NTX's use for alcohol dependence.

Keywords: cannabis, antagonist, opioid

Disclosure: M. Haney, Nothing to Disclose; G. Bedi, Nothing to Disclose; Z. Cooper, Nothing to Disclose.

W50. Increased Hippocampal Glutamate Correlates with Hippocampal Volumetric Deficits in Unmedicated Patients with Schizophrenia

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Background: Many studies have shown structural and functional changes in the hippocampus in schizophrenia. Interestingly, the hippocampus is thought to be more dependent on glutamate signaling than other neocortical structures; alterations in glutamatergic neurotransmission have been postulated to be a key pathophysiologic mechanism in schizophrenia.

Methods: We conducted a combined Voxel-Based-Morphometry (VBM) and Magnetic Resonance Spectroscopy (MRS) study to evaluate neurometabolite alterations and volumetric deficits in 27 unmedicated patients with schizophrenia (SZ) and 27 matched healthy controls (HC). All imaging was performed on a 3T head-only scanner (Magnetom Allegra, Siemens Medical Solutions, Erlangen, Germany), equipped with a circularly polarized transmit/receive head coil. A high-resolution structural scan was acquired for anatomic reference using the three-dimensional T1-weighted MPRAGE sequence (TR/TE/inversion time [TI] = 2300/3.93/1100 msec, flip angle = 12°, 256 × 256 matrix, 1-mm isotropic voxels). To examine hippocampal volumetric changes we performed VBM using the DARTEL algorithm. Data were processed using SPM8 implemented in MATLAB. Each subject's T1-MPRAGE image was segmented into grey matter, white matter, cerebrospinal fluid (CSF), skull, and scalp using the New Segment routine. The flow fields created by the DARTEL routine were used to generate both native space and spatially normalized, modulated, resliced (1.5 mm isotropic voxels), and smoothed (6 mm FWHM) grey and white matter images. MRS data were collected from a voxel in the hippocampus (2.7 × 1.5 × 1 cm). A series of sagittal, coronal, and axial T1-weighted anatomical scans (gradient-recalled echo sequence, TR/TE = 250/3.48 ms, flip angle = 70°, 5 mm slice thickness, 1.5 mm gap, 512 × 512 matrix) were acquired for voxel placement. Following manual shimming, water-suppressed spectra were acquired using the point-resolved spectroscopy sequence (PRESS; TR/TE = 2000/80 ms; 1200 Hz spectral bandwidth; 1024 points; number of averages = 640 (21 min 20 s). 1H-MRS data were analyzed in jMRUI. Spectra were quantified in the time domain

using the AMARES algorithm. N-acetyl-aspartate (NAA), and combined glutamate + glutamine (Glx) were quantified with respect to creatine (Cr). Differences in metabolite ratios were investigated with multivariate analyses of covariance using metabolites as within-group factors, disease state as between-group factor, and age and smoking (packs per day) as covariates. Statistical parametric maps of grey matter from SZ were compared to HC using an independent sample t-test in SPM. To evaluate correlations between hippocampal volume and neurometabolites, we performed separate regression analyses, corrected for age, smoking, and total intracranial volume in each group. VBM analyses were corrected for multiple comparisons.

Results: We found a significant hippocampal volumetric deficit located in the dentate gyrus extending posterolaterally to the Ammon's horn and the parahippocampal gyrus (Maximum intensity peak: $t = 4.47$, pFWE-corrected $= 0.025$, $kE = 46$, MNI coordinates: $x = -18$, $y = -30$, $z = -9$) and significantly increased hippocampal Glx/Cr (HC: 0.60 + /0.08; SZ: 0.66 + /−0.11; $F = 4.491$, $p = 0.04$) ratios in patients with schizophrenia compared to healthy controls. We also demonstrated significant correlations between hippocampal volume and Glx/Cr in patients with schizophrenia; two significant clusters were identified. The first maximum intensity peak was located in the dentate gyrus ($t = 4.81$, pFWE-corrected $= 0.021$, $kE = 110$, MNI coordinates: $x = -26$, $y = -32$, $z = -4$), the second maximum intensity peak was located in the Ammon's horn ($t = 4.96$, pFWE-corrected $= 0.041$, $kE = 110$, MNI Coordinates: $x = -36$, $y = -15$, $z = -16$).

Conclusions: To our knowledge, we are the first to report increased Glx/Cr and a link between hippocampal glutamate abnormalities and hippocampal volumetric deficits in unmedicated patients with schizophrenia, suggesting that glutamatergic excitotoxicity may cause hippocampal volumetric deficits. Our findings support the theory that altered hippocampal glutamatergic neurotransmission potentially accounts for structural deficits in the hippocampus observed in neuroimaging studies.

Keywords: schizophrenia, structural-MRI, Voxel Based Morphometry, Proton Magnetic Resonance Spectroscopy (1H-MRS)

Disclosure: N. Kraguljac, Nothing to Disclose; D. White, Nothing to Disclose; M. Reid, Nothing to Disclose; J. den Hollander, Nothing to Disclose; A. Lahti, Nothing to Disclose.

W51. Altered Cortical Activation During Episodic Memory Encoding and Recognition in First-Episode Psychosis

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Background: Cognitive impairments are a hallmark of schizophrenia. Elucidating the cerebral circuits that underlie these impairments is important to understanding the pathophysiology of this illness. Episodic memory has been shown to be impaired in schizophrenia. However, the neuroanatomical substrates responsible for dysfunction of the key components of episodic memory, encoding and recognition, are not well understood. Patients in their first episode of psychosis (FEP) are a desirable population in which to study cognitive impairment because the potential confounds of illness chronicity and prolonged antipsychotic drug exposure are limited. Using a visual episodic memory paradigm, we examined cerebral activation with fMRI in FEP and matched healthy controls.

Methods: The FEP subjects ($n = 19$, mean age 21.16 years, 15 male, mean months since first treatment 12.55, mean parental SES 2.95 - according to Hollingshead-Redlich criteria) were recruited through the Prevention and Recovery Center for Early Psychosis. The control group ($n = 11$, mean age 23.64 years, 8 male, mean parental SES 3.27) was comprised of healthy subjects who were free of major psychiatric disorders as determined by a structured diagnostic interview and matched for age, gender, and parental SES. Imaging studies were conducted on a Siemens 3T Tim Trio scanner while performing episodic memory tasks consisting of blocked visual scene encoding and recognition tasks. During the blocked-design encoding, trial subjects attempted to encode complex scenes for later recognition testing. The control condition consisted of repetition of a single degraded version of one of the encoding stimuli. During the event-related recognition trial, subjects view target scenes intermixed with foils, and are asked to decide which were presented during the encoding trial. The functional BOLD time-series underwent standard preprocessing (including motion correction, smoothing with a 6-mm FWHM Gaussian kernel and registration to a standardized Talairach brain) and was temporally filtered to include only signals between 0.01-0.1 hz. Whole brain activation analyses were conducted using SPM8. Comparison of activation differences within- and between-groups (FEP vs. control) were conducted on a voxel-by-voxel basis throughout the entire brain, using an overall p_{crit} of 0.01. FEP subjects and controls were administered the Brief Assessment of Cognition in Schizophrenia (BACS) which was used in analyses to examine the relationship between cognition and activation pattern. The BACS includes six cognitive domains (executive function, verbal fluency, attention, verbal memory, working memory and motor speed) comprised of seven tasks (verbal memory, digit sequencing, token motor, symbol coding, semantic fluency, letter fluency, and the Tower of London).

Results: *Encoding:* During the scene encoding task, both controls and FEP subjects showed bilateral activation in task-related circuitry, including visual cortex, fusiform gyrus, and medial temporal lobe (MTL) regions. Main effects for each group included bilateral MTL activation for controls, while FEP subjects demonstrated left but not right hemisphere MTL activation. Between-group comparisons revealed greater activation in controls than FEP subjects in bilateral sensory motor cortex and bilateral MTL, specifically hippocampus. There were no significant correlations with BACS tasks and regional activation during encoding tasks. *Recognition:* During detection of novel scenes (new > old contrast), both controls and FEP subjects showed hippocampal activation. Main effects for each group included bilateral hippocampal activation for controls, while FEP subjects had left but not right hippocampal activation. Between-group comparisons reflected greater activation in controls than FEP subjects during recognition of familiar scenes (old > new contrast) in bilateral prefrontal and retrosplenial cortices. In FEP subjects, digit sequencing correlated with activation in the retrosplenial cortex ($r = -0.55$, $p = 0.02$), left prefrontal cortex ($r = -0.53$, $p = 0.02$), and right prefrontal cortex ($r = -0.56$, $p = 0.01$). Right prefrontal activation was associated with processing speed on verbal fluency ($r = -0.55$, $p = 0.01$) and symbol coding ($r = -0.56$, $p = 0.01$). Left prefrontal activation was associated with processing speed on symbol coding ($r = -0.53$, $p = 0.02$). Retrosplenial cortex activation was associated with processing speed on verbal fluency ($r = -0.46$, $p = 0.05$).

Conclusions: These results suggest altered episodic encoding and recognition memory circuitry involving frontal and temporal regions in first-episode psychosis. Cognitive performance was related to activation of these cortical circuits. These findings add to a growing body of research implicating episodic memory circuitry in the pathophysiology of schizophrenia.

Keywords: First episode psychosis, episodic memory, cognition, fMRI

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W52. Transitive Inference in Relatives of Schizophrenia Patients

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Background: Relatives of schizophrenia subjects vary from controls in similar ways to schizophrenia subjects in symptomatology, genes and brain volume changes (McDonald et al., 2004; Lawrie et al., 2001). Deficits in relational memory also described as transitive inference (TI) have been reported in previous studies assessing memory impairment in schizophrenia (Ougur et al., 2006; Chin et al., 2005; Titone et al., 2004; Hutton et al., 2002). TI is the ability to infer relationships between indirectly related items that have not been previously presented together (Heckers et al., 2004; Ongur et al., 2005). The general network of brain areas previously identified to be associated with TI includes bilateral parietal cortex, prefrontal cortex, pre-supplementary motor area and the hippocampus (Heckers et al., 2004). In this study, we assessed TI in relatives of schizophrenia patients and compared them against healthy controls. We hypothesized that relatives will have impaired TI with regards to accuracy and response time compared to controls, especially for more complicated tasks.
Methods: Sample: A total of 74 relatively younger subjects comprised of 48 schizophrenia relatives (or 64.9%) and 26 healthy control subjects (35.1%) were evaluated using the Structural Clinical Interview for DSM Disorders (SCID) (Spitzer et al., 1990). Informed consent was obtained. Experimental details: This followed the paradigm earlier described (Heckers et al., 2004). Participants were trained to get $\geqslant$ 80.0% accuracy to identify 13 non-overlapping patterns (P & S) and 5 overlapping patterns (IP & IS). Training: In the beginning, participants were unaware of the ordered relationships for the 5 overlapping patterns and were informed that they would see pattern pairs and that behind one pair there would be a 'smiling face' ( ). Their task was to pick and recall the correct pattern hiding the smiling face. Participants indicated their answer by a button press in a response pad and received immediate feedback about their responses (if the participant guessed correctly, the selected pattern moves to uncover the smiling face and when the participants guess was wrong, the selected pattern moves but there would be no smiling face). Each condition comprised 144 training trials divided into 3 blocks: 60, 60 and 24 trials (Titone et al., 2004). Experiment: 160 trials of previously seen pairs ('P' and 'S') and novel pairs ('IP' and 'IS'). There were 16 blocks of 10 trials presented in a fixed order: P, IP, S, IS, P, IP, S, IS, P, IP, S, IS, P, IP, S and IS that took approximately 30 minutes to complete. Unlike the training trials, participants did not see the smiling face reinforcement during these 160 trials. The accuracy and response latency was calculated and analyzed by block and group (relatives versus controls). We further contrasted novel pairs that differ based on the number of items with an ambiguous prior reinforcement: zero (IP pairs), one (IS pairs except BD) or two ambiguous items (BD pairs).
Results: Almost 42.0% of relatives were first degree relatives (i.e. parent or sibling of a schizophrenia patient) while the rest were second degree relatives (i.e. cousin, uncle, aunt or grandparent with schizophrenia). Participant ages ranged from 13 years to 25 years, with the mean age being 19.7 years (standard deviation = 2.9 years). There were 38 male subjects (50.7%) and 37 female subjects (49.3%). The RT for schizophrenia relatives was shorter for all blocks except the novel overlapping pairs (IS) that had significantly longer duration with 11847.5 milliseconds for relatives versus 11190.1 milliseconds for controls $F(1,73) = 6.81$, $p = 01$. For accuracy, the controls performed better in all blocks, however, only the more complicated blocks overlapping pattern fills IP $F(1,71) = 6.00$, $p = 0.02$ & IS $F(1,71) = 12.02$, $p < 0.001$ reached statistical significance. Overall, RT for BD trials were longer than non-BD trials (12857.9 msec vs 9630.5 msec), while non-BD trials had better accuracy than BD trials (93.7% vs 79.3%). Relatives had longer RT and poorer accuracy for BD trials than controls 13134.0 milliseconds vs 12411.7 milliseconds and 74.5% vs 88.5% respectively with the relatives showing wider within group variation between BD and non-BD pairs. The two groups varied in accuracy $F(1,71) = 6.32$, $p < 0.0142$ for novel BD pairs.
Conclusions: These findings note better accuracy for TI in healthy controls versus accuracy in relatives of schizophrenia patients, and are comparable to previous findings assessing TI in schizophrenia patients (Ougur et al., 2006; Titone et al., 2004). Also similar to previous results in schizophrenia patients, schizophrenia relatives had significantly poorer accuracy and RT for the more complex overlapping pairs (IP & IS) as well as BD trials (Ougur et al., 2006; Titone et al., 2004). These findings support our *a priori* hypothesis and will further support the psychopathological features that may contribute to cognitive predictors of schizophrenia.
Keywords: SSchizophrenia relatives, Transitive inference, accuracy, response time, overlapping, non-overlapping
Disclosure: O. Onwuameze, Nothing to Disclose; B. Ho, Nothing to Disclose.

W53. Regionally Specific Theta, Alpha, and Gamma Resting State Abnormalities in Schizophrenia

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Background: fMRI studies indicate an overactive resting state network in patients with schizophrenia (SZ) (Fehr et al., 2003). To better understand resting state abnormalities in SZ, MEG localized resting state oscillatory activity in SZ and healthy controls (HC). Based on previous studies (see reviews in Siekmeier & Stufflebeam, 2010; Gandal et al., 2012), it was hypothesized that resting state low and high frequency abnormalities would be observed, with low frequency theta abnormalities most prominent in temporal regions and high frequency gamma abnormalities observed in multiple brain regions.
Methods: Twenty-one medicated patients with SZ (22-61 yrs) and 24 HC (21-58 yrs) participated. Six minutes of eyes–closed whole-head MEG data were collected. Frequency-domain VESTAL analyses (Huang et al., 2006) provided 3D maps of brain activity. Between-group t-tests examined 3D maps for delta, theta, alpha, beta, and gamma.
Results: Groups did not differ in delta or beta activity. Greater theta activity in right superior temporal gyrus (STG) and in right lateral occipital cortex (LOC) was observed in SZ than HC. Greater alpha activity in SZ than HC was observed in right STG, left parahippocampal gyrus, right superior frontal gyrus, left temporal pole, and right LOC. Greater gamma activity in SZ than HC was observed in left temporal pole, left LOC, and right middle frontal gyrus. Greater alpha activity in HC than SZ was observed in right frontal areas.
Conclusions: Greater gamma activity in SZ than HC was observed in multiple brain regions, a finding consistent with the hypothesis of greater baseline brain 'noise' activity in SZ (Gandal et al., 2012). However, findings here and in other studies showing increased baseline activity at lower frequencies suggest that baseline 'noise' abnormalities in SZ are not specific to gamma. Brain areas showing low and high frequency abnormalities in SZ did not completely overlap. This may indicate that there are distinct neural networks abnormalities in different brain regions in SZ.
Keywords: Schizophrenia, MEG, resting-state, alpha, theta, gamma
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W54. Association between the Change in Electrodermal Activity after Acute Tryptophan Depletion and Mood, Aggression and Venturesomeness in Young People with Attention Deficit Hyperactivity Disorder

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Background: The neurotransmitter serotonin (5-HT) has been shown to play an important role in the underlying neuobiological processes of aggressive behavior, with evidence coming from animal and human studies. However, few studies have been conducted in young people. The current pilot study was set out to investigate the influence of acute tryptophan depletion (ATD) on physiological arousal in young people with attention deficit hyperactivity disorder (ADHD), a population at risk for aggressive behavior. Here we aimed to explore if ATD, a physiological neurodietary method of decreasing central nervous 5-HT synthesis in humans, would result in changed physiological arousal in young people subjected to a task designed to elicit aggressive behavior when compared to a tryptophan (TRP) balanced control amino acid mixture (BAL).

Methods: ATD Moja-De is a physiological method of decreasing plasma levels of TRP, the physiological precursor amino acid (AA) of 5-HT. The administration of an AA beverage lacking TRP leads to a temporary decrease in 5-HT synthesis in the human brain as relevant AAs use the same L-1 transport system to overcome the blood brain barrier (BBB). Competitive antagonism of the AAs at L-1 leads to decreased substrate availability for tryptophan-hydroxylase 2 (TPH-2), the rate-limiting enzyme for central nervous 5-HT synthesis. As a consequence of decreased substrate availability for TPH-2 central nervous 5-HT synthesis is diminished. The Moja-De ATD protocol differs from classic ATD mixtures previously used in neuropsychiatric and pharmacological research. It involves a body weight-adapted dosing regime of relevant amino acids and also involves modified AA quantities. ATD Moja-De was proven to have acceptable tolerability while other AA mixtures previously used in ATD research were associated with side effects such as vomiting and nausea, thus allowing the use of ATD Moja-De in young people. The study design for this pilot study was a double-blind within-subject repeated measures crossover design. Participants were 9 to 15 year old boys ($n = 10$) and girls ($n = 10$) with a confirmed diagnosis of ADHD. Pregnancy tests (in female subjects) and drug screening tests were obtained in advance of each study day. The amino acid mixtures (ATD/BAL) were administered after an overnight protein fast on two separate study days. Reactive aggression was provoked using a point-subtraction aggression game (PSAG) 2.5 hours (time point marking a significant decrease in TRP influx across the BBB) after administration of ATD or the BAL control condition (AA mixture with TRP) on two separate study days. Externalizing behavior was assessed using the Child Behavior Checklist (CBCL). Impulsivity, venturesomeness and empathy were assessed using the IVE questionnaire (adapted German version of the Eysenck impulsivity questionnaire for young people). Mood states after administration of ATD/BAL were assessed using the ASTS mood questionnaire repeatedly during and after administration of the PSAG. While participating in the PSAG subjects' electrodermal activity (EDA) was recorded, serving as a biophysiological marker of sympathetic activity and physiological arousal. Numbers and extent of skin conductance responses (SCR) were evaluated.

Results: Significant positive correlations between the mean EDA difference from ATD to BAL (Δ $EDA_{ATD-BAL}$) and positive mood states were observed in both male and female participants. Δ $EDA_{ATD-BAL}$ was negatively correlated with anger and venturesomeness in both males and females, and with aggression in males. No significant differences in SCR were observed during the PSAG when comparing the ATD and the BAL condition.

Conclusions: The preliminary findings of the present investigation are somewhat in line with previous research indicating a potential link between amygdala activation and central nervous serotonin function. The correlation between Δ $EDA_{ATD-BAL}$ and positive mood could be seen as indicative for increased amygdala activity, in particular as previous research supports an association between increased amygdala activity and physiological arousal as indexed by SCR. As opposed to positive mood states, anger was negatively correlated with Δ $EDA_{ATD-BAL}$ as was aggressiveness. The latter findings might be interpreted in the contextual framework of the low arousal theory, suggesting that subjects with reduced physiological arousal tend to show elevated externalizing behavior. Because of the limited sample size the present findings must be considered preliminary and should be replicated in future large scale studies.

Keywords: serotonin, ADHD, aggression, acute tryptophan depletion, electrodermal activity

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W55. Longer-term Efficacy and Safety of Olanzapine and Fluoxetine Combination Versus Fluoxetine Monotherapy Following Successful Combination Therapy of Treatment-resistant Depression

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Background: Although 2nd generation antipsychotics are increasingly used as adjunctive therapies for treatment resistant depression (TRD), their longer-term (LT) efficacy and safety have not been well studied. The primary objective of this study was to evaluate LT efficacy and safety of olanzapine and fluoxetine combination (OFC) in TRD patients acutely treated and stabilized on OFC, measured by time to relapse (TTR) during 27 weeks of double-blind, randomized treatment with OFC or fluoxetine monotherapy (FL).

Methods: The multicenter, randomized, double-blind, active (FL)-controlled, parallel-group study assessed efficacy and safety of OFC in prevention of relapse in patients with TRD. Patients were 18-65 years with major depressive disorder (MDD) who failed to satisfactorily respond to at least 2 separate and different antidepressant treatments at adequate dose and duration (^{3}6 weeks) within the current MDD episode. The 47-week, 4-phase study included: screening (I); 6-8-week open-label (OL) acute treatment (II); 12-week OL stabilization (III); and 27-week double-blind relapse-prevention treatment (IV). Patients responsive to OL

OFC in acute treatment continued to stabilization phase. The 444 patients remaining stable were randomized 1:1 to either OFC (221) or FL (223) in phase IV. During phases II-IV, patients received 6 possible doses of OFC (3 mg olanzapine/25 mg FL/day introductory dose only, 6/25, 12/25, 6/50, 12/50, and 18/50); during phase IV, patients received either 25 or 50 mg FL-only fixed doses. Investigators and patients were blinded to precise duration of stabilization period, entry criteria for relapse-prevention phase and remission definition.

Primary efficacy outcome, TTR after randomization, was defined (primary definition) as meeting any of the following: a 50% increase in Montgomery-Åsberg Depression Rating Scale (MADRS) score with concomitant Clinical Global Impression-Severity of Depression (GCI-S) score increase to $\geqslant 4$; hospitalization for depression or suicidality; discontinuation for lack of efficacy or worsening. Response (acute phase) was defined as $\geqslant 50\%$ improvement from baseline on MADRS and CGI-S score of $\leqslant 3$. Patients were considered stabilized when maintaining $\geqslant 50\%$ from visit 2 on MADRS and $\geqslant 3$ CGI-S at stabilization-phase visits (up to 3 exclusions from criteria allowed, if did not occur at consecutive visits or visit prior to randomization). Remission = MADRS total score of $\leqslant 8$.

Results: Using the primary relapse criteria definition, TTR was significantly different in OFC group vs. FL group, in favor of OFC ($p < .001$). Using scale-based or discontinuation-based definitions, patients treated with OFC experienced significantly greater improvement than FL ($p < .001$, $p = .004$, respectively). There was no significant difference in patients treated with OFC and FL in TTR, using hospital-based definition. Rates of relapse and remission were statistically different between OFC and FL groups in favor of OFC ($p < .001$, $p = .047$, respectively). Statistically significant mean weight gain was seen as early as treatment week 1 in OFC group (OL phase), and 55.7% of patients treated with OFC experienced clinically significant weight gain (>7%). OFC treatment-emergent mean weight gain and categorical metabolic changes (glucose, lipids) were significantly higher than FL. A numerically, but not statistically different, frequency of discontinuations due to adverse events (AEs) was seen between OFC (8.6%) and FL (4.5%) ($p = .087$). No significant differences were seen between OFC and FL in extrapyramidal symptoms, serious AEs, frequency and nature of treatment-emergent AEs (with exception of depression and anxiety which were higher in FL group), or treatment-emergent mania.

Conclusions: OFC treatment compared to FL resulted in greater reductions in relapse in TRD patients who acutely responded and were later stabilized with OFC for at least 18 weeks. After 18-20 weeks, patients who continued with FL alone vs. OFC treatment for 27 weeks showed significant differences (favoring FL) in weight and metabolic parameters. The OFC safety profile was consistent with previous adult safety profiles. To our knowledge, this is the first adequately controlled relapse-prevention study in TRD that supports continued use of a 2nd generation antipsychotic beyond acute and stabilization phase, and provides substantial benefit/risk analyses, in LT treatment of patients with TRD.

Keywords: Olanzapine/fluoxetine, efficacy, safety, treatment-resistant depression

Disclosure: M. Tohen, **Part 1:** Formerly employed by Eli Lilly and Company (to 2008); spouse is a current employee and minor stockholder at Eli Lilly., **Part 3:** Have received honoraria or consulted for AstraZeneca, BristolMyersSquibb, Glaxo-SmithKline, Forest, Eli Lilly and Company, Johnson & Johnson, Merck, Otsuka, Sepracor, Sunovion, Lundbeck, and Wyeth.; E. Brunner, **Part 1:** Full-time employee and minor shareholder of Eli Lilly and Company. ; O. Osuntokun, **Part 1:** Full-time employee and minor shareholder of Eli Lilly and Company. ; J. Landry, **Part 1:** Full-time employee of Eli Lilly and Company. ; R. Schroer, **Part 1:** Full-time employee of Eli Lilly and Company. ; M. Thase, **Part 1:** Acted as advisor/consultant for: Alkermes; AstraZeneca; Bristol-Myers Squibb Company; Eli Lilly and Company; Dey Pharma; L.P.; Forest Laboratories; Gerson Lehman Group; GlaxoSmithKline; Guidepoint Global; H. Lundbeck A/S; MedAvante, Inc.; Merck and Co. Inc. (formerly Schering Plough and Organon); Neuronetics, Inc.; Novartis; Otsuka; Ortho-McNeil Pharmaceuticals (Johnson & Johnson); Pamlab, L.L.C.; Pfizer (formerly Wyeth Ayerst Pharmaceuticals); PGx Health, Inc; Shire US Inc.; Supernus Pharmaceuticals; Takeda; and Transcept Pharmaceuticals., **Part 3:** Served on Speakers Bureau for: AstraZeneca: Bristol-Myers Squibb Company; Dey Pharmaceutical; Eli Lillyand Company; Merck and Co. Inc.; and Pfizer (formerly Wyeth Ayerst Pharmaceuticals)., **Part 4:** Received grant support from Agency for Healthcare Research and Quality; Eli Lillyand Company; Forest Pharmaceuticals; Glaxo-SmithKline; National Institute of Mental Health; Otsuka Pharmaceuticals; and Sepracor, Inc.

W56. Uridine Reduces Symptoms in Adolescent Bipolar Depression: a Phosphorus-31 Magnetic Resonance Spectroscopy Study

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Background: Adolescent bipolar disorder is a significant public health concern. The neurobiology of pediatric BD is poorly understood, and novel treatments are urgently needed. Uridine is a pyrimidine previously studied as a treatment for bipolar depression in adults. Human and animal studies have shown that uridine administration impacts phospholipid synthesis in the brain. In addition to beneficial effects on cerebral phospholipid metabolism, pyrimidines improve catecholamine synthesis and mitochondrial function, all of which have been implicated in the pathophysiology of bipolar disorder (3). To investigate the neurochemistry of adolescent bipolar depression, the authors performed phosphorus-31 magnetic resonance spectroscopy (^{31}P-MRS) brain scans at baseline, and after 6 weeks of treatment with uridine, in depressed adolescents with bipolar disorder. A group of healthy control adolescents were scanned for comparison.

Methods: Adolescents who met the following inclusion criteria were recruited: 13-18 years of age with bipolar disorder type I, II or NOS as determined by the K-SADS-PL, a current depressive episode lasting $\geqslant$ 2 weeks, and a CDRS-R score > 40. Participants received open treatment with fixed-dose uridine 500 mg twice daily for six weeks. We used *in vivo* ^{31}P-MRS at 3 Tesla to measure pre- and post-treatment neurometabolites relevant to mitochondrial function in the frontal lobe. A group of matched healthy adolescent volunteers was recruited and underwent identical ^{31}P-MRS scans.

Results: 24 adolescents with bipolar depression and 24 healthy controls were enrolled. Baseline ^{31}P-MRS scans were obtained on ($n = 14$) bipolar adolescents, and post-treatment scans following 6 weeks of uridine were acquired on ($n = 12$) of these participants. At baseline, adolescents with bipolar depression showed alterations in phosphocreatine (PCr; $p = 0.03$) and inorganic phosphate (Pi; $p = 0.01$) levels compared with healthy adolescents. Post-hoc Tukey-Kramer analysis showed that unmedicated bipolar participants had decreased Pi compared with both healthy controls (17%; $p = 0.03$), and medicated bipolar adolescents (22%; $p = 0.02$). Treatment with uridine for 6 weeks was associated with an average decrease in CDRS-R score from 57.58 ± 13.05 to 32.83 ± 9.99 ($p = 0.0001$; Cohen's d effect size = 2.22). Uridine was well tolerated and participants experienced no SAEs, suicide attempts or hospitalizations.

Conclusions: Our results support the view that bioenergetic metabolism in the frontal lobe is altered in adolescents with bipolar depression, and may have implications for the use of Pi as

a biomarker. Placebo controlled studies of uridine as a treatment for depressed adolescents with bipolar disorder are warranted.
Keywords: adolescent bipolar depression neuroimaging spectroscopy
Disclosure: D. Kondo, Nothing to Disclose; X. Shi, Nothing to Disclose; Y. Sung, Nothing to Disclose; T. Hellem, Nothing to Disclose; R. Huber, Nothing to Disclose; B. Nickerson, Nothing to Disclose; L. Forrest, Nothing to Disclose; P. Renshaw, **Part 1:** Dr. Renshaw serves as a consultant to Kyowa Hakko. He has received research support from Roche and Bristol-Myers Squibb. He is an inventor on a patent application that describes the use of uridine as a treatment for bipolar disorder. This patent application is assigned to McLean Hospital and is licensed to the Repligen Corporation. The University of Utah manages conflicts of interest related to intellectual property. As part of this management, Dr. Renshaw did not evaluate any of the study participants at any point in time.

W57. A Randomized Trial Administering Aspirin, Minocycline or Pramipexole vs Placebo as add-on to Antipsychotics in Patients with Schizophrenia or schizoaffecive disorder

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Background: This is a randomized placebo controlled trial (RCT) testing the inflammatory hypothesis and elaborating on the dopamine hypothesis in schizophrenia. Aspirin, an inhibitor of both COX-1 and COX-2, and minocycline a tetracycline with anti-inflammatory effects (both of which showed in smaller trials some benefit in schizophrenia) were selected to test the anti-inflammatory hypothesis. Pramipexole, a pre-synaptic dopamine auto-receptor agonist, was chosen to elaborate on the dopamine hypothesis.
Methods: This multi-center, N = 400 trial was designed with one placebo arm to be employed as a comparator for 3 active arms. Inclusion criteria were 4 (moderate) or above on CGI-S and ³4 (moderate) score on two of the following four PANSS items: delusions, hallucinatory behaviors, conceptual disorganization or suspiciousness/ persecution, and/or a total PANSS negative symptoms score above 18. Before entering the trial and throughout the trial all subjects received anti-psychotics at doses within PORT recommendations. Upon entering the trial they were randomized to aspirin 1000 mg/d + pantoprazole 40 mg/d, minocycline 200 mg/d, pramipexole 1.5 mg, or placebo. Duration of the study was 16 weeks. Primary outcome measure was changes in total PANSS scores, secondary outcome measures included PANSS subscales and CGI.
Results: Mean age of patients was 42, 50% were females, mean duration of illness was 13 years, mean PANSS total score at baseline was 92, mean CGI at baseline was 4.7. The ANOVA for overall change for all comparison of 3 drugs and placebo for the primary outcome of the total PANSS scores was significant, p = 0.0343. Individual comparisons between each drug and placebo showed trends for significance (Effect size, ES = 0.26, p = 0.0561) for aspirin, and were non-significant for minocycline (ES = -0.14, p = 0.328) and for pramipexole (ES = 0.01, p = 0.952) For positive symptoms the overall ANOVA was not significant, p = 0.0842. Individual comparisons between each drug and placebo showed a trend for significance for aspirin (ES = 0.24, p = 0.079), and were non-significant for minocycline (Es = 0.04, p = 0.771) and pramipexole (ES = -0.11, p = 0.451). For negative symptoms the overall ANOVA was not significant, p = 0.0995, as were individual comparisons between each drug and placebo: aspirin (ES = 0.07, p = 0.586), minocycline (ES = -0.93, p = 0.095) and pramipexole (ES = 0.06, p = 0.451). For general psychopathology the overall ANOVA was significant, p = 0.0214. Individual comparisons between each drug and placebo were significant for aspirin (ES = 0.31, p = 0.040), non-significant for minocycline (ES = -0.16, p = 0.307) and pramipexole (ES = 0.05, p = 0.717). For CGI the overall ANOVA was significant, p = 0. 0.0140. Individual comparisons between each drug and placebo were non-significant: aspirin (ES = 0.23, p = 0.102), minocycline (ES = -0.24, p = 0.107) and pramipexole (ES = 0.04, p = 0.799).
Conclusions: This relatively large RCT was intended to provide a more definitive answer regarding the benefits of aspirin, minocycline and pramipexole reported in previous smaller trials. Although the overall ANOVA for PANSS total was significant, post-hoc analyses were only significant at trend level for aspirin, uncorrected for multiple comparisons, provided only a equivocal small advantage over placebo in total, positive and general psychopathology PANSS scores, and CGI. Based on these the failure to obtain the conventional .05 level, it is not possible to confirm the benefit of aspirin, nor to rule out the possibility that inhibition of COX-1 or COX-2, or other biological effects, both inflammatory and non-inflammatory of aspirin are implicated in the symptomatology of schizophrenia. It is not unusual to have pilot trials done by enthusiasts not confirmed. Although consistently replicated, the effect of aspirin in schizophrenia is too elusive and small to be of clinical significance. On the other hand these findings call for a renewed basic science effort to investigate what in the biological activity of aspirin is related to amelioration of the symptoms of schizophrenia.
Keywords: RCT, add-on, inflammatory hypothesis, aspirin
Disclosure: M. Weiser, **Part 1:** I have recieved travel awards and/or consultanats fees and/or speakers fees and/or research grants from Jansenn, Pfizer, Lundbeck, Teva, BioLineRx, Eli Lilly, Sanofi-Aventis, Roche; S. Burshtein, Nothing to Disclose; L. Fodoreanu, Nothing to Disclose; R. Chiriţă, Nothing to Disclose; G. Talău, Nothing to Disclose; D. Cirjaliu, Nothing to Disclose; J. Davis, M.D., Nothing to Disclose; M. Davidson, **Part 1:** Michael Davidson has received research grant support and/or travel support and/or speaker fees and/or consultancy fees from JNJ, Pfizer, Lundbeck, Teva, BioLineRx, Eli Lilly, Sanofi-Aventis, Roche, GSK, Envivo, Novartis, Abbott, Servier, and holds stocks in Tangent Data.

W58. The Value of Risk Reduction in CNS Drug Development: Use of Net Present Value as One Model

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Background: Data on the pharmaceutical industry demonstrates the probability of success in phase II has the largest influence on R & D productivity of any of the phases of discovery, preclinical, and clinical development. Further, failure rates in Phase II are quite high (Paul, et al., 2010). For phase II & III CNS clinical trials (e.g., major depressive disorder) when a drug known to be or subsequently proven to be effective is compared vs. placebo the probability of a statistically significant difference is approximately 50%, much lower than the 80% to 90% success rate expected from the powering of these studies (Khin, et al., 2011). Several methods have been proposed to reduce the risk of CNS trial failure in phases II and III (Mallinckrodt, et al., 2011). However, quantitative modeling has not been used to assess the value risk-reduction methods add to the R & D process.
Methods: We used the standard business tool of risk-adjusted net present value, also known as expected net present value (eNPV), as a quantitative assessment of value. This calculates all cash flow expected, adjusted for time and the probability of success. For example, a product that would return $100 immediately with a 50% chance of success has an eNPV = $50. A product that would return $100 in a year, with a 50% chance of success, would have an

eNPV = $50 less the annual discount rate (usually around 10%) so $45. We assumed a drug with 10 years of patent life at launch, a relatively rapid rise in yearly sales to a flat peak of $1B, followed by a rapid decline after patent expiry. We assumed standard rates of success in the various phases of drug development, taken from the data published by the Tufts Center for Drug Development. We further assumed a base 50% failure rate in phase IIa proof-of-concept studies for drugs that are in fact at least as effective as assumed in the powering of the study.

Results: Increasing the probability of success in phase IIa for effective drugs by 20% increased eNPV by $106 M. Increasing it just 1% increased eNPV by $5.3 M. Increasing the probability of success in phase III by 20% increased eNPV by $127 M. Increasing it just 1% increased eNPV by $8 M.

Conclusions: Quantifying the dollar value of reducing the risk of failure in phases II & III underscores the signficant return on investment afforded by methods that can reduce clinical attrition rates even slightly, not to mention their potential to advance medical science. Serious consideration should be given, from both a financial and medical perspective, to methods for reducing attrition, especially in disease states with known high rates of failed trials, such as MDD, CIAS, and many other CNS disorders. Several such methods have been proposed, including review of recorded assessments, novel clinical trial designs, central ratings and innovative statistical methods.

Keywords: clinical trials, phase II, signal detection, methodology

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W59. Personality Traits and Treatment of Major Depressive Episodes Associated with Bipolar I Disorder

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Background: Previous studies have suggested that the personality trait of Neuroticism is a risk factor for major depression (Barnettet al., 2012; Rosellini and Brown, 2011). There are currently limited data examining the impact of broader personality profiles on the outcome of treatment for major depression. The five-factor model of personality traits (NEO-FFI) includes Neuroticism (N), Extraversion (E), Openness to experience (O), Agreeableness (A), and Conscientiousness (C) is a self-report measure which scores invidulals against population norms. In this post-hoc analysis, we investigated the relationship between NEO-FFI domains individually and in combinations (defining personality styles) and treatment outcomes in a randomized, 6-week, double-blind, placebo-controlled study of lurasidone for the treatment of bipolar I depression.

Methods: Subjects meeting DSM-IV-TR criteria for bipolar I depression, with or without rapid cycling, with a Montgomery-Asberg Depression Rating Scale (MADRS) score $\geqslant$20 and a Young Mania Rating Scale (YMRS) score $\leqslant$12, were randomized to 6 weeks of once-daily, double-blind treatment with lurasidone 20-60 mg, lurasidone 80-120 mg (LUR), or placebo (PBO). Personality traits and styles were assessed at baseline. The NEO-FFI results were summarized using 5 levels of T-scores: very low range (T = 34 or lower), low range (T = 35 to 44), average range (T = 45 to 55), high range (T = 56 to 65), and very high range (T = 66 or higher) and used to categorize the sample in accordance with the ten NEO personality styles defined by Rosellini (based on scores above and below the average range on two personality domains. For example, combinations of N with E for the Well-Being style, N with O for Defense, N with A for Anger Control, N with C for Impulse Control, E with O for Interest, E with A for Interactions, E with C for Activity, O with A for Attitudes, O with C for Learning, and A with C for Character. ANCOVA (LOCF) was performed to examine treatment effects (LUR vs. PBO) by personality styles using statistical interaction tests.

Results: Baseline distributions of the personality T-scores showed that a majority of patients had high (52.2%) or very high (33.6%) Neuroticism (N), but low or very low T-scores in Extraversion (E) (81.2%), Openness to experience (O) (51.3%), Agreeableness (A) (83.9%), or Conscientiousness (C) (85.6%). Only 5 patients (0.03%) showed unawareness of their illness, signifying reduced insight as assessed by YMRS item 11. Statistical treatment-by-style interaction tests showed that 3 personality trait combinations predicted greater treatment benefits of lurasidone (20-60 mg/d or 80-120 mg/d vs. placebo), as assessed by endpoint reductions in MADRS scores: (1) Gloomy Pessimists [high N low E] ($p = 0.022$, vs. average or higher levels of Extraversion for the Well-Being Style), (2) Undercontrolled [high N low C] ($p = 0.046$, vs. average or higher levels of Conscientiousness for Impulse Control), and (3) The Lethargic [high E low C] ($p = 0.014$, vs. average or higher levels of Go-Getters style for the Activity style). Furthermore, a greater reduction in MADRS scores favoring lurasidone (vs. placebo) was found in five of the eight personality combinations involving high N (N+), 5 combinations involving low A (A-), 4 combinations involving low C (C-), and 4 combinations involving low E (E-). These include Gloomy Pessimists (N + E-, $p < 0.001$), Maladaptive (N + O-, $p < 0.001$), Hypersensitive (N + O+, $p = 0.012$), Temperamental (N + A-, $p < 0.001$), Undercontrolled (N + C-, $p < 0.001$), Homebodies (E-O-, $p < 0.001$), Competitors (E-A-, $p < 0.001$), The Lethargic (E-C-, $p < 0.001$), Resolute Believers (O-A-, $p < 0.001$), Free-Thinkers (O + A-, $p = 0.040$), Reluctant Scholars (O-C-, $p < 0.001$), and Undistinguished (A-C-, $p < 0.001$). A large placebo response was associated with the Overcontrolled style (N + C+) (LS mean change from baseline in MADRS at LOCF endpoint -17.73, 95% CI -27.86,-7.60, n = 17 placebo subjects), Mainstream Consumers (E + O-) (-13.05, 95% CI -24.6, -1.51, n = 13), By-the-Bookers (O-C+) (-22.63, 95%CI -32.61, -12.64, n = 12), and the Self-Promoter style (A-C+, -27.01, -47.14, -6.88, n = 16).

Conclusions: Our findings suggest that a high level of Neuroticism combined with low levels of Extraversion or Conscientiousness were associated with favorable outcomes of lurasidone monotherapy, in the treatment of major depressive episodes associated with bipolar I disorder. Lurasidone treatment also significantly reduced depressive symptoms in 5 of the 8 personality combinations involving low Agreeableness, and 4 combinations involving low Openness to Experience. These results suggest assessment of personality traits may be an important moderator of clinical trial outcome and can potentially be utilized as a predictor of treatment outcome.

Keywords: Bipolar, Depression, Personality, Moderater, Placebo response

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Massachusetts General Hospital, Owner, Collaborative Care Initiative, LLC (Private Practice), **Part 3:** Full time employee, Bracket, Partime employee, Massachusetts General Hospital, Owner, Collaborative Care Initiative, LLC (Private Practice), **Part 4:** None; C. Siu, **Part 1:** Full time Employee Data Power, Inc., Consultation Sunovion, **Part 2:** Full time Employee Data Power, Inc., **Part 3:** Full time Employee Data Power, Inc.; J. Cucchiaro, **Part 1:** Full Time Employee, Sunovion, **Part 2:** Full Time Employee, Sunovion, **Part 3:** Full Time Employee, Sunovion; R. Silva, Nothing to Disclose; F. Grossman, **Part 1:** Full Time Employee, Sunovion, **Part 2:** Full Time Employee, Sunovion, **Part 3:** Full Time Employee, Sunovion; J. Hsu, Nothing to Disclose; A. Kalali, **Part 1:** full time employee of Quintiles, **Part 2:** full time employee of Quintiles, **Part 3:** full time employee of Quintiles; A. Loebel, **Part 1:** Full Time Employee, Sunovion, **Part 2:** Full Time Employee, Sunovion, **Part 3:** Full Time Employee, Sunovion.

W60. Do Short-term Effects of Cholinesterase Inhibitors Predict Long-term Outcomes?

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Background: Cholinesterase inhibitors (ChEIs) are the standard of care for patients with mild to moderate Alzheimer's disease (AD). The choice of treatment is usually based on the results of controlled 6 to 12 month studies, yet patients are often treated for longer than this and there are few longer-duration trials. Placebo-controlled, multiple year studies of cholinesterase inhibitors have been conducted in patients with mild cognitive impairment (MCI). The purpose of the following analysis was to compare the long-term effects of cholinesterase inhibitors on MCI patients in order to intuit the long term effects of these drugs in AD patients, for whom long-term administration is a goal.
Methods: Long-term, double-blind, placebo-controlled MCI studies with ChEIs were compared, in which a primary outcome measure was conversion or time to conversion to AD. Donepezil was studied along with placebo and vitamin E in 769 patients with amnestic MCI (aMCI) and Clinical Dementia Rating (CDR) 0.5. Secondary outcome measures included the CDR sum-of-boxes (CDR-SB) Galantamine was studied in two cohorts from identical studies combined here, consisting of a total of 2048 subjects with MCI, having CDR 0.5. Secondary outcomes also included the CDR-SB. The rivastigmine study enrolled 1018 patients with MCI and a CDR of 0.5. The co-primary endpoint was the z-score on a neuropsychological test battery. Secondary outcomes included the CDR. Each study contained a subgroup of patients who received longitudinal MRI examinations in which global and hippocampal atrophy were evaluated, and these were compared. The ratio of drug to placebo patients converting from MCI to AD was calculated for each 6-month interval for each drug. Additionally, the rate of change in the CDR sum-of-boxes (CDR-SB) during each year of each study was calculated from available data.
Results: The overall rate of progression to AD in the donepezil trial was 16%/year. Donepezil did not reduce AD conversion over three years (hazard ratio 0.8, $p = ns$), however AD conversions were reduced as compared to placebo for year 1 ($p = .004$) and year 2 ($p = .03$). There were some differences in the change from baseline between donepezil and placebo on secondary measures, confined to the first half of the study. Differences between donepezil and placebo do not appear to have been assessed. In the combined galantamine studies, 15% of patients converted to dementia over 2 years. The mean decline in the CDR-SB at 24 months was significantly reduced by galantamine in Study 1 ($p = .028$), and tended to be reduced in Study 2 ($p = .056$), however this did not result in significant differences in dementia conversion. No significant between-treatment differences were seen in the secondary outcome measures. Over 4 years, 17.3% of 508 rivastigmine patients, as compared to 21.4% of 510 placebo patients, progressed to dementia (hazard ratio 0.85, $p = ns$). There was no significant difference on the z-score of the cognitive test battery. No secondary outcome measure differed between rivastigmine and placebo patients at any time point. Importantly, rivastigmine comparisons were corrected for multiple comparisons, donepezil and galantamine data were not. The ratio of dementia conversions in patients on donepezil compared to those on placebo was 0.7 at year 1; 1.7 at year 2, and 2.2 at year 3. The ratio of conversions in galantamine patients to placebo patients was 0.7 to 0.8 for each of the 6-month timepoints in the 2-year study. Rivastigmine conversion ratios were quite variable, ranging from 0.5 to 1.5 throughout the 4 year study, without a clear trend. Donepezil produced a numerical advantage on the CDR-SB in the first year which was lost over the next two years due to numerically greater deterioration in the donepezil than in the placebo group. In the combined studies, the pattern of CDR-SB scores in galantamine as compared to placebo patients did not change over two years. The CDR (global) was identical in rivastigmine and placebo patients at 2, 3 and 4 years. Neither donepezil nor rivastigmine had significant effects on MRI parameters. Galantamine-treated patients had a 33% reduction in the rate of global atrophy compared to placebo patients at 24 months. ($p = .003$)
Conclusions: The three ChEIs that were compared in these long-term studies of MCI patients showed different patterns of effect over time. Donepezil had a biphasic effect which, following a beneficial first year, subsequently promoted the conversion from MCI to AD in treated patients as compared to placebo patients. In contrast, the pattern of galantamine relative to placebo conversions did not change over two years. Similarly, donepezil's numerical benefit in change of the CDR-SB in the first year was lost in subsequent years, while galantamine's pattern remained constant. The long-term administration of galantamine resulted in a significant reduction in global atrophy that was not seen with donepezil or rivastigmine. This re-examination of the MCI studies shows substantial differences among the longer-term effects. Only galantamine's effects are steady over two years. The 6-month studies which have primarily guided therapeutic decisions in AD are not adequate to make those decisions.
Keywords: donepezil galantamine MCI MRI biomarkers
Disclosure: B. Davis, **Part 1:** Synaptec Inc, CEO and shareholder, Synaptec holds patents, no longer in force, for the use of galantamine for Alzheimer's disease and related dementias, and receives royalties, **Part 2:** Synaptec Inc, CEO and shareholder, Synaptec holds patents, no longer in force, for the use of galantamine for Alzheimer's disease and related dementias, and receives royalties, **Part 3:** Synaptec Inc, CEO and shareholder, Synaptec holds patents, no longer in force, for the use of galantamine for Alzheimer's disease and related dementias, and receives royalties; M. Sano, **Part 1:** Medivation, Novartis, Pfizer, Bristol-Myers Squibb, Eisai Pharmaceutical, Eli Lilly, Takeda, Sanofi-Aventis, Bayer, Medpace, **Part 2:** Medivation.

W61. Efficacy of Adjunctive Quetiapine SR in a Randomized, Double Blind, Placebo-Controlled Study of Mixed States (MS) in Bipolar Disorder (BD)

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Background: Mixed States (MS), an intrinsic presentation of bipolar disorders (BD), are severe and complex affective states that involve concomitant presence of both manic/hypomanic and depressive/dysphoric symptoms. Studies have shown that MS constitute >50% of all syndromal episodes in BD. Mixed states are associated with elevated risk for suicide in BD and are implicated in 11% of all completed suicides in BD. Observational evidence

indicates that MS are frequently associated withprominent anxiety, co-morbid substance use disorders and treatment refractoriness. Despite the common presentation of MS, and associated socio-occupational dysfunction, treatment options, both acutely and long term, are limited. Quetiapine is the only pharmacological agent that has demonstrated efficacy, as monotherapy, in the acute treatment of bipolar mania and depression as well as in prophylactic treatment of BD. To our knowledge, this is the first controlled study to assess the efficacy of quetiapine in the treatment of MS of BD. We hypothesized that the addition of quetiapine to ongoing treatment with mood stabilizers will lead to reduction in both the depressive and manic components of patients with an index episode of MS.

Methods: This prospective 24-week, double-blind, randomized study (n = 24) assesses the efficacy of quetiapine SR added to ongoing treatment regimen with mood stabilizers, lithium, valproate or lamotrigine or any combination of the three thereof, in the acute and maintenance treatment of patients with MS associated with BD. Primary efficacy was assessed by Mixed effects repeat measure of change from baseline in Bipolar Inventory of Signs and Symptoms (BISS) total score and, secondarily, manic and depression subscale scores. Response defined as 50% reduction in YMRS and MADRS and time to intervention or discontinuation for any mood episode were additionally used as efficacy measures. Assessments were performed at weeks 1, 2, 4, 8, 12, 16, 20 and 24.

Results: We conducted mixed effects repeat measures analyses including medication group, visit and medication by visit interactions. Mixed effects repeat measure analysis indicated significantly greater improvement in CGI-severity score for adjunctive quetiapine plus mood stabilizer group compared to mood stabilizer plus placebo group ($F = 6.52$, $P = 0.01$, $DF = 89$) as well as for GAF scores ($F = 6.60$, $P = 0.01$, $DF = 88$). MADRS total scores were significantly lower for adjunctive quetiapine plus mood stabilizer group compared to mood stabilizer plus placebo group ($F = 13.93$, $P = 0.0003$, $DF = 91$) as were CGI-depression scores ($F = 8.09$, $P = 0.005$, $DF = 89$). YMRS total scores did not differ between the two groups ($F = 2.67$, $P = 0.11$, $DF = 92$ nor did CGI-mania scores ($F = 1.66$, $P = 0.20$, $DF = 89$).

Conclusions: This study demonstrates the superiority of adding quetiapine SR to ongoing treatment with mood stabilizers compared to treatment with mood stabilizers alone. Quetiapine SR, compared to placebo, was more efficacious in the reduction of depressive symptomatolgy but did not differ from placebo on the manic facet of MS. This is the first report of a medication regimen more efficacious in reduction of depressive symptomatology of MS without concurrent greater reduction in manic symptomatology. Given that psychosocial impairment and risk of suicide in MS are a direct function of the intensity of depressive symptoms, findings from this study will have a clinical significance.

Keywords: mixed states, bipolar disorder, quetiapine, mixed mania,

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W62. Feasibility of Centralized Ratings for Mental Health Safety Screening in a Dermatology Trial

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Background: Clinical trials in non-CNS indications frequently include assessments of psychopathology to track associated symptoms and safety signals. Non-mental health sites may not be equipped to diagnose exclusionary mental disorders or follow-up on suicidality. Centralized ratings have proven feasible for assessment of adult psychiatric diagnosis, symptom severity, and suicidality across CNS disorders. Centralized ratings, in which independent remote raters interview subjects live by videoconferencing or telephone, may be used for safety assessments in non-psychiatric trials with sites that do not employ staff experienced in psychiatric assessment (e.g., dermatology). Centralizing assessments with mental health experts enables immediate clinical follow-up and actionable diagnostic support for investigators. This study examines the feasibility and acceptability of using centralized ratings in a Phase III dermatology clinical trial as a means of evaluating treatment effects and establishing safety indicators in adults and adolescents.

Methods: 7988 assessments were performed in the US and Canada via telephone on 1127 subjects who were patients at dermatology offices and enrolled in this clinical trial of a medication for their dermatologic condition. These assessments were done initially to assess study eligibility, basedon history, within study to determine treatment effects, and post-study to assess treatment sequelae. Subjects were a mix of adults (n = 630) and adolescents (n = 497). At screening, centralized raters administered the SCID-CT, C-SSRS Lifetime to assess suicidality, C-SSRS Last Year, and PHQ-8 for depressive symptom severity. At monthly visits, central raters performed the C-SSRS Emergent, PHQ-8, GAD-7 and assessed itemsdesigned to detect emergent psychotic symptoms.

Results: *Screening:* 34 subjects (3%) were excluded on the basis of SCID-CT diagnosis. Of these, 27 (2.4%) were excluded for a major depressive episode and one for hypomania in the past year, one for a lifetime major depressive episode, and five for a lifetime psychotic episode. On the basis of the SCID-CT or PHQ-8, subjects could be classified as being in no need of additional mental health services, or having psychiatric symptoms of mild severity (recommendation to refer to local mental health service provider; n = 33), moderate (immediate referral to psychiatric evaluation; n = 17), or severe (immediate escort to emergency room; n = 0). At screening one subject reported suicidal ideation defined as a score of 4 or 5 on the CSSRS, 1% reported self-injurious behavior (n = 10), and 0.5% reported suicidal behavior in the last year (n = 5). Scores on the PHQ-8 at screening ranged from 0–21 (M = 1.02; SD = 1.89). 54% of subjects scored a 0 on the PHQ-8 at screening (n = 612) and eight subjects had scores greater than 10. *Follow-Up:* No subjects reported suicidal ideation or suicidal behavior at any of the 6861 follow-up assessments. One subject reported self-injurious behavior and two subjects reported emergent psychotic symptoms. PHQ-8 and GAD-7 scores were stable within each subject over the course of the study. Mean within subject visit-to-visit change was .32 on the PHQ-8 (SD = .70) and .21 on the GAD-7 (SD = .51).

Conclusions: This study was conducted to support regulatory approval of a drug product, and supports the integration of centralized rating systems into non – psychiatric studies. It also established the feasibility and acceptability of routine screening and monitoring of psychopathology and suicidality in a non-psychiatric population. Central raters effectively identified subjects who did not qualify for entry at the beginning of the study because they had active suicidal ideation with intent and/or plan and significant active or recent mood disorder in the last year, or a lifetime incidence of psychosis. These subjects were excluded from the study and referred for clinical care. Throughout the study, central raters identified cases of emergent psychosis and mood disorder symptoms.

Keywords: Methodology, depression, clinical, suicidality, safety

Disclosure: J. Williams, **Part 1:** Full-time employee of MedAvante, Inc., **Part 2:** Full-time employee of MedAvante, Inc., **Part 3:** Full-time employee of MedAvante, Inc., **Part 4:** None.; D. Davis, **Part 1:** Full-time employee of MedAvante, Inc., **Part 2:** Full-time employee of MedAvante, Inc., **Part 3:** Full-time employee of MedAvante, Inc.,

Part 4: None; D. Popp, **Part 1:** Full-time employee of MedAvante, Inc., **Part 2:** Full-time employee of MedAvante, Inc., **Part 3:** Full-time employee of MedAvante, Inc., **Part 4:** None; J. Gross, **Part 1:** Employed as Vice President of Scientific Affairs for Cipher Pharmaceuticals, company that conducted study, No business propositions with ACNP, **Part 2:** Salary from Cipher Pharmaceuticals, **Part 3:** Employed as Vice President of Scientific Affairs for Cipher Pharmaceuticals, company that conducted study, No business propositions with ACNP, **Part 4:** Employed as Vice President of Scientific Affairs for Cipher Pharmaceuticals, company that conducted study.; D. Salvucci, **Part 1:** Full-time employee of MedAvante, Inc., **Part 2:** Full-time employee of MedAvante, Inc., **Part 3:** Full-time employee of MedAvante, Inc., **Part 4:** None; M. Detke, **Part 1:** Dr. Detke reports being an employee and major stockholder of MedAvante, Inc. and disclosed the provision of expert testimony for Eli Lilly and fees for consultation and participation on advisory boards for NIH, Roche, Sonkei, Phine Pharmaceuticals, Columbia NW Pharmaceuticals, Insight Neuropharma, Inc., and Jeevan Scientific, Inc, **Part 2:** Full-time employee of MedAvante, Inc., **Part 3:** Full-time employee of MedAvante, Inc., **Part 4:** Full-time employee of MedAvante, Inc.

W63. Imaging Cognition Circuits for Treatment Prediction in Major Depressive Disorder: Results from the International Study to Predict Optimized Treatment in Depression (iSPOT-D)

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Background: A better understanding of the brain networks involved in depression represents a promising way to optimize application of currently available therapeutic options for major depressive disorder (MDD), as well as to link the mechanisms of treatments to the hypothesized neural deficits involved in MDD. Abnormalities have been consistently identified in cortico-limbic circuitry (amygdala, anterior cingulate) in MDD, as well as in more traditional dorsolateral prefrontal-based executive control systems. Of these, the latter circuit is like involved in regulatory processes such as working memory updating, which are impaired in MDD, and likely to play a role in determining which patient remits and which patient does not. Here, we examined cognitive regulatory circuitry in the context of the International Study to Predict Optimized Treatment in Depression (iSPOT-D), which is a practical antidepressant treatment trial coupled with a suite of biomarkers, including functional MRI.
Methods: We used a standardized battery of tasks that measure cognitive regulatory functioning to identify brain circuits differentially engaged in 102 outpatients with MDD compared to 34 matched, healthy control participants. Among MDD patients, neural activation in these tasks was also used to predict treatment responses to Escitalopram, Sertraline, or Venlaflaxine after 8 weeks of treatment. Additionally, we examined moderating effects of clinically-defined MDD subtypes (i.e. anxious, melancholic) which may better disentangle the heterogeneity in the broader diagnosis of MDD.
Results: MDD participants were distinguished by a distinctive biosignature of hypoactivation of the dlPFC during working memory updating; hyperactivation of the dmPFC cortex during working memory and response inhibition cognitive regulatory tasks. Furthermore, treatment response was predicted by activation in the cognitive tasks, specifically during working memory load, and was moderated by medication arm and anxious subtype.
Conclusions: The findings provide the frame of reference for identifying neural circuit-based biomarker as predictors of treatment outcomes in MDD. Additionally, these findings suggest that using a standardized battery of emotion and cognitive functions coupled with imaging can be used to guide and personalize treatment options for MDD.
Keywords: Major Depressive Disorder, fMRI, treatment prediction
Disclosure: A. Gyurak, Nothing to Disclose; M. Korgaonkar, Nothing to Disclose; S. Grieve, Nothing to Disclose; L. Williams, Nothing to Disclose; A. Etkin, Nothing to Disclose.

W64. Six-Month Depot Naltrexone Treatment Reduces Relapse in Parolees Formerly Addicted to Opioids

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Background: Relapse to drug use is the fundamental problem of addiction. Vivitrol, (Alkermes Inc, Cambridge, MA) is an injectable extended-release formulation of naltrexone (XRNTX) that blocks opiate receptors for approximately one month after injection. XRNTX addresses the problem of noncompliance that limits the efficacy of oral naltrexone.
Methods: Multi-site randomized controlled trial of XRNTX at five sites: University of Pennsylvania (PA), Brown University/Rhode Island Hospital (RI), New York University (NY), Columbia University (NY) and Friends Research Institute (MD). Participants in this ongoing study are between 18 and 60 years old, have a DSM-IV-TR Diagnosis of opiate addiction and current or past history of conviction for a non-violent offence. They are randomized to six monthly depot-naltrexone injections (Vivitrol) or treatment as usual (TAU) and are followed up 12 and 18 months after the last XR-NTX. Outcome measures are urine drug screen (UDS) positive for opioids, new criminal convictions during the active phase of treatment and self-report of drug-related problems. Main hypothesis is that XR-NTX cohort will be show significantly lower rates of positive UDS at 6 months, new convictions, self reported drug problems and need for treatment.
Results: As of July 2012, the study recruited $n = 207$ (17% female, 50% AA, 20% Hispanic). Analysis of differences between the XRNTX and TAU cohorts (Chi-square, $p < 0.05$) showed that the XR-NTX cohort had significantly fewer positive urines at 6-months (16.9%) than the TAU group (32.9%), as well as significantly fewer self-reported days with drug-related problems (F 5.341, $p = 0.022$). There have been no significant differences in the new convictions or self-reported days of drug use. The 6-month retention rate ranged between 80 and 92% (Mean = 84%) at each site.
Conclusions: Our interim results confirm our previous reports (Cornish et al, JSAT, 14(6), 2006) that XR-NTX reduces relapse rates in opioid-dependent patients on parole and indicate that XR-NTX is an effective non-narcotic treatment for opiate dependence. Furthermore, our results show that XR-NTX has a much higher retention than what has been previously reported with non-opioid agonist therapies. The interim results did not yet show a reduction in criminal activity. This suggests that while XR-NTX is successful in curbing relapse, additional intervention such as psychotherapy may be required to assist parolees in changing their criminal behaviors.
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Keywords: Criminal Justice, Heroin, Opioid, Depot-Naltrexone, Vivitrol
Disclosure: J. Cornish, Nothing to Disclose; C. Nordeck, Nothing to Disclose; D. Langleben, **Part 4:** Investigator Sponsored Agreement with Alkermes Inc, to provide the study medication free of charge; D. Coviello, Nothing to Disclose; K. Lynch, Nothing to Disclose; T. Boney, Nothing to Disclose; C. O'Brien, **Part 2:** Occasional Consultant, Alkermes Inc, **Part 4:** Investigator Sponsored Agreement with Alkermes Inc, to provide the study medication free of charge. No other financial support.

W65. Non-Steroidal Anti-Inflammatory Drug Use is Associated with Lower Remission Rate with Escitalopram but Not with Other Antidepressants

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Background: Inflammation has recently been implicated in Major Depressive Disorder (MDD), raising interest in using anti-inflammatory agents as treatment. However, in a recent analysis of the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, use of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) was associated with worsened, rather than improved, outcome in subjects taking Citalopram, a Selective Serotonin Reuptake Inhibitor (SSRI). This report explores the use of both prescription and non-prescription NSAIDs in the COmbining Medications to Enhance Depression Outcomes (COMED) sample to determine whether concomitant use of NSAIDs affects antidepressant treatment outcome.
Methods: COMED randomized adults with chronic or recurrent MDD among one single-medication arm (escitalopram + placebo [ESC + PLA]) and two medication combination arms (bupropion SR + escitalopram [BUP + ESC] and venlafaxine XR + mirtazapine [VEN + MIR]) over a 12 week acute treatment phase. NSAID use data were extracted from patient reports of concomitant medications. Subjects reporting NSAID use at at least one post-baseline visit were classified as NSAID users. Unadjusted and adjusted generalized linear mixed models assessed the effect of NSAIDs on outcomes, including remission, response, and time to remission, comparing the three treatment arms. We also examined whether pain at baseline moderated outcome by including it in the model and examining the pain by treatment arm interaction.
Results: COMED subjects used NSAIDs at a high rate (381/633, 60.2%, median visits used 83.3%). There was a significant treatment arm × NSAID use interaction ($p = 0.05$; adjusted, $p = 0.04$). NSAID users in the ESC + PLA arm had lower adjusted remission rates (33.2%) than NSAID non-users (47.2%), while NSAID use was associated with higher adjusted remission rates than NSAID non-use in the combination arms (41.3% vs. 37.7% for BUP + ESC and 44.6% vs. 32.4% in the VEN + MIR arm).
Conclusions: These results support and extend findings from the STAR*D sample that NSAID use was associated with lower remission with SSRI treatment. We found a strong differential effect suggesting that NSAIDs may be beneficial when given with the non-SSRIs. Trials examining these results prospectively are needed to verify the effects of NSAIDs on antidepressant responses and the role of inflammatory markers with antidepressant efficacy.
Keywords: Major Depressive Disorder, antidepressant treatment, inflammation
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W66. Sensory-specific Satiety in Schizophrenia

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Background: Many patients with schizophrenia (SZ) exhibit deficits in the ability to engage in goal-directed behavior. It has been proposed that both positive and negative symptoms in SZ may derive, at least in part, from a disrupted ability to accurately and flexibly represent the value of stimuli and actions.
Methods: To assess relationships between dimensions of psychopathology in SZ, and the tendency to devalue food stimuli, on which subjects were fed to satiety, we administered a sensory-specific satiety (SSS) paradigm, in conjunction with fMRI scanning, to 23 schizophrenia patients and 31 controls. The paradigm involved feeding subjects 0.7-mm squirts of liquid foods (V8 vegetable juice and chocolate hazelnut drink), as well as a control solution (comprising the ionic components of saliva), in a pseudo-random order, using syringes. Subjects were instructed to roll the liquids around on their tongues for 10 s until receiving a cue (a green disc) to swallow. In each of 2 sessions, subjects received 16 squirts of each rewarding food and 32 squirts of the control solution. In between the 2 sessions, each subject was instructed to drink one of the foods (determined through counterbalancing) until he/she felt "full, but not uncomfortable". Using a Likert-type scale, from 0 to 8, subjects rated each liquid 10 times (at regular intervals, interspersed throughout the 2 sessions). We used ANOVAs with factors of GROUP, FOOD-TYPE (sated vs. unsated), and TIME OF RATING (pre- vs. post-satiety), to determine whether SZs and controls showed different sensory-specific satiety effects. We also analyzed correlations, within the patient group, between symptom measures from the SANS and BPRS, and changes in ratings of the sated and unsated foods (from the end of Session 1 to the beginning of Session 2).
Results: The ANOVA revealed main effects of FOOD-TYPE and TIME OF RATING, such that the entire sample of subjects devalued the sated food more than the unsated food, and gave foods lower ratings after satiety than before. Most importantly, these main effects were modulated by a GROUP × FOOD-TYPE-TIME OF RATING interaction [$F(1, 52) = 4.494$, $p = 0.039$], such that controls showed an effect of satiety that was sensory-specific

[F(1, 30) of FOOD-TYPE × TIME OF RATING interaction = 6.697, p = 0.015], whereas patients did not [F(1, 22) = 0.443]. Patients shows a main effect of TIME OF RATING [F(1, 22) = 6.226, p = 0.021]; that is, they showed an effect of satiety what was not sensory-specific. In controls, the sensory-specific satiety effect correlated negatively with self-reported physical and social anhedonia from the Chapman scales; the sensory-specific satiety effect was greater in those with lower reported anhedonia. In SZ patients, self-reported physical and social anhedonia predicted changes in self-reported hunger, but not changes in the valuation of foods.

Conclusions: Using an established probe of the ability to flexibly and rapidly update representations of the value of food stimuli, we found that patients with schizophrenia showed a reduced tendency to devalue food stimuli in a sensory-specific way. The ability to flexibly and rapidly update representations of the value of stimuli and actions figures critically in the adaptive motivation of goal-directed behavior. We argue that a reduced ability to precisely update value representations could contribute to motivational deficits observed in patients with schizophrenia.

Keywords: Schizophrenia, reinforcement learning, satiety, devaluation

Disclosure: J. Waltz, **Part 1:** Consulting agreement with F. Hoffmann-La Roche LTD; J. Brown, Nothing to Disclose; T. Ross, Nothing to Disclose; B. Salmeron, Nothing to Disclose; J. Gold, Nothing to Disclose; E. Stein, Nothing to Disclose.

W67. Reward Circuitry Function in Euthymic Adults with a History of Major Depressive Disorder

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Background: Although functional brain imaging has established that individuals with unipolar major depressive disorder (MDD) are characterized by frontostriatal dysfunction during reward processing, no research to date has examined the chronometry of neural responses to reward gains and losses in euthymic individuals with a history of MDD. Establishing neurofunctional characteristics of reward processing in euthymic individuals with a history of MDD is a critical step towards establishing functional brain markers predicting MDD risk. We previously reported that individuals with remitted major depressive disorder (rMDD) were characterized by relatively greater activation in anterior cingulate gyrus and right midfrontal gyrus during reward gain anticipation, and by relatively decreased activation in orbital frontal cortex, frontal pole, insular cortex, and thalamus during reward gain outcomes. We also found a relation between right frontal pole activation during reward anticipation and the number of lifetime depressive episodes within the rMDD group (Dichter, Kozink, McClernon, & Smoski, 2012). Here we report results of responses to reward loss anticipation and outcomes in the same rMDD sample.

Methods: A monetary incentive delay task was used during fMRI scanning to assess neural responses in canonical reward regions during anticipation and outcome of reward losses in 19 participants with remitted major depressive disorder (rMDD) and in 19 matched control participants.

Results: Responses during the anticipation and outcome phases of the task were analyzed separately. During loss anticipation, the rMDD group was characterized by relatively decreased activation in clusters within the pars triangularis in left inferior frontal gyrus, left frontal pole, and a cluster that included right caudate and thalamus. During loss outcomes, the rMDD group was characterized by relatively decreased activation in left and medial frontal pole clusters and the thalamus. No canonical reward processing regions showed greater activation in the rMDD group. Exploratory brain-phenotype analyses revealed a significant correlation between scores on the Ruminative Responses Scale (Nolen-Hoeksema & Morrow, 1991) and medial frontal pole (Brodmann's area 9) activation magnitudes during loss outcomes within the rMDD group.

Conclusions: Results indicate that euthymic adults with a history of major depression are characterized by hypoactivation in canonical reward regions during reward loss anticipation and reward loss outcomes. More broadly, these data combined with our previous findings of altered frontostriatal responses in this sample during reward gain anticipation and outcomes suggest that aberrant reward circuitry responses to rewards may potentially represent a trait marker for MDD, though future research is needed to evaluate the prospective utility of these functional neural endophenypes as a marker of MDD risk.

Keywords: Major Depressive Disorder, Remission, Reward, Magnetic Resonance Imaging

Disclosure: G. Dichter, Nothing to Disclose; C. Schiller, Nothing to Disclose; M. Smoski, Nothing to Disclose.

W68. Oxytocin Influences Response Bias in Men but Not Women in a Signal Detection Emotion Perception Task

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Background: Accumulating studies document changes in the perception of and response to socially mediated information, such as facial expressions, with administration of oxytocin. Across studies, however, its effects on emotion perception have been inconsistent. Outside the laboratory, affective judgments about another person (e.g., Is that person angry at me?) involve interpretation of perceptual uncertainty (e.g., scowls do not always indicate anger) and assessment of behavioral risk (e.g., the costs of inferring anger when it does not exist differ from the costs of missing anger when it does exist). An account of these decision variables is missing from studies of the effects of oxytocin on emotion perception. To characterize oxytocin's effects on emotion perception from a decision-making perspective, we utilized a task that combines perceptual uncertainty with behavioral economics in a signal detection framework (Lynn, et al., in press). We used the probability of encountering angry faces and the cost of misidentifying them as *not* angry (risk) to create a biased (biased towards reporting anger when not sure) perceptual environment. We measured the effect of oxytocin on perceivers' ability to achieve optimal bias in this environment. Based on prior data suggesting that oxytocin attenuates risk aversion, we hypothesized that receiving oxytocin would result in insufficient bias, due to under-estimating the probability of encountering angry faces and/or to under-valuing the cost of mistakes relative to placebo.

Methods: Forty psychotropic-free healthy control participants (age: M = 44.0 ± 10.32 [SD] years, 45% women) participated in a randomized double-blind administration of intranasal oxytocin or placebo prior to computer based tasks at the Center for Anxiety and Traumatic Stress Disorders (CATSD) at Massachusetts General Hospital. All were free of psychiatric disorders, per clinical interview with the Structured Clinical Interview for DSM-IV. Participants were given 30 IU of double-blind intranasal oxytocin (Syntocinon, Novartis) or placebo (oxytocin: n = 22, 9 women; placebo: n = 18, 7 women) thirty minutes before the computer tasks. In this signal detection framework, faces that depicted expressions ranging from relaxed to strongly scowling comprised two categories: "angry" (targets) and "not angry" (foils). Uncertainty was implemented by creating distributions of targets and foils which shared exemplars (i.e., the distributions overlapped on the perceptual domain: targets were M = 60 ± 15% (1 SD) scowl intensity, foils were M = 40 ± 15% (1 SD) scowl intensity).

Risk was created by earning or losing points for correct vs. incorrect categorization of targets and foils (i.e., categorizing a target as "not angry" cost more points than categorizing a foil as "angry"). Additionally, the base rate of targets was 0.6 (60% of trials were targets). The combination of relatively high missed detection cost and relatively frequent targets dictated a liberal optimal bias: a tendency to categorize faces as angry was required to maximize points earned. Over 230 trials, participants attempted to optimize their categorization of the faces, answering the on-screen prompt "Is this person angry?". Participants received immediate on-screen feedback ("Yes - that was right" or "No - that was wrong", points earned for the current trial, and cumulative points earned).

Results: Controlling for baseline perceived stress (Perceived Stress Scale) and trait anxiety (State Trait Anxiety Index, Trait Total Score) in this non-psychiatrically ill sample, we found a significant interaction of drug and gender on response bias (ANCOVA, $F(1,32) = 4.1$, $p < 0.049$), without main effects. Men who received oxytocin exhibited a significantly less liberal (less optimal, based on experimental parameters) bias for perception of anger in faces than those who received placebo (follow-up ANCOVA among men, $F(1,20) = 5.0$, $p < 0.037$). In contrast, women's bias was not significantly affected by oxytocin (follow-up ANCOVA among women, $F(1,12) = 0.6$, $p > 0.4$).

Conclusions: Participants attempted to optimize their judgments about angriness depicted in facial expressions, in the context of experimenter-defined values of target-foil perceptual similarity, payoffs (points earned/lost), and "anger" base rate. Men given oxytocin appeared less able to calibrate their emotion perception to the signal detection parameters that cause bias (payoffs, base rate, or both). As a learning experiment, our results suggest that oxytocin may impair men's ability to optimally adapt emotion perception (e.g., judgments of angriness from faces) to differences in risk and uncertainty that characterize different social contexts, while there was no effect of oxytocin for women. These data suggest that oxytocin might reduce (normalize) over-estimates of the base rate of threat or reduce (normalize) over-estimates of the magnitude of punishments that otherwise might contribute to excessive social withdrawal or reduced social approach behaviors. We cannot rule out, however, that by reducing the salience of risk, oxytocin treatment in men could potentially promote risk-prone decision-making in domains outside a patient's core symptomotology. More research is needed to understand the potential role and possible side effects of oxytocin in interventions.

Keywords: oxytocin, emotion perception, signal detection, gender

Disclosure: N. Simon, Nothing to Disclose; S. Lynn, Nothing to Disclose; E. Hoge, Nothing to Disclose; L. Fischer, Nothing to Disclose; L. Feldman Barrett, Nothing to Disclose.

W69. Deficits in Functional Capacity and Impaired Glycemic Control: Urban African Americans with Type 2 Diabetes

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Background: African Americans (AAs) suffer from an increased prevalence of both type 2 diabetes and its complications. Hyperglycemia can lead to deficits in cognition and possibly related skills such as performance of everyday living skills. We examined: a) performance-based measures of functional capacity among urban, AA patients with type 2 diabetes, and b) tested whether these deficits were associated with reduced response to an intervention aimed at attaining glycemic control.

Methods: At initial presentation to an inner-city diabetes clinic, 172 AA patients with type 2 diabetes were assessed with a variety of instruments, including the University of San Diego Performance Skills Assessment-Brief (UPSA-B). They then received a comprehensive diabetes management intervention, whose success was indexed by levels of glycosylated hemoglobin (HbA1c) at up to four reassessments over a one-year period. We used the mixed-effects model repeated-measures method to predict HbA1c during the following year while patients were receiving the intervention.

Results: The mean UPSA-B score was 81 (+/- 16). Scores on the UPSA-B predicted impaired glycemic control at baseline. After controlling for oral hypoglycemic medication and insulin dose intensification, and intervention attendance, the UPSA-B score predicted reduced benefit from a diabetes management program. Other factors such as depression and total illness burden also predicted the course of HbA1c. Thus, deficits in everyday functioning abilities appeared to be related to reduced benefits of treatment.

Conclusions: Deficits in functional capacity appeared to be related to reduced benefits of diabetes treatment during an intervention. Future studies will be needed to elucidate the mechanisms underlying these relationships, and to determine whether interventions targeted at these abilities can improve glycemic control.

Keywords: functional capacity, diabetes, minority, HbA1c, cognition

Disclosure: D. Musselman, Nothing to Disclose; M. McNutt, Nothing to Disclose; D. Ziemer, Nothing to Disclose; E. Royster, Nothing to Disclose; P. Harvey, **Part 1:** Consulting, less than $10,000, Abbott Labs, Amgen, Boeheringer Ingelheim, Bristol-Myers-Squibb, Forest Labs, Genentech, Johnson and Johnson, Pharma Neuroboost, Roche Pharma, Shire Pharma, Sunovion Pharma, Takeda Pharma, **Part 4:** Grant, Astra-Zeneca.

W70. Impulsivity in Relation to Emotional Stress in Borderline Personality Disorder

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Background: Impulsivity is regarded to be an important feature of borderline personality disorder (BPD). Clinical and empirical evidence indicates that impulsivity consists of a variety of components and can be considered as a trait as well as a state. In BPD, impulsive behavior appears to be associated with emotional stress. Therefore, the aim of this study was to investigate impulsivity on a multidimensional level in relation to emotional distress.

Methods: 32 unmedicated patients with BPD and 30 healthy controls completed different subjective and behavioral measurements of impulsivity (e.g. GoStop task). The investigation took place at two different days, one with and the other without stress induction. Stress was induced with a combination of mental arithmetics under time pressure, negative feedback, and aversive pictures.

Results: BPD patients showed heightened trait impulsivity compared to healthy controls. Participants in both groups had a stress-dependent increase of self-reported state impulsivity. We also found a change in reaction inhibition in the GoStop task after stress induction in both groups, with BPD patients revealing a stronger decline in reaction inhibition (ADHD symptoms were statistically controlled for).

Conclusions: Findings of this study suggest a strong relation between emotional dysregulation and impulsivity in Borderline patients, which may have important implications for the clinical setting.

Keywords: borderline personality disorder, impulsivity, reaction inhibition, stress

Disclosure: S. Cackowski, Nothing to Disclose; A. Krause-Utz, Nothing to Disclose; A. Reitz, Nothing to Disclose; C. Schmahl, Nothing to Disclose.

W71. Neural Mechanisms Associated with Switching Attention from an Internal to an External Focus

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Background: Efficient, adaptive behavior relies on the ability to switch attention flexibly between internal and external information. Internally focused cognitive processes, such as those involved in event imagination, autobiographical memory, and introspection, preferentially engage the "default mode network" (DMN) of brain regions, whereas attending to and acting on information in the external environment tends to recruit distinct neural systems in dorsal and lateral frontal and parietal cortex related to executive attention and motor control. Despite evidence indicating that internally focused thought processes may comprise, on average, 1/3 or more of awake cognition, the neural mechanisms associated with disengaging from an internal focus in order to direct attention externally remain unknown. Such an investigation is highly relevant for the understanding of internalizing psychiatric disorders such as obsessive-compulsive disorder, generalized anxiety, and depression, which are characterized by excessive self-focused fear or negative thoughts that could be related to an impaired ability to switch from an internal to external mode of cognition.
Methods: Fourteen healthy individuals performed a novel switching task while the functional magnetic resonance imaging blood oxygen level-dependent (fMRI BOLD) signal was measured. Subjects either imagined event scenarios (internal focus condition, IF) or performed a 2-back spatial working memory task (external focus condition, EF) for 12-18 s before switching to a target detection condition (TD) that required externallyfocused attention for 15 s. The block design was employed to reduce collinearity between sequential conditions, enabling the unique estimation of neural activity associated with the IF, EF, and TD blocks. Whole-brain analyses compared activity between IF and EF blocks and for TD blocks based upon prior block condition with a threshold of $p < .05$, cluster-level corrected using topological false discovery rate as implemented in statistical parametric mapping (SPM) version 8.
Results: As expected, an internal focus of attention during event imagination activated DMN regions (including ventromedial prefrontal cortex, posterior cingulate cortex, and limbic regions including hippocampus and amygdala) more than an external focus of attention during the working memory task. By contrast, EF elicited widespread activation of dorsal prefrontal cortex, precentral gyri, inferior frontal gyri/anterior insula, parietal cortex, thalamus, and midbrain. Despite the fact that all TD blocks were identical, brain activity differed significantly based upon the prior condition, such that engagement of dorsal frontal and parietal regions during TD was significantly reduced when subjects had been previously engaged in the IF as compared to EF task.
Conclusions: These data indicate that the recruitment of dorsal frontal and parietal regions during a task requiring externally directed attention depends on the cognitive processes engaged prior to performing the task. When individuals must disengage from internal information in order to focus on an external task, regions involved in executive attention and motor control are recruited less than when attention was already directed externally. These data have implications for understanding the neural circuitry of internalizing disorders, raising the possibility that excessive internal focus may be associated with impaired recruitment of frontal and parietal regions in response to external information.
Keywords: default mode; imagination; event simulation; internalizing.
Disclosure: E. Stern, Nothing to Disclose; A. Muratore, Nothing to Disclose; S. Taylor, Nothing to Disclose; J. Abelson, Nothing to Disclose; P. Hof, Nothing to Disclose; W. Goodman, **Part 4:** Research funding from Roche.

W72. Enhancing Self Control of Smoking with Real Time fMRI

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Background: Nicotine addiction is associated with dysregulated neural circuitry involved in reward and inhibitory control functions. Cue-induced craving has been found to trigger relapse in smokers as a result of these dysregulated brain systems. Smokers have demonstrated that they can effectively use emotion regulation strategies to modulate these brain systems in response to visual smoking cues. Real time fMRI (rtfMRI) neurofeedback may help people self-regulate their regional brain activity to improve control of their smoking behavior. In preliminary studies we found that smokers improved control of inhibition-related, but not reward-related, brain activity using rtfMRI neurofeedback. The goals of this study were to (1) develop an intuitive rtfMRI neurofeedback approach that helps smokers learn to self-regulate brain activation; (2) test whether neurofeedback training leads to improved self-control of inhibition-related brain activity; and (3) determine whether rtfMRI neurofeedback training results in improved clinical outcomes.
Methods: We collected data from 17 otherwise healthy, non-treatment-seeking cigarette smokers who completed two sessions of rtfMRI neurofeedback training. Participants performed a functional localizer task (Stop Signal Task) at each session in order to identify a region of interest (ROI) for neurofeedback training in the lateral inferior frontal cortex (LIFC), an area involved in inhibitory control. During each rtfMRI neurofeedback training trials, participants were instructed to either 'increase' or 'decrease' their own brain activity while they viewed an image of a person smoking. Participants then recorded their urge to smoke, ability to concentrate, ability to control their brain, or they were instructed to rest. Finally, participants received feedback about their level of brain activity in their LIFC ROI during the period they were instructed to self-regulate. Follow up visits to assess smoking behavior were conducted one week and one month after the second neurofeedback training session. One-way repeated measures ANOVAs and follow-up paired t-tests were used for all analyses.
Results: Participants reported a significant reduction in craving to smoke and number of cigarettes smoked per day one week and one month following neurofeedback training ($p < 0.05$). Unexpectedly, 8 of 17 subjects reported a plan to quit smoking within one year. Participants had variable success in self-regulating brain function across rtfMRI neurofeedback training trials.
Conclusions: Overall, rtfMRI neurofeedback appears to be an intuitive, user-friendly tool that may have clinical promise as evidenced by smokers demonstrating (1) modest improved control of inhibition-related brain activation and (2) decreased craving and number of cigarettes smoked and increased self-efficacy, and, in some cases, new plans to quit smoking following rtfMRI neurofeedback training. Data collection from two control groups is ongoing.
Keywords: real time fMRI neurofeedback smoking
Disclosure: L. Stoeckel, Nothing to Disclose; S. Ghosh, Nothing to Disclose; A. Keshavan, Nothing to Disclose; J. Stern, Nothing to Disclose; S. Whitfield-Gabrieli, Nothing to Disclose; J. Gabrieli, Nothing to Disclose; A. Evins, **Part 1:** Boehringer Ingelheim, Pfizer, **Part 4:** GlaxoSmithKline, Pfizer, Bowman Family Foundation.

W73. Lifetime Comorbidity of Obsessive-compulsive Disorder and Sub-threshold Obsessive-compulsive Symptomatology in the Community: Impact, Prevalence, Socio-demographic and Clinical Characteristics

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Background: The nosological status of obsessive-compulsive disorder (OCD) is currently under review. In the National Comorbidity Survey replication (NCS-R) of US adults, OCD was strongly associated with anxiety, mood, impulse-control and substance use disorders. Data from the Epidemiological Catchment Area (ECA) Study and the NSC-R also identified a greater likelihood of bipolar (especially bipolar-II) disorder comorbidity, compared with major depressive disorder in OCD. This study expands the available knowledge on OCD-comorbidity by investigating the prevalence and clinical impact on a group of individuals with OCD or subthreshold OC syndrome (OCS), prospectively followed-up over an extended period.
Methods: A stratified sample of the general population of Zurich, consisting of 591 subjects (292 males; 299 females) participated in a series of seven interviews over a 30-year period from age 20-50years. Psychologists or psychiatrists interviewed participants in their homes using the SPIKE, a face-to-face interview based upon DSM-criteria that covered the previous twelve months. The number and percentage of comorbid disorders were analysed with contingency tables. Odds ratios and their 95% confidence intervals were estimated with series of bivariate binary logistic regression models. Longitudinal associations between repeated distress and lifetime comorbid disorders were examined with generalized estimating equations. Individuals with OC states, with and without comorbidity, were compared to determine differences in socio-demographic factors, clinical characteristics, levels of distress, functional impairment, suicidality and treatment. Factors related to comorbidity were examined with series of multivariate logistic regression models. Meaningful and multivariately predominant predictors were extracted through the backward stepwise (Wald) exclusion method.
Results: Over the study period, 30 subjects, 11 males and 19 females (63%), were diagnosed with OCD, 98 with OCS and 107 with OC symptoms. Lifetime rates of psychiatric comorbidity were high and increased in prevalence across the OC severity spectrum. As many as 73% of individuals with OCD experienced an anxiety disorder and 60% an affective disorder. When compared to controls (i.e. subjects without any OC symptoms), the lifetime rates of several disorders were significantly associated with OCD (specifically, generalised anxiety disorder (GAD) 50%, $p<0.01$; social phobia 40%, $p<0.01$; agoraphobia 30%, $p<0.01$; panic disorder 17%, $p<0.05$; bipolar disorder 40%, $p<0.01$), whereas unipolar major depression and both alcohol and drug misuse disorders were not significantly more frequently associated with any diagnosis of OC severity-spectrum disorders. Most forms of comorbidity increased distress and impacted negatively on family and work relationships, though disorder-specific effects were observed. Thus, bipolar disorder, agoraphobia and GAD were associated with increased OCD-severity; bipolar disorder was associated with increased substance abuse and suicidal acts and panic disorder with increased treatment-seeking behaviour.
Conclusions: In a population-based sample, lifetime rates of psychiatric comorbidity were high and increased in prevalence across the OC severity spectrum. The American Psychiatric Association is actively considering removing OCD from the Anxiety Disorders group, where it is categorised in the DSM-IV (www.dsm5.org/). Comorbidity, *per se*, does not necessarily imply shared aetiology. The magnitude of the association that was found in this study between a broad range of anxiety disorders and OCD, which exceeded the association with lesser OC states, hints that one distinction between OCD and sub-threshold OC symptoms might involve the recruitment of neuropsychological mechanisms linked to pathological anxiety in the full-blown disorder, either as a causal or consequential factor. From a neuropsychological perspective, our finding of a specific relationship between OC states and bipolarity is intriguing and is consistent with the existence of as yet poorly defined, overlapping response-inhibition deficits that could possibly play an aetiological role both in the development of these disorders and in the progression to substance abuse and suicidal acts. These hypotheses merit further exploration using translational paradigms. Despite the statistical limitations imposed by the small sample-size, our findings additionally highlight the negative impact of psychiatric comorbidity on health and psychosocial function.
Keywords: Obsessive Compulsive Disorder, Ocd, Comorbidity, Lifetime, Prevalence
Disclosure: N. Fineberg, ; M. Hengartner, Nothing to Disclose; C. Bergbaum, Nothing to Disclose; T. Gale, Nothing to Disclose; K. Jefferies, Nothing to Disclose; W. Rössler, Nothing to Disclose; J. Angst, Nothing to Disclose.

W74. Attention and Positive Affect in Bipolar Disorder: An fMRI Study

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Background: Bipolar disorder is characterized by recurrent depressive and/or manic mood episodes that interfere with psychosocial functioning. A prominent feature of bipolar disorder is cognitive impairment, which contributes to impairment in psychosocial functioning. There is little information how affect interacts with concentration and memory in bipolar disorder. This study examined the impact of positive affect on neural networks involved in attention in patients with bipolar disorder with depressive symptoms.
Methods: 40 individuals with DSM-IV bipolar-I disorder (BP-I, 23 females, HAMD: $M=12.2$, $SD=6.6$; YMRS: $M=4.8$, $SD=5.1$) and 34 age- and education-matched healthy control participants (15 females; HAMD: $M=1.0$; $SD=1.4$; YMRS: $M=0.4$; $SD=0.9$) (all right-handed) completed an affective attention task while undergoing functional Magnetic Resonance Imaging (fMRI). MRI data were acquired using a 3.0-T whole-body scanner (Trio-System), equipped for echo planar imaging (Siemens Medical Systems, Iselin NJ) with a 3-axis gradient head coil. In the fMRI paradigm, subjects were shown three-digit numbers (100, 020 or 003). The task was to decide which number was different from the two other numbers (e.g. 1 0 0 – correct answer = 1; 0 2 0 – correct answer = 2). The numbers were superimposed on neutral or positive affectively valenced pictures taken from the International Affective Picture System (IAPS; Lang, Bradley, & Cuthbert, 2005). Data were analyzed with SPM 5 using a random effects model. Regions of activations with $p<.001$ are reported.
Results: For the contrast positive-neutral control subjects compared to bipolar patients had higher activations in the globus pallidus and the insula. Compared to controls, bipolar patients had higher activations in the middle frontal gyrus (Brodmann Area [BA 10]), in the inferior frontal gyrus (BA 45), in the parahippocampal gyrus, and in the superior temporal gyrus (BA 42).
Conclusions: To our knowledge this is the first study that investigates the functional neuroanatomy of task-irrelevant positive affect during concurrent completion of a cognitive task. There was increased activation for patients with bipolar disorder in frontal and temporal areas, which may reflect emotional

regulation processes during completion of the cognitive component of the attention task.
Keywords: bipolar, attention, affect, fMRI
Disclosure: T. Deckersbach, **Part 1:** MGH Psychiatry Academy, Brain Cells Inc., Systems Research and Applications Corporation, Boston University, the Catalan Agency for Health Technology Assessment and Research, the National Association of Social Workers Massachusetts, the Massachusetts Medical Society, Tufts University, NIDA, Oxford University Press, **Part 2:** None other than Massachusetts General Hospital/Partners Healthcare, **Part 4:** NARSAD, TSA, OCF, Tufts University, NIH, NIMH, NIA, AHRQ, Janssen Pharmaceuticals, The Forest Research Institute, Shire Development Inc., Medtronic, Cyberonics, Northstar; A. Corse, Nothing to Disclose; E. Greiter, Nothing to Disclose; A. Arulpragasam, Nothing to Disclose; N. Kaur, Nothing to Disclose; T. Chou, Nothing to Disclose; S. Rauch, **Part 1:** UTSW Grand Rounds – honorarium - 2010, Cleveland Clinic Grand Rounds – honorarium – 2010, NIMH Conte Center OCD Advisory Board – honorarium – 2010, Hall Mercer – Scientific Advisory Board – 2010, Oxford University Press – royalty 2010, APPI – royalty – 2010, NIMHH RDoC – honorarium – 2011, Oxford University Press – royalty 2011, APPI – royalty – 2011, **Part 2:** Primary employer: McLean Hospital/ Partners Healthcare, **Part 3:** None other than primary employer, **Part 4:** Cyberonics, Medtronic; A. Nierenberg, **Part 1:** American Drug Utilization Review, American Society for Clinical Psychopharmacology, Appliance Computing Inc. (Mindsite), APSARD, Astra Zeneca, Bayamon Region Psychiatric Society, Baystate Medical Center, Belvoir Publishing, Brain Cells, Inc., Brandeis University, Bristol Myers Squibb, Canadian Psychiatric Association, Clintara, Columbia University, Dianippon Sumitomo (now Sunovion), Douglas Hospital/McGill University, Eli Lilly and Company, EpiQ, Hillside Hospital, IMEDEX, International Society for Bipolar Disorders, Israel Society for Biological Psychiatry, Johns Hopkins University, Johnson & Johnson, Labopharm, Massachusetts Association of College Counselors, MBL Publishing, Physicians Postraduate Press, Slack Publishin, SUNY Buffalo, University of Florida, University of Miami, University of Wisconsin, University of Pisa, SciMed, Medscape, Merck, Methylation Science, MJ Consulting, New York State, Novartis, PamLabs, PGx Health, PR, San Juan, Shire, Shering-Plough, Takeda/ Lundbeck Pharmaceuticals, Targacept, University of Texas Southwestern Dallas, Infomedic.com, MGH Clinical Trials Network and Institute (CTNI), **Part 2:** None other than Massachusetts General Hospital/Partners Healthcare, **Part 4:** NIH, NIMH, NIA, Janssen Pharmaceuticals, Cephalon, AHRQ, PamLabs, Pfizer Pharmaceuticals, Shire; D. Dougherty, **Part 1:** Medtronic, **Part 4:** Medtronic, Cyberonics, Eli Lilly.

W75. Differences in Neural Response to Extinction Recall in Young Adults Characterized as Behaviorally Inhibited/noninhibited during Early Childhood

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Background: Anxiety is associated with difficulties distinguishing safety and danger cues in ambiguous contexts. Recent studies in anxious populations indicate that deficits in safety learning are mediated by impaired recruitment of ventromedial prefrontal cortex (vmPFC) when making difficult threat-safety discrimination (Lissek, 2009; Milad, 2009, Britton et al., under review). In addition, ventrolateral prefrontal cortex (vlPFC) has been implicated in attention to environmental threats (Monk et al., 2008). Fear conditioning and extinction are studied widely in healthy and anxious adults, but virtually no research extends this work to populations at-risk for anxiety. Behavioral inhibition (BI) is a temperament identified in early childhood, characterized by consistent vigilance towards novel and social situations, and predicts a 2 to 4 fold increase in risk for anxiety disorders (Chronis-Tuscano et al., 2009). The present study examined differences in extinction recall and its mediating neural architecture among young adults identified with BI in early childhood.
Methods: At 4 months, a large sample of typically developing infants were screened for motor and affective reactivity, and infants high on negative affect and motor reactivity were selected. From amongst this subsample, a composite score of BI was generated from maternal reports of child temperament and observations of behavior at 14, 24, and 48-months. At 19 years of age, 22 BI and 27 non-BI were recruited to participate in the current study. The first visit included fear conditioning followed by extinction. During fear acquisition, participants passively viewed neutral faces of two women, which served as conditioned stimuli (CS). One woman, the CS+, predicted the UCS "screaming lady", while the other woman, the CS-, did not. During extinction, the CS+ and CS- were presented in the absence of the UCS. In the second visit, two weeks later, participants underwent MRI scanning while being exposed to previously extinguished CS+. Using a series of morphed images, subjects were exposed to a continuum of stimuli ranging from the CS+ to the CS-, allowing the examination of generalization gradients in response. To assess threat appraisal and explicit memory, subjects were asked to answer one of two questions while viewing the morphed picture: (1) How afraid are you? (2) Did she scream in the past? Whole-brain analysis using linear mixed model approach was used to investigate complex interactions among BI status, cognitive instruction, and linear and quadratic trends across morphed images using an equivalent $p < 0.05$ corrected threshold based on a peak threshold, $p < 0.005$ and cluster size.
Results: In both groups, vmPFC was activated while subjects viewed the series of morphs ([6, 29, -14], $k = 75$), but no group interaction was noted. Preliminary results indicated an interaction between BI status and Morph levels in bilateral vlPFC (Right: [-39, -26, -4], $k = 65$; Left: [36, -24, -4], $k = 25$) and left insula ([39, 9, -6]; $k = 21$). Non-BI showed greater activation than BI in these brain regions, but only in response to morphs containing low levels of the CS+ face.
Conclusions: As demonstrated previously, extinction recall was associated with vmPFC activation. Comparing BI vs. non-BI, vlPFC and insula activation differed during the discrimination of safety and danger cues, but these between-group differences were present only when subjects viewed morphs containing low levels of the CS+ face. Thus, early childhood categorization of BI distinguishes neural response patterns during extinction recall in young adults. These results suggest that, when processing safety and danger cues, BI and anxiety disorders have overlapping as well as distinct neural correlates.
Keywords: Fear conditioning, extinction, fMRI, at-risk population, anxiety disorders
Disclosure: T. Shechner, Nothing to Disclose; N. Fox, Nothing to Disclose; J. Mash, Nothing to Disclose; C. Spiro, Nothing to Disclose; M. Hong, Nothing to Disclose; E. Leibenluft, Nothing to Disclose; D. Pine, Nothing to Disclose; B. Jenifer, Nothing to Disclose.

W76. The Neurosteroids Allopregnanolone and DHEA Enhance Emotion Regulation Neurocircuits and Modulate Memory for Emotional Stimuli

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Background: Allopregnanolone (ALLO) and dehydroepiandrosterone (DHEA) are endogenously-produced neurosteroids with

neuroprotective, anxiolytic, antidepressant, and antiglucocorticoid effects. Dysregulated release of these neurosteroids has been extensively linked to mood and anxiety disorders. Both neurosteroids are endogenously released in response to stress, and reduce negative affect when administered exogenously. Though these antidepressant and anxiolytic effects have been well established, no research to date has examined the neural pathways involved. In particular, brain imaging has not been used to link neurosteroid effects to emotion regulation neurocircuitry.

Methods: To investigate the brain basis of ALLO and DHEA's impact on emotional response and regulation, subjects were administered 400 mg of pregnenolone (N = 16), 400 mg of DHEA (N = 14), or placebo (N = 15) and underwent 3T fMRI while performing the Shifted-Attention Emotional Appraisal Task (SEAT), a test of emotional processing and regulation. FMRI data were analyzed in SPM8 random-effects models ($p < 0.05$, FWE-corrected for whole brain analyses, small-volume-corrected [SVC] for ROIs).

Results: Compared to placebo, ALLO and DHEA both reduced activity in the amygdala ([27,-1,-17]; $F(1,29) = 9.97$; [27,-10,-14]; $F(1,27) = 6.9$, $p < .05$, SVC). ALLO decreased activity in the insula ([42,8,4]; $F(1,29) = 10.97$, $p < .05$, SVC), whereas DHEA decreased activity in the hippocampus ([-33,-28,-11]; $F(1,29) = 22.07$, $p < .05$, SVC) and enhanced connectivity between the amygdala and hippocampus ([30,-13,-11]; $z = 3.40$, $p < .05$, SVC). DHEA enhanced activity in the rostral anterior cingulate cortex ([3,41,-2]; $F(1,29) = 13.3$, $p < .05$, SVC), whereas ALLO increased activity in the dorsal medial prefrontal cortex ([3,56,37]; $F(2,232) = 6.41$, $p < .05$, SVC) and enhanced connectivity between the amygdala and dorsal medial prefrontal cortex ([-30,-1,-23]; $t = 4.8$, $p < .001$), an effect that was associated with reduced self-report anxiety ($r = -.52$, $p = .046$). DHEA reduced memory accuracy for emotional stimuli (conjunctive d'; $t(27) = 2.31$, $p = .029$), and reduced activity in regions associated with conjunctive memory encoding.

Conclusions: These results demonstrate that ALLO and DHEA reduce activity in regions associated with generation of negative emotion and enhance activity in regions linked to regulatory processes. Considering that activity in these regions is altered in mood and anxiety disorders, our results provide initial neuroimaging evidence that these neurosteroids may be useful as pharmacological interventions for these conditions and invite further investigation into the brain basis of neurosteroid emotion regulatory effects.

Keywords: Allopregnanolone, Dehydroepiandrosterone, pharmaco-fMRI, Neurosteroid, Neuroactive steroid

Disclosure: R. Sripada, Nothing to Disclose; C. Marx, **Part 1:** Dr. Marx discloses that she is an unpaid scientific advisor to Sage Therapeutics, **Part 4:** Dr. Marx discloses that she is an applicant or co-applicant on pending U.S. patent applications on the use of neurosteroids and derivatives for the treatment of central nervous system disorders and for lowering cholesterol (no patents issued, no licensing in place); A. King, Nothing to Disclose; S. Garfinkel, Nothing to Disclose; J. Abelson, Nothing to Disclose; I. Liberzon, Nothing to Disclose.

W77. The Nicotinic Partial Agonist Varenicline Attenuates Visuospatial Working Memory Deficits in Schizophrenia Induced by Cigarette Smoking Abstinence

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Background: People with schizophrenia have pervasive cognitive deficits related to prefrontal cortical dopamine (DA) dysfunction (e.g. visuospatial working memory; VSWM). People with schizophrenia are more likely to smoke cigarettes than the general population. However, cigarette smoking abstinence worsens cognitive performance in schizophrenia and the presence of cognitive deficits in domains such as VSWM may predict smoking cessation failure in schizophrenia. VSWM could therefore be an important target for smoking cessation therapies in this population. Therefore, we evaluated the effects of the nicotinic partial agonist and smoking cessation medication varenicline tartrate (Chantix) on cognitive function in smokers with schizophrenia, in comparison to healthy control smokers, under smoking satiation, overnight abstinence and smoking reinstatement conditions.

Methods: A 3-day laboratory paradigm incorporating baseline smoking, overnight abstinence and smoking reinstatement conditions, was employed (*Sacco, KA et al., (2005) Arch Gen Psych 62: 649-59*). Across the three separate test weeks, schizophrenia (n = 12) and non-psychiatric control (n = 12) smokers were co-treated (using a counterbalanced sequence across subjects) with varenicline (0, 0.5 and 1 mg BID) during the 3 test days and assessed on the VSWM task (*Hershey et al., (1998). Neuropsychology, 12: 52-64*) under each smoking condition.

Results: Overnight smoking abstinence induced a deficit in VSWM, which was remediated by reinstatement of smokingin the schizophrenia (main effect of session: $p < 0.05$), but not in the control, group ($p = 0.374$). Varenicline treatment modulated VSWM as a function of smoking condition in the schizophrenia but not the control group (dose × session × diagnosis interaction: $p = 0.004$). Low dose varenicline pre-treatment (0.5 mg BID) attenuated changes in VSWM induced by smoking abstinence and reinstatement in the schizophrenia group (main effect of dose on change in VSWM induced by smoking abstinence: $p = 0.08$). In addition, in smokers with schizophrenia, the highest varenicline dose (1 mg BID) impaired VSWM compared to placebo in the baseline smoking condition ($p < 0.001$) but not in the abstinent or reinstatement smoking conditions.

Conclusions: We have replicated our previous finding that abstinence from cigarette smoking induces deficits in VSWM in schizophrenia but not controls. Moreover, the observation that low-dose subchronic varenicline (i.e., three days) attenuated abstinence-induced cognitive deficits in persons with schizophrenia suggest that it may counteract negative changes in VSWM during a quit attempt that may predispose to smoking cessation failure in this highly vulnerable group of smokers. This has important implications for the development of nicotinic partial agonists as treatments for tobacco dependence and cognitive dysfunction in people with schizophrenia.

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Keywords: schizophrenia, tobacco dependence, working memory, abstinence, varenilcine

Disclosure: V. Wing, Nothing to Disclose; C. Wass, Nothing to Disclose; T. George, **Part 1:** Grant Support from Pfizer, Inc., Member of Data Monitoring Committee for Novartis, **Part 4:** Grant Support from Pfizer, Inc.

W78. Decision Making and Psychological Pain in Acutely Suicidal Depressed Patients

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Background: Suicide is one of the most frequent causes of death in the United States, likely accounting for more than 40,000 deaths

this year. Suicide has been described by the noted columnist Art Buchwald as 'a permanent solution to a temporary problem', indicating that it is the result of flawed decision making. A variety of personality, emotional, and neurobiological factors has been associated with suicide; however, it is still singularly difficult to predict on an individual basis, who will go on to commit suicide. It has been proposed that suicide may be the consequence of poor decision making triggered by overwhelming psychological pain. Here, we interrogated decision making and psychological pain in depressed individuals after a recent suicide attempt.
Methods: We assessed decision making (temporal discounting), psychological pain and clinical characteristics including suicidality, depression, anxiety, hopelessness, childhood trauma and recent stressful events in four groups: (1) recent depressed patients within three days after a high lethality suicide attempt, (2) depressed patients with active suicidal ideation, (3) depressed controls without suicidal ideation, and (4) healthy controls ($n = 10$ per group). Group means were compared with ANOVA and T-Student test, and stepwise linear regression was used to create data explanatory models. Significance level was set as $p = 0.05$.
Results: The suicide attempt and ideation groups had higher levels of depression, suicidal ideation severity and intensity, psychological pain, childhood trauma and recent social stressful experiences than both the non suicidal depressed and healthy control groups. All of the depressed patient groups exhibited impaired decision making and greater impulsivity than healthy controls. Interestingly, there was no difference in decision making, psychological pain, suicidality, depression or anxiety scores between the suicide attempt and ideation groups. Within the suicide attempt group, individuals with persistent suicidal ideation exhibited more severe depression, anxiety and childhood physical abuse scores, and greater impaired decision making. On a follow up assessment, 7-10 days after the suicide attempt, suicide attempters showed a reduction in depression, hopelessness, suicidality and psychological pain scores, as well as in the impairment of decision. 70% of the depressed suicidal patients were already on selective serotonin reuptake inhibitor antidepressants.
Conclusions: Demonstrable but transient decision making abnormalities are found in a subset of depressed patients shortly after a recent suicide attempt. Overall, deficits in decision making and greater psychological pain were associated with presence of suicidal ideation rather than with suicidal behavior. Further studies are warranted to determine the contribution of depression severity in the development of decision making deficits and emotion processing associated with suicidal ideation.
Keywords: suicide, depression, decision making, temporal discounting, psychological pain
Disclosure: R. Caceda, **Part 2:** Astra Zeneca, **Part 3:** Astra Zeneca, **Part 4:** Arsht Foundation, Community Alliance Against AIDS; P. Harvey, **Part 1:** Abbott Labs, Amgen, Boeheringer Ingelheim, Bristol-Myers-Squibb, Forest Labs, Genentech, Johnson and Johnson, Pharma Neuroboost, Roche Pharma, Shire Pharma, Sunovion Pharma, Takeda Pharma, **Part 3:** Abbott Labs, Amgen, Boeheringer Ingelheim, Bristol-Myers-Squibb, Forest Labs, Genentech, Johnson and Johnson, Pharma Neuroboost, Roche Pharma, Shire Pharma, Sunovion Pharma, Takeda Pharma, **Part 4:** AstraZeneca, D. Durand, Nothing to Disclose; E. Cortes, Nothing to Disclose; S. Prendes, Nothing to Disclose; J. Wojas, Nothing to Disclose; C. Nemeroff, **Part 1:** Speakers Bureau, None, Consulting, Xhale, Takeda, SK Pharma, Shire, Roche, Lilly, Allergan, Stockholder, CeNeRx BioPharma, PharmaNeuroBoost, Revaax Pharma, Xhale, NovaDel Pharma, Other Financial Interests: CeNeRx BioPharma, PharmaNeuroBoost, Patents, Method and devices for transdermal delivery of lithium (US 6,375,990B1), Method of assessing antidepressant drug therapy via transport inhibition of monoamine neurotransmitters by *ex vivo* assay (US 7,148,027B2), Scientific Advisory Boards: American Foundation for Suicide Prevention (AFSP), CeNeRx BioPharma, National Alliance for Research on Schizophrenia and Depression (NARSAD), Xhale, PharmaNeuroBoost, Anxiety Disorders Association of America (ADAA), Skyland Trail, AstraZeneca Pharmaceuticals (2009), Board of Directors: AFSP, Mt. Cook Pharma (2010), NovaDel (2011), Skyland Trail, Gratitude America, ADAA, **Part 2:** AstraZeneca Pharmaceuticals, PharmaNeuroBoost, CeNeRx BioPharma, NovaDel Pharma, Reevax Pharma, American Psychiatric Publishing, Xhale, **Part 3:** Speakers Bureau: None, Consulting: Xhale, Takeda, SK Pharma, Shire, Roche, Lilly, Allergan, Stockholder: CeNeRx BioPharma, PharmaNeuroBoost, Revaax Pharma, Xhale, NovaDel Pharma, Other Financial Interests: CeNeRx BioPharma, PharmaNeuroBoost, Patents: Method and devices for transdermal delivery of lithium (US 6,375,990B1), Method of assessing antidepressant drug therapy via transport inhibition of monoamine neurotransmitters by *ex vivo* assay (US 7,148,027B2), Scientific Advisory Boards: American Foundation for Suicide Prevention (AFSP), CeNeRx BioPharma, National Alliance for Research on Schizophrenia and Depression (NARSAD), Xhale, PharmaNeuroBoost, Anxiety Disorders Association of America (ADAA), Skyland Trail, AstraZeneca Pharmaceuticals (2009), Board of Directors: AFSP, Mt. Cook Pharma (2010), NovaDel (2011), Skyland Trail, Gratitude America, ADAA, **Part 4:** National Institutes of Health (NIH), Agency for Healthcare Research and Quality (AHRQ).

W79. The Effects of Cannabis Abstinence on Neurocognitive and Clinical Symptoms in Cannabis Dependent Individuals with and without Schizophrenia

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Background: Cannabis dependence is common in persons with schizophrenia (SZ) and related psychoses, and there is evidence that cannabis misuse may hasten the onset of schizophrenia, and worsen positive, negative and neurocognitive symptoms. The majority of data on neurocognition come from cross-sectional studies, and overall these studies show mixed results; a meta-analysis of such studies controlling for other substance misuse suggested that cannabis use was associated with modest improvements in neurocognition in schizophrenia (Rabin et al., 2011). The present study uses a controlled prospective design to investigate the effects of cannabis abstinence from up to 28 days on psychotic and cognitive symptoms in cannabis dependent person with schizophrenia versus non-psychiatric healthy control (HC) subjects.
Methods: By study end, a total of 40 subjects (20 with SZ and 20 HC) will be enrolled in this study. To date, we have enrolled six subjects in the study (4 SZ, 2 HC) and 3/6 subjects have completed all assessments. Subjects undergoing cannabis abstinence were assessed at baseline, at Day 14 and Day 28 neurocognitive (tests of executive function, working memory, speed of processing, motivation, verbal memory) and clinical (PANSS, HDRS-17). Abstinence during the trial was assessed by self-report and twice weekly by objective measures. Urine specimens were screened with a novel semi-quantitative assay (NarcoCheck) of cannabis from urine, and negative samples were reinforced using low cost contingency management procedures (Petry et al., 2000). Urine samples were then tested by gas chromatography-mass spectroscopy (GC-MS) to obtain quantitative THC-COOH levels, normalized to urinary creatinine. Participants meeting both subjective and analytical criteria for cannabis abstinence are paid $300.
Results: Our preliminary data suggests the feasibility of these controlled cannabis abstinence procedures in an outpatient setting, and the emerging data on cognitive and clinical outcomes from this nascent cohort of SZ and HC subjects undergoing one month of cannabis abstinence will be presented.

Conclusions: We have developed a novel and feasible approach to studying the effects of extended cannabis abstinence in an outpatient setting in cannabis dependent subjects with and without schizophrenia. Our approach may yield important new information on the effects of cannabis abstinence on cognitive and clinical outcomes in persons with schizophrenia. *Supported in part by grants from the Canadian Institutes for Health Research (CIHR; MOP#115145), the Ontario Mental Health Foundation (OMHF) and the Chair in Addiction Psychiatry at the University of Toronto to Dr. George, and graduate fellowships from the CIHR Banting and Best Fellowship and the Ontario Graduate Studentship (OGS) (and OTSOF) to Ms. Rabin.*
Keywords: cannabis, abstinence, schizophrenia, cognition, psychotic symptoms
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W80. Conflict Monitoring and Adaptation in Individuals at Familial Risk for Developing Bipolar Disorder

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Background: Bipolar disorder is a highly heritable illness, with genetic influences explaining 60%-85% of risk variance. However, specific susceptibility genes or neurobiological markers remain unknown. In recent years, genetic and behavioral neuroscience has attempted to define endophenotypes that encompass deficits that are heritable, state-independent, and cosegregated with illness, as well as occur at higher rates in unaffected relatives than the general population. Plausible endophenotype candidates in bipolar disorder include impairments in specific neurocognitive domains. Cognitive impairments in individuals with bipolar disorder were traditionally thought of as mild and limited to acute mood episodes; however, a growing body of evidence challenges this assumption. Studying youth at familial risk for developing bipolar disorder (i.e. with a bipolar parent) could facilitate identifying cognitive endophenotypes. Nonetheless, recent studies suggest children of bipolar patients demonstrate specific deficits in executive function, particularly in tasks assessing cognitive interference and flexibility. Cognitive interference occurs when task-irrelevant background information impedes processing task-relevant information that forms the current focus of attention. Cognitive conflict may be best described as a special instance of cognitive interference in which task-irrelevant information induces incongruent or incompatible mental representations. Given this theoretical approach, selecting task-relevant over task-irrelevant information may be thought of as a core process in the resolution of cognitive interference, and the main goal of conflict monitoring. Similarly, changes in processing speed with shifting levels of conflict represent a measure of conflict driven adaptation.
Methods: Twenty-four adolescents (age 10-20 years) at risk of developing bipolar disorder were recruited from an ongoing longitudinal study assessing the neurodevelopment of adolescents with familial risk for bipolar disorder. "At-risk" (AR) subjects were defined by having at least one parent with bipolar I disorder and no current or past history of any mood or psychotic disorder in themselves. Twenty-three comparison subjects with healthy parents (HC), with no Axis I psychiatric disorder, and no first- or second-degree relative with any mood or psychotic disorder, were also recruited. Subjects in both groups were excluded for any lifetime history of substance use disorder or a pervasive developmental disorder, a total IQ score <80 (as determined by the Wechsler Abbreviated Scale of Intelligence), a loss of consciousness of $>$ 10 minutes, or any unstable neurological or medical illness. All subjects were medication free at the time of testing. Participants completed an arrow version of the Eriksen Flanker Task that included trials with three levels of conflict: neutral, congruent and incongruent flanks. Differences in performance were explored based upon the level of conflict in the current and previous trials.
Results: Examining the response time to the current trail, AR subjects performed slower throughout the EFT [$F(1,803) = 20$, $p < 0.001$]. Specifically, AR subjects displayed slower response times to neutral [$F(1,1771) = 17$, $p < 0.001$], congruent [$F(1,1809) = 15$, $p < 0.001$] and incongruent flanks [$F(1,1987) = 8$, $p = 0.004$] compared to HC subjects. There was no statistically significant group effect for current trial type [interaction group-current trial: $F(2,3386) = 0.92$, $p = 0.4$]. Examining the effect of previous trial type in the response to the current trial, we found that in both groups, there was a significant main effect of previous trial type on response time to the current trial [$F(2,4113) = 5$, $p = 0.008$]. Current trial type was also significantly associated with response time within each group [$F(2,3875) = 279.5$; $p < 0.0001$]. A sequence modulation of response time was observed in both groups [interaction term current trial $\times$ previous trial $F(4,3734) = 11$, $p < 0.001$]. A significant difference between groups in the sequence modulation of response time was detected through the interaction between previous trial type by current trial type by group [$F(4,3738) = 3$, $p = 0.03$]. Specifically, *post-hoc* analyses revealed that the AR group was significantly slower than the HC group in response to neutral, congruent and incongruent trials when preceded by an incongruent trial ($p = 0.006$; $p = 0.02$ and $p = 0.03$ respectively). AR subjects were also slower than HC in neutral and congruent trials when preceded by neutral trials ($p < 0.0001$ and $p < 0.001$ respectively) and to incongruent trials when preceded by congruent trials ($p < 0.01$).
Conclusions: Adolescents at risk for developing bipolar disorder displayed specific deficits in cognitive flexibility, which might be useful as biomarkers related to the development of bipolar disorder.
Keywords: Bipolar Disorder, at risk, youth, neurocognitive, conflict monitoring
Disclosure: L. Patino Duran, Nothing to Disclose; C. Adler, **Part 1:** Research Support (multi-site trials), AstraZeneca, Eli Lilly, Pfizer, Otsuka, Forest, Sunovion, Novartis, Glaxo Smith-Kline, Amylin, Research Support (direct research funding), AstraZeneca, Lecture Bureau, Merck, Consulting, Merck; N. Mills, Nothing to Disclose; S. Stephen, **Part 1:** Recent Research Support (grants to UC or UCP Psychiatry): as PI – NIMH; as co-investigator - Eli Lilly, Janssen/J&J, AstraZeneca, Sumatomo, Pfizer, NIDA, NIAAA, NIMH, NARSAD (details available with the University/UC Physicians)., Consultant: University of Nebraska - $3,500, Speaking:, Other:, CME companies get support from different pharmaceutical companies that can and does; D. Fleck, Nothing to Disclose; J. Welge, Nothing to Disclose; M. DelBello, **Part 1:** Research Support, AstraZeneca, Eli Lilly, Johnson and Johnson, Janssen, Pfizer, Otsuka, Sumitomo, NIDA, NIMH, NIAAA, NARSAD, Glaxo-SmithKline, Merck, Novartis, Lundbeck, Lecture Bureau, Bristol-Myers Squibb, Merck, Consulting/Advisory Board/Honoraria, Merck, Schering-Plough, Pfizer.

W81. Theta Power Modulation of Selective Encoding in Schizophrenia

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Background: Efficient episodic memory requires selective encoding of relevant versus irrelevant information, and this selectivity depends upon coordination of prefrontal-hippocampal neural

activity supported by slow wave oscillations in the theta range (~ 4-8 Hz). The current study utilized a selective encoding paradigm (CMET) and EEG waveform analysis to test the hypothesis that increased theta band power associated with selective encoding of a subset of test stimuli (variable rule condition) versus non-selective encoding of all test stimuli (fixed rule condition) is reduced in patients with schizophrenia.
Methods: Fifteen controls and sixteen patients alternated between two auditory word encoding conditions: 1) "Fixed Rule" – make living/nonliving judgment and remember all words. 2) "Variable Rule" – make living/nonliving judgment and try to remember only if word is a target (e.g., male voice), otherwise (e.g., female voice) "skip" the word. Recognition was tested for all of the words. Time-frequency transformations were performed using EEGLab with Morlet wavelet analysis. Delay period (0-1000 ms) for the theta frequency range was analyzed using a -200-0 ms baseline and a Gaussian kernel with a constant of 3. Bootstrap procedures revealed that the only significant group differences were during variable rule versus fixed rule task conditions, with patients showing reduced theta band activity in response to increased selection demand.
Results: Results converge with previous fMRI findings in suggesting that encoding deficits in schizophrenia are most prominent under high cognitive control conditions when rules must be used to guide response selection.
Conclusions: EEG data suggest that disrupted oscillatory activity in the theta range, which has been linked to dysfunctional parvalbumin containing interneurons in the prefrontal cortex, may be contributing to these selective encoding deficits.
Keywords: Episodic Memory, EEG oscillations, Cognitive Control
Disclosure: J. Ragland, Nothing to Disclose; J. Phillips, Nothing to Disclose; M. Minzenberg, Nothing to Disclose; T. Lesh, Nothing to Disclose; T. Niendam, Nothing to Disclose; M. Solomon, Nothing to Disclose; J. Yoon, Nothing to Disclose; C. Carter, Nothing to Disclose; C. Ranganath, Nothing to Disclose.

W82. Differential Roles of Basic Visual Information in Fear and Happiness Perception in Schizophrenia

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Background: Schizophrenia patients are impaired at recognizing facial emotions. This impairment is typically attributed to an affective processing deficit mediated in the limbic system. Processing of facial emotions also depends on inputs from the visual system. One approach to understanding the role of visual information in emotion recognition is to examine how manipulation of high and low spatial frequencies (HSFs and LSFs), which have differential modulatory effects on limbic and visual systems, impacts perception of emotions.
Methods: Perception of fear and happiness was measured with or without modulations of basic visual information. Visual information of face images was manipulated via high-pass (removing LSFs) and low-pass (removing HSFs) filtering. Twenty-eight patients and 27 controls judged which of two faces, differing only in spatial frequency content, was more fearful or happier. These judgments were made at three emotion salience levels (non-emotive, slightly emotive, highly emotive), and with three spatial frequency manipulations (high-passed, low-passed, unfiltered).
Results: Patients perceived images which contained LSFs (low-passed, unfiltered) as more fearful than those without LSFs (high-passed), across emotion salience levels ($p < 0.001$). This effect was not found in controls. Additionally, patients perceived images which contained HSFs (high-passed, unfiltered) as happier than those without HSFs (low-passed), across salience levels ($p < 0.001$). In controls, this effect was found only at low emotion salience.
Conclusions: These data indicate that low spatial frequency information, which rapidly projects to the limbic system, affects patients' fear perception to a greater extent than controls'. High spatial frequency information, which differentially activates the fusiform cortex, modulates happiness perception to a greater extent than LSFs in both groups. Yet, only in the patient group was this visual information modulation unaltered by emotion salience. Together, these results show that basic visual information has excessive modulatory effects on emotion perception in schizophrenia.
Keywords: Face perception, emotion, visual processing, schizophrenia, spatial frequency
Disclosure: Y. Chen, Nothing to Disclose.

W83. Parents of Low Socioeconomic Status: Brain Function and Structure is Affected by Perceived Social Status and Early Life Experience

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Background: One fifth of America's children grow up in families that suffer poverty. While there is good evidence that low socioeconomic status (SES) is harmful to development, health, achievement, and socio-emotional adjustment, very little is known about the role of the brain. Our primary aim is to determine how the chronic stress of childhood poverty influences adult brain physiology, including responses to emotionally salient, parent-related stimuli and structural analyses combined with objective and subjective measures of SES, perceived maternal care and stress. We hypothesize that young adults who experienced the chronic stress of childhood poverty will respond differentially to baby-cry stimuli depending on their parenting status. In addition, among low-SES parents, there will be differential responses to baby-cry and structural findings influenced by con-current subjective SES, stress and perceived early life maternal care measures.
Methods: Participants were recruited from an ongoing 16-year, longitudinal research program of low and middle-income individuals focused on childhood poverty, physiological stress, and socio-emotional development and recent brain imaging and coordinated psychometrics. Here, we analyzed a subset of low SES parents ($n = 11$) and non-parents ($n = 15$). Each subject completed psychometric evaluations, including demographics, subjective SES (ladder measurement), perceived psychosocial stress and maternal care (Parker Parental Bonding Instrument). To assess brain function, subjects performed an auditory baby-cry task in a 3T Phillips scanner, in which they listened to 20 second-blocks of baby-cry or pattern-matched white noise, prefaced by a primer: "a baby crying" or "your baby crying". Functional data were analyzed with SPM 8, with significance threshold for the whole brain set at $p < .005$ (uncorrected). Each subject also underwent a high-resolution T1-weighted MRI for thickness and volume analysis using Freesurfer software, correcting for gender and age.
Results: Within low SES subjects, parents ($n = 11$) as compared to non-parents ($n = 15$) exhibited increased activity in a network of brain regions including the midbrain, amygdala, insula, anterior cingulate, caudate and ventral striatum in response to "a baby crying" condition. Across the entire group ($n = 26$), responses in the ventral striatum and amygdala were proportional to the measure of subjectively perceived SES. This is consistent with the literature on emotional salience and reward circuits that are activated in parents in response to baby stimuli. Within the group of parents of chronic low SES ($n = 11$), the differential response to "own baby cry" in Insula was directly proportional to perceived SES, on the other hand the same response in habenula was

inversely related to perceived SES. Since insula activation in parenting studies has been associated with positive parenting thoughts and behaviors and habenula with learned helplessness, these results suggest that higher subjective SES may preserve positive caring neural responses in the insula and reduce negative responses in the habenula. Subjective SES rating in low-SES parents was inversely correlated with their current perceived stress level ($r = -0.692$, $p = 0.039$) and low perceived early-life maternal care ($r = 0.661$, $p = 0.005$). Structurally perceived early-life maternal care was inversely associated with the size of the regions within limbic brain circuits that may play a key role in parenting. Specifically, lower quality of early-life maternal care predicted smaller bilateral ventral striatum (left putamen, $p = 0.038$; right putamen, $p = 0.009$) and left amygdala ($p = 0.019$). These results suggest a link between specific aspects of low SES - such as early life maternal experience, current subjective social status and stress - and neural physiology in brain regions that are integral to emotion response, regulation and motivation in parents.
Conclusions: With the aid of neuroimaging techniques, we aim to characterize and differentiate the influence of objective and subjective socioeconomic status, early-life maternal care and current perceived stress on parent brain functions, among subjects that suffered chronic childhood poverty. Our finding support the literature suggesting the key role of specific brain circuits involved in emotional response and regulation in responding to baby cry. Within the subset of parents of low-SES, we find that subjective SES correlates with baby-cry response directly in insula and inversely in habenula, regions that are linked with positive parenting and helplessness respectively. Furthermore, structural findings suggest that perceived maternal care, which we found to be correlated with subjective SES, was linked to limbic brain volumes in regions that play roles in parenting. These findings suggest that subjective aspects of SES and early life experience impact brain function and structure relating to parenting with possible trans-generational implications.
Keywords: parental-brain fMRI insula striatum socioeconomic
Disclosure: J. Swain, Nothing to Disclose; S. Ho, Nothing to Disclose; G. Evans, Nothing to Disclose; X. Wang, Nothing to Disclose; R. Varney, Nothing to Disclose; I. Liberzon, Nothing to Disclose.

W84. Olanzapine, but Not Fluoxetine, Treatment Increases Survival in Activity-based Anorexia in Mice

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Background: Anorexia nervosa (AN) is an eating disorder characterized by extreme hypophagia, hyperactivity, and fear of weight gain. No approved pharmacological treatments exist for AN despite high mortality rates. The activity-based anorexia (ABA) phenomenon models aspects of AN in rodents, including progressive weight loss, reduced food intake, and hyperactivity.
Methods: First, we optimized the ABA paradigm for mice. We compared mouse strains (Balb/cJ, A/J) for susceptibility to ABA, and evaluated the effects of different food access durations (2, 4, 6, 8, and 10 h) on ABA measures. Then, we evaluated the effects of chronic treatment with fluoxetine (4 weeks) or subchronic treatment with olanzapine (OLZ) (1 week) on ABA in female BALB/cJ mice.
Results: Balb/cJ mice exhibited significantly shorter survival time (days until 25% bodyweight loss) in the ABA paradigm compared with A/J mice. Furthermore, 6 h of food access reduced survival in mice housed with wheels without reducing survival in mice housed without wheels. OLZ (12 mg/kg/day) significantly increased survival and reduced food anticipatory activity (FAA). However, OLZ did not alter food intake or running wheel activity during ad-lib feeding or restriction conditions, or in mice housed without wheels. Fluoxetine (18 mg/kg/day) increased food intake and reduced FAA, but did not alter survival. Here, we report for the first time that OLZ, but not fluoxetine, reduces ABA in mice.
Conclusions: Our findings indicate further need for clinical investigations into the effects of OLZ, but not selective serotonin reuptake inhibitors, on core features of AN.
Keywords: atypical antipsychotic, SSRI, survival, anorexia, ABA
Disclosure: S. Dulawa, Nothing to Disclose; S. Klenotich, Nothing to Disclose; M. Seiglie, Nothing to Disclose; M. McMurray, Nothing to Disclose; J. Roitman, Nothing to Disclose; D. Le Grange, Nothing to Disclose; P. Dugad, Nothing to Disclose.

W85. Antipsychotic use, Cardiometabolic health and Care Coordination: Implementation of Metabolic Monitoring Guidelines in a Large Outpatient Psychiatry Clinic

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Background: Use of antipsychotics (AP) has been on the rise secondary to broader Food & Drug Administration approved indications which now includes bipolar disorder and adjunctive treatment for depression/anxiety. Use of APs, however, has also been associated with higher risk of serious medical consequences. A recent study suggested that antipsychotic use is independently associated with cardiometabolic risks, even after adjusting for patient's lifestyles characteristics. Other factors such as race, ethnicity, socioeconomic status, comorbidities, and non-compliance with treatment/monitoring recommendations might play a role in increasing cardiometabolic risks. In the present study, AP use, their indications, demographic and clinical profiles of patients receiving APs was investigated in a large outpatient psychiatry clinic at the University of Connecticut Health Center (UCHC). Monitoring of cardiometabolic health by patient's psychiatric and medical providers was also investigated per the American Psychiatric Association/American Diabetes Association (APA/ADA) guidelines. Finally, we conducted a survey of medical and psychiatric providers on the issue of coordination of care specifically focusing on this issue.
Methods: The project was approved by the UCHC Institutional Review Board. Patients receiving APs were randomly selected from the case load of six clinicians in the outpatient psychiatry clinic. A retrospective chart review was conducted using an assessment form specifically designed for the project. The assessment form gathered following information: patient demographic factors (age, gender, education, race and ethnicity), APs and indications for their use, comorbidities including cardiovascular issues and diabetes, familial risk factors, current monitoring of cardiometabolic health; specifically weight/height, waist circumference, vitals and metabolic monitoring (as recommended by the APA/ADA consensus statement, 2004). A total of 15 psychiatric prescribers and 19 internists were anonymously surveyed on the issue of AP use and cardiometabolic health. The survey included nine questions about clinician's knowledge of APs, APA/ADA monitoring guidelines and coordination of care between two specialties.
Results: A total of 93 patient charts were reviewed (46 males and 47 females). Patients were primarily white ($n = 61$). More than half (55%) had high school education or less. Risperidone ($n = 30$) was the most frequently prescribed antipsychotic, followed by quetiapine ($n = 23$) and aripiprazole ($n = 20$). The indications included psychosis ($n = 29$), bipolar disorder ($n = 28$), adjunctive treatment for depression/anxiety ($n = 15$) and off-label indications ($n = 21$) such as impulse control disorder. A total of 12 patients were receiving two APs simultaneously. Approximately two third of patients carried a secondary psychiatric diagnosis and almost all (95%) were receiving concomitant psychotropic medications.

Approximately one third of patients (n = 29) had known cardiovascular comorbidities and similar number of patients (n = 24) were diagnosed with diabetes. Preliminary analyses showed significant gaps in monitoring of cardiometabolic health of these patients and lack of coordination between the psychiatric prescriber and patent's medical providers. More than half of medical providers surveyed stated that psychiatric prescribers are responsible for monitoring of cardiometabolic issues. About two third of internists were not aware of the existence of the APA/ADA monitoring guidelines. Comprehensive data on the AP use, gaps in monitoring and survey results will be presented.
Conclusions: A survey of major public and private mental health systems in 2010 found that adherence to APA/ADA monitoring guidelines remains limited due to a number of impediments. The present study results confirmed significant gaps in monitoring of cardiometabolic health of patients receiving APs in the outpatient psychiatry clinic and found that APs are being prescribed more often for non-psychotic indications. The findings suggested that lack of coordination between psychiatric and medical providers was one of the primary reasons for the gaps in monitoring. A second-phase of the project is currently underway to implement monitoring as recommended by the APA/ADA guidelines and to rigorously assess risk-benefit ratio when prescribing APs.
Keywords: Antipsychotics, cardiometabolic monitoring, care co-ordination
Disclosure: J. Kamath, Nothing to Disclose; K. Nawrocki, Nothing to Disclose; R. Andrews, Nothing to Disclose.

W86. Brain GABA in Schizophrenia and Bipolar disoders

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Background: GABAergic dysfunction may underlie some of the symptoms in schizophrenia (SZ) and has been suggested by genetic and postmortem studies (Lewis and Burgos, 2006). However, *in-vivo* tissue measurement of GABA is challenging and currently limited to the proton magnetic resonance spectroscopy methodology. Four studies have examined GABA in SZ, with MEGA-PRESS, an editing sequence, but the results have been inconsistent. The specificity of GABA abnormalities in SZ compared to subjects with bipolar disorder with psychotic features (BP), has not been examined. We present preliminary results from an ongoing investigation in these populations.
Methods: We used a MEGA-PRESS (Mescher *et al*, 1998) sequence (TR = 3 s, TE = 68 ms) to acquire localized, water suppressed spectra from a 20 cc voxel in the posterior medial parietal cortex, with a 3T Siemens Trio scanner. The subtraction of signals from alternate EDIT-on and EDIT-off scans results in selective observation of the outer lines of the GABA triplet plus macromolecules (GABA +). We integrated the area for GABA + with MATHLAB and referenced to the water area from an unsuppressed scan, to calculate GABA + /H20 concentrations for each subject. Initially, we assessed the test-retest reliability of this method in 5 SZ and 4 healthy control (HC) subjects. Each subject was scanned, pulled out of the scanner for 5 mins and re-scanned. Subsequently, we measured GABA + /H20 in medicated, clinically stable outpatients with SZ (n = 27) and BP (n = 9), as well as in HC (n = 17).
Results: The Coefficient of Variation (CV) for GABA + /H20 was 12% (11.9% for SZ and 12.3% for HC). The mean (standard deviation) GABA + /H20 for the three groups was: SZ = 0.93 (0.21), BP = 0.99 (0.18), and HC = 0.95 (0.19). One-way ANOVA did not reveal any group differences (f = 0.39, p = 0.68).
Conclusions: In this study we fail to detect GABA abnormalities in SZ or BP subjects, in the posterior medial parietal cortex. These patients were clinically stable and treated with antipsychotic medications. These preliminary results are consistent with the report from Kegeles *et al* (2012), which found GABA + /H20 elevations in unmedicated SZ patients, but normal concentrations in medicated subjects, in the anterior medial frontal cx. Antipsychotic treatment may restore GABAergic function in SZ and BP disorders.
Keywords: GABA, MEGA-PRESS, Schizophrenia, Bipolar
Disclosure: J. Bustillo, **Part 1:** Novartis study AQW051A2202 member of the Independent Data and Safety Monitoring Board.; H. Chen, Nothing to Disclose; T. Jones, Nothing to Disclose; N. Lemke, Nothing to Disclose; C. Abbott, Nothing to Disclose.

W87. A Brain-selective Prodrug of 17β-estradiol in the Male Mouse: Implications for the Use of Estrogen in Men who Suffer from Mood and Anxiety Disorders

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Background: The male brain contains significant levels of estrogen receptors and 17β-estradiol, the latter due to conversion from testosterone by aromatase. Estrogen replacement therapy (ERT) has been suggested as a treatment for neuropsychiatric disorders. Interestingly, in severe cases of schizophrenia or cognitive deterioration ERT showed therapeutic capacity in men. However, there are several concerns when treating men with estrogen, especially with regard to its peripheral activity and associated negative side effects. Recently we found that treatment with DHED, named from its chemical acronym and representing a novel brain-specific bioprecursor/prodrug of 17β-estradiol without peripheral estrogenic action, elicited antidepressant- and anxiolytic-like effects in female mice. Based on these results the current study was designed to test the utility of brain-selective estrogen therapy to modify depression- and anxiety-like behaviors in male mice.
Methods: Ten week old gonadally intact male C57BL/6J mice were treated (s.c., 2 h prior to each procedure) with vehicle, DHED (1, 3 10 μg/kg/4 ml) or 17β-estradiol (25 μg/kg/4 ml), and tested in behavioral procedures that assess antidepressant- and anxiolytic-like action in the mouse. Mice were tested following a single injection in the forced swim test (FST; a screening tool for antidepressant action). A different cohort was treated chronically (first test was conducted following the 7th injection) with vehicle, DHED (1, 3 μg/kg/4 ml) or 17β-estradiol (25 μg/kg/4 ml) and tested in the following procedures. To assess locomotor activity and anxiety-like behaviors animals were tested in the Elevated Plus Maze (EPM), and Open Field (OF). To assess antidepressant-like action animals were tested in the Tail Suspension Test (TST), and Learned Helplessness (LH).
Results: Administration of DHED, similarly to 17β-estradiol, reduced immobility time in the FST and TST, implicating an antidepressant-like action of both treatments. In the LH, although DHED increased escape behavior, this trend did not reach statistical significance. However, treatment with 17β-estradiol yielded a significant increase in escape behavior, supporting an antidepressant action of estrogen in male mice. DHED treatment resulted in an increase in the time mice spent in the open arms of the EPM, without affecting locomotor activity as measured in the OF or EPM. Neither 17β-estradiol nor DHED treatment had an effect on body weight throughout the chronic administration. However, treatment with 17β-estradiol resulted in a significant reduction of testicular weight, an effect which was not observed with DHED.
Conclusions: These findings provide support for antidepressant-like capacity of estrogens in male mice. Importantly, the lack of estrogenic-like activity on testicular weight suggests that DHED's conversion to 17β-estradiol is restricted to the brain, similarly to our previous findings in female mice. Furthermore, behavioral

results suggest some superiority of DHED even in the context of neuropharmacological effects, since in addition to the antidepressant-like action of DHED in the TST and FST this treatment also elicited anxiolytic-like action in the EPM which was not observed following treatment with 17β-estradiol. Thus, the use of a unique brain-selective prodrug of 17β-estradiol that does not expose the periphery to estrogens, while eliciting estrogenic modulation of behaviors in the male mouse, may provide a novel and promising potential treatment for men who suffer from psychiatric disorders.
Keywords: mood disorders; animal model; estrogen; para-quinol; 10β-Hydroxyestra-1,4-diene-3-one
Disclosure: M. Arad, Nothing to Disclose; S. Piantadosi, Nothing to Disclose; K. Tatrai-Prokai, Nothing to Disclose; I. Merchenthaler, Nothing to Disclose; L. Prokai, Nothing to Disclose; T. Gould, Nothing to Disclose.

W88. Haste or Speed? Balancing Speed and Accuracy during a Motivated Reaction Time Task in Remitted and Depressed Patients with Bipolar Disorder

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Background: A variety of evidence to suggest that bipolar disorder is associated with disruptions of reward related processes, although the properties and scope of these changes are not well understood. A possible empirical approach to this question is to examine the effect of bipolar disorder on the modulation of performance of a cognitive or sensorimotor task in the presence of incentives.
Methods: In the present study, we aimed to address these issues by examining performance of patients with bipolar disorder (24 depressed bipolar; 32 euthymic bipolar) on a motivated choice reaction time task with established sensitivity to manipulations of serotoninergic neurotransmission (Cools et al, 2005; Roiser et al. 2006). We compared performance with a group of healthy control individuals ($n = 43$) and a group of patients with unipolar depression ($n = 38$), who were matched on several demographic variables. The task consists of an 'odd-one-out' discrimination, in the presence of a cue signaling the probability of reward on a given trial (10%, 50% or 90%) given a sufficiently fast response. Previous studies with this task observe a reliable shortening of reaction times in the high compare to low reward cue, and consequently we compared performance on these conditions in our analysis.
Results: All groups showed similar reaction time performance, and similar shortening of reaction time following the presentation of a reward related cue. However, compared to healthy individuals, the euthymic bipolar group, and to a lesser extent the depressed bipolar group, showed a relative increase in error rate during the high reward compared to low condition (euthymic bipolar vs control *post hoc* p value: $p = 0.008$; depressed bipolar vs control: $p = 0.088$). In other words, rather than optimize their performance for the high reward condition, error rates were increased despite a similar pattern of reaction times. Further analysis revealed that in the healthy control and unipolar depression groups, relative increase in error rate during the high compared to low reward condition was negatively correlated with relative reaction time speeding during the high compared to low reward condition, across participants ($r's < -0.42$, $p's < 0.006$). By contrast, reward related speeding and reward related increase in errors were uncorrelated in both bipolar groups ($p's > 0.68$). The difference of correlation coefficients between individuals with a bipolar diagnosis (euthymic and depressed) and those without was significant ($z = 2.77$, $p = 0.0056$).
Conclusions: These findings suggest that although reaction time performance on the present task is relatively well matched, there may be a specific failure to calibrate reaction time speed and accuracy in a strategic fashion in the presence of reward-related stimuli. Across individuals without a diagnosis of bipolar disorder, a relative speed/accuracy trade off was observed, such that relatively enhanced reaction time performance on the high compared to low reward condition came at the expense of increased a relative increase in error rate. However, individuals with a diagnosis of bipolar disorder showed no such calibration, and also tended to show relatively increased error rates in the high reward condition. We suggest that this may be related to a hypersensitivity to rewarding cues leading to excessive arousal, which has a deleterious effect on strategic control of reaction time performance. Although the measures could not be used to discriminate individuals with a bipolar diagnosis from those without, the findings were suggestive that a similar dysfunction may be present across different phases of the bipolar illness, and may represent an important target for future research.
Keywords: Bipolar Disorders, Depression, Reaction time, incentives, speed accuracy trade off
Disclosure: H. Chase, Nothing to Disclose; H. Aslam, Nothing to Disclose; J. Almeida, Nothing to Disclose; M. Phillips, Nothing to Disclose.

W89. An Improved Framework for Confound Regression and Filtering for Control of Motion Artifact in the Preprocessing of Resting-state Functional Connectivity Data

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Background: Several recent reports in large, independent samples have demonstrated the influence of motion artifact on resting-state functional connectivity MRI (rsfc-MRI). Standard rsfc-MRI preprocessing typically includes regression of confounding signals and band-pass filtering. However, substantial heterogeneity exists in how these techniques are implemented across studies, and no prior study has examined the effect of differing approaches for the control of motion-induced artifacts.
Methods: To better understand how in-scanner head motion affects rsfc-MRI data, we describe the spatial, temporal, and spectral characteristics of motion artifacts in a sample of 348 adolescents. Analyses utilize a novel voxelwise description of head motion. Building on this information, we systematically evaluate the efficacy of a range of confound regression and filtering techniques for the control of motion-induced artifacts.
Results: Results reveal that the effectiveness of preprocessing procedures on the control of motion are heterogeneous, and that improved preprocessing provides a substantial benefit beyond typical procedures. An optimized pipeline including a 36-parameter confound regression model as well as spike regressors in combination with band-pass filtering at 0.01-0.08 Hz provides a dramatic improvement over typical processing pipelines according to every outcome measure evaluated.
Conclusions: These results demonstrate that the effect of motion on rsfc-MRI can be substantially attenuated through improved preprocessing procedures, but not completely removed. All studies of functional connectivity relating to individual differences in clinical or developmental populations should report and account for motion artifact that is present in the data.
Keywords: motion, artifact, fMRI, connectivity, development, adolescence, network, connectome, resting-state
Disclosure: T. Satterthwaite, Nothing to Disclose; M. Elliott, Nothing to Disclose; R. Gerraty, Nothing to Disclose; K. Ruparel, Nothing to Disclose; J. Loughead, Nothing to Disclose; M. Calkins, Nothing to Disclose; S. Eickhoff, Nothing to Disclose; H. Hakonarson, Nothing to Disclose; R. Gur, Nothing to Disclose; R. Gur, Nothing to Disclose; D. Wolf, Nothing to Disclose.

W90. Effects of Yoga on Cognition, Psychiatric Symptoms, Weight and Biochemical Changes in Chronic Schizophrenic Patients

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Background: A few studies have suggested that Yoga may be effective in improving psychiatric symptoms, quality of life measures, and cognition in schizophrenic patients Studies in non-psychotic patients with type -2 diabetes show Yoga effects on weight reduction and improvement in glucose-lipid parameters. Studies in non-psychotic patients have also shown reduction in cortisol, TSH and alteration in ACTH response. Studies of response in glucocorticoid receptors in brain and blood cells have shown that behavioral treatments related to maternal care, maternal depression or stress and childhood abuse can alter glucorticoid receptors and their epigenetic control. We present results from a preliminary study of the effects of Yoga on these multiple aspects of clinical, cognitive, and biochemical response in schizophrenic patients.
Methods: We conducted a study of Yoga in 21 chronic schizophrenic outpatients (schizophrenia or schizoaffective diagnosis) who participated in 12 weeks (1 h sessions 3x/week) of Hatha Yoga (group 1) or later a modified Yoga concentrating more on Qigong movements and procedures (group 2). Both groups practiced Coherent Breathing, gentle breathing at 5 breaths per minute with equal inhalation and exhalation. Patients entered had BMI $\geqslant 27.5$, and/or fasting glucose >100 mg. Subjects were evaluated at baseline and end for a) Cognition (RBANS), b) Psychiatric Symptoms (PANSS), c) glucocorticoid receptor mRNA in lymphocytes, and d) appetite measures in response to a test meal. They were evaluated monthly for e) fasting glucose and lipid measures, f) cortisol, and ACTH, TSH, and g) weight and waist measures. Statistical analysis used paired sample t-test and repeated measures analyses of variance.
Results: Three months of Yoga treatments produced significant *increases* in Cognitive Scores on RBANS Total Scores and Sum of Index Scores ($P = .001$) and increases in RBANS sub-scores of Attention, Delayed Memory, Figure Copy, Visual- Spatial Construction, Semantic Fluency and Language Index. There were no significant changes in PANSS scores, although there was a trend for decrease on the Depression factor ($P = .08$) and PANSS General Factor ($P = .06$), and other scores showed a slight trend for decrease. There were no significant changes in weight or glucose and lipid measures, but Waist and Hip circumference significantly decreased ($P = .001$). In the test meal volume of meal consumed was decreased after Yoga treatment. There was a trend ($P = .2$) for increase in serum ACTH and a tendency for increased cortisol in Yoga group 2. Serum cortisol and ACTH were highly correlated at baseline ($r = .69$, $P = .001$), but not correlated by 8 or 12 weeks of Yoga treatment (r's = 0.07.-.0.13). In preliminary analysis from data form Yoga group 1, 9 patients showed approximately 50% decrease in lymphocyte glucocorticoid receptor mRNA (GR mRNA (baseline) 4.51 vs. (end) 2.08, $P = .030$).
Conclusions: Our results suggest that Yoga improves cognitive function in schizophrenic patients and may modify glucocorticoid receptor function. Studies with appropriate controls, including exercise controls, are needed to further specify these effects. Longer periods of breathwork while walking may produce stronger effects.
Keywords: Yoga, Schziophrenia, Cognition, Glucocorticoid Receptor
Disclosure: R. Smith, **Part 1:** Grants from Stanley Foundation; Research Drug supplied by Pfizier and Takeda; M. Mathew, Nothing to Disclose; L. Maayan MD, Nothing to Disclose; Gerbarg, M.D, Nothing to Disclose; R. Brown MD, **Part 1:** a possible conflict with a pending patent, Confirmation No. 9891, using 7-keto, DHEA for the treatment of Post Traumatic Stress Disorder; E. Visceglia M.D, Nothing to Disclose; H. Sershen, PhD, Nothing to Disclose; A. Lajtha PhD, Nothing to Disclose; S. Boules MD, Nothing to Disclose; J. Auta, Ph.D, Nothing to Disclose; A. Guidotti, M.D, Nothing to Disclose; J. Davis, M.D, Nothing to Disclose.

W91. Depression-associated Risk Variant in GRM7 Predicts Vulnerability in Offspring at Risk for Major Depression and is Associated with Cortical Thickness Patterns

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Background: Longitudinal studies of at-risk populations including offspring of affected parents represent an important research strategy to map the trajectory into illness and study intermediate phenotypes and genetic determinants of vulnerability. Here, we have a unique opportunity to integrate genetic data and neuroimaging endophenotypes in the context of a family-based 3-generation sample of participants at risk for Major Depressive Disorder (MDD). As part of an ongoing study to identify genes that confer risk to MDD in the High Risk sample, we selected three candidate SNPs mapping in the gene encoding the *metabotropic glutamate receptor 7* (*GRM7*), based on the positive results of a previous GWAS that identified *GRM7* variants associated to depression.
Methods: Three candidate SNPs, i.e., rs9870680, rs9815274, and rs1569285, were tested in 70 multi-generational pedigrees. The pedigrees comprise the original sample probands, defined as G1, their offspring in the second generation, G2, and the third generation, G3. MDD of the original G1 probands was assessed using SADS-L. G2 and G3 participants were identified as at high risk for MDD or at low risk based on the clinical diagnosis of MDD of the G1 probands from which they descend. Based on the risk status classification, the final analysis comprised 118 high risk (HR) and 43 low risk (LR) nuclear families. Genotyping was conducted with TaqMan assays under standard conditions. Famtypes software was used to parse pedigree information. Both quality control and association analyses were conducted using PLINK. In the Part 1 of the analysis, we used the transmission disequilibrium test (TDT) to test for distortion in transmission of alleles from heterozygous G1 affected parents to G2 and G3 at-risk offspring. PLINK TDT decomposes large pedigrees into individual nuclear families which are treated as independent in most of the calculations. In a separate analysis, the same approach was applied to test for distortion in the LR nuclear families as a control. In Part 2, we tested if risk variants identified in part 1 analysis influence cortical thickness patterns prior to the manifestation of clinical symptoms. Data from a previous brain imaging study on the same sample showed significant differences in cortical thickness patterns between HR and LR participants, providing evidence of a valid endophenotype related to the vulnerability to the disease in at-risk subjects. Data were available only for a subset of the original sample, comprising 57 HR and 46 LR participants. An exploratory analysis tested for the association of the risk alleles with 23 brain region volumes of the right hemisphere using the family-based association tests for quantitative traits implemented in the QFAM tool of PLINK, adjusting for gender, age and risk status. We used a within-family approach to provide a test robust to population stratification and adaptive permutation to account for family structure.

Results: Part 1: After quality control procedures to filter for Mendelian errors and after verifying that the three SNPs were in Hardy Weinberg Equilibrium, we performed the TDT, using 118 nuclear families. TDT analysis in parent-proband trios from the High Risk Study sample revealed that the minor allele T variants of 2 of the 3 SNPs of GRM7 are significantly under-transmittedfrom parents to their HR offspring (rs9870680: T/U = 14/29, P = 0.02; rs9815274: T/U = 14/29, P = 0.02). The two SNPs are in strong Linkage Disequilibrium ($r^2 = 0.94$). The same TDT analysis was performed in the LR subgroup and no distortion in the transmission of the risk alleles was detected. In Part 2, the same T allele of SNP rs9815274 was found associated with regional volume of gray matter in the right para-hippocampal gyrus (rPHG) using the family-based association tests for quantitative traits implemented in the QFAM tool of PLINK (T-test = 6.38, P = 0.02, Nperm = 10,000). Overall, SNP rs9815274 significantly predicts differences in HR vs. LR regional volume of gray matter in rPHG, with larger volumes for HR subjects.
Conclusions: We observed a significant distortion in the transmission of the T allele of SNPs rs9870680 and rs9815274 of the gene *GRM7*. These findings suggest that this distortion could be potentially related to the transmission of susceptibility to MDD from affected parents to at-risk offspring who had not yet progressed to full development of the clinical symptomatology. In the second and third generation, the T alleles are significantly less transmitted than expected by chance. We have identified a potential association between the T allele of SNP rs9815274 and a neuroimaging endophenotype of MDD in an at-risk population. These findings suggest that *GRM7* might modulate grey matter volume in the rPHG, a cortical brain region known to be involved in memory encoding and retrieval. While far from definitive, this study may serve as an illustration of the power to efficiently integrate genetic and brain-imaging data in the context of family-based multi-generation design to elucidate the biological underpinnings of susceptibility to MDD in genetically at-risk populations.
Keywords: High Risk Design, MDD, Family-based association, GRM7, Para-hippocampal gyrus
Disclosure: G. Guffanti, Nothing to Disclose; P. Wikramaratne, Nothing to Disclose; A. Talati, Nothing to Disclose; R. Bansal, Nothing to Disclose; S. Hodge, Nothing to Disclose; C. Erdman, Nothing to Disclose; V. Warner, Nothing to Disclose; P. Adams, Nothing to Disclose; M. Gameroff, Nothing to Disclose; Z. Odgerel, Nothing to Disclose; B. Peterson, **Part 4:** Lilly Research Laboratories Functional and Anatomical MRI changes after treatment of chronic depression with Duloxetine (Investigator-initiated study: D. Hellerstein & B. Peterson, co-PIs); M. Weissman, Nothing to Disclose; S. Hamilton, Nothing to Disclose.

W92. Assessments of Everyday Functioning in Schizophrenia

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Background: The VALERO study is aimed at refinement of the assessment of everyday outcomes in schizophrenia with a focus on the validity of rating scales that could be used to measure treatment outcomes. We have previously identified rating scales with higher correlations with performance-based measures of cognition and functioning and have shown that self-report on the part of patients fails to converge with either informant reports or performance-based measures. In this phase of the study, we examined the association between achievement of functional milestones in several domains and clinical ratings of functioning generated with a comprehensive assessment procedure, as well as self-assessment of abilities.
Methods: Patients were rated by interviewers on 6 everyday functioning rating scales, on the basis of interviews with patients and informants. They also performed neuropsychological and functional capacity testing and rated their own everyday functioning. Achievement of functional milestones in domains of vocational (ever employed/currently employed), residential (living independently/financially responsible), and social (ever married or equivalent) domains were identified with a comprehensive procedure. We then related total and subscale scores on functional status rating scales to achievement of milestones, and compared the self-reports of patients who had and had not achieved functional milestones.
Results: Achievements of functional milestones were weakly convergent, with the highest correlation between any two milestones at $\varphi = .18$. Total scores on the interviewer rated functional outcomes scales were uncorrelated with achievement of functional milestones, while subscales aimed at vocational and residential outcomes were significantly ($p < .005$) related to lifetime employment, independence in residence and financial responsibility. When self-reports were examined, individuals who had never achieved the functional milestones rated themselves as at least as capable as those who had. However, both cognitive test and functional capacity performance were superior in individuals who had been employed and were independent in their residential functioning, to those who had never achieved these milestones.
Conclusions: Milestone achievements seem relatively independent of each other and not related to global real-world functional ratings. Further, global clinical ratings did not predict milestone achievements. More specific targeted assessments of functional abilities seem required to predict achievement of functional milestones, suggesting that total scores on rating scales may not be specific enough to be valid as treatment outcomes. Finally, individuals who never achieved functional milestones consider themselves as (or more) competent compared to those who have experienced real-world achievements. Increasing the level of realism in self-assessment of functioning may be a critical treatment target in schizophrenia.
Keywords: schizoprenia, scales, self-assessment, functional capacity, self-report
Disclosure: S. Sabbag, Nothing to Disclose; F. Gould, Nothing to Disclose; D. Durand, **Part 1:** Otsuka America Pharmaceutical, Inc.; P. Harvey, **Part 1:** Abbott Labs, Amgen, Boeheringer Ingelheim, Bristol-Myers-Squibb, Forest Labs, Genentech, Johnson and Johnson, Pharma Neuroboost, Roche Pharma, Shire Pharma, Sunovion Pharma, Takeda Pharma, **Part 2:** Consulting, less than $10,000, **Part 4:** Astra-Zeneca

W93. Genetic Association between Dopamine Signaling Molecules and Striatal Presynaptic Dopamine

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Background: Dopamine- and cAMP-regulated phosphoprotein of 32 KDa (DARPP-32) and the D_2receptor are central, closely-linked mediators of dopamine signaling, which have been implicated in the pathophysiology of several heritable neuropsychiatric illnesses, including schizophrenia. In medium spiny neurons of the striatum, D_2 receptor activation obstructs phosphorylation of DARPP-32, curtailing its ability to inhibit protein phosphatase 1, thereby affecting the phosphorylation status of a multitude of downstream targets. The genes coding for DARPP-32 and D_2 receptor contain frequent, functional variations in humans, which have demonstrated associations with dopamine-dependent cognitive measurements, striatal activity and connectivity by functional magnetic resonance imaging (MRI), and, in select experiments, modest association with schizophrenia. These variants are a 7-marker haplotype in the gene coding for DARPP-32 which predicts altered mRNA expression in postmortem prefrontal cortical

samples, and a single nucleotide polymorphism (SNP) in the D_2 receptor gene (rs6277), which affects protein folding and stability. Though the growing literature of association studies examining dopamine-related neurocognitive phenotypes forward interpretation that these DARPP-32 and D_2 receptor gene variants alter dopamine system physiology, there is little direct, consistent evidence for this from *in vivo* human studies.

Methods: As a well-validated method of assaying striatal presynaptic dopamine synthesis, ^{18}F-FDOPA PET was employed in 82 healthy Caucasian adults under 50 years of age who also underwent genotyping for DARPP-32 and D_2 receptor variants with Taq-Man 5′-exonuclease assay. After carbidopa pretreatment to prevent peripheral tracer degradation and at least 6 hours of fasting to limit tracer competition for central nervous system access, 8-16 mCi of ^{18}F-DOPA were injected intravenously and 90 minutes of dynamically binned images were acquired. These images were attenuation-corrected, realigned, coregistered to a structural MRI obtained in a separate session, warped to standard space using ANTS software and smoothed. The Patlak method was adopted to calculate the specific uptake constant K_i using an occipital reference region. Striatal region of interest and voxel-wise regression analyses queried K_i maps for genotype and gene-gene interaction effects, controlling for sex.

Results: Genotype groups were well-matched for age. The non-risk genotypes for DARPP-32 (haplotype non-homozygotes) and D_2 receptor (T homozygotes) were associated with greater K_i in the caudate ($p = 3.7 \times 10^{-3}$ uncorrected, and $p = 1.5 \times 10^{-2}$ FWE-corrected, respectively). When examined together, there existed a gene-by-gene interaction in the caudate head, where subjects who were both DARPP-32 non-homozygotes and D_2 receptor T homozygotes had far greater K_i than other groups ($p = 1.0 \times 10^{-2}$, FWE-corrected).

Conclusions: In line with previous data from animal studies suggesting an influence of DARPP-32 and D_2 receptor genes on presynaptic dopaminergic characteristics, our results indicate that the studied variants – or those in linkage disequilibrium with them – may bias striatal dopamine synthetic function in the living human brain. Though their direction does not support a straightforward presynaptic mechanism of schizophrenia risk, these findings provide preliminary evidence in favor of a dopaminergic explanation to previous neurocognitive and neurophysiological associations with these genetic polymorphisms. The described epistasis suggests that in the cognitive caudate, presynaptic dopaminergic tone may be regulated by a network of proteins extending at least to post-synaptic terminals, and future work is needed to comb this understudied pathway for novel targets in the treatment of dopamine-related neuropsychiatric disease.

Keywords: Dopamine, DARPP-32, D2, genetics, PET

Disclosure: D. Eisenberg, Nothing to Disclose; J. Masdeu, Nothing to Disclose; P. Kohn, Nothing to Disclose; B. Kolachana, Nothing to Disclose; D. Weinberger, Nothing to Disclose; K. Berman, Nothing to Disclose

W94. Correlation of Cortisol but Not BDNF Levels with Hippocampal Activation in Depressed Patients

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Background: The hippocampus seems to be affected in major depressive disorder (MDD). While brain-derived neurotrophic factor (BDNF) has positive effects on neurogenesis within hippocampus, cortisol has opposite effects. Dysfunctional hippocampal functioning in depressed patients is thought to be mediated by BDNF and cortisol, relating with the pathophysiology of the disease.

Methods: We looked at the correlation between serum cortisol and plasma BDNF levels, and hippocampal activity. Functional magnetic resonance imaging (fMRI) responses of the brain were examined in individuals with depression versus controls. FMRI was examined during associative memory task that involved the encoding and retrieval of word and face pairs. The word and face pairs consisted of either negative or positive words with neutral faces.

Results: While the bilateral hippocampus activation during negative encoding was found in patients alone, the bilateral hippocampus activation during positive retrieving was commonly found in controls and patients. Relative to controls, patients exhibited an increased activity in the right hippocampus during negative encoding. Within the MDD group, cortisol levels correlated negatively with hippocampal activity during negative encoding. On the other hand, within control group, cortisol levels correlated positively with left hippocampal activity during positive retrieving. There were no significant associations between BDNF levels and hippocampal activity.

Conclusions: Distinct patterns of associations between cortisol levels and hippocampal activity during affective memory were detected in depressive patients.

Keywords: Depression, Imaging, BDNF, Cortisol, Hippocampus, Memory.

Disclosure: S. Toki, Nothing to Disclose; Y. Okamoto, Nothing to Disclose; M. Takamura, Nothing to Disclose; T. Matsumoto, Nothing to Disclose; S. Yoshimura, Nothing to Disclose; T. Yamamoto, Nothing to Disclose; S. Yamawaki, Nothing to Disclose.

W95. Electroconvulsive Therapy Response in Major Depressive Disorder: a Pilot Functional Network Connectivity Resting State fMRI Investigation

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Background: Electroconvulsive therapy (ECT) remains the gold-standard treatment for severe, treatment-resistant patients with major depressive disorder (MDD) where a rapid and definitive response is indicated. The short time interval and magnitude of response make ECT an ideal therapeutic intervention to assess biomarkers of treatment response in MDD with resting state functional magnetic resonance imaging (fMRI). Spatial independent component analysis (ICA) utilizes a data-driven multivariate approach to identify distinct brain regions with temporally coherent hemodynamic signal change. In the present investigation, we apply ICA-derived functional network connectivity (FNC), a measure of between network temporal correlations, to assess the potential impact of between network connectivity differences associated with ECT response. We hypothesize that ECT response will be associated with normalization of aberrant between network relationships.

Methods: Depressed subjects met the following inclusion criteria: 1) DSM-IV TR diagnosis of MDD; 2) the clinical indications for ECT; and 3) a Hamilton Depression Rating Scale–24 item (HDRS–24) $\geqslant$ 21. ECT response was defined as a maximum post-treatment HDRS-24 score of 10. Matched healthy comparison subjects (HC) were recruited from the same demographic area and completed one session of resting state fMRI. MDD subjects received 11.17 (+ /- 3.33) ECT treatments (stimulus delivery determined by titration of seizure threshold). MDD subjects were concurrently treated with antidepressant medications. fMRI parameters were as follows: FOV 24 cm, matrix size 64×64, TR/TE = 2000/30 msec, and slice thickness 3.5 mm. fMRI data was preprocessed with SPM5 and INRIalign. We analyzed the preprocessed data using the Group ICA fMRI Toolbox (GIFT, http://mialab.mrn.org/software/gift) with a higher model order (e.g. 75 components). We focus our

analysis on four networks in MDD associated with increased functional connectivity: the subcallosal cingulate gyrus, default mode network, dorsal lateral prefrontal cortex, and dorsal medial prefrontal cortex. Three raters selected these components of interest with visual inspection of spatial maps and power spectra. Using the Functional Network Connectivity Toolbox (FNCtb, http://mialab.mrn.org/software/fnc) we bandpassed filtered the ICA time courses from 0.01 to 0.10 hertz and computed the differences in lagged correlations (+ /- 3 seconds) between pairs of the selected components (6 components, 15 pairs of correlations). Each correlation was converted to a z-score using the Fisher's transformation prior to the statistical test.

Results: The average age for the depressed subjects ($n = 12$) was 66.42 years + /-9.78 (4 males/8 females). HC ($n = 12$) were matched for age and gender. The post-ECT HDRS-24 confirmed clinical response from a pre-ECT assessment of 34.56 + /-10.03 to a post-ECT assessment of 2.89 + /-2.93 post-ECT for nine of the twelve subjects ($t_8 = 9.50$, $P < 0.001$). The average post-ECT HDRS-24 for the non-responders was 18.33 + /-3.51. For the pre-/post-ECT contrast, the dorsal medial prefrontal cortex (C36)/posterior default mode (C63) had a significant ($P_{FDR} < 0.05$) increase in FNC measures or temporal dependencies after ECT response ($t_8 = -5.38$, $P < 0.001$). The posterior default mode (C63)/dorsal lateral prefrontal cortex (C67) also had a significant increase in temporal dependencies after ECT response ($t_8 = -3.85$, $P = 0.0049$). Relative to HC, the pre-ECT subjects had significant lower FNC measures between the dorsal medial prefrontal cortex (C36) and the posterior default mode network (C63) ($t_7 = -2.71$, $P = 0.01$). The pre-ECT and HC contrast was not significant between the posterior default mode (C63) and the dorsal lateral prefrontal cortex (C67) ($P > 0.05$). The post-ECT and HC contrasts for both network pairs were not significant ($P > 0.05$). Pairwise correlations between changes in functional network connectivity and symptom changes were not significant ($P > 0.05$). The two-factor ANOVA comparing groups (ECT responders and non-responders) and time (pre- and post-ECT assessments) had significant group × time interactions for the dorsal medial prefrontal cortex (C36)/posterior default mode (C63) ($f_{1, 20} = 4.58$, $P = 0.045$) and the posterior default mode (C63)/dorsal lateral prefrontal cortex (C67) ($f_{1, 20} = 7.52$, $P = 0.013$).

Conclusions: This investigation assessed changes in functional network connectivity associated with ECT response in subjects with MDD. ECT response appears to reverse the relationship from negative to positive between two pairs of networks: the dorsal medial prefrontal cortex (C36) / posterior default mode (C63) and the posterior default mode (C63) / dorsal lateral prefrontal cortex (C67). These between network changes appear to be in the direction of normalization. In other words, significant differences between post-ECT and HC subjects were no longer evident after the ECT series. The ECT non-responders failed to exhibit the same pattern of between network changes. The differences between ECT responders and non-responders suggest that these between network changes may be related to the therapeutic underpinnings of ECT as opposed to epiphenomenon.

Keywords: major depressive disorder, electroconvulsive therapy, resting state fMRI, ICA

Disclosure: C. Abbott, Nothing to Disclose; N. Lemke, Nothing to Disclose; S. Gopal, Nothing to Disclose; R. Thoma, Nothing to Disclose; J. Bustillo, Nothing to Disclose; V. Calhoun, **Part 1:** Dr. Calhoun has received research support from the National Institutes of Health, National Science Foundation, Department of Energy, has done some legal consultation, has performed grant reviews for the National Institutes of Health and other agencies; has guest-edited journal sections; has given academic lectures in various scientific venues; has received support for various training courses; and has generated books or book chapters for publishers of various texts; J. Turner, Nothing to Disclose.

W96. Methylome Sequencing in the Alcohol Post-dependent Rat Model

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Background: Emerging evidence suggests a role of DNA methylation in alcohol dependence. For instance, clinical studies have shown an association between alcoholism and global DNA hypermethylation. Here, we investigated the distribution pattern of DNA methylation at genomic level for a comprehensive understanding of the role of DNA methylation in alcohol dependence.

Methods: Alcohol dependence was induced by exposing rats to alcohol vapor for 7 weeks, 14h/day. To identify persistent neuroadaptations rather than transient changes associated with acute intoxication or withdrawal, behavioral and molecular tests were performed 3 weeks after completion of alcohol exposure. Alcohol consumption was assessed using a 2-bottle-free choice paradigm. The methylated DNA fragments were captured with MBD2b/MBD3L1 heterodimer and sequenced following the DNA ChIP sequencing protocol (Illumina). Log2 transformation and normalization of the raw data using the Limma package from Bioconductor was used. DNA ChIP sequence reads were mapped to rat genomic sequences (UCSC rn4) using Bowtie.

Results: Post-dependent rats showed escalated alcohol consumption. DNA sequencing generated a total of 22 million reads. Analysis of the DNA ChIP sequencing data shows 6880 significant differences in methylation levels between the control and post-dependent rats. Most of the differencies were found in exonic and intronic regions. Recent studies suggest that intragenic DNA methylation may be involved in the regulation of alternative splicing. Thus, changes in intragenic DNA methylation pattern induced by chronic alcohol exposure may reflect different expression in splice variants. Furthermore, bioinformatics analysis indicates that glutamate release and CREB signaling which are well known to be involved in addiction are amongst the top significant pathway.

Conclusions: Our results show a significant alteration of DNA methylation pattern in the mPFC following a history of alcohol dependence. Our bioinformatics analysis suggests that alcohol exposure may affect splice variant of genes involved in processes related to addiction. Future experiments are needed to confirm these primary data.

Keywords: epigenetic, DNA methylation, splice variant, alcohol dependence

Disclosure: E. Barbier, Nothing to Disclose; J. Tapocick, Nothing to Disclose; N. Jurgens, Nothing to Disclose; J. Schank, Nothing to Disclose; K. Schuebel, Nothing to Disclose; Z. Zhou, Nothing to Disclose; Q. Yuan, Nothing to Disclose; D. Goldman, Nothing to Disclose; M. Heilig, Nothing to Disclose

W97. Effects of Pharmacogenetic Manipulation of the Nucleus Accumbens on Neuronal Activity and Alcohol Seeking Behaviors

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Background: Chronic alcohol intake leads to long lasting changes in reward- and stress-related neuronal circuitry. The nucleus accumbens (NAc), an integral component of this circuitry, receives inputs from the ventral tegmental area, amygdala, and prefrontal cortex. Dysregulation of this circuitry underlies alcohol seeking and stress-induced relapse-like behavior in animal models. Promising clinical trials have shown that deep brain stimulation of the NAc decreases alcohol craving and relapse in alcohol

dependent subjects (Azorin et al., 2010; Ulf et al., 2011). Further, animal studies have demonstrated that activation of NAc neurons elicits reward-related behaviors, findings that have vast implications for addiction research. Here we use designer mutant muscarinic receptors that are exclusively activated by designer drugs (DREADDs). These receptors represent a powerful pharmacogenetic tool for remotely controlling the activity of discrete populations of neurons *in vivo* (Rogan and Roth, 2011). We used the mutagenized G protein-coupled receptor hM3Dq, which is selectively activated by the pharmacologically inert and orally bioavailable drug, clozapine-N-oxide (CNO), to assess acute and chronic induction of neuronal activity and plasticity in the NAc.
Methods: Initial experiments were carried out to identify CNO doses needed to induce activity in the NAc. Mice were sterotaxically injected with AAV5-hSyn-HA-hM3D(Gq)-IRES-mCitrine bilaterally into NAc (bregma: angle 10°, A/P +1.6 mm, M/L +1.5, D/V -4.4) and allowed to recover and habituate to individual housing for four weeks. One group of mice were given acute doses of CNO (0.0, 0.5, or 1.0 mg/kg i.p.) and sacrificed by intracardial perfusion 90 minutes later. Another group of mice were given CNO chronically (0 mg/ml or 0.2 mg/ml CNO in drinking water) and perfused after 7 days. Validation of viral injection placement was assessed using an HA antibody and neuronal activity was assessed using antibodies for c-Fos (acute dosing) or FosB/DFosB (chronic dosing). In another group of mice, we are currently testing whether increased neuronal activity in the NAc during alcohol withdrawal reduces subsequent alcohol seeking. Mice were habituated to a reverse light/dark cycle, trained to lever press for food (right lever), surgically implanted with an indwelling jugular catheter and stereotaxically injected with AAV-hM3D (or GFP) into the NAc, and allowed to recover several days before chronically self-administering IV ethanol (right lever) in daily two hour sessions. CNO is administered in drinking water during withdrawal (7 days) and alcohol-seeking behaviors are assessed in extinction and reinstatement sessions.
Results: Acute administration of CNO (0.5 or 1.0 mg/kg) dramatically increased c-Fos in HA-hM3D(Gq) positive cells in the NAc. In the chronic CNO experiment, control mice drank approximately twice as much fluid as mice consuming CNO in their drinking water; however, both groups exhibited similar body weights at the beginning and end of the experiment. Experimental mice chronically consumed an average of 23 (+/- 4) mg/kg CNO/day. This chronic activation of hM3D by CNO resulted in increased FosB/DFosB in HA-hM3D(Gq) positive cells. Data regarding the chronic use of the DREADDS in the NAc during alcohol withdrawal will be presented.
Conclusions: These experiments demonstrate that neuronal activity can be increased in a spatial and temporal specific manner using a pharmacogenetic approach. We hypothesize that chronic increases NAc activity during withdrawl can decrease alcohol seeking behaviors.
Keywords: DREADD, CNO, c-Fos, deltaFosB, Alcohol
Disclosure: A. Ozburn, Nothing to Disclose; J. Kern, Nothing to Disclose; K. Purohit, Nothing to Disclose; C. McClung, **Part 1:** honorarium: Johnson & Johnson; Servier, **Part 4:** Research funding: IMHRO and Johnson & Johnson, Pfizer, Glaxo Smith Kline.

W98. Anhedonia and Neural Response to Social Reward in Adolescents

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Background: Anhedonia is a feature of several types of psychopathology—notably, affective and substance-use problems—that arise during adolescence. Efforts to examine the etiology and pathophysiology of such disorders have been limited by heterogeneity within diagnostic categories and possibly artificial distinctions between categories. To obtain a more thorough understanding of the development of adolescent psychopathology, it is valuable to focus on a coherent dimension with relevance to psychopathology across diagnostic categories and a known neural basis. Anhedonia is an excellent candidate for such an approach. It reflects disruption in positive valence systems, and it has a neural basis in reward circuitry. Specifically, function in regions such as the striatum and medial prefrontal cortex is altered in anhedonia (Der Avakian & Markou, 2012; Keedwell et al., 2005; Wacker et al., 2009). Anhedonia is likely to increase during adolescence, a sensitive developmental period involving decrease in positive affect (Larson & Sheeber, 2008) and the emergence of affective disorders (Seeley & Lewinsohn, 2008) and substance use (Vega et al., 2002). Adolescence also involves continued development in neural reward circuitry (Spear, 2000) and dramatic changes in social context, both of which could contribute to vulnerability to anhedonia-related problems. While response to monetary reward has been studied in adolescent development and affective problems, response to social reward has been relatively neglected, despite the importance of peer social contexts during this period.
Methods: 28 late adolescents aged 18-21 (M age = 20.36 years; 51.9% female; 77.8% European American) participated in a functional magnetic resonance imaging study in a Siemens Trio 3T scanner using a block-design social reward task. Using photo stimuli from similar-age peer strangers, participants received feedback about whether others had rated them as likeable. Preprocessing and analyses were conducted in using statistical parametric mapping (SPM8) software. Analyses focused on the contrast between blocks in which participants received positive evaluations from people whom they rated as highly likable (high positive) and blocks in which they received positive evaluations from people whom they rated as less likable (low positive). Regression models examined the association of neural response to social reward with self-reported social anhedonia (Revised Chapman Social Anhedonia Scale; Eckblad, Chapman, Chapman & Mishlove, 1982) and depressive symptoms (Center for Epidemiologic Studies Depression Scale; Radloff, 1977).
Results: High social anhedonia and high depression symptom severity were both related to greater medial prefrontal cortex (mPFC) response to high positive versus low positive feedback (anhedonia: 15 voxels, $t = 2.67$, $p_{FWE} < 0.046$, Talairach coordinates:-9,33,34; depression: 13 voxels, $t = 2.64$, $p_{FWE} < 0.02$, Talairach coordinates: -10,33,34).
Conclusions: Our findings indicate that anhedonia is related to sensitivity to social reward, particularly in situations involving positive evaluations of others or mutual positive regard. Anhedonia was associated with function in the mPFC, a region implicated in self-processing and mentalizing, as well as in reward processing generally. This suggests that disruption of social and self-relevant cognition might be especially important to adolescent anhedonia, and it supports the use of social reward paradigms in future studies. Finally, consistent with the role of anhedonia in depression, depressive symptom severity was also related to response to social reward in a similar region of the mPFC. Altered responding to social reward could contribute to the etiology and pathophysiology of reward-related problems in adolescence.
Keywords: reward, anhedonia, brain function, adolescence, depression
Disclosure: E. Forbes, Nothing to Disclose; K. Healey, Nothing to Disclose; T. Olino, Nothing to Disclose; E. Coffman, Nothing to Disclose.

W99. Characterizing the Splicing Variants of ZNF804a in Human Brain

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Background: *ZNF804a* consists of 4 exons, and produces a protein with a C2H2-type domain that has been associated with the zinc-

finger protein family. Multiple genome-wide association studies (GWAS) have identified *ZNF804a* as a risk gene for schizophrenia and bipolar disorder. Studies of its mouse homologue, znf804a, suggest that this gene may regulate aspects of early brain development, including neurite outgrowth, and axonal and dendritic branching. Allelic variation at rs1344706, the most robust genome-wide associated SNP in ZNF804a, was also associated with expression of ZNF804a in human brain. Specifically, the risk allele was associated the higher expression of ZNF804a. A recent study of schizophrenia-derived induced pluripotent stem cells showed the expression of ZNF804a radically increased during the transition from a pluripotent stem cell to early differentiating neurons, suggested the abnormal higher expression of ZNF804a in schizophrenia patients in early brain development. Best estimates suggest that 90% of multi-exon genes, including ZNF804a, undergo alternative splicing. In light of these findings, we conducted a series of experiments in the postmortem human brain to identify and characterize alternative transcripts of ZNF804a in order to increase our understanding of its role in the brain development and psychiatric disorders.

Methods: *RNA seq:* To find potential splicing variants, RNA sequencing were performed on two commercial (Clontech) pooled poly A+ RNA samples (human fetal brain poly A+ RNA and human adult brain poly A+ RNA). The results were mapped to GRCh37/hg19 by TopHat. 5′ cDNA RACE: To identify potential 5′ cDNA ends of ZNF804a in human brain, we carried out rapid amplification of 5′ cDNA ends, using fetal and adult brain poly A+ RNA with ZNF804a gene-specfic antisense primers binding at exon 4. We used the SMART RACE cDNA Amplification Kit (Clontech) for these assays and all RACE products were cloned into pCR4-TOPO vector (Invitrogen) and sequenced. End-to-end PCR: Based on the previously identified ZNF804a gene exons, RNA sequencing results and RACE results, we designed primer pairs to amplify full-length and portions of ZNF804a transcripts using Platinum Taq DNA polymerase (Invitrogen). All PCR products were cloned into pCR4-TOPO vector (Invitrogen) and sequenced. Quantitative real-time PCR and genotyping: Postmortem brains were collected at the CBDB, NIMH with informed consent of the next kin under NIMH protocol 90-M-0142 and the BTBDD at the NICHHD under contracts NO1-HD-4-3368 and NO1-HD-4-3383. The expression level of ZNF804a transcripts are being measured in a large postmortem DLPFC sample cohort using the TaqMan qRT-PCR method. Genotyping is underway using the TaqMan 5′ exonuclease allelic discrimination assay (Applied Biosystems).

Results: The RNA sequencing results based on the two commercial pooled poly A+ RNAs suggested that the full length transcript of ZNF804a was the main splicing variant in the fetal brain but not in the adult brain. In addition, there is a possible transcript with an exon2 deletion in the fetal brain. The end-to-end PCR by using primer pairs picking up the full length transcript showed a clear band of the predicted size in fetal brain but not in adults. By cloning and sequencing the end-to-end PCR products from fetal brain, we identified two splicing variants in fetal brain, full length ZNF804a and a transcript composed of part of exon1 and exon4. To confirm the RNA sequencing data of ZNF804a on adult brain RNA expression, we conducted the 5′ RACE. In adult human brain, there are at least 2 potential 5′ start sites for ZNF804a. One is in exon2 and the other is located in intron 2. 5′ RACE results confirmed the presence of the transcript with an exon2 deletion in adult brain. In general, we found one truncated transcript in fetal brain and at least 3 truncated transcripts in adult brain. Currently, we are performing 5′RACE with the same primer pairs in fetal brain to define the library of potential transcripts. After we have the trancriptome map of ZNF804a in human brain, we will measure their expression level in our postmortem sample cohort to evaluate the possible effects of diagnosis and allelic variation, focusing on schizophrenia and GWAS-positive SNPs in particular.

Conclusions: ZNF804a is a strong candidate gene for neuropsychiatric disorders based on the results of GWAS. Though its function is still unclear, accumulated evidence suggests that ZNF804a plays an important role in multiple biological processes during brain development, and it may regulate a transcriptional network of additional schizophrenia-associated genes. Our current results suggest that the splicing of ZNF804a is complicated in the human brain, and dominant transcripts of ZNF804a differ between the fetal and adult brain. Careful characterization of the splicing variants of ZNF804a in the human brain will help define the mechanisms by which allelic variation in this gene leads to increased risk of neuropsychiatric illness.

Keywords: ZNF804a, Splicing Variants, Schizophrenia, Human Postmortem Brain

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W100. Antidepressant Effects of Optogenetic Control of Nucleus Accumbens Neurons

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Background: The nucleus accumbens (NAc) plays a crucial role in regulating mood, including maladaptive behaviors seen in depression and anxiety disorders. Recently, deep brain stimulation (DBS) to the nucleus accumbens was shown to alleviate depression and anxiety symptoms in patients suffering from treatment resistant depression.

Methods: To investigate the role of NAc medium spiny neurons (MSNs- the NAc projection neurons), which are differentially enriched in dopamine receptor 1 (D1) vs. dopamine receptor 2 (D2), in mood regulation we selectively express optogenetic proteins in each MSN to alter activity during mood regulated behaviors. First, we optogenetically activate specific NAc neuronal subtypes expressing ChR2(H134) with 10 Hz blue light stimulation during acute mood-regulated behaviors including tail suspension test (TST–a form of stress) and elevated plus maze (EPM–a measure of anxiety). Next we express ChR2(H134), ChETA, or ChR2(E123A) in NAc neurons in animals exhibiting social avoidance (a depression-like behavior) during social interaction after repeated social defeat stress. We then activate NAc neurons with low frequency or higher frequency stimulation, the latter similar to DBS, during social interaction or repeatedly for 5 days prior to social interaction.

Results: We demonstrate that 10 Hz blue light activation of ChR2(H134) in D1+ MSNs during acute mood-regulated behaviors decreased time spent immobile during the TST and increased time in the open arms in the EPM. Additionally, repetitive high frequency activation but not low frequency activation of NAc neurons reversed the social avoidance seen after repeated social defeat stress.

Conclusions: We show that activation of D1+ NAc neurons is important for mediating acute mood-regulated behaviors, since activation of these neurons has antidepressant- and anxiolytic-like effects. Additionally these studies have implications into the mechanism of DBS in the NAc of human depressed patients, since directly activating NAc neurons with high frequency blue light pulses can alleviate depression symptoms displayed after repeated social defeat stress. We are currently investigating whether this effect is mediated through D1+ or D2+ MSNs.

Keywords: nucleus accumbens, depression, optogenetics, medium spiny neurons, social defeat stress

Disclosure: T. Francis, Nothing to Disclose; J. Lenz, Nothing to Disclose; E. Finkel, Nothing to Disclose; D. Chaudhury, Nothing to Disclose; M. Han, Nothing to Disclose; M. Lobo, Nothing to Disclose.

W101. Ketamine and Neurocognition in Depression: The Modulating Effects of Lamotrigine

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Background: Ketamine – a noncompetitive N-methyl-d-aspartate (NMDA) glutamate receptor antagonist – is associated with rapid-onset antidepressant effects in treatment resistant major depressive disorder (TRD). Acute disruptions in neurocognitive functioning associated with ketamine have been reported in healthy volunteers. No study to date has examined the acute cognitive impact of ketamine in depressed patients or the association between neurocognitive functioning and treatment response. We measured neurocognition in individuals with TRD prior to and immediately following the 40-minute ketamine infusion. We further measured the effect of a single pre-treatment dose of the glutamate inhibitor lamotrigine in modulating ketamine's impact upon neurocognition.
Methods: Primary efficacy and safety data of ketamine in this sample has been previously reported (Mathew et al, 2010). Briefly, TRD subjects received a single open-label 40-minute intravenous (IV) infusion of ketamine (0.5 mg/kg) following a 2-week washout of psychotropic medication and completed safety and efficacy measures at baseline and then at several time points during and after the infusion. One hour prior to the ketamine infusion, participants were administered a single oral 300 mg dose of lamotrigine or placebo. The primary efficacy outcome was change in Montgomery–Asberg Depression Rating Scale (MADRS) score from baseline to 24 hours post-infusion. Antidepressant response was defined as $\geqslant$ 50% reduction in MADRS scores from baseline. Neurocognitive functioning was assessed at baseline using a comprehensive battery: estimated premorbid IQ (WRAT Reading), current IQ (WAIS Vocabulary and Matrix Reasoning), and the MATRICS battery (MCCB) [Trails A&B, WMS Spatial Span, Letter-Number Sequencing, Hopkins Verbal Learning Test (HVLT), Brief Visual Memory Test (BVMT), Category Fluency, and the Continuous Performance Test (CPT I/P)]. We created domain scores in line with the MCCB domains using our own normative MCCB data to create z-scores from a demographically-matched healthy sample (n = 150), as the MCCB published norms do not include ages >59 years (20% of our sample falls in this range). We then calculated mean z-scores to form 4 key domains (processing speed; attention; verbal learning; and visual learning). At 40 minutes post-infusion, we repeated the HVLT and Category Fluency in order to measure the effect of ketamine on verbal learning and executive functioning. For baseline data, we entered clinical response group [responders (n = 16) vs. non-responders (n = 9)] into a logistic regression including demographics, baseline symptom ratings, and neurocognitive domains to identify possible clinical and cognitive predictors of ketamine response. Next, we evaluated the effect of acute ketamine on cognitive performance using paired t-tests to assess the overall effect regardless of response status. Finally, to address the heterogeneity in cognitive response, we categorized subjects based on whether they evidenced cognitive impairment (n = 16) or showed no change/improvement in performance (n = 9) at 40 minutes. Cognitive subgroups were compared on several features.
Results: Our subjects (n = 25) had a mean age of 49.0 ± 11.2, a mean duration of illness of 29.6 ± 13.4 years and a mean premorbid IQ of 108.4 ± 9.3. At baseline, regression models indicated that two variables were independently predictive of response: Age, and Processing Speed. Individuals who showed a good clinical response to ketamine were older [Wald = 2.9; df = 1; p = 0.09; Exp(B) = 1.15] and had *slower* processing speed at baseline (mean z-score = -0.39 + /-0.35) than those individuals who did not respond [mean z-score = 0.58 + /-0.84; Wald = 4.2; df = 1; p = 0.04; Exp(B) = 0.12]. There was no significant effect of ketamine at 40 minutes post-infusion on HVLT learning (t = 0.96; df = 24; p = 0.35) or semantic fluency (t = 0.17; df = 23; p = 0.87); however, HVLT *delayed* recall showed significant worsening at 40 minutes (t = 2.1; df = 24; p = 0.04). In order to investigate a potential association between acute neurocognitive changes and clinical response to ketamine, we analyzed subjects who demonstrated (n = 16) and those who did not demonstrate (n = 9) impairments in HVLT recall following ketamine. Subjects with impaired memory at 40 minutes were *less* likely to respond clinically (37.5% response rate) than those subjects who did not evidence impairment (77.7% response rate; $Chi^2 = 3.7$; p = 0.05). Finally, pre-treatment with lamotrigine appeared to protect against short-term cognitive side effects. Specifically, those subjects who were treated with lamotrigine prior to ketamine infusion (n = 10) were significantly less likely to experience cognitive side effects at 40 minutes (40% worsened) than those who did not receive lamotrigine (80% worsened; $Chi^2 = 4.2$; p = 0.04).
Conclusions: In the current study we show that (1) slower baseline processing speed is associated with better antidepressant response to ketamine; (2) less cognitive impairment at 40 minutes is associated with better antidepressant response and; (3) lamotrigine appears to attenuate the short-term cognitive impairment associated with ketamine. These results provide preliminary support for a specific baseline neurocognitive marker of treatment response to ketamine and a potential role for adjunctive lamotrigine in ketamine treatment for major depression.
Keywords: ketamine, cognition, side-effects, lamotrigine, depression
Disclosure: J. Murrough, **Part 2:** Dr. James Murrough is a fulltime employee of Mount Sinai Medical Center and receives research mentoring from Dr. Dennis Charney, Dean of Mount Sinai School of Medicine. Dr. Charney has been named as an inventor on a use-patent of ketamine for the treatment of depression. If ketamine were shown to be effective in the treatment of depression and received approval from the Food and Drug Administration for this indication, Dr. Charney and Mount Sinai School of Medicine could benefit financially. This conflict is currently being managed by the Mount Sinai School of Medicine Financial Conflict of Interest Committee, **Part 4:** In the past two years, Dr. James Murrough has served as a site PI on industry-sponsored clinical trials involving the following companies: Evotec, Janssen Pharmaceuticals; L. Wan, Nothing to Disclose; B. Glicksberg, Nothing to Disclose; K. Collins, Nothing to Disclose; S. Mathew, Nothing to Disclose; D. Charney, **Part 1:** Patent pending: Ketamine - for the treatment of depression, Dr. Charney and Mount Sinai School of Medicine have been named on a use patent application of Ketamine for the treatment of depression. If Ketamine were shown to be effective in the treatment of depression and received approval from the Food and Drug Administration (FDA) for this indication, Dr. Charney and Mount Sinai School of Medicine could benefit financially, D. Iosifescu, **Part 1:** CNS Response Inc: Consultant, **Part 4:** Since 2010 Dr. Iosifescu has received grant/research support through Mount Sinai School of Medicine from Brainsway, Euthymics Bioscience Inc, Neosync and Shire. In the next two years it is likely he will receive grants from Hoffmann-La Roche Inc and Astrazeneca LP.; K. Burdick, **Part 1:** Ai Cure, **Part 4:** 2012: Ai Cure - site PI.

W102. A New Animal Model of the Pathophysiology of Tourette Syndrome: Parallel Characterization of Humans and Mice with a Disruption of the Histidine Decarboxylase (Hdc) Gene

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Background: Tourette syndrome (TS) is a neurodevelopmental disorder characterized by tics and sensory gating abnormalities.

Available treatments are limited, and its neurobiological underpinnings are not well understood. Pathophysiological analysis of such conditions in animal models can provide key insight; however, modeling complex neuropsychiatric conditions presents daunting challenges. TS has a heritability of 30-60%, but causative mutations and risk alleles have proven elusive, attesting to a complex, heterogeneous genetic architecture. In this setting, the investigation of rare, highly penetrant mutations is of particular value. A recent study of a dense 2-generation TS pedigree identified a rare segregating nonsense mutation, *Hdc* W317X, in the *l-histidine decarboxylase (Hdc)* gene. A subsequent CNV study has further supported a connection between dysregulated histaminergic neurotransmission and TS. We describe parallel analysis of TS patients carrying the *Hdc* W317X mutation and mice lacking one or both copies of the *Hdc* gene and establish that reduction in histamine (HA) biosynthesis produces key phenomenological, pharmacological, and neurochemical features of TS.

Methods: 9 TS patients carrying the *Hdc* W317X mutation were characterized clinically and in prepulse inhibition (PPI). Adult male HDC knockout mice were tested in parallel behavioral assays (stereotypy; PPI) with or without pretreatment with the D2 antagonist haloperidol. Striatal dopamine in knockout mice and in HDC KO mice after HA infusion was assessed by *in vivo* microdialysis. Dopamine D2/D3 receptors were quantified *in vivo* in patients carrying the *Hdc* W317X mutation by positron emission tomography (PET) with the D3-preferring ligand PHNO, and *in vitro* in mice using the D2/D3 ligand raclopride.

Results: All patients carrying the *Hdc* W317X mutation had current and/or past tics; patients also had a deficit in auditory PPI. Heterozygous and homozygous knockout mice had reduced brain histamine and exhibited parallel behavioral symptomatology, with enhanced stereotypy after amphetamine administration and a deficit in PPI. The stereotypy phenotype was mitigated by haloperidol pretreatment, establishing predictive validity. Wild-type mice showed decreased striatal DA by *in vivo* microdialysis after central HA infusion; conversely, KO mice showed enhanced striatal DA. Both patients and mice showed an elevation in D2/D3 receptor binding in the substantia nigra; this is consistent with the upregulation of D3 receptors in this structure seen in other contexts after chronic dopamine elevation.

Conclusions: Pathophysiological modeling of disease based on causal mutations has been a fruitful strategy in many areas of medicine and holds great promise, but there are few examples of the successful application of this approach to the study of common neuropsychiatric conditions. A high-penetrance loss-of-function *Hdc* allele was recently identified as a candidate rare cause of TS by a linkage study in a high-density TS pedigree. We have used this connection as the basis for a new pathophysiological animal model of TS; our parallel characterization of mice and TS patients confirms a causal connection between disruption of histaminergic neurotransmission and core features of TS and establishes the construct, predictive, and face validity of this model, shedding new light both on the normal role of histaminergic modulation of the basal ganglia circuitry and on the mechanistic link between HA dysregulation and TS. While *Hdc* mutations appear to be a very rare cause of TS, we anticipate that further mechanistic investigations in this model may shed light on the pathophysiology of the disorder more generally.

Keywords: Animal models Tourette syndrome Histamine Basal ganglia

Disclosure: L. Baldan, Nothing to Disclose; K. Williams, Nothing to Disclose; J. Gallezot, Nothing to Disclose; M. Crowley, Nothing to Disclose; V. Pogorelov, Nothing to Disclose; R. Gorczyca, **Part 1:** Employee of Pfizer Neuroscience, Cambridge, MA; G. Anderson, Nothing to Disclose; B. Leventhal, Nothing to Disclose; H. Ohtsu, Nothing to Disclose; Z. Hughes, **Part 1:** Full-time employee of Pfizer Neuroscience; J. Krystal, **Part 1:** Consultant: Aisling Capital, LLC; AstraZeneca Pharmaceuticals; Biocortech; Brintnall & Nicolini, Inc.; Easton Associates; Gilead Sciences, Inc.; Glaxo Smith Kline; Janssen Pharmaceuticals; Lundbeck Research, USA; Medivation, Inc.; Merz Pharmaceuticals; MK Medical Communications; F. Hoffman-La Roche, Ltd; SK Holdings Co., Ltd; Sunovion Pharmaceuticals, Inc.; Takeda Industries; Teva Pharmaceuticals, Ltd, Scientific Advisory Board: Abbott Laboratories; Bristol-Myers Squibb; Eisai, Inc.; Eil Lilly and Co.; Forest Laboratories, Inc.; Lohocla Research Corporation; Mnemosyne Pharmaceuticals, Inc.; Naurex, Inc.; Pfizer Pharmaceuticals; Shire Pharmaceuticals, Exercisable warrant options: Tetragenex Pharmaceuticals (value less than $150), Patents (none of relevance to the current work): Seibyl JP, Krystal JH, Charney DS, Dopamine and noradrenergic reuptake inhitors in the treatment of schizophrenia, Pat #5,447,948. Coric V, Sanacora GS, Krystal JH, filed patent application related to targeting the glutamatergic system in the treatment of neuropsychiatric disorders (PCTWO06108055A1); pending application on intranasal ketamine in the treatment of depression; L. Mayes, Nothing to Disclose; I. de Araujo, Nothing to Disclose; Y. Ding, Nothing to Disclose; M. State; C. Pittenger, **Part 1:** Consultant: F. Hoffman-La Roche, Ltd.

W103. The Effects of Heterozygous Knockout of the Vesicular Monoamine Transporter (VMAT2) and Transgenic Overexpression of Alpha-synuclein (SYN) on Locomotor Behavior in Mice

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Background: Compartmentalization of dopamine is determined largely the plasma membrane dopamine transporter (DAT; SLC6A3), and the vesicular monoamine transporter (VMAT2; SLC18A2). By regulating cytosolic/extra-vesicular dopamine levels these transporters are likely to influence behavior mediated by dopaminergic systems, including locomotor behavior and responses to psychostimulant drugs such as amphetamine. α-synuclein is thought to play a role in Parkinson's disease by affecting the function of the dopamine transporter. The normal function of α-synuclein is uncertain but it appears to affect responses to psychostimulant drugs via effects on the dopamine transporter. Therefore, the effects of heterozygous VMAT2 knockout (KO) and transgenic overexpression of α-synuclein (SYN) on basal and amphetamine-stimulated locomotor behavior were examined in mice.

Methods: Crosses of VMAT2 KO mice and α-synuclein overexpressing mice resulted in double transgenic mice of 4 genotypes: VMAT2 +/+ SYN -, VMAT2 +/-SYN -, VMAT2 +/+ SYN +, and VMAT2 +/-SYN +. Male and female mice of all 4 genotypes were initially placed in a locomotor testing apparatus for two hours to test locomotion in a novel environment. In 4 subsequent locomotor tests, mice were placed in the apparatus for 1 h prior to injection with d-amphetamine (0, 0.3, 1.0 or 3.0 mg/kg i.p.) and locomotor activity was assessed for another hour.

Results: Locomotor activity was reduced by heterozygous VMAT2 KO and α-synuclein overexpression (VMAT2 +/-SYN – and VMAT2 +/+ SYN + versus VMAT2 +/+ SYN -). This was observed during the initial (novel) locomotor test, as well as during the subsequent habituation periods prior to amphetamine injection. Locomotor activity in these mice remained below wildtype (WT: VMAT2 +/+ SYN -) levels even at the end of the initial 2 h test session. By contrast to the effects of each transgenic manipulation alone, combined transgenic manipulation of both VMAT2 and α-synuclein (VMAT2 +/-SYN +) restored locomotion in all circumstances to WT levels. Similarly to the effects of each of the manipulations alone on basal locomotion, amphetamine-stimulated locomotion was also reduced by heterozygous VMAT2 KO and α-synuclein overexpression alone, but normalized by combined manipulations in VMAT2 +/-SYN +

mice. Although the differences were slightly greater at higher amphetamine doses they were also observed after saline administration, so presumably reflect the different initial levels of baseline locomotion in each strain.
Conclusions: Both heterozygous VMAT2 KO and α-synuclein overexpression affected locomotor activity and locomotor responses after amphetamine treatment. However, the combination of two transgenic manipulations normalized the differences in locomotor behavior produced by each manipulation alone. This suggest that both of these genes may be important in behavior regulated by dopaminergic systems, inlcuding locomotor function and drug reward. *(Support: NIDA-IRP)*
Keywords: Dopamine, transgenic, knockout, α-synuclein, vesicular monoamine transporter
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W104. Adult Hippocampal Neurogenesis Modulates Excitability of the Dentate Gyrus

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Background: Adult hippocampal neurogenesis is a unique form of plasticity that generates new neurons in the dentate gyrus (DG) throughout life. Convergent lines of evidence have suggested a role for adult-born neurons in disambiguating or distinguishing between similar representations, a process known as pattern separation. Although pattern separation has largely been recognized as important for formation of new memories of places and events or episodic memories, impairments in pattern separation may also contribute to overgeneralization of fear in neutral contexts resembling previously encountered aversive events, a hallmark of anxiety disorders such as post-traumatic stress disorder (PTSD). Recently, we have found that ablation or genetic enhancement of adult hippocampal neurogenesis is sufficient to impair or improve discrimination between fearful and safe contexts that are very similar, respectively. These observations beg the question how a small number of adult-born neurons modulate pattern separation in the DG to influence contextual discrimination learning. Bridging these gaps in our understanding of how adult hippocampal neurogenesis influences encoding may generate insights into the therapeutic potential for targeting this form of neural plasticity to treat encoding impairments in PTSD.
Methods: Here, we used immediate early genes (IEG) to map neuronal activation patterns in the DG of mice in which levels of adult hippocampal neurogenesis were selectively manipulated. To selectively increase adult hippocampal neurogenesis, we used a recently developed genetic gain-of-function system in which we can inducible increase the number of adult generated dentate granule neurons. We used targeted hippocampal x-irradiation to selectively block hippocampal neurogenesis in the adult DG. We complemented the IEG based approach with fast voltage-sensitive dye imaging (VSDI) combined with laser photostimulation and electrical stimulation to examine how increased or decreased adult neurogenesis in the DG affects local circuit activity and signal propagation. This method allows for high spatiotemporal-resolution imaging of the entire circuit including the DG, CA3 and CA1 subregions, and also enables effective mapping of local functional circuit connections. Analysis and quantification of GABAergic terminals was performed by VGAT immunohistochemistry followed by confocal microscopy.
Results: IEG based circuit mapping showed thatincreasing adult hippocampal neurogenesis increased the sparseness of activation in the DG. Consistently, VSDI in combination with photostimulation via glutamate uncaging or electrical stimulation revealed a reduction in lateral spread of activity in the DG of mice in which we inducibly increased adult hippocampal neurogenesis. Furthermore, measurements of VSD response strength at stimulation sites in these mice also uncovered a reduction in DG excitability. Interestingly, DG->CA3 output in response to stimulation remained unchanged in mice in which adult hippocampal neurogenesis was increased. Complementing these findings, blockade of adult hippocampal neurogenesis increased excitability of the DG. Analysis of the GABAergic presynaptic marker VGAT in the hilus, molecular layers and granule cell layer did not detect a difference in mice with increased adult hippocampal neurogenesis and controls.
Conclusions: A hypothesis that has emerged from computational models and neuroanatomical properties of the DG-CA3 circuit is that sparseness of activation is important for pattern separation. The implicit idea is that a sparse code facilitates the distribution of similar entorhinal input patterns across the granule neuron population to decorrelate overlapping representations. Here, we show that levels of adult hippocampal neurogenesis inversely regulate the degree of sparseness of activation in the DG. Several models may explain these observations. First, the integration of new neurons into the DG may facilitate input-expansion of entorhinal inputs. Second, synaptic competition between adult-born neurons and pre-existing mature granule neurons may result in a redistribution of synaptic weights. Third, adult-born neurons may exert feedback inhibition onto the DG by recruiting hilar interneurons and mossy cells. Since the photostimulation was done in the granule cell layer, the effects of increasing adult neurogenesis on lateral spread and excitability are likely to be due to changes in local circuit properties or connectivity downstream of dentate granule neurons. The lack of a change in VGAT in the DG of experimental and control mice examined suggest that the number of inhibitory inputs onto the DG is unchanged. However, it may be that the excitatory drive onto hilar interneurons and mossy cells is greater when neurogenesis is increased. Together these data suggest that increased adult neurogenesis enhances pattern separation by increasing response threshold and increasing the sparseness of activation in the DG while maintaining a similar level of output to CA3.
Keywords: adult hippocampal neurogenesis, dentate gyrus, anxiety disorders, pattern separation, PTSD
Disclosure: A. Sahay, Nothing to Disclose; T. Ikrar, Nothing to Disclose; S. Levinson, Nothing to Disclose; A. Besnard, Nothing to Disclose; A. Hill, Nothing to Disclose; R. Hen, **Part 1:** Lundbeck and Roche; X. Xu, Nothing to Disclose.

W105. Neuronal Signatures of Self-control in Anterior Cingulate Cortex

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Background: Addiction, obsessive compulsive disorder (OCD), and Tourette Syndrome (TS) are diseases in which the core symptoms include deficits in self-control. Recent studies have begun to identify the key brain areas that govern our ability to resist temptation, but the circuit-level mechanisms of self-control remains poorly understood. Of the core elements of self-control, delay of gratification, or persistent commitment to the choice of a delayed option, has been identified as especially important. Inspired by the recent development of delay-of-gratification tasks for rhesus macaques, we have developed corresponding tasks that are usable with single unit recordings. We focused on the dorsal anterior cingulate cortex (dACC). The dACC has been linked overcoming impulsive behaviors, to self-control, and to executive control more broadly. Lesions to dACC produce frank deficits in self-control and variations in structure and function in dACC predict susceptibility to addiction, OCD, and TS.

Methods: On each trial of our task, one of several possible options (colored rectangles) appears at the top of a computer monitor and quickly glides down the screen. Monkeys can accept or reject this option by fixating on it. Once an option is accepted, the monkey must maintain gaze on it for several seconds in order to obtain a reward. Failures to maintain gaze for the duration of the shrinking period (several seconds) are considered persistence failures and lead to no reward. Options vary in their benefit (reward amount offered) and cost (delay until reward). We recorded firing rate activity of 125 single neurons in the dACC while two macaques performed this task.
Results: We found that monkeys' chose approximately optimally and that their choices reflected a balance between costs and benefits for each option. Neuronal activity was tonically enhanced throughout the hold period, suggesting that it contributes to active resistance to temptation. Consistent with this idea, we found that variations in dACC activity predicted accept or reject decisions for individual stimuli, and in approximately one quarter of neurons, firing rate during the second before the stimulus appeared predicted the monkeys decision. When monkeys made a decision and stuck with it past 750 ms, they proceeded to successfully maintain gaze on it for about 90-95% of trials. On the remaining trials they failed to maintain gaze and let the option disappear. These trials are demonstrably suboptimal because, due to the structure of the task, it was always better to reject any option immediately. We therefore classify these trials as self-control failures. In approximately 20% of dACC neurons, we found a slight but significant suppression in neuronal activity during the half second before the failed self-control gaze shifts. These reductions in activity are therefure predictive of self-control failures.
Conclusions: Our results indicate that dACC plays a direct role in controlling delay-of-gratification decisions in a macaque self-control task. Specifically, they suggest that dACC provides a proactive control signal that facilitates persistent commitment to an abstemious decision. These results therefore constitute the first putative self-control signal observed at the single neuron level in macaques. Past studies have generally emphasized the importance of dACC for monitoring and for reactive control; the present results demonstrate its key role in proactive control as well. It is likely that dACC is only one of several brain areas important for self-control. The dorsolateral prefrontal cortex and ventromedial prefrontal cortex has been hypothesized to play distinct roles in self-control decisions as well. Our results suggest that dACC may be a high-level controller that tunes activity in these other areas during self-control decisions. More broadly, these results offer a potential explanation for the observed diminution in self-control that accompanies addiction, OCD, and other diseases associated with aberrant structure and function of the dACC. Finally, these results suggest that dACC may be a good target for future therapies, such as deep brain stimulation, that aim to improve self-control in severe psychiatric conditions.
Keywords: self-control, addiction, OCD, macaque, anterior cingulate cortex
Disclosure: B. Hayden, Nothing to Disclose; T. Blanchard, Nothing to Disclose.

W106. GLYX-13, an NMDA Receptor Glycine-site Functional Partial Agonist, Induces Rapid Antidepressant-like Effects without Ketamine-like Side Effects

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Background: Recent clinical studies with NMDA receptor (NMDAR) antagonists such as ketamine have established the NMDAR as a novel target of high interest in the treatment of depression. GLYX-13 is a glycine-site functional partial agonist (GFPA) at the NMDAR, with a unique pharmacological profile compared to other NMDAR modulators. GLYX-13: 1) simultaneously enhances the magnitude of long-term potentiation (LTP) while reducing long-term depression, 2) enhances learning in hippocampus-dependent learning tasks in both young and learning-impaired aging rats, 3) reduces cell death in the hippocampus following carotid occlusion in gerbils, 4) produces analgesic effects in the rat formalin and Bennett models, and 5) and potentiates positive emotional learning in rats. Here we examined GLYX-13 for its potential as a clinically relevant antidepressant using multiple rat models of depression, and tested for ketamine-like side effects in rats. We also determined if the antidepressant-like effects of GLYX-13 required AMPA glutamate receptor activation, and we examined if GLYX-13 could facilitate metaplasticity.
Methods: *Behavioral Pharmacology*: Male Sprague-Dawley (SD) rats (2-3 Months old) were given injections of GLYX-13 (1-56 mg/kg IV; 1-100 mg/kg SC; 0.1-10 μg MPFC), ketamine (10 mg/kg IV; 0.1-10 μg MPFC), fluoxetine positive control (three doses at 10 mg/kg SC) or sterile 0.9% saline vehicle, either 20-60 min or 24 hrs before Porsolt testing. Pretreatment with NBQX (10 mg/kg IP) was used to test the role of AMPAR in the antidepressant-like effect of GLYX-13 (3 mg/kg IV) in the Porsolt test. Antidepressant-like drug effects were measured by decrease in floating time in the Porsolt test, decreased feeding latency in a novel but not familiar environment for the novelty-induced hypophagia (NIH) test, and decreased number of escape failures in the learned helplessness (LH) test. Ketamine-like abuse potential and reward was measured by ketamine-like responding in drug discrimination testing and time spent in the drug paired side in the conditioned place preference assay. Ketamine-like disruptions in sensory-motor gating were measured by decreased pre-pulse inhibition. Ketamine-like sedation was measured by decreases in open field locomotor activity and operant response rate in a drug discrimination study. *Molecular Pharmacology*: Adult male SD rats were dosed with GLYX-13 (3 mg/kg IV), ketamine (10 mg/kg IV) or saline vehicle and sacrificed 24 hrs post dosing. MPFC and hippocampal slices were prepared, and cell surface expressing proteins were cross-liked by biotinylation. Cell surface expression of GluR1 and NR2B were measured by Western blot. *Electrophysiology*: Hippocampal slices were prepared from adult male SD rats 24 hours after a single injection of GLYX-13 (3 mg/kg IV), ketamine (10 mg/kg IV) or vehicle. LTP at Schaffer collateral-CA1 synapses was measured in response to three submaximal bouts of high-frequency Schaffer collateral stimulation (2×100 Hz/800 ms). The percent contribution of NR2B and NR2A-containing NMDARs to pharmacologically isolated total NMDAR conductance were measured in Schaffer collateral-evoked EPSCs of CA1 pyramidal neurons by using the NR2B-selective NMDAR antagonist ifenprodil (10 μM), and the NR2A-NMDAR selective antagonist NVP-AM077 (100 nM).
Results: *Behavioral Pharmacology*: GLYX-13 (3-10 mg/kg IV; 10-30 mg/kg SC) produced robust antidepressant-like effects in the Porsolt, LH and NIH tests that were comparable to ketamine and fluoxetine. The antidepressant-like effect of GLYX-13 (3 mg/kg IV) and ketamine (10 mg/kg IV) persisted at 24 hrs post-dosing in the Porsolt test. The antidepressant-like effect of GLYX-13 (3 mg/kg IV) was completely blocked by co-administration of a silent dose of the AMPAR antagonist NBQX (10 mg/kg IP). MPFC injections of GLYX-13 (1-10 μg), but not ketamine (1-10 μg), also produced a robust antidepressant-like effect in the Porsolt test. In contrast, ketamine (10 mg/kg IV, IP, SC), but not GLYX-13 (3 mg/kg IV), elicited conditioned place preference, inhibited pre-pulse inhibition, and reduced locomotor activity in the open field. GLYX-13 (3-170 mg/kg SC) did not substitute for ketamine (10 mg/kg IP), and did not suppress operant responding. *Molecular Pharmacology*: Twenty-four hrs post-dosing, GLYX-13 (3 mg/kg IV) and ketamine (10 mg/kg IV) both increased cell surface expression of NR2B and GluR1 proteins in the MPFC and hippocampus assessed by

Western blot analysis. *Electrophysiology*: Both GLYX-13 (3 mg/kg IV) and ketamine (10 mg/kg IV) increased Schaffer collateral-evoked NR2B-specific NMDAR current in CA1 pyramidal neurons and facilitated the formation of LTP in hippocampal slices 24 hrs after a single drug dose.
Conclusions: Our data show that GLYX-13 produces a robust and long-lasting antidepressant-like effect in multiple models, without any ketamine-like side effects. The long-lasting antidepressant-like effects of both GLYX-13 and ketamine appear to be triggered by an NMDAR-mediated metaplastic enhancement of LTP resulting from an up-regulation of NR2B-containing NMDARs. GLYX-13 is currently in a Phase II clinical development program for treatment-resistant depression.
Keywords: Depression
Disclosure: J. Burgdorf, **Part 1:** Naurex Inc.; X. Zhang, **Part 1:** Naurex Inc.; K. Nicholson, **Part 1:** Naurex Inc.; R. Balster, **Part 1:** Naurex Inc.; J. Leander, **Part 1:** Naurex Inc.; P. Stanton, **Part 1:** Naurex Inc.; R. Kroes, **Part 1:** Naurex Inc.; J. Moskal, **Part 1:** Naurex Inc.

W107. Chronic Unpredictable Stress Dysregulates Glutamate Neurotransmission, Neuronal Plasticity and Cognitive Flexibility in the Rat Medial Prefrontal Cortex

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Background: Impairments in cognitive flexibility represent a major component of stress-related psychiatric disorders, such as depression, and are likely to reflect dysregulation of the prefrontal cortex (PFC). Neuro-imaging studies have shown that depression is associated with hypoactivity and reduced glutamate levels in the PFC (Hasler et al., 2007). We have demonstrated that rats exposed to chronic unpredictable stress (CUS) express cognitive deficits related to mPFC dysfunction (i.e., cognitive set-shifting) on an attentional set-shifting test (AST) (Bondi et al., 2008). Conversely, we have investigated the use of AST as a potential model of cognitive behavioral therapy (CBT), by engaging animals in a task requiring cognitive flexibility. In preliminary studies, repeated performance on the AST produced antidepressant-like effects on the forced swim test, and reversed chronic stress-induced deficits in extinction learning. We hypothesize that chronic stress may compromise cognitive function, and that performance on the AST may enhance it, by altering glutamate neurotransmission and plasticity in the mPFC. To test this hypothesis, we measured afferent-induced *fos* expression and acute stress-induced glutamate release in the mPFC, as well as expression of the plasticity-related immediate early gene, ARC in CUS and non-stressed rats after performance on the AST.
Methods: To determine the effects of CUS on glutamate afferent-induced activation of the mPFC, bicuculline was infused into the mediodorsal thalamus 24 hr after the last CUS or control handling session, and *fos* expression was measured in the mPFC by *in situ* hybridization. In another study, a guide cannula was implanted unilaterally in the mPFC, and a microdialysis probe inserted 24 hr after the last CUS or control session. Glutamate release was assessed at baseline and in response to 30 min immobilization stress. In a third study, rats were exposed to CUS or control conditions and tested on the AST 3 days after the last session (i.e., following habituation and training days). Rats were sacrificed 30 min after completing the set-shifting task and the mPFC was removed to measure ARC expression using qRT-PCR and western blots.
Results: Glutamate afferent-induced *fos* expression was reduced in the mPFC of CUS treated rats ($p<0.05$). Acute stress-evoked glutamate release in the mPFC was also attenuated in CUS treated rats compared to non-stressed controls ($p<0.001$). Preliminary results indicate that performance on the cognitive set-shifting task significantly induced ARC expression in the mPFC of control rats ($p<0.001$). Studies are ongoing to determine if this response was altered in CUS-treated rats, concordant with the stress-induced cognitive deficit.
Conclusions: These results show that CUS dysregulates glutamate neurotransmission in the mPFC, and that engaging rats in a behavioral task requiring cognitive flexibility increased expression of ARC, a marker of neuronal plasticity in the mPFC. This suggests that the beneficial effects of behavioral therapies such as CBT may be related to restoration of plasticity and glutamate neurotransmission in the mPFC. Future studies will determine if AST, as a model of CBT, also restores glutamate release and functional activity in the mPFC of CUS-treated rats.
Keywords: depression, cognitive flexability, chronic stress, glutamate, cognitive behavioral therapy
Disclosure: J. Jett, Nothing to Disclose; B. Bingham, Nothing to Disclose; D. Morilak, **Part 1:** Consultant for Dey Pharmaceuticals (now Mylan), Consultant for Actavis, **Part 2:** 2012, consultant for Actavis (income, no equity), **Part 4:** Research funding from Forest Laboratories and Lundbeck. None of these activities were related to the research reported in this abstract.

W108. Cognitive Features after Long Term Breast Cancer Survival: Longitudinal Evaluation of Neuropsychological Function into Later Life

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Background: The present study examined the long-term cognitive implications of cancer treatment among breast cancer survivors aged 65 years and older. The aim was to better understand the possible effects of previous treatment, including chemotherapy, and how these effects may interact with cognitive aging in later life.
Methods: Women who had undergone successful treatment of breast cancer with surgery and chemotherapy at least 10 years prior to enrollment were examined, as well as women who had also received treatment for breast cancer with surgery but who did not receive chemotherapy. Longitudinal neuropsychological testing was performed to evaluate for evidence of late life cognitive decline. Participants were screened to be free of recurrent cancer for the preceding ten years at the time of enrollment and were free other exclusionary medical conditions. Subjects underwent comprehensive neuropsychological testing at intake and repeat testing after two years to examine the possibility of cognitive decline. Performance at two year follow-up was compared to baseline testing for each group.
Results: Cancer survivors who received chemotherapy 10 or more years previously demonstrated a decrease in performance over two year follow-up on the COWA ($p=.035$), BVRT errors ($p=.035$), and BVRT correct ($=.002$). However they also showed improved scores over follow-up on the MMSE ($p=.043$), Digit Span reverse ($p=.01$), and Digit Span total ($p=.002$). For women who received surgery but no chemotherapy, performance decreased over time on the COWA ($p=.001$) and BVRT correct ($p=.004$), but improved on Trails A ($p=.045$), Digit Span reverse ($p=.023$), Digit Span total ($p=.015$), and Complex Figure delay ($p=.009$).
Conclusions: Overall these mixed results do not indicate a uniform pattern of cognitive changes among older cancer survivors, nor do they suggest that in later life women who have survived breast cancer treatment are at risk for progressive cognitive decline. Additional research may clarify relevant predictors of late life cognitive outcomes among cancer survivors. This research was supported by R01CA122934.
Keywords: aging, cognition, cancer, medical conditions.
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W109. Nonconscious Color Priming Reveals Intact Feedforward Visual Processing in Schizophrenia

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Background: Visual perceptual impairments are widely reported in patients with schizophrenia, including deficits in motion perception, backward masking, and perceptual closure. What is unclear is how early in the visual processing stream dysfunction occurs. Some studies have reported deficits occurring as early as the retina. Most other studies show impairments at later stages of processing where a percept is formed and must be identified. However, it is unclear whether visual processing deficits start before the formation of percepts as visual processing studies in schizophrenia have typically examined the processing of consciously registered stimuli. One way to examine early, preperceptual processing is using a masked color priming paradigm. In this task, a small disc serves as a prime and a surrounding ring serves as a target and is presented slightly after the disc. When the disc and ring are of incongruent colors, reaction times are slowed when identifying the color of the ring compared to when the disc and the ring color are congruent; this effect is referred to as color priming. Importantly, color priming can occur when the disc is not consciously perceived by the observer, indicating that nonconscious, stimulus-dependent levels of visual processing are involved. We utilized this paradigm to determine if this very early stage of visual processing is intact in patients with schizophrenia. If nonconscious color priming effects are as large in schizophrenia patients compared to healthy controls, this would indicate that visual processing is intact at this early, feedforward stage that occurs before the formation of precepts.
Methods: Both nonconscious and conscious color priming was assessed in an initial sample of 181 schizophrenia patients and 85 healthy control subjects. We assessed the effectiveness of the masking effect in the nonconscious condition and excluded subjects who did not exhibit masking of the disc. This resulted in a final sample of 148 schizophrenia patients and 54 healthy controls. Subjects were instructed to identify the color of the ring that was preceded by a disk (prime). The disc and the ring could be either the same color (congruent) or a different color (incongruent). In the nonconscious condition, the disc was masked by the ring using an SOA of 62.5 ms; in the conscious condition the ring did not mask the disc by using a long SOA of 200 ms.
Results: Schizophrenia patients and healthy controls exhibited longer reaction times of similar magnitude in the incongruent vs. congruent trials for both nonconscious and conscious color priming. That is, both groups showed a similar magnitude color priming effect in both nonconscious and conscious conditions. However, healthy controls had a significantly larger priming effect in the nonconscious vs. conscious condition, but patients did not show a significant difference in priming effects between the two conditions. Color priming in either condition did not correlate with BPRS or SANS ratings in the patients.
Conclusions: We utilized color priming to examine early, preperceptual stages of visual information processing. Schizophrenia patients showed color priming effects that were similar in magnitude to healthy controls during nonconscious color priming. These results suggest that stimulus-dependent, feedforward (i.e., from retina to V1) processing is intact in schizophrenia patients. Our results imply that the well-documented visual processing deficits in schizophrenia occur at later percept-dependent, cortico-cortical stages of processing. Our results have implications for dysfunctional neurotransmitter systems in schizophrenia, namely the GABA system.
Keywords: Schizophrenia; Visual processing; Color priming; Nonconscious; Feedforward

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W110. Neuropsychological Performance in Phenotypes of Pediatric Bipolar Disorder

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Background: Once thought to be exceedingly rare, pediatric bipolar disorder (BD) is a growing public health concern. Specifically, studies in the U.S. and abroad suggest that from the mid-1990 s to the present, increasing percentages of children and adolescents are being diagnosed with BD.[1–3] These studies highlight the need for greater understanding of the brain/behavior interactions underlying pediatric BD. To advance what is known about cognitive function in children and adolescents with bipolar spectrum disorders, we evaluated neuropsychological performance in children and adolescents with BD types I, II, and not otherwise specified who were participating in the Course and Outcome of Bipolar Youth (COBY) study using tasks from the Cambridge Neuropsychological Testing Automated Battery (CANTAB). We were particularly interested in between-group differences in cognitive flexibility and reversal learning on the intra-dimensional/extra-dimensional shift task (IDED).[4]
Methods: a) Sample: This study was IRB approved and conducted at the three participating COBY study sites: Brown University, University of Pittsburgh, and University of California Los Angeles. Children and adolescents ages 7 to 17 years 11 months with BD-I (N = 81), BD-II (N = 11), or BD-NOS (N = 28). *After informed parent consent/child assent,* psychiatric diagnoses were assessed using the Schedule for Affective Disorders and Schizophrenia for School-Age Children, Present and Lifetime Version (KSADS-PL). Longitudinal changes in psychiatric symptomatologywere assessed using the Longitudinal Interval Follow-up Evaluation (LIFE) and tracked on a week-by-week basis using this instrument's Psychiatric Status Rating (PSR) scales. b) CANTAB testing: Included the following tasks: (1) intra-dimensional/extra-dimensional shift (IDED; computerized version of Wisconsin Card Sorting Task; probes reversal learning and cognitive flexibility), (2) rapid visual information processing (RVP; evaluates sustained attention akin to the continuous performance task), (3) pattern recognition memory (PRM; participants see a set of shapes and then pairs of shapes are presented, one novel and one from original set. Participants must select the familiar, rather than novel, shape), (4) spatial span memory (SSP; test of working memory akin to Corsi Block test), (5) Affective Go/No-Go (AGN; evaluates information processing for positive and negative words). c) Statistical Analyses: Analysis of variance (ANOVAs) implemented in Statistical Package for Social Sciences (SPSS v17) were calculated for each separable domain of our CANTAB neuropsychological battery to evaluate between-group differences between BD-I, BD-II, and BD-NOS participants.
Results: With respect to our primary evaluation of reversal learning as indexed by the simple reversal stage of the IDED task, we found a main effect of group in our 2-way comparison of BD-I and BD-II participants vs. BD-NOS [Wilks lambda = 0.95, $F(2,117) = 3.15$, $p = 0.05$]. Further analyses showed that there was a between-group difference in total number of trials [$F(1,118) = 4.25$ $p = 0.04$], but not total errors [$F(1,118) = 1.55$, $p = 0.22$] required to complete the stage 2 simple reversal stage. Post-hoc pair-wise analyses showed that the difference in total trials was driven by

BD-I/II participants requiring more trials than BD-NOS participants ($p = 0.04$). With respect to broader evaluation of neuropsychological performance, we did not find a main effect of group differentiating BD-I, II, or NOS participants on the overall measures of PRM, IDED, SSP, RVIP, or AGN task performance, whether using participants' raw scores or the z-scores from their performance using CANTAB's age-normed data.
Conclusions: In sum, our study begins to shed light on neuropsychological performance in children and adolescents suffering from different phenotypes of BD. Our study suggests that BD-I and -II participants have greater difficulty on reversal learning tasks than BD-NOS participants, which aligns with other studies showing similar impairments in youth with distinct episodes of mania. Further work is necessary to see the interaction between neurocognitive performance and longitudinal illness course and development, as these COBY BD participants become young adults. Reference List: (1) Blader JC, Carlson GA. Increased Rates of Bipolar Disorder Diagnoses Among U.S. Child, Adolescent, and Adult Inpatients, 1996-2004. *Biol Psychiatry* 2007;62:107-114. (2) Moreno C, Laje G, Blanco C, Jiang H, Schmidt AB, Olfson M. National trends in the outpatient diagnosis and treatment of bipolar disorder in youth. *Arch Gen Psychiatry* 2007;64:1032-1039. (3) Holtmann M, Duketis E, Poustka L, Zepf FD, Poustka F, Bolte S. Bipolar disorder in children and adolescents in Germany: national trends in the rates of inpatients, 2000-2007. *Bipolar Disord* 2010;12:155-163. (4) Dickstein DP, Nelson EE, McClure EB et al. Cognitive flexibility in phenotypes of pediatric bipolar disorder. *J Am Acad Child Adolesc Psychiatry* 2007;46:341-355.
Keywords: bipolar disorder, child, adolescent, neuropsychological performance
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W111. Impaired Reward Responsiveness during Nicotine withdrawal in Rats and Humans Assessed in a Translational Behavioral Procedure

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Background: Nicotine withdrawal produces negative affective symptoms similar to those seen in depression. It is hypothesized that chronic drug exposure and withdrawal promotes the abnormal processing of rewards, which may contribute to addictive behaviors and negative affect during withdrawal that in turn may lead to relapse. Clinical evidence suggests that depressed subjects display abnormal processing of positively reinforcing stimuli (i.e., anhedonia, or decreased interest in rewards) when assessed using the Response Bias Probabilistic Reward Task [Pizzagalli et al. (2008) J Psychiatr Res *43*, 76-87]. Briefly, this task involves exposure to two different visual stimuli that are difficult to discriminate, each requiring a different response to lead to reinforcement. Correct responses to one stimulus are rewarded three times more frequently (i.e., rich) compared to correct responses to the other stimulus (i.e., lean). Non-depressed human subjects modulate their behavior during testing as a function of prior reinforcement by gradually developing a biased response toward the rich stimulus. In contrast, depressed subjects fail to develop this response bias for the more frequently rewarded stimulus. The result is a quantitative task that objectively measures deficits in reward processing in depressed individuals. The goal of the present study was to determine whether nicotine withdrawal is associated with impaired reward responsiveness similarly in rats and humans using the Response Bias Probabilistic Reward Task originally developed in humans and recently adapted for rats. We hypothesized that nicotine withdrawal would be associated with similarly decreased reward responsiveness in rats chronically exposed to nicotine and heavy smoking human subjects.
Methods: *Rats:* Male Wistar rats were food restricted and trained in operant boxes to press a lever to receive a food pellet as a reward. Rats were then presented with either a short or long tone (identical in all parameters other than duration) and trained to discriminate the tones by pressing one of two levers associated with each tone duration. Once these associations were learned, defined as more than 70% accuracy, the difference between the two tone durations was made more ambiguous during a 100-trial test session split into three blocks. Correct responses on the lever associated with either the short or the long tone (counterbalanced) were reinforced three times more frequently (i.e., rich) than correct responses on the other lever (i.e., lean). After this baseline test, rats were surgically prepared with subcutaneous osmotic minipumps delivering either 6.32 mg/kg/day nicotine (base) or saline vehicle for 28 days. After 28 days, minipumps were removed and rats were tested again 24 hr later during withdrawal. **Humans:** Participants classified as heavy smokers were presented on a computer screen with one of two mouths varying slightly in length on a schematic face, and instructed to discriminate the mouths by pressing one of two keys on a keyboard associated with each mouth length. During a 300-trial session split into three blocks, correct responses for either the long or short mouth (counterbalanced) resulted in presentation of a monetary reward (5 cents) three times more frequently than correct responses for the other mouth. At the end of the session, participants were given the amount of money won. In one session, participants were smoking at their usual rate prior to testing. In another session, participants were instructed to be 24 hr smoke-free prior to testing (i.e., withdrawal), which was biologically verified. The smoking and abstinence sessions were randomly counterbalanced across subjects and were approximately one-week apart.
Results: *Rats:* Saline-treated rats developed a response bias towards the rich stimulus, which was comparable to the response bias previously quantified in non-depressed human subjects. In contrast, response bias was significantly decreased in rats exposed to nicotine withdrawal ($p < 0.05$). Humans: In heavy smokers, response bias was significantly decreased within subjects during 24 hr abstinence relative to the smoking session ($p < 0.05$). Collectively, control rats and heavy smokers when smoking (relative to their abstinence day) responded more toward the rich stimulus than the lean stimulus. However, rats and humans experiencing withdrawal from nicotine responded similarly with less overall responsiveness toward the rich stimuli despite the fact that correct responses for the rich stimuli were reinforced more frequently.
Conclusions: The results indicate that withdrawal from nicotine significantly impairs reward responsiveness in both rats and humans as assessed using the Response Bias Probabilistic Reward Task. This impairment of reward responsiveness is reflected by an inability to alter behavioral responding as a function of prior reinforcement experience. Being able to identify reward processing impairments that are analogous across species will facilitate translational research investigating the behavioral and neurobiological mechanisms that underlie nicotine reward and withdrawal.
Keywords: Anhdonia, Nicotine Withdrawal, Reward, Depression, Animal Model

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W112. Loss Aversion with Respect to Prospect Theory and Relative Preference Theory

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Background: Loss aversion (LA) has been defined as "losses loom larger than gains" by Prospect Theory (PT)(Kahneman & Tversky, 1979), which was the basis of a Nobel Prize in Economics for 2002. LA has been quantified and replicated across multiple studies (Kahenman et al., 1990; Tversky & Kahneman, 1991; Barberis et al., 2001). LA under PT can be estimated in terms of the absolute value of the ratio between the slopes of the negative value/utility function (s-) and positive value/utility function (s+) (i.e. |s-/s+|) (Wakker & Tversky, 1993; Bowman et al., 1999; Neilson, 2002), with healthy control subjects giving losses from 1.74 to 4.8 times the weight that they give gains (Abdellaoui et al., 2007). However, these estimates are almost always measured in the stimulus domain of money, which has a different contextual meaning for psychiatric populations that may not have similar economic opportunities. Relative preference theory (RPT)(Kim et al. 2010) offers a framework for computing loss aversion that is complementary to PT, and broadens the approach that can be used to study loss aversion along with negative and positive valence systems with non-monetary stimuli, in a broad array of populations, particularly psychiatric populations. In this study, we sought to evaluate if RPT-based LA produced parameter estimates similar to PT-based LA, even if these frameworks differed with regard to the stimulus used (money vs. non-monetary stimuli), measure of behavior (ratings vs. keypress), and mode of LA measured – namely global vs. local loss-aversion (e.g., using the whole curve or just the curve next to the origin)(Abdellaoui et al., 2007).
Methods: 22 healthy control subjects completed both the PT-based monetary task and the RPT-based keypress task. For a task in the framework of PT, we used a monetary game of chance (Breiter et al., 2001), with controlled expectancy and outcomes that followed PT. Two spinners with different weightings of gain (+$10) and loss (-$8) were used, with actuarial outcomes of -$2 (Bad Spinner), and +$4 (Good Spinner) overall. Behaviorally, subjects made ratings of their emotional responses to the spinners with a potentiometer while an arrow was rotating around the sectors of the spinner, reflecting their anticipated utility. They also rated their emotional response during the outcome phase when the arrow stopped rotating, indicating the subject had won or lost that amount of money (reflecting outcome utility). For the non-monetary task outside the framework of PT, we used a validated keypress procedure derived from the operant conditioning literature (Aharon et al., 2001; Kim et al., 2010), wherein subjects trade effort for increasing, decreasing, or not changing viewing time of pictures of non-monetary stimuli (e.g., facial expressions from Ekman and Friesen (1974)). Data analysis produced three LA estimates: "anticipation LA" from the monetary game of chance; "outcome LA" from the monetary game of chance; and "keypress LA" from the RPT-based task.
Results: LA for the anticipation phase of the PT-based monetary task involved a "global" measure which produced mean ± SE estimates for s+, s-, and the absolute value of s-/s+ (i.e., |s-/s+|) of 0.69 ± 0.05, 1.37 ± 0.12, and 1.93 ± 0.16, respectively. For the outcome phase of the PT-based monetary task, s+, s-, and the absolute value of s-/s+ (i.e., |s-/s+|) were 0.35 ± 0.03, 0.39 ± 0.04, and 1.11 ± 0.05, respectively. LA for the decision and outcome phases of RPT-base keypress task involved a "local" estimate, producing s+, s-, and an absolute values of s-/s+ (i.e., |s-/s+|) of 1.39 ± 0.53, 1.49 ± 0.51, and 2.12 ± 0.36, respectively. The 95% confidence interval for the RPT-based keypress task alone overlapped the estimate of 2.25 published by Kahneman and Tversky (1992). A significant effect ($r = 0.610$, $p < 0.003$) was observed in the correlation of anticipation LA (via the PT-base monetary task) with the RPT-based keypress task. The correction for multiple comparisons was $p < 0.05/3 = 0.17$, for three comparisons.
Conclusions: These data indicate that a task based on PT, using monetary stimuli, and a task based on RPT, using non-monetary stimuli, can produce similar loss aversion estimates across experiment phases. The correlation between the anticipation phase of the monetary game of chance and the keypress task occurred despite these tasks differing in three domains: (1) monetary vs. non-monetary stimuli; (2) ratings (PT) vs effortful keypressing (RPT: representing a transaction between motor action and viewing time), and (3) "global" vs. "local" methods for computing LA. The similarity of LA estimates between the two tasks, despite significant differences in (1) – (3), argues that LA represents a general weighting between approach and avoidance decisions when uncertainty is present. Given the ease with which RPT-based keypress tasks can be used on the Internet, or in animal studies, these findings open a broader range of applications for the study of rewards and sanctions, including loss aversion, than can be studied with PT. RPT-based keypress tasks hold significant promise in their use for studying psychiatric populations for which socio-economic factors and income disparities may not make matching easy between affected and non-affected control cohorts.
Keywords: loss aversion, neuroeconomics, decision-making, reward, preference
Disclosure: S. Lee, Nothing to Disclose; M. Lee, Nothing to Disclose; J. Gilman, Nothing to Disclose; B. Kim, Nothing to Disclose; J. Kuster, Nothing to Disclose; A. Blood, Nothing to Disclose; H. Breiter, Nothing to Disclose.

W113. Probabilistic Reinforcement Learning in Young Adults with Autism Spectrum Disorders Reflects Cognitive Control Deficits

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Background: Individuals with autism spectrum disorders (ASD) display a unique pattern of learning strengths and challenges. They show intact (or even enhanced) lower-level learning of stimulus response associations, of single items of information, of facts, of habits, and of information learned implicitly. However, they display deficits in *generalizing* (or transferring) what they have learned during training to new similar situations. Generalization problems have a profound impact on the academic, social, and adaptive functioning of persons with ASD, and have not been well studied. The goal of the current research is to illuminate the neural mechanisms of learning differences in persons with ASD using neuroimaging, and to translate findings into clinically relevant insights.

Methods: To better understand how the neural mechanisms underlying feedback processing contribute to learning challenges characteristic of ASD, we used rapid event-related functional magnetic resonance imaging (fMRI), and a probabilistic selection task where participants were trained to choose the correct stimulus in three different stimulus pairs (AB, CD, EF) presented with feedback that was valid 80%, 70%, and 60% of the time, respectively. Participants had to determine which was the rewarded stimulus from this relatively unpredictable reward-related feedback (i.e. they had to generalize the meaning of the feedback across multiple trials). Participants were young adults aged 18-40 years with ASD, who were largely medication free and evaluated using gold standard autism diagnostic measures (n = 22), and young adults with typical development (TYP; n = 25). Whole brain voxel-wise analyses were conducted using Bayesian state-space learning curves and prediction errors as parametric modulators. We interrogated regions of interest in the striatum, prefrontal cortex (PFC), and medial temporal lobes, and conducted functional connectivity analyses using these regions as seeds.

Results: As in our previous behavioral study, individuals with ASD learned the task to comparable rates as TYP by the end of training, but were slower to learn. Early in learning, the ASD group showed less benefit from positive feedback as evidenced by reduced tendency to continue selecting previously rewarded choices, although they used negative feedback comparably to the TYP group. Whole brain and ROI analyses showed that the ASD group exhibited greater striatal and medial temporal lobe activation during early learning that was related to task performance. There was less activation in prefrontal regions throughout learning in the ASD group. For the TYP group, activation in the striatum and the orbito-frontal cortex (OFC), was significantly related to the probability of having learned, whereas these relationships did not hold for the group with ASD. Indices of activation of the striatum also were positively associated with the presence of restricted interests and repetitive behaviors in individuals with ASD.

Conclusions: Results suggest that individuals with ASD accomplish probabilistic reinforcement learning differently than TYP. Throughout learning, they activate prefrontal regions less than their TYP counterparts, and OFC activation is not related to their probability of having learned. Instead, young adults with ASD appear to rely on striatal, and medial temporal lobe regions to a greater extent than TYP, suggesting the use of these brain regions may be compensatory. Activation of the striatum during early learning also was related to symptoms of restricted interests and repetitive behaviors, illustrating there may be a relationship between the learning style of those with ASD and their repetitive behavior symptoms. Overall, those with ASD have cognitive control related learning deficits. Consequently they rely on a rote learning-based strategy as opposed to a more flexible one that can incorporate rapid updating of reward contingencies, and integrate this information in the service of goal directed behavior. Those with ASD exhibit sparing of processes thought to rely on the striatum and the hippocampus, and deficits in those thought to require intact functioning of the OFC and PFC. This interpretation of findings also is supported by the systems-level computational modeling work of Frank et al. (2004, 2005, 2006).

Keywords: autism spectrum disorders, reinforcement learning, striatum, hippocampus, orbito-frontal cortex

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W114. Respective Contributions of Alcoholism and Bipolar Disorder to Neurocognitive Deficits in Adults with Co-occurring Bipolar Disorder and Alcohol Dependence: Impact of Abstinence

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Background: Bipolar disorder (BPAD) is associated with higher rates of alcoholism than any other Axis I psychiatric illness. Both BPAD and alcohol dependence (AD) are associated with discrete neurocognitive impairments that may impede treatment adherence and remission from each disorder. Individuals with both BPAD and AD may have more severe cognitive deficits than those with either disorder alone, but previous research on the comorbid population is limited and equivocal. Most previous studies have evaluated bipolar subjects with past, rather than current, AD, and to date, all previous neurocognitive studies have compared bipolar alcoholics only with healthy controls or bipolar subjects without a history of alcoholism. To better understand the respective roles of alcoholism and bipolar disorder in cognitive deficits evident in adults with co-morbid illness, the current study employed a full factorial design comparing cognition in subjects with AD alone, BPAD alone, both BPAD and AD, and healthy controls. All subjects were evaluated for global intellectual function and for performance on tests of attention/processing speed, verbal fluency, verbal memory, visuospatial memory, executive function, and impulsivity. Secondary analyses were conducted comparing cognition in abstinent (>35 days) vs. currently drinking bipolar alcoholics.

Methods: Treatment-seeking adults age 18-65 with co-occurring alcohol dependence and bipolar disorder were recruited for a randomized, placebo-controlled 12-week clinical trial designed to test the effects of lamotrigine on drinking, mood, and cognitive outcomes. Enrollment eligibility required subjects to have consumed alcohol in the past 30 days ($\geqslant$35 drinks/week for men, $\geqslant$ 28 drinks/week for women in the month prior to last alcohol use) and to be maintained on stable doses of lithium or antipsychotic medications for 1 month at the time of randomization. Trial participants were evaluated for neurocognitive performance at baseline (Week 0) and after 12-weeks of treatment with placebo or lamotrigine, titrated to 200 mg/day. Comparison subjects (healthy control (HC), AD only (AD), BPAD only (BP), and alcohol-dependent subjects with BPAD (BP + AD) who failed to meet alcohol use or medication inclusion criteria) were recruited for neurocognitive testing only at Week 0. Baseline results were analyzed by ANOVA with Bonferroni adjustment for *post hoc* multiple comparisons. Baseline vs. endpoint comparisons in BP + AD trial completers were analyzed using within-subjects ANOVA.

Results: Seventy-eight subjects, including N = 41 BP + AD participants, were enrolled for baseline neurocognitive testing. Of 27 BP + AD subjects who met alcohol use criteria, N = 25 were enrolled in the medication trial and N = 11 subjects completed both baseline and endpoint cognitive test batteries. At baseline, no group differences were evident in attentional, verbal fluency, or visuospatial memory domains. In contrast, verbal memory impairments were observed in AD, BP, and BP + AD subjects relative to controls. Significant executive function impairments included total errors and non-perseverative errors on the Wisconsin Card Sorting Test (WCST), whereas group differences in performance on the classic, alcohol, or emotional variants of the Stroop task did not survive Bonferroni adjustment. Deficits on the WCST were most severe in the two alcohol-dependent groups, with significantly worse impairment in BP + AD as compared with BP subjects. Impulsivity was highest in the two bipolar groups (BP + AD $\geqslant$ BP > AD > HC) across all dimensions of the Barratt Impulsiveness Scale (BIS-11). Among BP + AD subjects, current drinkers exhibited lower verbal IQ and greater impairments of executive

function than abstinent subjects on both the WCST and classic and emotional variants of the Stroop task. However, no improvement of executive function impairments was observed from baseline to endpoint in BP + AD trial completers despite reduced drinking or full, sustained abstinence in all subjects over 12 weeks.
Conclusions: The current results indicate that alcoholism and bipolar disorder are associated with discrete and partially dissociable impairments of verbal memory and executive function in adults with co-morbid BPAD and AD. Additive cognitive impairments associated with AD and BPAD were evident only for WCST measures of executive function in this sample. Given the lack of improvement in executive function over the 12 weeks from baseline to endpoint in BP + AD trial completers, cross-sectional differences in Stroop and WCST performance detected between abstinent and current drinkers may be a marker of alcoholism prognosis rather than the result of abstinence in bipolar alcoholics.
Keywords: Alcohol, cognitive impairment, comorbidity, executive function, impulsivity
Disclosure: B. Tolliver, Nothing to Disclose; J. Prisciandaro, Nothing to Disclose; D. Brown, Nothing to Disclose; K. Brady, Nothing to Disclose.

W115. Does Targeted Social Cognitive Training Enhance Cortical and Subcortical Activation in Schizophrenia during Reward Processing?

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Background: Schizophrenia patients (SZ) suffer from deficits across a range of cognitive, social and affective processes, including impairments in reward processing and motivated behavior. Some basic and clinical evidence suggests that there may be an association between dysfunction in social cognitive processing and motivated behavior. In the present study, we examined whether intensive targeted training of basic cognitive and social cognitive processes would enhance behavioral performance and brain activation patterns during reward processing on a monetary incentive delay task.
Methods: SZ and healthy comparison subjects (HC) performed a Monetary Incentive Delay task during fMRI scanning at baseline. Patients then received approximately 80 hours of intensive computerized cognitive plus social cognitive training over a 16 week period. Subjects underwent a second fMRI session after training was completed. BOLD fMRI was measured on a 3T-Siemens scanner. Images were analyzed using SPM8.
Results: At baseline, during monetary reward incentive trials versus control non-incentive trials, HC subjects showed increased activation in the medial prefrontal cortex (mPFC) and insula during the cue phase, signaling anticipation of reward. During the feedback phase, signaling reward outcome, HC subjects revealed activation in mPFC and basal ganglia (globus pallidus and putamen), in accordance with prior research. By contrast, SZ patients showed impaired performance compared to HC subjects, activation in posterior brain regions such as the posterior cingulate cortex, and no activation in either mPFC or basal ganglia during either the reward incentive cue or feedback phase. Preliminary data indicate that after 16 weeks of intensive social cognitive training, SZ- subjects show increased activation in mPFC and basal ganglia (putamen and globus pallidus) during both the reward incentive cue and outcome phases, similar to what is seen in HC subjects at baseline.
Conclusions: The findings from this experiment suggest that: 1) At baseline, and as expected, SZ patients reveal impaired performance and disrupted neural activation patterns during reward processing on the monetary incentive delay task 2) Intensive computerized social cognitive training may "normalize" some of these disrupted patterns of neural activity, with subjects showing evidence of activation in the appropriate neural networks during both anticipation of reward and during positive reward outcome after the intervention. These findings may be the result of non-specific effects of training due to the high reward schedule and adaptive nature of the exercises, or may reflect the more specific effects of improving basic social cognition and enhancing the salience of appropriately rewarding social stimuli in the environment.
Keywords: fMRI, cognitive training, schizophrenia, plasticity
Disclosure: S. Vinogradov, **Part 4:** Dr. Vinogradov is a consultant to BrainPlasticity Institute, a company with a financial interest in cognitive training software. She is also a consultant to Genentech, Amgen, and Hoffman-LaRoche; K. Subramaniam, Nothing to Disclose; S. Nagarajan, Nothing to Disclose; C. Hooker, **Part 4:** Dr. Hooker is a paid consultant on an NIMH BRDG-SPAN grant to Brain Plasticity Inc., a company with a commercial interest in the cognitive training software used in the present study.

W116. Catechol-O-Methyltransferase (COMT) Genotype as a Predictor of Response to Computerized Cognitive Remediation in Schizophrenia and Schizoaffective Disorders

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Background: Neurocognitive deficits are core features of schizophrenia and have a significant impact on functional outcome. Reports have suggested that a functional polymorphism of the catechol-*O*-methyltransferase (COMT) gene (Val158Met) partially influences cognitive performance both in schizophrenia patients and in healthy controls by modulating prefrontal dopaminergic activity. Our aim was to evaluate the effect of the association of the COMT $Val^{108/158}$ Met genotype with the response to a computerized neurocognitive rehabilitation treatment (CRT) in patients with chronic schizophrenia. Our hypothesis was that (1) the COMT low-activity Met allele will be associated with better neurocognitive performance at the end of CRT in working memory performance, attention, and cognitive flexibility in patients with schizophrenia and that (2) the COMT high-activity Val allele will be associated with lesser improvement in these areas after CRT.
Methods: Patients with a DSM-IV diagnosis of schizophrenia or schizoaffective disorder were genotyped for the COMT $Val^{108/158}$ Met polymorphism. All patients had been assigned to 3 hours per week of CRT for a total duration of 12 weeks and were evaluated on a standardized battery of neuropsychological assessments, a brief assessment of functional skills, and clinical symptoms (PANSS) at baseline and at endpoint (Week 12). Met homozygous patients were combined with Met carriers (Met/Val = 48) and Met homozygotes (Met/Met = 9) in one group and compared to Val homozygotes (Val/Val n = 45). Response to CRT was defined as $\geqslant$ 20% performance improvement on the Trail Making tests and Continuous Performance Test, Identical Pairs version (CPT-IP) as a cut-off criterion to categorize patients into two groups: (1) Responders and (2) Non-responders.
Results: 125 patients have been enrolled. No significant demographic, neuropsychological or functional differences were seen between groups at baseline. Mean overall PANSS score was 78.89 ± 13.11. Genotype data was available for 108 patients. A mixed model linear regression for each cognitive domain (Executive Functioning, Processing Speed, working Memory, Attention/Vigilance, Global Cognitive Index) was based on all Met/Val + Met/Met patients (n = 49 + 11) vs. Val/Val patients (n = 48). A significantly greater improvement was found for the global cognitive index score ($p = 0.050$; partial eta square = .231), Trail Making Test scores measuring processing speed ($p = 0.049$; partial

eta squared = .291) and working memory tasks (*Wechsler Memory Scale*—3rd Ed. (WMS-III): Spatial Span, *Letter-Number Span*; p = 0.048; partial eta squared = .231) for the (Met/Val + Met/Met) group compared to the Val/Val group. For the Attention/Vigilance domain we used the CPT-IP. The primary outcome variable for the CPT-IP was the signal discrimination index d'. Mean d' was 1.17 ± 1.1 for the Val/Met + Met/Met genotypes, and 0.91 ± 1.0 for Val/Val. The linear mixed model that included d' as a dependent measure indicated a significant effect of COMT genotype (p = 0.05; partial eta-squared = 0.251), and years of education (p = 0.05; partial eta-squared = 0.201). There were no significant interactions. Fisher's Exact Test did not show any significant difference between responder vs non-responder classification and the COMT classification groups (Met/Val + Met/Met vs. Val/Val).

Conclusions: These findings support the hypothesis that COMT polymorphism influences cognitive functioning through CRT, and represents a model of personalized therapeutic approach by using patients' genotype as predictor of response. The caveat is that because of the small sample size, the positive findings could be due to Type I Error. Primarily, the presence of Met allele was associated with significantly greater improvements in overall neurocognitive functioning after 12-weeks of CRT. As we accrue a larger sample size we may be able to determine if the two effects (i.e., improvement from CRT and COMT polymorphism) act at different levels.

Keywords: Schizophrenia, Cognitive remediation, COMT genotype

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W117. Multimodal Neuroimaging of Networks Associated with Working Memory Performance

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Background: Recently there has been a focus on understanding the interaction of task-based and resting networks and the relative roles of each network in cognitive performance. Here we sought to combine data across modalities to understand the contributions of both resting and task-based network activity to working memory (WMem) performance.

Methods: A sample of 115 healthy adults was recruited as a part of the Consortium for Neuropsychiatric Phenomics (CNP). We performed functional magnetic resonance imaging (fMRI) while the participants performed a Sternberg-style spatial working memory task as well as a separate resting-state fMRI (rsMRI) scan. Using data from both scans we evaluated performance-related variation across task-based and resting networks in the same participants. To accomplish this, we performed a network interaction analysis using three independent approaches. First, in the task-based analysis, to predict WMem performance, we used activation and deactivation across a series of regions as well as a metric summarizing the difference between the degree of activation and deactivation in certain regions, which was intended to capture network coordination. Next, in the rsMRI analysis we assessed the relationship of performance with the Default Mode Network (DMN), the fronto-parietal Executive network, as well the relationship between the two networks. Finally, we assigned participants to two groups those who were in the top and the bottom quartiles of performance, and created a profile of relative activation and deactivation across regions of interest (ROIs) for each group. This enabled us to test for a difference in the overall shape of the neural profiles between high and low performers in a multimodal fashion.

Results: In the task-based analysis, there were no significant associations between performance and activation in the WMem circuitry or deactivations in DMN associated regions. However the difference between the activation and deactivation of network node was the most significant predictor of performance. Supporting this finding outside the context of task performance, the rsMRI investigation revealed that the degree of independence between the task-associated and DMN networks also was also the most highly significant predictor of behavioral performance. Finally, the "profile-analysis" showed that across regions, the shape of the neural profiles differed significantly between high and low performing individuals. The regions with the largest group differences were right parietal cortex during task, the difference between DMN and Executive networks during rest, and right dorsolateral prefrontal cortex during task.

Conclusions: Overall, this pattern of results suggests that while both task-based and resting networks are individually important, functional interactions between task-based and resting networks are also uniquely informative. In addition, this study supports the use of novel analytic approaches, such as the profile analysis and the network difference scores, for combining data across modalities. Such an approach ultimately could be applied to analyses including more modalities, or to other applications, such as determining the key differences in neural profiles between patient groups.

Keywords: working memory, resting state, functional mri, neuroimaging, cognition

Disclosure: K. Karlsgodt, Nothing to Disclose; G. Hellemann, Nothing to Disclose; J. Mumford, Nothing to Disclose; E. Congdon, Nothing to Disclose; C. Sugar, Nothing to Disclose; A. Bato, Nothing to Disclose; F. Sabb, Nothing to Disclose; E. London, Nothing to Disclose; R. Poldrack, Nothing to Disclose; R. Bilder, **Part 1:** Cypress Bioscience, Inc., Johnson & Johnson, Merck, Novartis, Takeda Pharm, **Part 2:** Johnson & Johnson, **Part 4:** Johnson & Johnson; T. Cannon, Nothing to Disclose

W118. Low Frequency Neural Oscillations Associated with Age and Processing Speed in Early- and Adult-onset Schizophrenia

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Background: Behavioral measures of cognitive processing speed have been reliably associated with schizophrenia symptom expression, impaired real-world functioning, and genetic vulnerability. Additionally, a number of studies have demonstrated that controlling for variance in cognitive processing speed eliminates patient-control differences in several cognitive domains, including attention and working memory. Collectively, these findings have been taken as evidence that slowed cognitive processing speed reflects a fundamental aspect of schizophrenia-related impairment. Measures of cognitive processing speed, such as digit-symbol coding tasks, are thought to rely on the efficient creation and coordination of task-specific neural networks, since they require fast integration of a number of more basic cognitive functions supported by disparate brain areas (e.g., visual scanning, associative memory, response mapping). Due to abnormalities at the synaptic level and/or the level of white matter structure, schizophrenia appears to affect the ability to manage these functional networks efficiently, possibly explaining cognitive slowing in patients. Typically, adolescence entails a significant

reorganization within the brain, bridging inefficient, localized functional organization of neural networks in childhood with a more efficient, long-range neural integration in adulthood. In fact, cognitive processing speed does not reach optimal levels until people reach their early-to-mid 20's, after structural connections between frontal and posterior regions mature. Previously, we studied behavioral performance on a digit-symbol coding task and found that onset of schizophrenia was associated with a deviation away from a typical developmental trajectory. Specifically, controls show age-related improvement in processing speed, well into adulthood, but early onset patients show a failure to modulate processing speed with age. Together, these findings suggest that schizophrenia onset is associated with a failure to optimize immature, frontally-mediated neurocognitive networks so that they may support efficient task performance. A more direct test of this hypothesis requires temporally-precise measurement of large-scale neural network activity and a broad age range among participants. Neuroimaging techniques measuring blood flow oxygenation or glucose uptake, however, are unable to investigate such quickly occurring network activity on a trial-by-trial basis. Therefore, studies of the neural activity associated with this important cognitive construct are practically absent from the literature.
Methods: The present study represents an initial step toward characterizing neurocognitive development in the context of psychosis by examining data from adolescent-onset (ages 12-18) and older (ages 19-55), adult-onset SZ patients (total patient $N = 20$), and matched controls ($N = 20$). Participants performed a computerized digit-symbol coding task, previously shown to be sensitive to both schizophrenia diagnosis and age, while 64-channel electroencephalographic (EEG) data were recorded. Matched numbers of correct trials of EEG were then subjected to independent components analysis, and component mean event-related spectral perturbation and inter-trial coherence were calculated. In addition to testing potential diagnostic group differences, we investigated age-by-diagnosis interactions suggestive of abnormal age-related changes in the patient group.
Results: In addition to group differences in behavioral performance, event-related EEG activity in the theta (4-8 Hz) and, to a greater extent, alpha (8-12 Hz) ranges was predicted by a group-by-age interaction. This effect was stronger for stimulus detection and evaluation than for response execution, and was centered over frontal scalp regions. Critically, patients did not show age-related changes in this frontal alpha component, while controls showed a characteristic decrease in event-related power with increasing age – consistent with a failure of maturation among frontal brain areas in patients.
Conclusions: The present results provide novel insight into the neurophysiological underpinnings of slowed cognitive processing speed in schizophrenia, demonstrating that oscillations in frontal alpha band (8-12 Hz) activity at the time of stimulus onset reflect age-related changes in cognitive processing speed among controls, but not among people with schizophrenia. Alpha activity in similar task contexts has been associated with efficient deployment of selective attention, as well as with encoding of mental representations. Physiologically, alpha oscillations may result from cortico-thalamic neural network activity, although that possibility remains controversial. Overall, the present findings demonstrate that a temporally-specific physiological mechanism indexed by lower frequency EEG activity is related to the constrained development of cognitive processing speed among schizophrenia patients – a bottleneck which may have important implications for general cognitive impairment and real-world functioning.
Keywords: psychosis, cognitive processing speed, EEG, electrophysiology, neural development
Disclosure: P. Bachman, Nothing to Disclose; Z. Moran, Nothing to Disclose; M. Jalbrzikowski, Nothing to Disclose; D. Glahn, Nothing to Disclose; T. Cannon, Nothing to Disclose; C. Bearden, Nothing to Disclose.

W119. Relationship between Anxiety and Vascular Function in Older Individuals with and without Atherosclerotic Vascular Disease

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Background: Anxiety is a significant risk factor for cardiovascular events, although the mechanism of this relationship remains unclear. The current study was conducted to test the hypothesis that anxious symptoms are significantly related to vascular dysfunction in older individuals with and without atherosclerotic vascular disease (AVD).
Methods: Anxious symptoms were measured with the Symptom Checklist-90-Revised in 89 participants with clinically-diagnosed AVD and 54 healthy comparison participants. Forearm conduit vessel function was measured using brachial flow-mediated dilatation and forearm resistance vessel function was measured using intra-arterial drug administration and plethysmography.
Results: Anxious symptoms were not significantly associated with forearm conduit vessel function in either group. However, in participants with AVD, anxious symptoms were significantly and inversely associated with forearm resistance vessel function ($R^2 = .12$, $p = .001$). Adjustment for medication, risk factors and depressive symptoms did not alter the association between anxiety and resistance vessel dysfunction, except for Body Mass Index (BMI); (R^2 decreased from 0.12 to 0.07; $p = 0.03$). While BMI was more strongly associated with resistance vessel function than anxiety was, together, BMI and anxiety accounted for more variance in resistance vessel function than either did separately. In the healthy comparison group, no relationship was found between anxious symptoms and resistance vessel function.
Conclusions: Anxious symptoms are significantly related to resistance vessel damage in individuals with AVD. This relationship was independent of medication, depression and cardiovascular risk factors, with the partial exception of BMI. These findings support the concept that anxiety potentially increases risk for vascular events through worsening of vascular function in older individuals with AVD.
Keywords: Anxiety, vascular function, atherosclerosis, obesity
Disclosure: A. Stillman, Nothing to Disclose; D. Moser, Nothing to Disclose; J. Fiedorowicz, Nothing to Disclose; H. Robinson, Nothing to Disclose; P. Nopoulos, Nothing to Disclose; W. Haynes, Nothing to Disclose

W120. Expectation and Hedonics Activate Specific Neural Networks during Reward

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Background: Reward processing from anticipation, to action to hedonic response, involves a complex network of cortical and subcortical brain regions that have been implicated in several psychiatric disorders. EEG permits an understanding of temporally specific cortical brain responses during timed tasks and may provide a window into normal and aberrant cortical function. EEG activity in midline cortical regions has been demonstrated to be dependent on the magnitude and valence of rewards. Previous studies have emphasized particular midline electrodes and compared different tasks during cued expectancy and outcome. In this study, we explored expectation, action and hedonic responses simultaneously using one task as measured by Event Related Potentials (ERP) in healthy subjects over a larger portion of the scalp than previously published. Most previous studies compared winning to losing or winning to no reward, when reward was expected. In this study, we compared ERPs when reward was

expected to when it was not expected during each phase of a monetary reward task.
Methods: 15 healthy controls without psychiatric history were recruited and consented to participation in our IRB approved protocol. 64 channel EEG data were collected while subjects performed the monetary incentive delay task (MID). There were 240 trials comprised of 4 reward levels; 0, $0.25, $0.50, and $1.00, with 80% chance of winning on reward trials. Subjects were allowed to keep their winnings. Each trial included 3 phases: Cue (signifying reward potential of the trial), Target (alerting the subject to respond) and Feedback (informing subjects what they won that trial and what their total winnings were). Continuous EEG data were recorded from all subjects and reviewed offline for eye blinks and artifacts. Only artifact free trials were included in the analyses, resulting in the exclusion of 3 subjects who had a small number of artifact free trials. 1500 ms epochs were created for each phase and were time locked to stimulus onset such that epoch onset was 100 ms pre-stimulus and ended 1400 ms post stimulus. For each subject, an average of all trials within a reward condition was created and mean amplitude averages obtained for each 100 ms bin, starting at 100 ms post stimulus onset and extending for 700 ms, for each of the 3 phases. Repeated measure ANOVAs were performed using mean amplitudes from 25 fronto-parietal electrodes. For each of the 100 ms bins, ANOVA factors included condition ($0, $1), laterality (5) and electrodes (5). Greenhouse-Geisser corrections were applied to all comparisons.
Results: We found an interaction of condition and electrode starting 300 ms after Target onset ($F = 3.9$, $p = .05$), lasting 200 msec ($F = 7.9$, $p = .005$). For Feedback, this interaction was significant at 400 msec ($F = 4.7$, $p = .021$) and lasted 400 msec ($F = 3.6$, $p = .04$). For target alone, we found a main effect of laterality at 300 ($F = 4.1$, $p < .03$) and lasting 300 ms ($F = 3.5$, $p < .05$). Amplitudes were higher in the reward condition (compared to no reward), were more posterior during Target and Feedback and greater from midline to the right during Target only. Although we did not find a significant amplitude difference in ERPs of the Cue and we did not find a significant difference in negativity at 300 ms during the Feedback phase, there were trends for both.
Conclusions: These data replicate previous findings of reward magnitude dependent effects on prediction cue and feedback stimulus. Greater amplitudes were found with expected reward compared to no reward expectation. We expanded on these findings with similar effects found during target, lateralization of the effect on the right during target and amplitude differences lasted longer in all phases than previously reported. In addition to a negativity captured at 300 ms, we observed more dramatic positive amplitude differences at 400 ms and beyond. These data demonstrate that a particular network of activity is involved during reward processing that extends beyond the midline across phases of reward processing. Further analyses will delineate spatial localization. Differences in scalp recordings between patients and healthy populations may reveal pathophysiology underlying abnormalities in expectation and hedonia.
Keywords: Reward, ERP, EEG, expectation, feedback
Disclosure: A. Stanford, Nothing to Disclose; S. Lisanby, **Part 3:** None, **Part 4:** Research Grants: Brainsway, NeoSync, ANS/St Jude, Equipment support: from Magstim and Magventures; D. Malaspina, Nothing to Disclose; Y. Cycowicz, Nothing to Disclose.

W121. Inhibitory Control Deficits in Autism Spectrum Disorders (ASD)

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Background: Studies of response inhibition in ASD have yielded inconsistent findings. Discrepancies between studies of voluntary manual motor and oculomotor response inhibition, albeit not yet compared directly in the same patient cohort, raise questions about the neural system specificity of inhibitory control deficits in ASD.
Methods: Forty-five individuals with ASD and 40 healthy controls matched on age (range 6-38 years) and Performance IQ were administered manual motor and oculomotor stop-signal tasks (SST) and baseline measures of reaction time. During the SST, subjects were instructed to either press a button (manual version) or make a saccade (oculomotor version) when a peripheral target appeared ('Go' trials), or inhibit these responses when a central stop signal appeared at some point following the appearance of the peripheral "Go" cue ('Stop' trials) on 40% of trials. We examined subjects' reaction times during both baseline (100% Go trial condition) and SST Go trials, as well as the rate at which they failed Stop trials (i.e., they pressed a button or looked towards the peripheral target).
Results: Subjects with ASD made more stop trial errors than healthy controls on the manual motor and oculomotor SSTs ($p's < .05$). Stop trial error rates were associated with the degree to which subjects slowed their reaction times from baseline trials to task Go trials, such that increased slowing was associated with fewer Stop trial errors ($p < .01$). Subjects with ASD did not slow their reaction times as much as controls ($p < .05$). Increased age was associated with fewer Stop trial errors and increased slowing of reaction times in healthy controls ($p's < .01$), but not in subjects with ASD. For both tasks, adults ($\geqslant 18$ years) with ASD were relatively more impaired than children and adolescents with ASD suggesting diminished improvement in this cognitive ability with age. Increased Stop trial error rates were related to increased rates of repetitive behaviors for individuals with ASD ($p < .05$).
Conclusions: These results indicate that individuals with ASD show inhibitory control deficits that affect both manual motor and oculomotor systems. Both of these deficits appear to reflect a reduced ability to strategically slow reaction times to enhance the ability to suppress unwanted or context inappropriate responses. Inhibiting unwanted behaviors involves frontostriatal suppression of motor pathways. The application of strategic biases during SST performance has been shown to recruit medial prefrontal cortical regions including supplementary motor cortex and supplementary eye fields. Our findings suggest that the maturation of frontostriatal and medial prefrontal brain systems that support the capacity for successful response inhibition may be disrupted during adolescence – a critical epoch for the development of inhibitory control. Alterations within frontostriatal brain systems affecting inhibitory control in ASD also appear to be related to the disabling repetitive behaviors characteristic of this disorder. Future treatments targeting the biological mechanisms underlying these behaviors may be able to facilitate the continued maturation of behavioral abilities through adolescence and early adulthood even after early emerging impairments associated with ASD have been established.
Keywords: autism, response inhibition, stop signal test, oculomotor, manual motor
Disclosure: M. Mosconi, Nothing to Disclose; M. Ragozzino, Nothing to Disclose; L. Schmitt, Nothing to Disclose; E. Cook, **Part 4:** Seaside Therapeutics; J. Sweeney, **Part 1:** I consult to Lilly, Takeda, Roche, BMS and Pfizer, **Part 4:** grant from Janssen providing study drug.

W122. Violation of Temporal Expectancy Triggers Lability of Amygdala-dependent Memories

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Background: Making associations and learning the temporal relationship between events permits organisms to acquire adaptive

behaviors. When previously consolidateda versive memories are reactivated, plasticity-dependent reconsolidation processes are triggered in the lateral amygdala (LA), resulting in a time window during which the memory is labile and subject to change. However, memory reconsolidation has boundary conditions and the exact rules governing reconsolidation are poorly understood.

Methods: Rats with bilateral cannulae in the lateral amygdala (LA) were submitted to a strong auditory fear conditioning training paradigm. The next day, they were presented with a single conditioned stimuli paired with and unconditioned stimuli (CS-US) trial with the same CS-US interval or an interval different than during training. Immediately after anisomycin (an inhibitor of protein synthesis) or vehicle was infused into the LA. The next day, freezing to the CS alone was tested. In a different group of rats, the brain was removed 90 min after memory reactivation and inmunohistochemistry assay for Zif-268 was performed.

Results: Here we show that changing the temporal relationship between the conditioned (CS) and unconditioned (US) stimulus is sufficient to trigger synaptic plasticity and reconsolidation of a strong fear memory in the LA. The change in the temporal architecture of the association is detected after a single CS-US pairing. Thus, a mismatch between the expected and experienced temporal relation between events is a key trigger for updating aversive memories in the amygdala.

Conclusions: Our results demonstrate that time is a core part of the CS-US association and in order to trigger reconsolidation of aversive memories new information is needed at the time of reactivation. In sum, our study provides new and better understanding of the precise requirements and rules of memory reconsolidation, opening a new basic framework for developing strategies to effectively treat strong traumatic memories.

Keywords: fear conditioning, memory reconsolidation, timing, traumatic memories, anisomycin

Disclosure: L. Diaz-Mataix, Nothing to Disclose; R. Martinez, Nothing to Disclose; G. Schafe, Nothing to Disclose; J. LeDoux, Nothing to Disclose; D. Valerie, Nothing to Disclose

W123. Fine-grained Working Memory Load Manipulation Reveals Absence of Normative Inverted-U Activation in Schizophrenia

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Background: Patients with schizophrenia exhibit serious and clinically relevant deficits in working memory (WM). However, investigations of WM in patients with schizophrenia using functional Magnetic Resonance Imaging (fMRI) have largely failed to reveal a consistent abnormality in brain activation in patients. One hypothesis is that patients exhibit a disordered relationship between the extent of activation in dorsolateral prefrontal cortex (DLPFC) and WM load, for example a left-shift in an inverted-U relationship (Callicott et al., 2003; Manoach, 2002, 2003), such that patients exhibit greater activation relative to healthy individuals at low WM loads and less activation at high loads. To test this hypothesis, we employed a version of the self-ordered working memory task (SOT) for use with fMRI that provides a finer-grained variation in WM load than existing tasks.

Methods: Thirteen patients with schizophrenia and eighteen control participants matched on age, gender, and parental socioeconomic status performed the SOT during the acquisition of Blood-Oxygen Level Dependent fMRI images from a Philips 1.5 Tesla Intera scanner (2 s TR, 40 slices of a 64×64 plane, 3 mm isotropic voxels). In each trial of the SOT participants are presented with eight line drawings of 3D objects in an array. On each step of the trial the object positions are pseudo-randomly rearranged, and participants must select any object that they have not previously selected, thereby producing a gradual increase in WM load over the eight steps of each trial. Whole-brain fMRI activation data during correctly performed steps was analyzed in a two-way between-groups repeated measures ANOVA with factors Diagnosis (two levels) and Step (eight levels), using the Greenhouse-Geisser correction for non-sphericity. Regions showing a main effect of Step in either group were further analyzed in a random-effects polynomial regression to determine the shape of the change in activation over steps.

Results: Patients and controls exhibited above chance accuracy and monotonic declines in performance from steps two through eight, with patients also performing significantly worse than controls at these steps. Healthy controls exhibited a significant ($p < 0.05$, FDR corrected) negative quadratic polynomial (inverted-U) response to increasing WM load in the SOT in bilateral DLPFC, posterior parietal cortex (PPC), lateral occipital cortex, fusiform gyrus, and left putamen. Patients with schizophrenia exhibited no significant main effect of step in any brain region, even at a relaxed statistical threshold ($p > 0.25$, FDR corrected). Significant between-group differences in the pattern of activation was observed at a relaxed threshold ($p < 0.25$, FDR corrected) in bilateral DLPFC, right PPC, and right cuneus and fusiform gyrus.

Conclusions: The present findings support the hypothesis of an inverted-U relationship between DLPFC activation and WM load in healthy individuals, as proposed by Callicott et al. (2003) and Manoach (2002, 2003), and this relationship was also observed in several other brain regions known to be involved in WM. However, there was no evidence to suggest a left-shift in this inverted-U in patients with schizophrenia; rather, the normative inverted-U relationship was absent in patients. While specification of the functional significance of this inverted-U relationship remains somewhat speculative, the fact that healthy individuals maintained high levels of performance at later steps, and yet showed decreasing activation during correct performance in brain regions known to subserve WM, suggests that healthy individuals may have exhibited a flexible shift in strategy (e.g. to a familiarity-based long-term memory strategy) as their WM capacity was exceeded. Critically, patients with schizophrenia failed to show this shift at high WM load, raising the possibility that they either have a fundamental impairment that makes such a strategy shift a non-optimal approach to performing the task, or that they were exhibiting perseveration on the earlier-adopted strategy. This study is arguably the most comprehensive investigation of the impact of variation in WM load on brain activation in patients with schizophrenia and matched controls carried out to date, and reveals several new directions for research into the functional impairment underlying WM deficits in patients with schizophrenia.

Keywords: Schizophrenia, working memory, functional neuroimaging, inverted-u

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W124. If I Do It, It Must be Important: An Inhibition Deficit Model of Obsessive Compulsive Disorder

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Background: Current psychological models of obsessive-compulsive disorder (OCD) suggest that catastrophic misinterpretations of (normally occurring) intrusive thoughts underlie etiology and maintenance of OCD symptoms. However, little is known about the reasons causing some individuals to develop beliefs leading to this misinterpretation of intrusive thoughts. Repeated checking, a compulsive behavior (e.g., whether the gas stove was turned off), was found topromote rather than decrease uncertainty even in healthy controls. However, why do s ome individuals tend to check more than others? OCD patients were found to exhibit various deficits in executive functions. One of the executive functions in which results have been particularly robust and consistent is response inhibition. OCD patients and their family members were found to present with deficits in response inhibition relative to healthy controls (comparable to deficit found in patients with attention deficit hyperactivity disorder). However, to date, no studies have proposed an OCD model integrating this basic cognitive deficiency with current OCD models. The current study aimed at investigating whether inhibition capability is related to the degree of uncertainty caused by repeated checking.
Methods: Fifty-five healthy participants completed self-report questionnaires measuring OCD symptoms, OCD beliefs, anxiety levels and depressive symptoms. Subsequently, they carried out a stop-signal task (measuring response inhibition) followed by a repeated-checking task. Participants were assigned to two conditions: (1) relevant checking (checking a virtual gas stove), and (2) irrelevant checking (checking virtual light bulbs). Importantly, uncertainty indices were calculated by the changes in memory confidence, memory vividness, and memory details between two trials of virtual gas checking, separated by 20 trials of either virtual gas stove checking (relevant checking), and virtual light bulbs checking (irrelevant checking). At the end of the checking task, participants were told that they have completed their participation and may terminate participation and receive their credit. They were further instructed that in case they are interested, they may press any key to check whether their last response was correct. However, the answer will take 20 seconds to upload.
Results: Confirming our hypothesis, participants with poor inhibitory capabilities demonstrated greater uncertainty and memory distrust as a consequence of (relevant) repeated checking than participants with good inhibitory control. Subjects who engaged in relevant checking were further twice as likely to remain an additional 20 seconds in order to check their responses after being informed they have completed their participation in the experiment (relative to subjects in the control condition of irrelevant checking).
Conclusions: We propose a modified OCD model for individual proneness to OCD in which weaker response inhibition may result in a greater tendency to (subtly) respond to intrusive thoughts. These reactions may become automatic over time and underlie the development and maintenance of OCD beliefs and symptoms (i.e., as if saying, if I do it, it must be important).
Keywords: OCD, repeated-checking, response-inhibition, obsessive-beliefs
Disclosure: G. Anholt, Nothing to Disclose; O. Linkovski, Nothing to Disclose; E. Kalanthroff, Nothing to Disclose; A. Henik, Nothing to Disclose.

W125. Selective Manipulation of Striatal Circuitry with Serotonin-6 Receptors: Pathway Specific Targeting of 5-HT6 Receptor Overexpression has Opposing Effects on Behavioral Acquisition and Expression of Habits

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Background: Serotonin-6 (5-HT_6) receptor overexpression via viral mediated gene transfer (VMGT) in discrete areas of striatum alters the expression of subregion-specific striatum-dependent behaviors. Specifically, VMGT to overexpress 5-HT_6 receptors in the posterior dorsomedial striatum disrupts acquisition of simple action-outcome operant task associations in naïve rats. In rats over-trained to habitually press a lever, overexpression of 5-HT_6 receptors in the dorsolateral striatum disrupts habitual responding thereby enabling behavioral flexibility. 95% of the neurons in the striatum are medium-spiny neurons (MSNs) that segregate into two into main pathways based on their gene expression profile and the brain areas they project to, referred to as direct (striatonigral) and indirect (striatopallidal).
Methods: In these studies we further probe striatal function by using Herpes Simplex Virus vectors utilizing cell-specific promoters to understand how 5-HT_6 receptors in specific neuronal subpopulations mediate behavioral acquisition of discrete action-outcome tasks and alter the behavioral inflexibility of habitual responding in rat models.
Results: 5-HT_6 receptor overexpression in direct or indirect pathway MSNs of the posterior dorsomedial striatum appear to enhance or impair acquisition of a discrete action-outcome task, respectively. Additionally, 5-HT_6 receptor overexpression in indirect pathway MSNs of the dorsolateral striatum interferes with habitual responding allowing for behavioral flexibility during an omission contingency session.
Conclusions: Together these findings support a role for indirect pathway MSN 5-HT_6 receptor signaling in attenuating habitual responding. This provides a potential target for treating striatal based neuropsychiatric disorders such as obsessive-compulsive disorder, Tourette syndrome and addiction disorders.
Keywords: Serotonin, 5-HT6, habit, viral-mediate-gene-transfer, striatum.
Disclosure: D. Eskenazi, Nothing to Disclose; J. Neumaier, Nothing to Disclose.

W126. A Novel Task Probing Neural Substrates of Approach-Avoidance Conflict: Implications for Understanding Anxiety Disorders

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Background: Conflict situations occur when a person or animal is faced with opposing drives, or incentives to act, that are incompatible with one another. Animal approach-avoidance conflict paradigms have been used extensively to characterize effects of anxiolytic agents and probe neural circuitry related to anxiety. However, there is a lack of paradigms measuring conflict decision-making in human populations, limiting translation of preclinical findings to human clinical research. We recently developed a novel human paradigm of approach-avoidance conflict (AAC) for which behavior related to measures of anxiety sensitivity and behavioral activation (Aupperle et al., 2011). The current study used this paradigm in conjunction with functional neuroimaging to delineate neural substrates underlying conflict decision-making in humans.

Methods: Fifteen healthy adults (8 male) completed the AAC computer task during functional magnetic resonance imaging (fMRI). For decision phases of the AAC, participants were shown a runway with pictures on each side to represent two potential outcomes. Each outcome included an affective stimulus (positive or negative) and reward points (0, 2, 4, or 6). Participants moved an avatar on the runway to indicate their preference for each potential outcome. There were three trial types: (1) 'Avoidance-only', in which 0 points were offered for both outcomes, so that subjects chose between viewing a positive or negative affective stimulus. (2) 'Approach-only', in which positive affective stimuli were associated with both outcomes, so that the subjects chose between receiving 0 versus 2 points. (3) Three levels of 'Conflict' in which the same outcome was associated with both reward (2, 4, or 6 points) and "punishment" (negative affective stimulus). The outcome phase consisted of presentation of the corresponding affective stimulus followed by presentation of the point reward. Repeated measures ANOVA was used to compare conflict decision trials of the AAC to non-conflict trials for the decision phase and paired samples t-tests were used to compare negative versus positive affective stimuli for the outcome phase. Analyses were considered significant at $p < .05$, corrected for whole-brain and region of interest (ROI) voxel-wise analyses. Percent signal change (PSC) was extracted from activated regions and correlation analyses examined the relationship to task behavior.

Results: Conflict decision-making was associated with greater activation in bilateral anterior insula (BA 13), right anterior cingulate cortex (ACC; BA 32,6,9), and dorsolateral prefrontal cortex (dlPFC; BA 9) and less activation in left superior parietal cortex (BA 5,7) and superior frontal gyrus (BA 6,8) as compared to non-conflict trials. ROI analyses additionally revealed a cluster within left caudate that was greater for conflict than non-conflict trials. Extracted PSC for each of these regions revealed that bilateral anterior insula, caudate, and ACC activation related to greater average avoidance behavior on the task and that ACC and dlPFC activation related to self-reported difficulty making decisions on the task. Amplitude modulation analyses revealed a region within the dlPFC that was greatest for trials in which behavior was more indecisive (e.g., moving avatar in the middle of the two outcomes). While amygdala regions were not identified as being recruited for conflict decisions, analyses of the outcome phase indicated that amygdala activation was greater when processing negative versus positive affective stimuli.

Conclusions: The AAC paradigm was sensitive to neural circuits related to affective processing (insula), reward processing (caudate), and decision-making (medial and lateral PFC). The dorsolateral PFC may play a central role in weighing relative values of approach- and avoidance-related outcomes to produce decisional behavior. Amygdala regions may be more involved in processing affective outcomes to conflict situations. These results support the AAC as a useful probe for neural substrates of approach-avoidance conflict. The AAC could therefore be a potential tool for linking preclinical animal research and human clinical research relevant to anxiety disorders and anxiolytic treatment.

Keywords: Conflict, Decision making, functional MRI, Anxiety, Avoidance

Disclosure: R. Aupperle, Nothing to Disclose; S. Sullivan, Nothing to Disclose; A. Melrose, Nothing to Disclose; M. Paulus, Nothing to Disclose; M. Stein, **Part 1:** Dr. Murray Stein has in the past 3 years received compensation for his work as Psychiatry Co-Editor-in-Chief for Up-to-Date, and Deputy Editor for the journal Depression and Anxiety.

W127. Relationship between Plasma Peptide YY and Cardiometabolic Disease Risk Factors in a Cohort of Older Psychiatric Patients

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Background: Peptide YY (PYY) is an endocrine hormone that regulates appetite and marks obesity and metabolic syndrome risk in the general population. Its usefulness in the psychiatric population as a biomarker of cardiometabolic disease risk has not been examined. The objective of this study was to determine if plasma PYY was associated with cardiometabolic disease risk factors in patients with psychosis aged > 40 years. Furthermore, we explored if the patients' psychiatric diagnosis and antipsychotics use contributed to different levels of cardiometabolic disease risk factors.

Methods: All patients were recruited originally for an antipsychotic clinical trial involving four commonly used atypical antipsychotics (NCT00245206). At the baseline visit, plasma PYY and peripheral cardiometabolic disease risk factors (anthropometric measurements, lipid panel, blood pressure, glucose, insulin, leptin, adiponectin, and high-sensitivity C-reactive protein [hs-CRP]) were measured in 174 patients aged >40 years (114 men, 60 women) who had psychosis associated with schizophrenia, mood disorders, PTSD, or dementia. We also extracted the information on the type of antipsychotics the patients took *prior to* randomization to the trial medication for the present cross-sectional analysis. Each patient was either taking no medication, or was on aripiprazole, quetiapine, risperidone, or olanzapine. Quantitative phenotypes were log-transformed before statistical analysis. Association analyses were conducted using correlation coefficient, ANOVA, and linear regression models in R vs.2.14.2.

Results: Plasma PYY level was not associated with age, race, psychiatric diagnosis, or type of antipsychotics the patients were taking. PYY was significantly higher in women compared to men (172.4 vs. 147.8 pg/mL, $p = 0.03$). Surprisingly neither body weight, waist-hip ratio, nor body adiposity index was found to correlate with PYY levels. However, PYY significantly correlated with levels of LDL cholesterol ($R = -0.16$, $p = 0.03$), insulin ($r = 0.18$, $p = 0.01$), and high sensitivity-C-Reactive Protein or hs-CRP ($r = 0.21$, $p = 0.005$). Stratifying the patients by the type of antipsychotics they were taking, the most significant correlation observed between PYY and hs-CRP was in patients receiving quetiapine ($r = 0.3331$, $p = 0.04$), whereas PYY and LDL correlations were most striking in patients receiving no medication ($r = -0.399$, $p = 0.03$) and those on olanzapine ($r = -0.532$, $p = 0.002$). Our exploratory analysis revealed that diastolic blood pressure, waist-hip-ratio, triglyceride, and adiponectin levels were significantly different among the diagnosis classes; whereas triglyceride and leptin levels were significantly different among the medication types, after adjusting for age, gender, and race as covariates.

Conclusions: Cardiometabolic burden is significantly higher in the psychiatric population compared to the general population, especially in the older age group. Risk factors contributing to this heightened risk include medications, sedentary life-style, and possibly neuroendocrine abnormalities that result in dysregulated satiety signaling. Our results suggest that, contrary to what is observed in the general population, PYY did not correlate with anthropometric measurements and body weight. However, PYY significantly correlated with a marker of inflammation, hs-CRP, especially in patients taking quetiapine. This finding might be relevant to the discontinuation of quetiapine during the 3rd year of our clinical trial due to high risk of serious adverse events. Overall high correlation between PYY and LDL, especially in patients receiving no medication and those on olanzapine, suggests that PYY may be a marker of lipid abnormalities that is independent of

the weight- or body fat- effect in this population. Finally, several cardiometablic disease risk factors are associated with psychiatric diagnosis and type of antipsychotic the patients are taking. These findings warrant a replication study using a larger cohort in order to identify the magnitude of impact that diagnosis and medication have on cardiometabolic disease risk factors in older psychiatric patients, and to identify the role PYY may play in LDL cholesterol metabolism and inflammation, both of which contribute to the accelerated rates of cardiometabolic disease in patients with psychiatric illnesses.
Keywords: Peptide YY, Cardiometabolic risk, Antipsychotic medication, Psychosis
Disclosure: P. Shih, Nothing to Disclose; H. Jin, Nothing to Disclose; S. Mudaliar; R. Henry, Nothing to Disclose; D. Jeste, Nothing to Disclose.

W128. The Influence of the Brain-derived Nuerotrophic Factor Val66Met Genotype and HMG-CoA Reductase Inhibitors on Insulin Resistance in the Schizophrenia and Bipolar Populations

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Background: The Brain-derived Neurotrophic Factor (*BNDF*) Val66Met variant and HMG-COA reductase inhibitors (statins) have been implicated in insulin resistance and diabetes risk. We sought to determine the effect of the *BDNF* Met variant and statin use on insulin resistance in schizophrenia and bipolar disorder using the homeostasis model assessment of insulin resistance (HOMA-IR).
Methods: A cross-sectional design was used and patients with diabetes or receiving medications affecting glucose regulation were excluded. Associations between insulin resistance and genotype were analyzed by ANOVA and regression analysis. Subjects were grouped by *BDNF* genotype as well as statin use.
Results: 252 subjects with a mean age of 44 years were included. The group was 53% male and 59% had a schizophrenia diagnosis; 78% and 19% were receiving atypical antipsychotics (AAPs) and statin medications, respectively. Analysis showed schizophrenia subjects with the *BDNF* met allele as well as schizophrenia subjects with the *BDNF* met allele and statin combination had significantly higher HOMA-IR values compared to the other groups ($p = 0.046$ and $p = 0.016$, respectively).
Conclusions: These results suggest that in the metabolically high-risk population of schizophrenia the *BDNF* met allele alone and in combination with statin medications is associated with higher insulin resistance values. This was not seen in the bipolar population. Further validation of these associations remains necessary.
Keywords: BDNF, Insulin Resistance, Schizophrenia, Bipolar Disorder, Statins
Disclosure: K. Burghardt, Nothing to Disclose; R. Pop-Busui, Nothing to Disclose; M. Bly, Nothing to Disclose; T. Grove, Nothing to Disclose; S. Taylor, Nothing to Disclose; V. Ellingrod, Nothing to Disclose.

W129. Relationship between Reactivity to Heroin-related Cues, Craving, and Self-administration in Buprenorphine-maintained Heroin Abusers

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Background: Exposure to drug-related cues is thought to play an important role in relapse to drug use. Indeed, several recent studies have demonstrated activation of specific brain areas (e.g., nucleus accumbens, amygdala, hippocampus, prefrontal cortex) in response to heroin-related cues among recently abstinent heroin users (Langleben et al., 2012; Li et al., 2012; Lou et al., 2012). However, the relationship between cue reactivity, craving, and drug-taking behavior among heroin users has received less experimental attention. The purpose of the present study was to examine cue reactivity and drug craving in participants who were given the opportunity to self-administer heroin or placebo for 4 days prior to cue exposure.
Methods: Non-treatment seeking intravenous (i.v.) heroin abusers participated in a 3-week inpatient study examining the effects of pioglitazone on opioid dependence. Reinforcing (i.e., self-administration), subjective (craving), and physiological (galvanic skin response (GSR), skin temperature (ST)) responses were evaluated during the study. Participants received sublingual buprenorphine/naloxone (8/2 mg) each evening at 8 pm throughout the study. They also received one of 3 possible doses of pioglitazone (0, 15, or 45 mg) each evening at 8 pm. For the current analysis, the data were pooled for all of the participants because the sample sizes per group were too small to make meaningful comparisons as a function of pioglitazone dose. During Week 1, participants were stabilized on buprenorphine/naloxone and pioglitazone. Test sessions occurred on Mon-Fri during Weeks 2 and 3. Active heroin (12.5 mg, i.v.) was available during one of the weeks and placebo (saline, i.v.) was available during the other week; doses were administered under double-blind conditions and in random order. On Mon-Thu of each test week, participants were given 5 opportunities per day to choose between $10 and drug (0 or 12.5 mg heroin) using a verbal choice procedure; the percentage of drug choices across the week was calculated. On Fri of each test week, participants received 12.5 mg heroin in the morning, followed by a cue exposure session consisting of presentation of neutral stimuli (bottle of water, glass cup) and then drug-related stimuli (powder, spoon, tourniquet, water, syringe and needle). After the cue exposure session, participants were given 10 opportunities to choose between $1/10^{th}$ of the heroin dose administered that morning (12.5 mg) and $2 using a modified progressive-ratio choice procedure. The amount of effort (taps on a computer mouse) participants were willing to expend to receive heroin was measured by breakpoint values (largest ratio completed for drug). Repeated measures analyses of variance (SuperANOVA, v.1.11, Abacus Concepts, Inc.) were used to analyze each endpoint. Results were considered statistically significant when p values were $\leqslant 0.05$.
Results: Preliminary analyses were performed on 10 heroin abusers (9 M, 1F; 1 Asian, 1 Mixed, 3 White, and 5 Hispanic) who used an average of 7.6 ± 1.2 bags of heroin per day. Participants self-administered significantly more heroin (57%) than placebo (26%) during the choice sessions on Mon-Thu ($p < 0.05$). The dose $\times$ day interaction was also significant ($p < 0.05$), with participants self-administering equivalent amounts of heroin and placebo on Mon (heroin: 60%; placebo: 52%), but different amounts by Thu (heroin: 56%; placebo: 6%). During the cue exposure session on Fri, GSR increased and ST decreased during presentation of the drug cues compared to the neutral cues ($p < 0.01$). Although there was no statistically significant difference in GSR to the drug cues when participants received placebo compared to heroin on Mon-Thu ($p = 0.1$), the response tended to be more robust during the placebo week. No difference in ST during the cue session was observed as a function of the available dose (heroin or placebo) on Mon-Thu. Consistent with the physiological responses, craving was greater after presentation of the drug cues relative to the neutral cues (38.5 versus 34.3, respectively; $p < 0.05$), but no difference in craving was observed as a function of the available dose on Mon-Thu. Breakpoint values for heroin during the self-administration session after the cue exposure session also did not significantly vary as a function of the available dose on Mon-Thu.
Conclusions: These preliminary results show that self-administration of placebo extinguished within approximately 4 days when

participants were given the opportunity to choose between placebo and $10. Although physiological responses and craving were elicited by the presentation of drug-related cues, these responses did not vary as a function of the availability of active heroin or saline during the 4 days prior to cue exposure; breakpoint values for heroin also did not vary after cue exposure as a function of available dose. These data may have important implications for the treatment of opioid dependence in that subjective, physiological, and behavioral responses to drug-related cues appear to remain high regardless of short-term access (or lack of access) to heroin.
Keywords: heroin, abuse, cue reactivity, craving, self-administration, humans
Disclosure: S. Comer, **Part 2:** Grunenthal GmbH, **Part 3:** Grunenthal GmbH, **Part 4:** Reckitt Benckiser, Johnson & Johnson, Endo; A. Bisaga, Nothing to Disclose; J. Jones, **Part 1:** Reckitt-Benckiser, Endo, Johnson & Johnson, MediciNova, **Part 4:** Reckitt-Benckiser, Endo, Johnson & Johnson, MediciNova; S. Mogali, **Part 1:** Reckitt-Benckiser, **Part 4:** Reckitt-Benckiser; J. Manubay, **Part 1:** Reckitt-Benckiser, Endo, Johnson & Johnson, **Part 4:** Reckitt-Benckiser, Endo, Johnson & Johnson; M. Sullivan, **Part 1:** Reckitt-Benckiser, **Part 4:** Reckitt-Benckiser; S. Vosburg, ; Z. Cooper, Nothing to Disclose; P. Roux, Nothing to Disclose; J. Fogel, Nothing to Disclose; L. Shiffrin, Nothing to Disclose.

W130. Combined Effects of Antipsychotic Medication and Hypoglycemia upon Microglial Activation

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Background: Hypoglycemic episodes are a common occurrence among diabetic patients. An important interaction between hypoglycemia and antipsychotic medications, however, has gone largely unnoticed in the medical community. Typical antipsychotic medications such as haloperidol elevate extracellular glutamate through antagonist effects on both dopamine D2 and serotonin 5HT1A receptors. In contrast, serotonin 5HT2A receptor antagonists oppose this action and inhibit glutamate release. Glutamate is directly excitotoxic through effects on ionotropic receptor channels, and may have additional synergistic effects with other neurotoxic pathways activated by hypoglycemia, such as oxidative stress pathways. Preclinical studies demonstrate adverse effects of insulin-induced hypoglycemia including neuronal cell death and cognitive impairment mediated by elevated glutamate release. By further elevating extracellular glutamate, it is predicted that haloperidol worsens the neurotoxic potential of insulin-induced hypoglycemia. In contrast to haloperidol, the atypical antipsychotic medications quetiapine and aripiprazole 1) have transient or partial agonist dopamine D2 receptor effects, 2) higher relative 5HT2A receptor antagonism, and 3) are 5HT1A receptor partial agonists. These three independent pharmacological actions should each limit extracellular glutamate and subsequent neurotoxicity. In order to test this model we treated rats with haloperidol, quetiapine, or vehicle and then measured microglial activation following insulin-induced hypoglycemia. We predicted insulin-induced hypoglycemia would activate microglia to the highest levels in haloperidol-treated rats.
Methods: Male Sprague-Dawley rats were treated with haloperidol (1 mg/kg/day), quetiapine (6 mg/kg/day), or vehicle for 21 days. Insulin (7.5U/kg) or saline were injected to induce moderate hypoglycemia for 30 minutes, followed by rescue with an injection of 20% d-glucose. Rats were sacrificed 24 hours after the hypoglycemic episode. Microglia were stained with IBA-1, and the activation phase of microglial cells within brain regions of interest determined by a rater blinded to treatment group.
Results: Round "activated" microglia were significantly increased, while numbers of ramified "resting" microglia were decreased in haloperidol-treated rats following insulin-induced hypoglycemia. In contrast, there were no significant changes in the levels of activated or resting microglia in quetiapine-treated rats following insulin-induced hypoglycemia.
Conclusions: These observations demonstrate direct evidence of elevated inflammatory mediators following insulin-induced hypolglycemia during treatment with haloperidol. Further study is needed to determine consequences in terms of neuronal cell loss and behavior, and also to determine clinical and epidemiological consequences of similar exposures in human populations.
Keywords: inflammation; diabetes; schizophrenia; neuroleptic; NMDA
Disclosure: N. Richtand, **Part 1:** Consultant: Bristol-Meyers Squibb, Gerson Lehrman Group, Sunovion Pharmaceuticals Inc./ Sepracor, Speaker's Bureau: Bristol-Meyers Squibb, Otsuka America Pharmaceutical, Schering - Plough Corporation/ Merck, Novartis Pharmaceuticals, Sunovion Pharmaceuticals Inc./ Sepracor, Grant/Research Support: Ortho-McNeil Janssen Scientific Affairs, LLC; AstraZeneca Pharmaceuticals, **Part 2:** Speaker's Bureau: Bristol-Meyers Squibb, Otsuka America Pharmaceutical, Sunovion Pharmaceuticals Inc./ Sepracor, **Part 3:** Speaker's Bureau: Bristol-Meyers Squibb, Otsuka America Pharmaceutical, Sunovion Pharmaceuticals Inc./ Sepracor; A. Isom, Nothing to Disclose; R. Ahlbrand, Nothing to Disclose; G. Gudelsky, Nothing to Disclose.

W131. Substance Use during Cannabis Withdrawal in People with Schizophrenia

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Background: Cannabis is the most widely used illicit substance, consumed by between 125 and 203 million people worldwide in 2009, an annual prevalence rate of 2.8-4.5%. People with schizophrenia have an even higher rate of cannabis use than the general population, in the range of 17-80%. Many cannabis users stop use without formal treatment. Cannabis withdrawal syndrome (CWS) is well documented in human studies, and withdrawal symptoms may lead to relapse. Cannabis use is prevalent among people with schizophrenia, yet little is known about their experience of cannabis withdrawal. The objective of this study was to examine the withdrawal symptoms and pattern and frequency of substance use during cannabis withdrawal.
Methods: Participants were enrolled from among patients undergoing treatment at psychiatric facilities in the Baltimore, Maryland area affiliated or collaborating with the Maryland Psychiatric Research Center, University of Maryland School of Medicine. A convenience sample of 120 outpatients with schizophrenia or schizoaffective disorder who had been using cannabis at least weekly and made a quit attempt without formal treatment while not in a controlled environment were administeredthe Marijuana Quit Questionnaire (MJQQ), a 176-item semi-structured questionnaire, to collect information on characteristics of subjects' "most serious" (self-defined) quit attempt. Descriptive statistics are reported as N (%), median or mean, and range. All analyses were performed using SAS version 9.1.3 (SAS Institute, Inc; Cary, NC).
Results: A majority of the patients were male (76.7%), African-American (62.5%), and never married (N = 95, 79%). Mean (range) age was 41.5 (21-63) years. Mean (range) education level was 11.4 (3-18) years. Withdrawal symptoms were reported by 118 (98.3%) participants, with 80.8% reporting >4 symptoms (out of a total of 40 possible symptoms). The most frequently reported symptoms were craving for cannabis (69.2%), feeling sad or depressed (57.5%), feeling anxious (56.7%), feeling bored (56.7%), feeling irritable or jumpy (50.8%), feeling restless (48.3%), and trouble falling asleep (35.8%). During the index quit attempt, pre-existing use of psychoactive substances often increased (N [% of pre-

existing users]): caffeine 46 (42.2%), alcohol 39 (39.0%), nicotine 54 (48.6%), sedatives 2 (10.0%), sleeping aids 6 (37.5%), stimulants 9 (31.0%), narcotic pain medications 3 (37.5%), other narcotics such as heroin 3 (27.3%), and non-narcotic pain medications 13 (19.4%). In contrast, initiation of use was infrequent (N [% of non-users]): caffeine 4 (36.4%), alcohol 1 (5.0%), nicotine 5 (55.6%), sedatives 2 (2.0%), sleeping aids 5 (4.8%), stimulants 11 (12.1%), narcotic pain medications 1 (0.9%), other narcotics such as heroin 6 (5.5%), non-narcotic pain medications 3 (5.7%), hallucinogens 2 (1.8%), and phencyclidine 2 (1.9%).

Conclusions: Cannabis withdrawal symptoms are common among people with schizophrenia making a "serious" quit attempt, with psychological symptoms much more common than physical symptoms (e.g., headache, tremor, nausea, diarrhea). During quit attempts, pre-existing use of psychoactive substances increased substantially, perhaps to self-medicate withdrawal symptoms, while initiation of use is uncommon except for caffeine and nicotine. The absolute and relative prevalence of individual withdrawal symptoms is roughly comparable to that found in a study using the MJQQ in 469 adult cannabis smokers with no serious psychiatric co-morbidity (Levin et al., 2010). The proportion of subjects initiating or increasing caffeine, alcohol, or tobacco use is also roughly comparable, while subjects with schizophrenia were more likely to initiate or increase their use of other psychoactive substances during the quit attempt, suggesting that cannabis withdrawal might put them at risk for substance abuse. This study has several strengths, including the large sample size (N = 120) and a detailed evaluation of 40 individual cannabis withdrawal symptoms. The study is limited because the data were collected by retrospective self-report without external corroboration from a convenience sample. CWS is a major public health problem leading to relapse of cannabis use. Understanding CWS and associated substance use is critical and timely because CWS criteria have been proposed for DSM-V. Because there are no approved pharmacological treatments for CWS, there is a clinically unmet need for improved psychosocial treatment interventions. Future studies should focus more on the symptoms and signs of the cannabis withdrawal syndrome proposed for DSM-V and use more rigorous prospective study designs to evaluate how individuals cope with cannabis withdrawal.

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Keywords: Schizophrenia, Cannabis Withdrawal Syndrome, Substance use, People with Dual Diagnosis

Disclosure: M. Koola, Nothing to Disclose; D. Boggs, Nothing to Disclose; D. Kelly, **Part 1:** Grant support from Bristol Myers Squibb and Ameritox Ltd; F. Liu, Nothing to Disclose; J. Linthicum, Nothing to Disclose; H. Turner, Nothing to Disclose; R. McMahon, **Part 1:** Statistical consultant for Amgen, Inc, within the last year; D. Gorelick, Nothing to Disclose.

W132. Familial Internalizing and Externalizing Liability Factors Contribute to Borderline Personality Disorder

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Background: Individuals with borderline personality disorder frequently display comorbid mental disorders. These disorders include "internalizing" (such as major depressive disorder and anxiety disorders) and "externalizing" disorders (such as substance use disorders and antisocial personality disorder). It is hypothesized that these disorders may arise from latent "internalizing" and "externalizing" liability factors. Factor analytic studies suggest that borderline personality disorder is influenced by both internalizing and externalizing factors, but the extent to which such contributions are familial is unknown. This study was performed to examine the association of borderline personality disorder with internalizing and externalizing liability factors, and to assess the extent to this association is attributable to familial contributions.

Methods: The study design was a family study with direct interviews of probands and relatives. The participants were 368 probands (132 with borderline personality disorder; 134 without borderline personality disorder; and 102 with major depressive disorder) and 885 siblings and parents of probands. Participants were administered the Diagnostic Interview for DSM-IV Personality Disorders (for borderline personality disorder and antisocial personality disorder); the Revised Diagnostic Interview for Borderlines (DIB-R) (for borderline personality disorder); and the Structured Clinical Interview for DSM-IV (for Axis I disorders). Within person associations of borderline personality disorder with internalizing and externalizing latent factors was assessed by confirmatory factor analysis. Within-family associations were assessed using Cholesky decomposition structural equation models of familial and non-familial factors for borderline personality disorder (using internalizing and externalizing latent variables on which the corresponding disorders loaded).

Results: On confirmatory factor analysis of within-person associations of disorders, borderline personality disorder loaded moderately on internalizing (factor loading .53, SE .10; $p < .001$) and externalizing latent variables (.48, SE .10; $p < .001$). In a Cholesky decomposition model, 84% (SE 19%; $p < .001$) of the correlation of borderline personality disorder with internalizing and externalizing factors was accounted for by familial contributions.

Conclusions: Familial contributions to internalizing and externalizing liability factors also mutually contribute to borderline personality disorder. These contributions account for the great majority of the association of borderline personality disorder with internalizing and externalizing factors.

Keywords: borderline personality disorder genetic epidemiology internalizing disorders externalizing disorders family study

Disclosure: J. Hudson, **Part 1:** Alkermes, Genentech, HealthCore, Lilly, Otsuka, Pfizer, Roche, Shire, **Part 2:** Pfizer, **Part 3:** None, **Part 4:** Lilly, Otsuka, Shire; M. Zanarini, Nothing to Disclose; K. Mitchell, Nothing to Disclose; L. Choi-Kain, Nothing to Disclose; M. Tsuang, Nothing to Disclose; J. Gunderson, Nothing to Disclose.

W133. Depression Symptoms Associated with Cannabis Dependence in an Adolescent American Indian Community Sample

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Background: Depression and substance use disorders, including cannabis dependence, arise during adolescence, are frequently comorbid, and represent major health burdens in the general U.S. population. Native American adolescents have the highest rates of major depression and substance use, including cannabis use, disorders of any U.S. adolescent ethnic population. Morbidity and mortality associated with these disorders is also substantial. Despite this high burden of morbidity and mortality, little is known about the association of depression symptoms with cannabis and other substance use and use disorders in Native American adolescents. The goal of this study was to assess and

compare in boys vs. girls the relationship between lifetime DSM-III-R depression symptoms and major depression episode (MDE), considered as independent of and induced by substance use, and cannabis use and dependence in a community sample of reservation dwelling American Indian adolescents.
Methods: This study used the Children's Semi-Structured Assessment for the Genetics of Alcoholism (Adolescent Version) to obtain demographic information; substance use history; and lifetime DSM-III-R diagnoses from a community sample of 202 (98 boys, 104 girls) American Indian adolescents living on contiguous reservations. Rates of depression symptoms, MDE, major depression disorder independent of substance use (MDD), other substance use history and dependence disorders, and early conduct disorder (CD), considered as onset of full CD prior to age 13 years, were assessed. Logistic regression was used to assess the co-morbidity of depression symptoms and MDE in the presence of five potentially confounding covariates: age, gender, heavy substance use, early substance use, and CD. We also characterized the temporal relationship between onset of depression symptoms and MDE with first cannabis use in the subsample who had experienced depression symptoms and used cannabis. Gender comparisons were made in all analyses.
Results: Thirteen percent of boys and 38% of girls had a lifetime DSM-III-R major depression disorder (MDD) independent of substance use. Fifteen percent of boys and 41% of girls had a major depression episode (MDE) either coincident with or independent of cannabis use. MDE and several individual depression symptoms were significantly associated with cannabis dependence in boys but not in girls. Proportions of depression symptoms and MDE that first occurred at the same age or later than the age of first cannabis use were not different in boys as compared to girls. The median ages of onset of MDE and most depression symptoms were the same in the boys and girls who had experienced both depression and cannabis use.
Conclusions: The findings of this study are consistent with the notion that depression and cannabis use co-emerge in late childhood and early adolescence. These findings suggest that the association of depression with cannabis dependence is more significant in boys than girls in this population of adolescents. One biological explanation for this difference may be that cannabis induces neurochemical changes, perhaps in the central corticotropin-releasing factor mediated stress system, in the adolescent male brain which makes it more vulnerable to depression symptoms because of the presence of male sex hormones. Alternatively, or in addition, gender differences in vulnerability to specific psychosocial stressors, may underlie the difference in association of depression with cannabis use in boys as compared to girls in this sample.
Keywords: depression, cannabis, adolescents, American Indian
Disclosure: D. Gilder, Nothing to Disclose; C. Ehlers, Nothing to Disclose.

W134. Mental Disorders in Adolescence and Young Adulthood: Homotypic and Heterotypic Longitudinal Associations

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Background: Few epidemiologic studies examined prospectively the longitudinal associations of narrowly defined mental disorders in childhood, adolescence and young adulthood. These studies find homotypic longitudinal associations for several mental disorders, demonstrating persistence or recurrence over time. Many mental disorders also show heterotypic longitudinal associations, predicting elevated risks for other mental disorders. However, our current knowledge on the specificity and non-specificity in the course of narrowly defined mental disorders from adolescence to young adulthood remains limited for several reasons: First, only few prospective studies starting in childhood or adolescence have extended their follow-up to age 25 or higher. Second, only few studies considered a broader range of disorders and accounted for comorbidity when assessing homotypic and heterotypic longitudinal predictions. Third, most studies are based on cross-sectional diagnoses rather than lifetime or between-assessment-interval diagnostic information which might influence association patterns particularly for episodic disorders. Therefore, the current study examines the homotypic and heterotypic longitudinal associations of a range of specific DSM-IV defined mental disorders from adolescence (up to age 20) to young adulthood (age 21 to 34) while considering lifetime/interval diagnostic information and accounting for comorbidity.
Methods: A representative community sample of 3,021 adolescents and young adults aged 14 to 24 at baseline (T0) was prospectively followed-up in up to 4 assessment waves (T1, T2, T3) over a time period of up to 10 years. Mental disorders (anxiety, mood, substance use, eating, and somatoform disorders) were assessed according to DSM-IV criteria using the computerized lifetime (T0) and interval versions (T1, T2, T3) of the Munich Composite International Diagnostic Interview (DIA-X/M-CIDI); separation anxiety (T0/T1), conduct problems (T1/T2), antisocial personality (T2) and psychotic symptoms (T2/T3) were assessed using embedded assessment modules. Longitudinal associations (Odds Ratios, OR) with 95% Confidence Interval were examined via logistic regression analyses. To account for comorbidity, multiple logistic regression analyses containing all predictor disorders were conducted in addition to the univariate analyses examining the crude associations.
Results: Univariate analyses revealed strict homotypic predictions (same diagnosis later in time) for most disorders under consideration (exceptions: Generalized Anxiety Disorder and Obsessive Compulsive Disorder). Broader homotypic predictions (disorder of same diagnostic class) and heterotypic predictions (across disorder classes) were also found, but these were usually weaker than the strict homotypic associations. Multiple logistic regression analyses accounting for comorbidity revealed overall fewer associations. While the strict homotypic predictions largely remained, many broader homotypic and heterotypic associations were attenuated to non-significance.
Conclusions: Findings suggest strong homotypic longitudinal predictions for most mental disorders from adolescence to young adulthood even when accounting for comorbidity. Some homotypic associations may have been underestimated in previous studies. For example, our study revealed homotypic predictions also for depression even when accounting for comorbidity. Overall, findings suggest disorder-specificity in course of mental disorders albeit comorbidity or development of other conditions across time is a frequent phenomenon.
Keywords: psychopathology, course, continuity, prediction
Disclosure: K. Beesdo-Baum, Nothing to Disclose; D. Pine, Nothing to Disclose; R. Lieb, Nothing to Disclose; H. Wittchen, **Part 1:** Pfizer, Servier, Lundbeck, Novartis, Wyeth, **Part 4:** Novartis, Pfizer, Eli Lilly, Wyeth, Servier, Essex, Lundbeck, Sanofi Aventis.

W135. Migraine Comorbidity Worsens Course of Illness in a Longitudinal Study of Bipolar Disorder

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Background: Migraine headaches have been shown to be more common in people with bipolar disorders, however, the impact on the clinical features of bipolar disorder, and the impact by gender, are not yet clear.

Methods: We investigated comorbid migraine in 419 subjects with BP (272 F; 147 M) and 157 healthy control subjects (86 F; 71 M) followed in the Prechter Longitudinal Study of Bipolar Disorder for up to five years with depression (PHQ-9) and mania (Altman Self-Rating Mania Scale) ratings every 2 months. Control subjects were screened for personal and family mental illness, but were not screened for medical illness upon admission to the study. Frequencies of migraine, history of suicide attempts, psychosis, and mixed symptoms were compared between BP with migraine and BP without migraine groups using chi-square. Logistic regression was used to determine the impact of BP diagnosis on risk for migraine. Age at onset (AAO), number of episodes, maximum severity, frequency, and variability of mood symptom scores during followup were compared using the Mann Whitney U test for non-parametric distribution.
Results: Migraine headaches were more common in the bipolar disorder group than the control group. When corrected for age, sex and BMI, BP increased the odds of migraine by 6. The age at onset of BP (AAO) was significantly less with migraine than without (mean 16 vs 22). Mean AAO of migraine (age 22) occurred after the mean AAO of BP. Subjects with migraine had a history of more depressions and more hypomanias at initial interview than those without migraines. Some measures of severity differed by gender: women with BP and migraines had more likelihood of history of mixed symptoms, but there was no difference in psychosis or suicide attempts in either gender or both genders together. Longitudinal follow-up of subjects showed that subjects with BP and migraine had worse severity of depression, more frequent depressions, more variability of depression scores and more frequent mixed symptoms than BP subjects without migraines.
Conclusions: Comorbidity with migraine changed the course of illness of BP, and may point to a common biological mechanism linking the two illnesses. Targeted treatment for migraine may improve course of illness in BP.
Keywords: migraine, bipolar disorder, mood disorder, medical comorbidity, outcome
Disclosure: E. Saunders, Nothing to Disclose; M. Kamali, Nothing to Disclose; A. Gelenberg, **Part 1:** Eli Lilly, Pfeizer, Best Practice, AstraZeneca, Wyeth, Glaxo Smith Kline, ZARS Pharma, Jazz Pharmaceuticals, Lundbeck, Takeda, E-research Technology, Inc. Dey Pharma, PGxHealth, Myriad Genetics, Zynx Health, Healthcare Technology Systems, Inc., Forest Pharmaceuticals, Allergan, **Part 4:** Eli Lilly, Glaxo Smith Kline, Pfeizer; M. McInnis, **Part 1:** Janssen, Eli Lilly, Merck Pharmaceuticals.

W136. Childhood Sexual and Emotional Abuse Related to Multiple Unfavorable Bipolar Disorder Illness Characteristics

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Background: Research indicates bipolar disorder (BD) patients with compared to without childhood sexual/physical (and to a more limited extent emotional) abuse have increased unfavorable BD illness characteristics. We examined relationships between these and other types of early life stress (ELS) and unfavorable BD illness characteristics.
Methods: We assessed relationships between ELS and BD illness characteristics in 93 BD outpatients (mean ± SD age 47.7 ± 14.1 years; 62.4% female; 47 Type I, 39 Type II, 7 Type Not Otherwise Specified) assessed with the Systematic Treatment Program for BD (STEP-BD) Affective Disorders Evaluation, monitored with the STEP-BD Clinical Monitoring Form, and receiving open naturalistic evidence-based care in the Stanford Bipolar Disorders Clinic, who completed the Childhood Trauma Questionnaire.
Results: Patients with compared to without childhood sexual abuse had increased rates of preteen onset (48.3% versus 15.6%, $p = 0.002$), BD family history (62.1% versus 36.1%, $p = 0.025$), prior suicide attempt (41.4% versus 17.7%, $p = 0.021$), and personality disorder history (17.2% versus 1.6%, $p = 0.011$). Moreover, patients with compared to without childhood emotional abuse had increased rates of preteen onset (33.9% versus 13.5%, $p = 0.031$), mood disorder family history (83.0% versus 62.2%, $p = 0.03$), other psychiatric disorder history (74.5% versus 54.1%, $p = 0.047$), and posttraumatic stress disorder history (PTSD, 18.2% versus 2.9%, $p = 0.045$). Even after controlling for effects of potential confounding variables, childhood sexual abuse remained significantly associated with preteen onset of illness ($B = -1.4$, S.E. $= 0.5$, $df = 1$, $p = 0.009$), and BD family history ($B = -1.1$, S.E. $= 0.5$, $df = 1$, $p = 0.020$), and tended to be associated with an increased rate of personality disorder ($B = -2.1$, S.E. $= 1.2$, $df = 1$, $p = 0.066$), while childhood emotional abuse remained significantly associated with preteen onset ($B = -1.3$, S.E. $= 0.6$, $df = 1$, $p = 0.023$) and mood disorder family history ($B = -1.1$, S.E. $= 0.5$, $df = 1$, $p = 0.029$), and tended to be associated with an increased rate of PTSD ($B = -2.1$, S.E. $= 1.1$, $df = 1$, $p = 0.054$). In contrast, physical abuse/neglect and emotional neglect had more limited relationships with unfavorable BD illness characteristics.
Conclusions: Additional studies are needed to assess our findings that not only sexual but also emotional abuse is related to unfavorable BD illness characteristics, and that physical abuse/neglect and emotional neglect may have more limited relationships to unfavorable BD illness characteristics.
Keywords: bipolar disorder; childhood abuse; CTQ; sexual abuse; emotional abuse
Disclosure: S. Miller, **Part 1:** Pamlab, Inc: honorarium; S. Parameshwaran, Nothing to Disclose; F. Hooshmand, Nothing to Disclose; P. Wang, Nothing to Disclose; T. Ketter, **Part 1:** Dr. Ketter has received grant/research support from Agency for Healthcare Research and Quality, AstraZeneca Pharmaceuticals LP, Teva Pharmaceuticals/Cephalon Inc., Eli Lilly and Company, National Institute of Mental Health, Pfizer Inc., Sepracor Inc./Sunovion Pharmaceuticals; has served as a consultant for Allergan Pharmaceuticals, Avanir Pharmaceuticals, Teva Pharmaceuticals/ Cephalon Inc., Forest Pharmaceuticals, Janssen Pharmaceutica Products, LP, Merck & Co., Inc., Sunovion Pharmaceuticals; has received CME Lecture Honoraria (NOT Speaker's Bureau fees) from AstraZeneca Pharmaceuticals LP and Otsuka Phramaceuticals; his spouse (Nzeera Ketter, MD) is an employee of and owns stock in Janssen Pharmaceutica Products, LP/Johnson & Johnson, **Part 2:** For Terence Ketter only Otsuka Pharmaceuticals for 2012; for Nzeera Ketter only Janssen Pharmaceutica Products, LP/Johnson & Johnson for each year, **Part 3:** For Terence Ketter none; for Nzeera Ketter only Janssen Pharmaceutica Products, LP/Johnson & Johnson for each year, **Part 4:** C10953/3072 (SPO # 48966) (Ketter Site-PI) Teva Pharmaceuticals/Cephalon Inc. "A Double-blind, Placebo-controlled, Parallel-group, Fixed-dosage Study to Evaluate the Efficacy and Safety of Armodafinil Adjunctive Therapy in Adults With Major Depression Associated With Bipolar I Disorder" - 3/4/11 - 12/31/11 - $140,131, WS819640 (SPO # 49927) (Ketter PI) Pfizer Pharmaceuticals. "Effectiveness of Ziprasidone in a Clinical Setting" 12/01/10 – 11/01/11 - $77,044, D1050256 (SPO # 45413) (Ketter Site PI). Quintiles, Inc. (Prime Sponsor: Sepracor Inc./Sunovion Pharmaceuticals) "A 24-Week, Flexible-Dose, Open-Label Extension Study of Lurasidone for the Treatment of Bipolar I Depression" – 8/25/10 – 8/24/12 – $120,624, D1050235 (SPO # 45621) (Ketter Site PI) Quintiles, Inc. (Prime Sponsor: Sepracor Inc./ Sunovion Pharmaceuticals) "A Randomized, 6-Week, Double-Blind, Placebo-Controlled, Flexible-Dose, Parallel-Group Study of Lurasidone Adjunctive to Lithium or Divalproex for the Treatment of Bipolar I Depression" – 8/25/10 – 8/24/12 – $166,596, IRUSQUET0463 (SPO # 41037) (Ketter PI). AstraZeneca. "The

Long Term Effectiveness of Quetiapine plus LTG Therapy in Bipolar Patients" – 2/27/07 – 6/30/11 – $43,005, F1D-US-X279 (SPO # 30246) (Ketter PI). Eli Lilly and Company. "Double-Blind Placebo-Controlled Olanzapine Monotherapy in the Treatment of Acute Syndromal And Subsyndromal Exacerbations of Bipolar Disorders" – 6/28/05 – 9/30/11 – $150,000, IRUSQUET0333 (SPO # 30119) (Ketter Site PI). AstraZeneca. "A Double-blind, Placebo-controlled Trial of Seroquel for the Treatment of Dysphoric Hypomania in Bipolar II Patients" – 1/1/04 – 06/30/11 – $355,098.

W137. PTSD is Associated with an Increased Prevalence of Autoimmune Disorders

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Background: Accumulating evidence links post-traumatic stress disorder (PTSD) with elevated inflammatory activity. However, the clinical significance of this association is unclear. Though inflammation could increase the risk of autoimmune disease, little is known about whether patients with PTSD are at increased risk of developing autoimmune disorders.
Methods: We conducted a retrospective cohort study of 673,277 Iraq and Afghanistan veterans under 55 years old who received VA healthcare from October 1, 2005 to March 31, 2012 with at least one year of follow up. Department of Veterans Affairs administrative data were used to identify ICD-9 codes for mental health and autoimmune disorders and to obtain sociodemographic, military service, and health service utilization information. Generalized Linear Models were used to ascertain the association of PTSD with subsequent autoimmune diagnoses after adjusting for age, race and number of primary care visits.
Results: The sample was 88% male and 49% white with a mean age of 31.3 years (+/- 8.7). PTSD was diagnosed in 206,623 (31%) veterans and mental health disorders other than PTSD were diagnosed in an additional 132,242 (20%) veterans. Compared to veterans with no mental health diagnoses, those diagnosed with PTSD had increased risk for subsequent diagnosis with thyroiditis (Adjusted Relative Risk [ARR] = 1.74; 95% CI, 1.67, 1.82), rheumatoid arthritis, (ARR = 1.92, 95% CI, 1.67, 2.20), inflammatory bowel disease (ARR = 1.32, 95% CI, 1.20, 1.46), multiple sclerosis (ARR = 2.23, 95% CI, 1.88, 2.64), systemic lupus erythematous (ARR = 1.81, 95% CI, 1.48, 2.23) and any of these disorders alone or in combination (ARR = 1.50, 95% CI, 1.45, 1.56). Moreover, while there was an increased risk for each of these disorders in veterans with mental health disorders other than PTSD, the risk was consistently higher in those diagnosed with PTSD. Women had significantly higher risk for autoimmune disorders overall, but the pattern of results was similar in men and women.
Conclusions: Veterans with PTSD appear to be at increased risk for autoimmune disorders compared to those with no or other mental health diagnoses. Future prospective longitudinal cohort studies are needed to establish causality, measure inflammatory markers in conjunction with PTSD, and evaluate whether successful treatment of PTSD reduces risk of autoimmune disorders.
Keywords: PTSD, Autoimmune Disorders, Multiple Sclerosis, Lupus, Thyroiditis
Disclosure: A. O'Donovan, Nothing to Disclose; B. Cohen, Nothing to Disclose; D. Bertenthal, Nothing to Disclose; M. Margaretten, Nothing to Disclose; K. Seal, Nothing to Disclose; T. Neylan, Nothing to Disclose.

W138. Metabolic Syndrome and Outcomes in Individuals with Bipolar II Disorder

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Background: Recent studies demonstrate a clear association between (CV) risk and bipolar disorder (BP). The metabolic syndrome is defined as a clustering of CV risk factors including insulin resistance, abdominal obesity, mild dyslipidemia, and hypertension which appears to identify substantial risk for CV disease beyond any single risk factor. The metabolic syndrome and BP appear to share common risk factors, including inflammatory changes, dysregulation of the sympathetic nervous system, and behavior patterns, such as physical inactivity and overeating. Problematically, many of the medications used to treat BP contribute to CV risk by causing weight gain and metabolic disturbances. Elevated CV risk factors are associated with worse psychiatric outcomes in BP samples and premature mortality. While elevated CV risk factors have been well-characterized in individuals with BP I disorder, it is unclear whether individuals with BP II disorder have similar CV risk profiles to those with BP I disorder and whether there are relationships among CV risk, BP subtype, and psychiatric outcomes.
Methods: 350 participants (274 BP I, 76 BP II) age 18-66 enrolled in the Bipolar Disorders Center for Pennsylvanians were included in the analyses. Participants were assessed at baseline, 12 months and 18 months. Outcome measures included the Medical Outcome Study Short Form-36 (SF-36) and the Cumulative Illness Rating Scale (CIRS). Multiple linear regression models were conducted, controlling for age, gender, and baseline scores.
Results: 28.1% (n = 77) and 23.7 % (n = 18) of individuals with BP I and BP II, respectively, met criteria for the metabolic syndrome. 38% (n = 133) were on atypical antipsychotic medications. The physical component subscale score of the SF-36 was significantly lower (worse) at 12 months ($F = 4.47$, $df = 1$, $p < .05$) and 18 months ($F = 4.13$, $df = 1$, $p < .05$) in subjects meeting criteria for the metabolic syndrome. When BP subtype was added to the model, it did not account for any additional variance suggesting that it does not moderate the relationship between SF-36 scores and metabolic syndrome. There were no differences in CIRS scores between groups over time.
Conclusions: Individuals with the metabolic syndrome had worse scores on the physical component subscore of the SF-36 over time, regardless of BP subtype. There were no statistically significant differences in the percentage of individuals with BP I versus BP II meeting criteria for the metabolic syndrome, and cumulative illness ratings over time did not differ between the BP subtypes. Similarity in medical burden and CV risk profiles between BP I and BP II groups suggests that the need for interventions to monitor and modify CV risk in individuals with BP II disorder.
Keywords: Bipolar disorder, cardiovascular risk, metabolic syndrome
Disclosure: H. Swartz, **Part 1:** Speaking honoraria from Servier International, Sanofi-Aventis, Astra-Zeneca France; Royalties from UpToDate; A. Fagiolini, **Part 1:** Dr. Fagiolini is/has been a speaker and a consultant for Angelini, Bristol-Myers Squibb, Boehringer-Ingelheim, Lundbeck, Pfizer, Eli Lilly, GlaxoWellcome, Janssen, Novartis, Sigma tau and Takeda; P. Rucci, Nothing to Disclose; E. Frank, **Part 1:** Consultant: Servier, Vanda Pharmaceuticals, Royalties: Guilford Press, American Psychological Association Press; D. Kupfer, Nothing to Disclose.

W139. Juvenile Antioxidant Treatment Prevents Behavioral and Prefrontal Cortical Deficits in a Developmental Model of Schizophrenia

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Background: Strong evidence suggests schizophrenia is a disorder arising from combined genetic risk factors and environmental insults during development, with symptoms becoming evident during adolescence. The neonatal ventral hippocampal lesion (NVHL) model produces prefrontal cortical deficits with adolescent onset in the rat. We have observed that cortical GABA interneurons are affected in this model, yielding cortical disinhibition in adult rats. Here, we examined whether increased levels of oxidative stress are causative to the behavioral and cellular changes observed in the NVHL model. We investigated the levels of oxidative stress in prefrontal cortical interneurons in juvenile and adult NVHL and control rats. Next, we administered the antioxidant N-acetylcysteine (NAC) between postnatal day 5 and 45 to determine whether antioxidants prevent cellular, behavioral, and electrophysiological deficits.
Methods: Rats received either an NVHL or sham surgery at postnatal day (P) 6-8. Half of those animals are given NAC in their drinking water starting at P5 and continuing into P45. Both at P21 and at P60 the amount of oxidative stress in the cingulate cortex was assessed using immunohistochemistry for 8-oxo-dG, a marker for mitochondrial DNA oxidation. We also measured the density of parvalbumin (PV) interneurons using unbiased stereology. In another set of rats, we examined the effect of NAC on the deficits in prepulse inhibition NVHL rats exhibit, and on the altered modulation of prefrontal cortical neurons using *in vivo* and *in vitro* electrophysiological recordings.
Results: Rats with an NVHL exhibited higher levels of oxidative stress but no loss of PV in the prefrontal cortex at P21. At P60, the levels of oxidative stress had decreased, and there was a significant loss of PV interneuron labeling. NAC treatment prevented the increase in oxidative stress and the loss of PV labeling. Oxidative stress was observed in 50% of PV interneurons, but not observed in calretinin or calbindin interneurons, indicating in may occur only in fast-spiking neurons. NAC also prevented prepulse inhibition deficits in adult NVHL rats.
Conclusions: Oxidative stress levels are higher in the cingulate cortex of a developmental animal model of schizophrenia, and controlling redox balance prior to the onset of deficits can prevent the deleterious effects of developmental insults on adult brain function. This is consistent with human data indicating antioxidant adjuvant treatment may be beneficial, and highlights the potential neural population and pathophysiological mechanisms involved in the NVHL model. Early antioxidant treatment may prove an effective way to reduce risk for conversion in people at risk for psychiatric disorders.
Keywords: schizophrenia, animal model, prefrontal cortex, oxidative stress, electrophysiology
Disclosure: D. Counotte, Nothing to Disclose; H. Cabungcal, Nothing to Disclose; P. Piantadosi, Nothing to Disclose; E. Sullivan, Nothing to Disclose; E. Lewis, Nothing to Disclose; G. Calhoon, Nothing to Disclose; H. Tejeda, Nothing to Disclose; M. Cuenod, Nothing to Disclose; K. Do, Nothing to Disclose; P. O'Donnell, **Part 1:** Consultant for Roche Pharmaceuticals.

140. RNA Editing of an AMPA Receptor Subunit is Altered in Major Depression and Suicide

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Background: Major depression is a common and severely debilitating mental illness which is partially heritable and poorly understood. One brain region of interest, the dorsolateral prefrontal cortex (DLPFC), is important for the regulation of executive function. Consistent data from several previous studies indicate that cortical 5-HT2C RNA editing is increased in major depression and in suicide victims (Niswender et al., 2001; Gurevich et al., 2002; Iwamoto et al., 2003; Dracheva et al., 2008). This form of RNA editing is a post-transcriptional process which is catalyzed by enzymes called Adenosine Deaminases Acting on RNAs or 'ADARs'. RNA editing alters the physiological functions of AMPA and kainate glutamate receptors, and 16% of known microRNAs, in addition to the 5-HT2C receptor (Nishikura, 2011). Our previous studies show that the increased level of 5-HT2C RNA editing in mood disorders and suicide may be a consequence of altered activity of the RNA editing enzyme, ADAR1, in these subjects (Simmons et al., 2010). Moreover, recent studies indicate that the glutamatergic system may play a role in the pathophysiology of mood disorders, since ketamine, an antagonist of the NMDA glutamate receptor, has rapid antidepressant effects in patients. In addition to NMDA receptor antagonists, drugs which potentiate AMPA receptor activity have been found to produce antidepressant effects in animal models. Since the RNA editing process alters AMPA receptor function, we have tested the hypothesis that there is a generalized change in RNA editing which influences glutamatergic signaling in major depression and suicide.
Methods: Postmortem subjects diagnosed with major depression and a comparison group of subjects without psychiatric illness were included in this study. RNA was extracted from the DLPFC of 93 major depressive suicide cases and 46 control subjects. All cases included in these analyses were tested for the presence of antidepressants on toxicology screens. Quantitative polymerase chain reaction (QPCR) was conducted for the ADAR enzymes. QPCR data were normalized to the expression of housekeeping genes and analyzed using the relative standard curve method. Subsequently, levels of RNA editing and alternative splicing of the AMPA receptor subunit, GluR2, were measured using QPCR-restriction fragment length polymorphism (QPCR-RFLP) in these subjects.
Results: Our data indicate that GluR2 RNA editing at the Q/R site was 100% in the human DLPFC. The two GluR2 isoforms produced by R/G site editing were both detectable after RT-PCR followed by sequencing, and subsequently using a QPCR-RFLP method. ADAR1 but not ADAR2 expression showed a gender by diagnosis interaction ($F = 7.03$, $df = 1, 138$, $p = 0.009$). Expression of the GluR2 edited isoform was not correlated with ADAR1 expression. However, increased GluR2 RNA editing was detected in major depressive suicide cases compared with controls ($F = 12.2$, $df = 2, 70$, $p = 0.001$).
Conclusions: We report that ADAR1 gene expression is differentially altered in males and females with major depression. However ADAR1 gene expression was not correlated with RNA editing of the GluR2 subunit of the AMPA receptor. Instead, our results indicate that increased GluR2 RNA editing occurs in major depressive suicides. This RNA editing event in GluR2 has been shown to produce a faster time to desensitization and resensitization of AMPA receptors containing GluR2. AMPA receptor potentiators have been shown to exert efficacy in rodent models of depression and the mechanisms by which these effects occur is uncertain. Our findings implicate the RNA editing process and also AMPA

receptor activity in the pathophysiology of suicide in major depression. Therefore these data indicate that the AMPA receptor GluR2 subunit may be a novel target for antidepressant drug development.
Keywords: glutamate, ADAR, prefrontal cortex, gene expression
Disclosure: M. Sodhi, Nothing to Disclose; D. Mount, Nothing to Disclose; T. Hyde, Nothing to Disclose; J. Kleinman, Nothing to Disclose.

W141. Higher Insula Connectivity in Abstinent Stimulant Users

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Background: Stimulant dependence is a disorder that has been characterized by an inability to control impulsive and compulsive internal urges needed to inhibit stimulant consumption. An increasing number of studies suggest that insula, a region known to integrate internal (e.g. limbic) and external (e.g. cortical) information processing, plays an important role in addiction and abstinence maintenance. Little is known, however, about whether insula's functional connectivity patterns are different between individuals with stimulant dependence versus non-substance abusing controls.
Methods: Resting state functional magnetic resonance imaging data were collected to examine insula's functional connectivity between 18 short-term abstinent stimulant addicts (STAS; 4-week abstinent) and 19 non-substance abusing controls (NSAC). We used seed-based region of interest analysis to identify regions with significant functional connectivity with bilateral insula.
Results: Compared to NSAC, STAS showed significantly higher synchrony between insula (a) and cortical executive processing regions such as right dorsolateral prefrontal cortex (Brodmann area 10) and left inferior parietal lobule (Brodmann area 40), (b) and limbic reward processing regions such as bilateral thalamus and left lentiform nucleus.
Conclusions: We find that STAS have higher resting state synchrony than NSAC between insula and both executive control and reward processing regions. We propose that the increased synchrony results from the STAS group's ongoing need to mediate control on reward seeking behavior. Results are consistent with the role of insula as a region involved in the integration of executive and reward functions, an interaction needed to control craving and avoid relapse in individuals with substance dependence.
Keywords: stimulant dependence, insula, reward network, executive control, functional connectivity
Disclosure: J. Camchong, Nothing to Disclose; S. Specker, Nothing to Disclose; V. Slaymaker, Nothing to Disclose; B. Mueller, Nothing to Disclose; A. MacDonald, Nothing to Disclose; K. Lim, Nothing to Disclose

W142. Schizophrenia Subtypes: Going, Going, Gone

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Background: For the past half century, psychiatric nosology has relied on "subtypes" as a scientific, clinical and conceptual framework for understanding "the group of schizophrenias". In this context, Bleuler's original turn of the (past) century conceptualization that schizophrenia consists of subtypes or groups has proved to be uncannily accurate. From a descriptive standpoint, schizophrenia subtypes evolved via Bleuler and Kraepelin's careful observations and the descriptive Research Diagnostic Criteria (RDC), and thence the DSM in its various iterations as a cornerstone of clinical practice and research. For many years, the paranoid/non-paranoid nosological dichotomy was paramount in psychometric research of "The Group of Schizophrenias" as described by Bleuler. This dichotomy was elaborated further in the DSM. Support for the use of subtypes in schizophrenia treatment and research comes from many traditional clinical studies. In contrast, subtypes have been challenged because: ● traditional subtypes are not strong heuristically ● patients are not necessarily stable in their subtype over the course of the illness ● genetic difference between paranoid and hebephrenia subtypes do not appear to be sufficient to keep the 2 categories separate. ● latent class/genetic studies tend to reinforce the newer deficit subtype, not the existing DSM-IV subtypes. ● nominating the deficit subtype is not wise if the other subtypes are unknown and just referred to as "other" ● focusing on specific pathology domains is a better heuristic than traditional subtypes based on admixture of psychopathologies ● endophenotypes have not yet produced a comprehensive alternative for schizophrenia subgroups at the level of classification. This study examined 5 of the highest rated prime journals in neuropsychiatry (Journal of Molecular Psychiatry, American Journal of Psychiatry, Archives of General Psychiatry, Biological Psychiatry, and Schizophrenia Bulletin to see the frequency with which DSM IV subtypes are actually used in the high impact psychiatric neuroscience literature. To do this, we reviewed all articles published with a keyword "schizophrenia" from a 2010 to 2011 interval to see what percentage of these articles actually used DSM subtypes. Our general hypothesis was that less than 50% of these articles would use subtypes in their design, methods and results.
Methods: The "top 5" journal articles on schizophrenia were reviewed to see if DSM-IV subtypes were used.

Journal	# Articles/ Schizophrenia	Subtypes Used?
Schizophrenia Bulletin	35	9
American Journal of Psychiatry	43	3
Journal of Molecular Psychiatry	22	0
Archives of General Psychiatry	30	2
Biological Psychiatry	83	0
Total	**213**	**14**

Results: Less than 10% of studies utilize schizophrenia subtypes (Year- 2010-11).
Conclusions: As psychiatric research has progressed, the use of traditional (i.e. RDC, DSM) subtypes for schizophrenia is now being utilized in less than 10% of "prime journal" articles. From a scientific perspective, perhaps SANS and SAPS ratings, deficit vs. non-deficit categorization or the use of genes and endophenotypes has replaced "old" DSM subtypes. From a nosological standpoint, the diminished use of DSM IV subtypes in the literature speaks for itself: DSM IV subtypes are a faint signal in the literature of the 21st century. Alfred Adler said "If you want to understand (someone) look at the tongue in his shoes (behavior), not the tongue in his mouth (pronouncements)". Our field, especially in the publication realm has rendered its verdict: DSM IV subtypes are simply not being used. Whatever the explanation, this will undoubtedly lead to and also reflects the diminished importance of scientifically ambiguous and perhaps empirically unsupported subtypes used in DSM-IV. Thus, DSM-V should take into account this strong "non-use" trend. Also, it appears as if researchers are relying on other (non DSM-IV subtype) domains (deficit type, SANS/SAPS, neurocognitive status, endophenotypes, genes) while exploring

the clinical, neurobiological, genomic and treatment domains of schizophrenia.
Keywords: Schizophrenia, Subtypes, DSM, Nosology
Disclosure: D. Braff, Nothing to Disclose; A. Rissling, Nothing to Disclose; S. Langton, Nothing to Disclose; W. Carpenter, **Part 1:** 2010-2012: Advisor jobs to Shire, Astrazeneca, Geneotech, and Merck

W143. Seasonality and Diurnal Rhythms of Sleep and Activity Assessed by Mobile Technologies in a Community Based Population Study

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Background: Increasing evidence suggests that disruptions in circadian clock genes impair sleep-wake cycle and social rhythms which can have a major impact on mood disorders. In addition, seasons represent a major environmental effect on both circadian and homeostatic patterns of sleep regulation and activity. However, there is relatively little research on seasonal fluctuations of sleep and activity in normal and pathological human states. A study of white-crowned sparrows (*Zonatricia leucophrys gambelii*) shows that while in captivity these birds show periods of migratory restlessness and increased rates of goal-directed behavior and impulsivity during times of the year when they would usually be migrating. The goal of this poster is to repeat similar analysis done in this sparrow population to examine the effect of seasonality on objectively-assessed patterns of activity and sleep in a large population based sample.
Methods: This sample consisted of 266 participants from a community based family study of affective spectrum disorders, with an age range from 10-80. Participants were characterized by use of diagnostic interviews of psychiatric illness and sleep disorders. Objective measures of activity counts and sleep duration were obtained by combined actigraphy and experiential momentary sampling over a two week period.
Results: There were no significant differences in the mean activity counts and sleep duration across the two weeks by the self-reported morningness-eveningness groups. However, there was greater variability in sleep duration such that those with eveningness had greater variability (s.d. = 97) compared to intermediate (s.d. = 79) and morningness (s.d. = 73) groups. With respect to seasonal differences, there was greater average activity (counts per minute across two weeks) in the summer compared to winter and fall ($p = 0.022$), as well as greater variability in mean activity counts during the summer as compared to the fall ($p = 0.06$). Mixed model analysis corrected for age showed an earlier decline in activity during the day in the winter and fall months as compared to the spring and summer. There was also an increase in sleep duration in the winter compared to the summer. We plan to use functional data analysis, a new statistical technique, to further analyze the impact of seasonality on the circadian rhythm of sleep and activity across mood disorder subgroups.
Conclusions: These preliminary findings demonstrate subgroup differences in diurnal and seasonal patterns of objectively-assessed sleep duration and activity in a community based sample. Future analyses will examine how disruptions in such patterns may be associated with mood disorders. Linking seasonal and circadian patterns in animals and humans will facilitate our understanding of the biological pathways and environmental correlates of normal and disrupted human sleep and activity.
Keywords: Seasonality Sleep Activity Mood Disorders
Disclosure: A. Taylor, Nothing to Disclose; F. Lamers, Nothing to Disclose; J. Zhang, Nothing to Disclose; R. Benca, Nothing to Disclose; K. Merikangas, Nothing to Disclose.

W144. Pediatric Bipolar Disorder and Mixed Mood Symptoms: Moderately Prevalent in Community Mental Health and Underdiagnosed by Practitioners

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Background: There has been a tremendous increase in the rate of diagnosis of pediatric bipolar disorder in the last decade based on reviews of billing diagnoses (Moreno et al., 2007; Blader & Carlson, 2007). It is unclear whether this represents a correction to the previous practice of underdiagnosing bipolar disorder or whether pediatric bipolar disorder is now being over-diagnosed. Epidemiologicalestimates from nonclinical samples indicate that 2 to 4% of youths may be on the bipolar spectrum (Van Meter et al., 2011; Merikangas et al., 2011). The purpose of the present study is to compare the agreement between clinical intake diagnoses –also used for billing– of bipolar disorder in a community mental health center versus research "LEAD standard" (Spitzer, 1983) diagnoses of bipolar spectrum illness, benchmark LEAD vs. clinical agreement kappas about bipolar against other more common diagnoses, and provide a clinical epidemiological set of base rates for bipolar spectrum and other pediatric diagnoses.
Methods: Participants ($N = 618$) were randomly selected from families presenting with a youth for outpatient community mental health services at urban clinics. Patient ages ranged from 4.9 to 18.0 years, 60% were male, and 88% African-American. LEAD diagnoses combined results from a semi-structured diagnostic interview with caregiver and youth (KSADS), plus family psychiatric history and prior treatment history. Bipolar spectrum diagnoses followed strict and unmodified DSM-IV criteria and required a clear change in functioning and evidence of spontaneous mood shifts during episode. NOS could be due to insufficient duration or insufficient number of manic symptoms. Current mood was characterized usingestablished thresholds on interview-based mood severity ratings that required the mood to be episodic or a change in functioning (Algorta et al., 2011; Duax et al., 2007).
Results: Based on the LEAD diagnoses, the most common diagnoses were ADHD (65%), ODD (37%), unipolar depression (30%), any anxiety disorder (26%), adjustment disorder (16%), conduct disorder (13%), bipolar spectrum (12.6%: 2.7% bipolar I, 1.3% bipolar II, 3.9% cyclothymic disorder, and 4.7% bipolar NOS), and PTSD (10%). Rates of the most common clinical diagnoses were statistically significantly lower for all these categories. The most common clinical diagnoses were ADHD (42%), depression (25%), ODD (19%), and adjustment disorders (12%). Based on the clinical intake/billing diagnoses, 0.2% were diagnosed on the bipolar spectrum, and 2.3% had a "rule out of bipolar." Including "mood NOS" raised the potential clinical intake "potential bipolar" prevalence to 8.7%. Agreement between the LEAD and clinical diagnoses of bipolar spectrum illness was poor to moderate. Focusing on the "potential bipolar" clinical definition, overall agreement was $k = .32$, $p < .00005$, with the clinical diagnosis sensitivity = 33%, specificity = 95%, positive predictive value = 48%, and a negative predictive value = 91%. The more conservative clinical definition (diagnosing bipolar or a "rule out" of bipolar, but not mood NOS) had a specificity = 100% and PPV = 100%, but sensitivity = 1% and a NPV = 88%. LEAD diagnoses identified significantly more Axis I diagnoses with a mean of 2.6 diagnoses versus 1.6 diagnoses clinically, $t = 18.93$, $p < .0005$. With regard to mixed mood presentation based on elevated interview ratings of severity (Algorta et al., 2012), 88% of bipolar I and 66% of the rest of the bipolar spectrum cases had a mixed presentation, making it the most common mood presentation within LEAD diagnosed bipolar spectrum disorders. Mixed

depressive and manic symptoms (not meeting full DSM criteria) also occurred in 7% of depressed, 3% of ADHD/Disruptive Behavior cases with no DSM mood disorder, and 6% of other diagnoses, reflecting an overall moderate degree of specificity of mixed mood (70%) to the bipolar spectrum. LEAD bipolar II was most likely to be clinically diagnosed "depressed" on the billing sheets (63%) and cyclothymia most commonly was clinically labeled disruptive behavior or ADHD (63%).

Conclusions: Agreement between clinical/billing diagnoses and research diagnoses was only fair to poor. Consistent with prior work (Rettew et al., 2009), clinical diagnoses were significantly less sensitive to diagnoses, but especially so for conduct disorder and bipolar disorder. Discussion with clinicians indicates that these are considered particularly serious diagnoses that they were hesitant to assign at intake. Clinical diagnoses tend to underestimate comorbidity compared to systematic research diagnoses. Bipolar spectrum disorder affected roughly 13% of the outpatient sample, with rates roughly double to triple that found in thegeneral population (cf. Van Meter et al., 2011; Merikangas et al., 2011). Mixed mood states are the most common presentation among pediatric bipolar cases. Mixed mood is moderately specific to LEAD diagnoses of bipolar disorder when emphasizing episodic presentation, and appears to contribute to diagnostic uncertainty in clinicians, who focused on the salient mood and oftenignored the second mood component in assigning diagnoses.

Keywords: diagnostic agreement, clinical epidemiology, pediatric bipolar disorder

Disclosure: E. Youngstrom, **Part 1:** Consulted with Lundbeck; received travel support from Bristol-Myers Squibb; J. Youngstrom, Nothing to Disclose; G. Algorta, Nothing to Disclose; R. Findling, **Part 1:** Alexza, American Psychiatric Publishing, AstraZeneca, Bristol Myers Squibb, Dainippon Sumitomo Pharma, Forest, GlaxoSmithKline, Guilford Press, Johns Hopkins U Press, Johnson & Johnson, Kempharm, Lilly, Lundbeck, Merck, NIH, Novartis, Noven, Otsuka, Pfizer, Physicians Postgraduate Press, Rhodes, Roche, Sage, Schering Plough, Seaside Therapeutics, Sepracor, Shire, Stanley Medical Research Institute, Sunovion, Supernus, Transcept, WebMD.

W145. Clinical Characteristics of Visual Hallucinations in Psychotic Disorders: A Cross-sectional Study

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Background: Visual hallucinations (VH) are frequently reported in adult psychotic disorders, childhood onset schizophrenia (COS) and Parkinson's disease (PD). Studies in adult psychotic disorders show rates of VH ranging from 12% to 72%, varying according to study design and samples. While VH are an understudied dimension of all psychoses, there is surprisingly limited data on VH and associated factors in adult psychotic disorders. The present study examines the association of VH with other clinical features, including psychotic symptoms and illness severity, in a well-characterized sample of inpatients with psychotic disorders.

Methods: In this cross-sectional study, we examine VH in a large cohort of patients with schizophrenia, schizoaffective disorder and bipolar I disorder with psychotic features. Subjects were recruited for a genetic association study of mood and psychotic disorders. Scales used to measure psychiatric symptoms included the Structured Clinical Interview for DSM-IV-TR, Positive and Negative Syndrome Scale, Young Mania Rating Scale and the Montgomery-Asberg Depression Rating Scale.

Results: In a previous sample of 420 patients from our genetic association study, visual hallucinations were common and present across diagnoses, in 32 (24.1%) patients with schizophrenia, 29 (28.7%) patients with schizoaffective disorder and 30 (16.1%) patients with bipolar I disorder. 256 (61%) patients in the total sample had hallucinations in any modality. We have now recruited over 800 patients and are performing analyses of associations to VH in this larger sample. The association of VH with factors related to illness severity, including age of onset and functional status is being studied. We examine VH in relation to demographic factors, hallucinations in other sensory modalities (auditory, olfactory, tactile and gustatory hallucinations), specific delusions (persecutory, grandiose, reference, control and somatic delusions), other psychotic symptoms and to lifetime history of major depressive episode, manic episode, catatonia, substance abuse disorders and family history of psychosis and mood disorders.

Conclusions: Lifetime and current VH are often noted in patients across the three diagnostic categories of psychotic disorders studied, suggesting a dimensional approach may be useful in studying the significance of VH in psychosis. Hallucinations in all sensory modalities are also present across the three psychotic disorders. The proposed analyses will define clinical characteristics of visual hallucinations and their association to other factors related to illness presentation and severity. A 1990 study in 117 patients with schizophrenia and schizoaffective disorder reported that global severity of illness was associated with VH. In COS and PD, VH are more common and have been strongly associated with severity of illness. COS is a form of schizophrenia with greater genetic loading, on average, and the NIMH COS study showed a high rate of VH (80.3%, 94/117). To date, more studies on VH and associated factors have been done in PD. Dopamine and dopaminergic therapies were considered the primary risk factor of VH in PD, but VH are no longer considered simple side effects of dopaminergic agents. The involvement of the cholinergic system in VH is suggested by effects of anticholinergic drugs, neuropathology and imaging studies in PD patients with VH. Overall, our study is designed to contribute to an improved understanding of visual hallucinations from a symptom dimension perspective, across diagnostic categories of psychosis, including schizophrenia, schizoaffective disorder and bipolar I disorder.

Keywords: visual hallucinations, psychotic disorders, schizophrenia, schizoaffective disorder, bipolar disorder

Disclosure: V. Chouinard, Nothing to Disclose; D. Ongur, **Part 2:** Associate Editor for Archives of General Psychiatry, **Part 4:** Principal Investigator for research grant with Rules Based Medicine Inc.; G. Chouinard, **Part 1:** Has received consulting fees/honoraria from Pfizer; B. Cohen, Nothing to Disclose.

W146. Risk-taking in Schizophrenia and Controls with and without Cannabis Dependence

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Background: The appreciation of risk is a vital aspect of decision-making. Both schizophrenia and illicit drug use are associated with altered risk-based decision-making, including differences from healthy controls on measures of impulsivity, optimistic bias, and sensation-seeking. The combined impact of schizophrenia and a co-occurring substance use disorder on decision-making is poorly understood. Given that the prevalence rate of substance use disorders in people with schizophrenia is nearly five times that of the general population, it is important to examine how these illnesses may interact on decision making. This study examined measures of risk-taking and decision-making in people with schizophrenia (SZ, $n = 24$), cannabis dependence (CD, $n = 21$), schizophrenia and co-occurring cannabis dependence (SC, $n = 18$), and healthy controls (HC, $n = 24$).

Methods: Participants were recruited from the community via advertisements. Presence or absence of psychiatric diagnoses was confirmed by the Structured Clinical Interview for DSM-IV. Participants completed multiple symptom, risk, cognitive, and addiction assessments during one visit. This report highlights the Balloon Analog Risk Task (BART) and the Impulsive Sensation-Seeking Scale from the Zuckerman-Kuhlman Personality Questionnaire (ImpSS). Group comparisons used chi-square, ANOVA, and t-tests as appropriate.
Results: There were significantly fewer pumps on the BART trials in the SZ group (28.8 ± 12.2) compared to the SC (35.4 ± 12.5; $t(79) = 1.94$, $p = 0.055$), CD (39.6 ± 7.7; $t(79) = 3.15$, $p = 0.001$), and HC (35.6 ± 9.3; $t(79) = -2.18$, $p = 0.03$) groups. The SZ group also had fewer balloon explosions (6.5 ± 3.7) compared to the SC (9.6 ± 4.3; $t(79) = 2.34$, $p = 0.02$), CD (11.5 ± 3.8; $t(79) = 4.13$, $p = 0.0001$), and HC (9.2 ± 4.7; $t(79) = -2.28$, $p = 0.03$) groups. There were no differences in pumps or explosions among the SC, CD, and HC groups. There were no differences in the amount of money earned by any group; SZ ($13.39 \pm 5.00), SC ($14.89 \pm 3.91), CD ($15.23 \pm 1.64), and HC ($15.10 \pm 2.35; $F(3,81) = 1.35$, $p = 0.26$). On the ImpSS, the HC scored significantly lower on impulsivity (1.92 ± 1.28) compared to the SZ (3.79 ± 2.11; $t(85) = 3.70$, $p = 0.0004$), SC (3.39 ± 1.82; $t(85) = 2.69$, $p = 0.009$), and CD (3.17 ± 1.72; $t(85) = 2.46$, $p = 0.02$) groups. The HC group was also lower on sensation-seeking (3.63 ± 2.84) than the CD group (6.04 ± 2.93; $t(85) = 2.72$, $p = 0.008$). The SZ (4.71 ± 3.37) and SC (5.17 ± 3.01) groups did not differ from the other groups on sensation-seeking.
Conclusions: The BART measures actual risk-taking behavior in a laboratory setting, while the ImpSS assesses self-reported preferences in reference to real-life events. On the BART, the SC group was most similar to the groups without schizophrenia (CD, HC), rather than to the SZ group. On the ImpSS, the SC group was most similar to the other illness groups (CD, SZ), rather than to the HC group. This suggests that people with schizophrenia and cannabis dependence may have a profile of risk-taking behavior and related decision-making similar to people with cannabis dependence alone or with non-ill persons. Self-reported impulsivity, however, appears similar across the three diagnostic groups, with less impulsivity reported by the non-ill control subjects.
Keywords: schizophrenia, cannabis dependence, co-occurring disorders, risk-taking, impulsivity, decision-making
Disclosure: B. Fischer, Nothing to Disclose; R. McMahon, Nothing to Disclose; D. Kelly, **Part 4:** Ameritox, Ltd; Bristol Myers Squibb; H. Wehring, Nothing to Disclose; W. Meyer, Nothing to Disclose; S. Feldman, Nothing to Disclose; W. Carpenter, **Part 1:** Shire; AstraZeneca; Genotech, **Part 4:** N/A; D. Gorelick, Nothing to Disclose.

W147. The Influence of Social Setting on Acute Alcohol Effects in Humans

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Background: Social settings are known to enhance acute responses to alcohol, and alcohol is known to affect social behavior. Despite these known interactions with social setting, laboratory-based studies usually test the effects of alcohol under socially isolated conditions. Thus, the current study addressed a critical gap in the scientific literature by investigating 1) the acute subjective, physiological, and behavioral effects of alcohol in a social, compared to an isolated context; 2) the effects of alcohol on social interaction; and 3) the role of the co-participant's drug state on an individual's response to alcohol.
Methods: Healthy volunteers ($N = 44$) with moderate alcohol use completed this 4-session, within-between-participant, double-blind study. Participants were randomly assigned to either the social group (SOC) in which two individuals participated together in the same room, or the isolated group (ISO) in which participants were tested alone. During each session, participants received either oral alcohol (0.8 g/kg) or placebo. Within the SOC condition, participants received alcohol once when the co-participant received alcohol and once when s/he received placebo, and received placebo once when the co-participant received alcohol and once when s/he received placebo. In the ISO condition, participants received alcohol and placebo twice in a randomized order. Cardiovascular measures, breath alcohol concentrations, and subjective effects were assessed before and after consuming the beverages. In the SOC group, measures of social interaction were also obtained.
Results: Alcohol produced its expected effects overall, on alcohol concentrations, feelings of alcohol-related intoxication, stimulation, and other "positive" subjective effects (e.g., 'Like Drug', 'Want More Drug': $p < 0.01$ for all comparisons). The SOC group reported greater alcohol-induced "positive" subjective effects and feelings of intoxication compared to the ISO group ($p < 0.05$ for all comparisons), but the groups did not differ in breath alcohol concentrations. Within the SOC group "positive" subjective effects were greater when both participants received alcohol ($p < 0.05$ for all comparisons). Finally, compared to placebo, alcohol increased measures of social interaction (e.g., ratings of emotional responsiveness: $p < 0.05$).
Conclusions: These data show that the acute effects of alcohol are enhanced by a social setting, in this case the presence of another individual, and that alcohol increases social interaction. Additionally, the drug state of another individual influences the subjective effects of alcohol. Overall, these findings demonstrate that non-pharmacological factors, specifically social factors, influence the subjective response to a drug. The social context in which drugs are used are likely to play an important role in their use, and abuse.
Keywords: Alcohol, social interaction, subjective effects, humans
Disclosure: M. Kirkpatrick, Nothing to Disclose; H. de Wit, **Part 3:** Dr. de Wit has received support from Unilever for a research project, unrelated to this study.

W148. Anatomy of the "Neuropsychiatric Translational Research Revolution": Challenges Abound

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Background: Psychiatric neuroscience has undergone a dramatic "revolution" over the past few decades spurred on by new facts from interrelated fields such as neuroimaging to genomics. Nevertheless, our success in integrating the plethora of new facts (knowledge) about psychiatric disorders into a coherent "whole" (wisdom) has arguably lagged, leading to a "Pretense of Wisdom Syndrome" (Braff 2012). The field may be so fixated on fascinating but clinically ambiguous facts that only a Procrustean view could lead us to believe that the interesting new knowledge fits into a coherent *clinically relevant* translational neuroscience framework for fully understanding and advancing our knowledge regarding the etiology and treatment of complex neuropsychiatric disorders.
Methods: In order to determine whether the issues described above are also of concern to senior neuropsychiatric Thought Leaders (TLs), we administered a Translational Research Questionnaire (TRQ) that included questions about the relative importance TLs place on emerging facts and patient contact and other issues. TLs were drawn in part from the 2011 Program Committees of the ACNP and Society of Biological Psychiatry.

Some answers (other details will appear in the Poster) (numbers vary)

- We asked "What is your Highest Degree": Respondents: MD-20; Ph.D.-19; Both M.D., Ph.D.-12.
- The Mean was 23 Years to, "How Many Years Ago Did you Obtain Your Terminal Degree?"
- We asked the question, "How Important Do You Think It is For Translational (T-1: "Bench to Bedside") Researchers To See at Least 30 patients with the disorder they are studying?" Of the respondents, 6 replied Not at All Important; 5 responded Moderately, 10 responded Important, 10 responded Very Important, and 24 responded Essential.
- Final (Yes or No) Question (presented orally after questionnaire was filled out):
- Do you believe that research in high impact journals, such as Science and Nature, reflect the level of familiarity with neuropsychiatric disorders that is needed to meaningfully understand these disorders? Yes – 18; No – 40

Conclusions: Based on the results of the TRQ and the opinions of Thought Leaders, translational researchers could benefit from stepping back from our focus on mechanistic, "micro" level knowledge to examine how we design, interpret and frame our work in terms that resonate beyond our own specialty. To these ends, we respectfully suggest a number of recommendations for the field in order to create a more relevant translational research environment and narrow the basic to clinical gap.

- Realistic timeframes: It is important to present the public with a realistic bench to bedside timetable for the clinical applications of basic science findings.
- Patient contact: Bench researchers need contact with patients in order to contextualize molecular facts, understand the complexity of mental disorders, and link etiology to treatment interventions. Likewise, clinicians should spend some time in the laboratories with which they collaborate.
- Psychosocial interventions: We must consider how *both* biological and psychosocial interventions may lead to effective brain changing therapeutics for our patients.
- Collaborative relationships: To accomplish these goals, we must forge closer, collaborative relationships between basic and clinical scientists.

Nobel Laureates Goldstein and Brown, warned us in 2008 that "elite" basic science journals presented research that was disarticulated from clinical realities in medicine. Our TLs are similarly concerned with this basic-clinical science gap. Our patients would greatly benefit from better contextualized interpretations of research efforts in our exciting neuroscience domain. The neuropsychiatric "translational revolution" is in a very early stage with basic advances occurring in rapid order: too rapid for their clinical implications to be quickly tested. Additional suggestions for dealing with this basic-clinical time gap will be offered and solicited.

Keywords: Translational Research, Neuropsychiatry

Disclosure: D. Braff, Nothing to Disclose; L. Braff, Nothing to Disclose.

W149. Utilization of Patient-derived Neuronal Cells for Disease Modeling and Hypothesis Building in Neuropsychiatric Disease Research

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Background: Recent technical advances in human neuronal cell culture methods have provided opportunities to examine neuronal cells derived from accessible patient tissues/cells and gain insight into the mechanisms underlying neuropsychiatric diseases. Full potentials of such human neuronal cells need to be addressed in light of other promising approaches such as neuroimaging, postmortem brain studies, and animal models.

Methods: We have optimized the methods to obtain live neuronal cells, in particular dissociated olfactory epithelium-derived cells (olfactory cells) and induced neuronal cells (iN cells), from the patients with schizophrenia and other neuropsychiatric diseases. Genome-wide molecular profiling (mRNA and epigenetic modifications) and cell biology experiments were performed to explore new hypotheses and model key disease phenotype(s). Animal model experiments were used to complement some aspects of the mechanistic studies.

Results: We have found that olfactory cells and iN cells are suitable for molecular/biochemical studies and cell biology assessment, respectively. Indeed, combined approaches of gene expression microarray and ChIP-seq using olfactory cells from the patients with schizophrenia have identified a group of genes related to phase II detoxification system as one of the most altered genes in schizophrenia. Further mechanistic studies focusing on neuron-glia interaction and brain inflammatory cascades are in progress. Using iN cells, we have successfully recapitulated a key pathological features of lysosomal storage disease (Tay-Sachs disease): accumulation of glycosphingolipids (GM2 gangliosides). These results demonstrate their utility for the investigation of neuropathogenic mechanisms and for screening potential therapeutic chemical compounds.

Conclusions: Our studies demonstrate that live human neuronal cells will provide unique opportunities to build new hypotheses as well as faithfully model key disease features. We have also addressed some of the advantages and disadvantages of currently available human neuronal cell cultures. *In vitro* human neuronal cell approach, together with other approaches, will be an essential part the comprehensive study platform for neuropsychiatric diseases.

Keywords: olfactory epithelium, gene expression microarray, ChIP-seq, schizophrenia, induced neuronal cells

Disclosure: S. Kano, Nothing to Disclose; G. Maegawa, **Part 1:** Consultant for Biomarin Inc. and Shire HGT; Z. Zhou, Nothing to Disclose; R. Cardarelli, Nothing to Disclose; C. Colantuoni, Nothing to Disclose; Q. Yuan, Nothing to Disclose; F. Han, Nothing to Disclose; A. Wilson, Nothing to Disclose; N. Cascella, Nothing to Disclose; H. Ji, Nothing to Disclose; P. O'Donnell, **Part 1:** Consultant for Roche Pharmaceuticals; D. Goldman, Nothing to Disclose; A. Sawa, **Part 1:** Research Funding, Astellas, Takeda, Tanabe-Mitsubishi, Dainippon-Sumitomo, Consultant, Pfizer, Asubio, Sucampo, Eli Lilly, Taisho, Amgen, Collaboration, Pfizer, Afraxis, Sanofi-Aventis, Astrazeneca, Johnson and Johnson.

W150. Prepulse Inhibition Detects Evidence of Neurodevelopmental Differences in Individuals at Greatest Risk for Psychosis: Findings from the North American Prodromal Longitudinal Study (NAPLS)

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Background: The NAPLS Consortium is a multisite longitudinal study that investigates risk, prediction and mechanism of psychosis in individuals at clinical high risk (CHR) for psychosis. The startle prepulse inhibition (PPI) paradigm, an important biobehavioral marker in psychopathology research, was administered as part of the test battery.
Methods: A total of 367 CHR subjects between the ages of 12 and 30 were compared to 187 normal comparison (NC) subjects on the PPI paradigm. The paradigm includes startle pulse alone stimuli (115 dB white noise) presented alone or preceded by a prepulse stimulus (86 dB) at 3 different interstimulus intervals (30, 60 and 120 ms). Electromyographic (EMG) responses were recorded using a Biosemi system equipped with EMGelectrodes that record eye blink at the obicularis oculi muscle.
Results: There were significant age ($F[1,549] = 17.11$, $p < 0.001$) and gender ($F[1,549] = 4.50$, $p < 0.05$, Males > PPI than Females) main effects but no significant group effects. The age effects were present only in the CHR sample and showed significant positive correlations with age. Comparison of age regression between CHR and NC subjects was at a trend level ($p = 0.06$). One year clinical follow-up data was available for 306 CHR subjects. Of those, 34/306 (11%) had developed a psychotic illness and also showed significant positive correlations between PPI and age that differed from NC's (Age × Group Regression comparison: $F[2,489] = 3.72$, $p < 0.05$). Male CHR subjects who went on to develop a psychotic illness ($N = 26$) had significantly greater ($p < 0.05$) PPI than those CHR who did not develop a psychotic illness by one year ($N = 156$) and male NC subjects ($N = 99$).
Conclusions: Although PPI appears to be fully developed by adolescence in NC subjects, subjects at greatest risk for psychosis demonstrate evidence continued PPI development past early adolescence. In contrast to findings in chronically psychotic patients, male CHR subjects who later developed a psychotic illness had greater PPI than observed in CHR subjects who did not convert to psychosis and NC's, replicating findings in a separate dataset that suggest compensatory brain changes or perhaps a period of neurotoxicity may characterize the period prior to the onset of psychosis. Taken together, the hypothesized neurodevelopmental abnormalities of the prodromal phase of psychotic illness appear to be indexed with PPI and may represent a risk factor that can provide insight into neuropathological changes early in the course of illness.
Keywords: prepulse inhibition, prodrome, schizophrenia, neurodevelopment
Disclosure: K. Cadenhead, Nothing to Disclose; J. Addington, Nothing to Disclose; T. Cannon, Nothing to Disclose; B. Cornblatt, Nothing to Disclose; D. Mathalon, Nothing to Disclose; T. McGlashan, Nothing to Disclose; D. Perkins, Nothing to Disclose; L. Seidman, Nothing to Disclose; M. Tsuang, Nothing to Disclose.

W151. Relationships between Mismatch Negativity, Auditory Emotional Processing, and Psychosocial Functioning in Schizophrenia

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Background: Schizophrenia (SZ) patients exhibit a range of symptoms from deficits in early perceptual processing to impairments in social cognition and daily functioning. Early perceptual processing deficits can be demonstrated by a reduction in mismatch negativity (MMN), an event-related potential (ERP) that is elicited when an infrequent, task-irrelevant oddball stimulus occurs in a sequence of frequent standard stimuli. Previous studies have demonstrated that reduced MMN in SZ patients is associated with deficits in social cognition and everyday psychosocial functioning. In this study, we examined the relationships between MMN deficits, affective perception and semantic identification of environmental sounds and psychosocial functioning in schizophrenia patients.
Methods: SZ patients ($n = 27$) and nonpsychiatric comparison subjects ($n = 21$) underwent MMN testing. In a separate behavioral testing session, participants listened to 6-second sound clips taken from the International Affective Digitized Sound (IADS) collection and performed affective rating and semantic identification of these sounds. SZ patients were assessed on the Scale of Functioning (SOF), a well-validated multidimensional 15-item clinician rating scale that was designed in order to characterize the functional status of an adult across psychological, social and occupational domains.
Results: Schizophrenia patients had a significantly reduced amplitude of MMN at electrode site Fz, consistent with previous results ($t(35) = 2.92$, $p < 0.007$). After listening to the IADS sounds, patients demonstrated significant impairments in semantic identification of sounds ($t(35) = 5.44$, $p < 0.001$), but there was no difference in affective ratings between patients and controls, even when examining ratings of only correctly identified sounds. Impaired semantic identification in the patient group was significantly associated both with MMN deficits and with SOF scores ($p < 0.05$). MMN deficits significantly predicted environmental sound processing ($b = 0.46$, $t(19) = 2.24$, $p < 0.05$) and explained a significant proportion of variance in environmental sound identification ($R^2 = 0.21$ to 0.33, all $F's > 5.00$, all $p's < 0.05$). Environmental sound identification significantly predicted social functioning when controlled for MMN deficits ($b = -0.59$, $t(18) = -1.96$, $p < 0.05$). Environmental sound identification also explained a significant proportion of variance in social functioning after controlling for MMN ($R^2 = 0.30$, $F(2,18) = 3.78$, $p < 0.05$). Regression analyses, however, failed to reveal a direct relationship of MMN with social functioning in schizophrenia patients.
Conclusions: Patients demonstrated impairment in sound identification, but when examining correctly identified sounds, their affective ratings were similar to controls. This suggests that imprecision of auditory information processing of real-world emotionally evocative sounds can be dissociated from the subjective experience of valence and arousal. MMN amplitude was predictive of emotionally salient sound identification, which was likewise predictive of social functioning. The current findings are consistent with a model in which early sensory auditory processing influences complex sound processing which, in turn, impacts psychosocial and daily functioning in schizophrenia patients.
Keywords: Mismatch Negativity, Environmental Sound Processing, Affective Perception, Social Functioning
Disclosure: B. Breteinstein, Nothing to Disclose; W. Chang, Nothing to Disclose; A. Rissling, Nothing to Disclose; R. Sharp, Nothing to Disclose; C. Sugar, Nothing to Disclose; R. Malaguti, Nothing to Disclose; M. Pela, Nothing to Disclose; J. Sprock, Nothing to Disclose; D. Braff, Nothing to Disclose; G. Light, **Part 1:** Dr. Light has received compensation from Astellas for one-time participation in a scientific advisory boad unrelated to this study.

W152. Relationship between Auditory Processing and Affective Prosody in Schizophrenia

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Background: Emotion perception is a fundamental aspect of social cognition. Patients with schizophrenia have well-established

deficits in their ability to identify other people's emotion from facial expression and tone of voice. Despite strong evidence that basic visual processing deficits contribute to impaired facial affect recognition in schizophrenia, very few studies have examined the mechanisms underlying poor ability to detect emotion in voice tone. In this study, we explored the link between different stages of auditory processing, using event-related potentials (ERPs), and affective prosody detection in schizophrenia.
Methods: Thirty-six schizophrenia patients and 18 healthy control subjects participated in the study. Duration mismatch negativity (MMN) and P300 were measured using two auditory oddball paradigms, a passive one for MMN and an active one for P300. Subjects were also administered tasks of affective prosody, facial emotion identification, and tone matching. The affective prosody task consisted of audio recordings of actors saying semantically neutral sentences with different voice tones. Participants were asked to identify the emotion conveyed in each sentence.
Results: Patients had significantly reduced MMN and P300 amplitudes, impaired auditory and visual emotion recognition, and poorer tone matching performance, relative to healthy controls. Within the patient group, correlations among the ERP and behavioral measures revealed significant associations between affective prosody recognition and both MMN and P300 amplitudes. These relationships were modality-specific: MMN and P300 did not correlate with facial emotion recognition. A linear regression with MMN and P300 entered simultaneously as independent variables and affective prosody as the dependent variable revealed significant regression coefficients for both factors. The two ERP waves accounted for 49% of the variance in the task performance.
Conclusions: Our results support previous findings of a relationship between basic auditory processing abnormalities and affective prosody dysfunction in schizophrenia and they extend the findings to include ERPs. Our results are consistent with a cascade model in which perceptual processes lead to social cognitive abilities. Early and late auditory ERPs independently contributed to the ability to recognize emotions from voice tone. Hence, both relatively automatic pre-attentive processes (measured with MMN), and also later attention-dependent processes (measured with P300) are needed for accurate auditory emotion identification. These findings provide some support for bottom-up (e.g., perceptually based) cognitive remediation approaches.
Keywords: schizophrenia; auditory processing; affective prosody; mismatch negativity; P300.
Disclosure: C. Jahshan, Nothing to Disclose; J. Wynn, Nothing to Disclose; J. Avila, Nothing to Disclose; M. Green, Nothing to Disclose.

W153. Diffusion Tensor Imaging of the Thalamus in Cocaine Dependent Subjects: Association with fMRI and Treatment Response

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Background: Prior studies have shown evidence of impaired white matter integrity in cocaine dependent subjects as measured by diffusion tensor imaging (DTI). In another study, we showed that cocaine dependent subjects had lower brain activation in the thalamus than healthy controls and that the level of brain activation was related to treatment outcome. As the thalamus is a critical relay between cortical and subcortical structures one potential reason for the reduced thalamic activation in cocaine users could be altered microstructural integrity within this region.
Methods: Nineteen cocaine dependent subjects and 12 non-drug using controls who had previously participated in an fMRI study of working memory took part in this study to examine the white matter microstructure in the thalamus using DTI. Cocaine dependent subjects were randomized to treatment studies after the scan. Whole brain DTI data were acquired on a Philips 3.0 T Intera system with a six-channel receive head coil (Philips Medical Systems, Best, Netherlands). DTI images were acquired in the transverse plane using a single shot spin-echo diffusion sensitized echo-planar imaging (EPI) sequence (21 gradient directions plus bo image, b factor = 1000 s/mm2, repetition time = 6100 ms, echo time = 84 ms, 44 contiguous axial slices, field-of-view = 240 mm × 240 mm, 112 × 112 acquisition matrix, 256 × 256 reconstructed matrix, 0.9375 mm × 0.9375 mm reconstructed in-plane resolution, slice thickness = 3 mm. The right and left thalamus were segmented into gray and white matter regions following a DTI atlas-based validated procedure implemented in SPM as described elsewhere (4). Statistical comparisons of fractional anisotropy (FA) and mean diffusivity (MD) between cocaine users and controls were performed using a Mann-Whitney U test due to non-normal data distributions. Correlations between fMRI and DTI as well as DTI and treatment outcome were performed using Spearman correlations.
Results: Cocaine dependent subjects had significantly lower FA (Man Whitney $U = 41.5$, $p = 0.003$) and significantly higher MD (Mann Whitney $U = 40.0$, $p = 0.003$) in the right thalamus compared to non-drug using controls. There was no significant difference between groups in the left thalamus for FA ($p = 0.133$) or MD ($p = 0.152$). For all subjects (cocaine users and controls), thalamic fMRI activation while performing a working memory task significantly correlated with FA in the right thalamus (Spearman $r = 0.613$, $p < 0.001$), and MD in the right thalamus (Spearman $r = -0.536$, $p = 0.002$), but there was no significant correlation between left thalamus FA ($p = 0.236$) or MD ($p = -0.145$) and fMRI activation. Within cocaine dependent subjects there was a significant correlation between right thalamus FA and treatment effectiveness score (Spearman $r = 0.633$, $p = 0.004$).
Conclusions: This study shows that cocaine dependent subjects have evidence of altered integrity within the right thalamus compared to non-drug using controls and that fMRI activation within the thalamus significantly correlated with white matter integrity. Moreover, within cocaine users white matter integrity in the thalamus was related to treatment outcome for the cocaine users. Further studies on the relationship between white matter integrity and brain activation in cocaine dependent subjects are warranted.
Keywords: Cocaine, Diffusion Tensor Imaging, fMRI
Disclosure: F. Moeller, **Part 1:** Consultant for Boehringer Ingelheim; K. Hasan, Nothing to Disclose; J. Steinberg, Nothing to Disclose; L. Ma, Nothing to Disclose; J. Schmitz, Nothing to Disclose; S. Lane, Nothing to Disclose; P. Narayana, **Part 1:** Consultant for GenZyme.

W154. Tolcapone Modulates Working Memory Load Related DLPFC Activity and Coupling in Patients with Schizophrenia

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Background: Deficits in working memory (WM) have consistently been reported in patients with schizophrenia (Dickinson et al, 2007) and abnormal dorso-lateral prefrontal cortex (DLPFC) activation has been implicated to underly these deficits (e.g. Callicott et al, 2003). Evidence from recent studies suggests that not only DLPFC activation, but also its abnormal coupling with subcortical structures, such as hippocampal formation (HF), may play a role in the WM deficits (Rasetti et al, 2011). Converging

evidence suggests dopamine (DA) dysregulation in the DLPFC as one of the factors related to the abnormal prefrontal cortical physiology and WM deficits seen in patients with schizophrenia. Cortical DA signaling can be modulated through pharmacological approaches including inhibition of catecholamine-O-methyltransferase (COMT), an enzyme that plays a unique role in regulating DA flux in the PFC. In the current study, we evaluated the effect of tolcapone, a potent COMT inhibitor which penetrates the blood brain barrier, on prefrontal cortical information processing in a sample of patients with schizophrenia while they perform a task with increasing working memory load.

Methods: We performed a double-blinded, placebo controlled, and crossover study in which placebo or coded tolcapone at a dose of 100 mg three times a day on the first day and then at a dose of 200 mg three times a day was administered orally for the next 6 days. fMRI was performed on the seventh day. After a one-week wash-out period following the first arm, the subjects who received coded tolcapone received coded placebo three times a day and those who started on the coded placebo received coded tolcapone three times a day, in both cases for 7 days. Twenty-seven patients with schizophrenia (22 males, 5 females; Mean age = 25.8 years) underwent BOLD fMRI (3T) while performing the N-Back task with increasing WM load (1-Back and 2-Back). Differences in activation (in the whole brain and within DLPFC as an *a priori* region of interest) and differences in DLPFC coupling with hippocampus formation (HF) evaluated with PPI (seed right DLPFC), between working memory loads (1-back and 2-back) were investigated during placebo and with tolcapone treatment using the repeated measures ANOVA design in SPM5.

Results: During placebo condition, a significant effect of load was observed in activation of the PFC and parietal regions ($pFWE < 0.05$ corrected for whole brain), with 2-Back condition showing greater activity in these areas compared to 1-Back condition, despite similar accuracy. With tolcapone, a significant load by drug interaction was observed ($p_{FWE} = 0.05$ corrected within DLPFC ROI). Specifically, while there was a significant reduction in DLPFC activation with tolcapone during the 2-Back task, a similar reduction was not observed during the 1-Back task. Post-hoc analyses confirmed this observation (2-Back pla > tol $p_{FWE} = 0.02$ corrected within DLPFC ROI; no significant effect of tolcapone on DLPFC activation during the 1-Back task). On PPI analysis there was no significant main effect of WM load, or tolcapone on rDLPFC-HF coupling. However, tolcapone significantly increased rDLPFC - bilateral HF coupling during the 2-Back condition (rHF $p_{FWE} = 0.032$, lHF $p_{FWE} = 0.072$ corrected within bilateral HF ROI). A similar effect was not observed during the 1-Back condition.

Conclusions: These data complement our prior work in healthy normal controls (Apud et al., 2007) and show that tolcapone enhances prefrontal cortical efficiency as well as its coupling with HF in patients with schizophrenia. Most importantly, they show that these effects are more apparent at higher working memory loads (i.e. 2-Back task) suggesting that treatment with tolcapone could enhance the working memory capacity in patients with schizophrenia.

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Keywords: tolcapone, schizophrenia, fMRI, DLPFC, coupling

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W155. Behavioral Economics for Standardized Metrics in CNS Drug Development and Regulation

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Background: Novel CNS acting drugs and formulations offer considerable promise for a broad range of neurocognitive and behavioral disorders, but increasing concerns about prescription drug abuse complicate development, regulatory evaluation, and marketing. Some drugs in development assumed to pose low risk of Controlled Substance scheduling may be scheduled like other compounds (e.g., pregabalin, lacosamide, fospropofol). Approval of new submissions based on previously approved molecules has either been delayed or rejected due to concerns about the formulation (e.g., transdermal methylphenidate, buprenorphine, and fentanyl products). The challenges faced by the FDA and industry are well illustrated by the OxyContin experience. Its rate of abuse was due, in part, to the ease of tampering enabling rapid absorption of high doses of oxycodone by swallowing, nasal insufflation, and injection. Development of the new formulation was complicated by the absence of standardized protocols for *in vitro* formulation assessment and lack of valid quantitative metrics for predicting reduced attractiveness to drug abusers. Formulation assessment is urged in FDA's 2010 Draft Guidance to Industry on Abuse Potential Assessment, but the guidance is very general. Recent innovations in Behavioral Economics (BE) may provide a credible conceptual, methodological, and analytical framework for abuse liability quantification at multiple levels to inform research, development, and marketing as well as surveillance, policy, and public safety.

Methods: Abuse liability may be assessed via BE "demand curves" that quantify drug consumption across a range of increasing prices. "Price" can be anything of value such as money, effort, or time, and consumption may be actual (e.g., self-administration), hypothetical (e.g., purchase task questionnaire), or reported (e.g., self-report or epidemiological data). The recently introduced Exponential Model of Demand (Hursh & Silberberg, 2008) is a descriptive nonlinear regression-based model for demand curve data that yields highly sensitive metrics that mathematically separate endogenous biological and dose/potency confounds from drug-seeking persistence. The latter is quantitatively expressed as a rate constant for decreasing consumption across the entire range of increasing prices, thereby representing the sensitivity to price or "essential value" of the reinforcer.

Results: Reviews of the emerging human literature base reveal that hypothetical demand curves follow the same exponential demand function as found with actual consumption in animal models and predict self-reported use, biomarkers of recent use, and actual self-administration in humans. Hypothetical demand functions are also sensitive to pharmacological treatment interventions and contextual effects of future adverse consequences of consumption. In their longitudinal study of prescription opioid abusers, Cicero et al. (2012) reported that preference for OxyContin was reduced by 57% following replacement with the new formulation, suggesting a remarkable reduction in abuse liability of the same active molecule solely as a function of the tamper-resistant formulation. We will present analyses of these and forthcoming pilot data suggesting that a BE-based approach could have predicted both the rapid uptake of OxyContin by drug abusers as well as the relative decline in abuse and street value of the new formulation.

Conclusions: BE methods like hypothetical demand curves permit informative standardized comparisons across compounds and formulations/packaging within the same drug class, as well as

comparisons throughout the research and development process in controlled animal and human studies, and then in market research, post-market surveillance, and policy analysis (Hursh and Roma, in press). BE analyses may also complement traditional abuse liability assessment and integrate with data from *in vitro* formulation assessment and other potential factors that may influence the risk of abuse. Behavioral Economic methods may facilitate development and regulation of CNS compounds by providing standardized quantitative metrics for assessing abuse liability across molecules, formulations, and packaging.

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Keywords: Abuse Liability Drug Scheduling Risk Management Behavioral Economics Drug Development

Disclosure: J. Henningfield, **Part 1:** Through my position at Pinney Associates, I provide consulting services on drug development, abuse liability assessment, *in vitro* drug formulation assessment, risk management/REMS, and FDA drug regulation to pharmaceutical firms that are developing and marketing new drugs and formulations. I also share a financial interest in patents for a new oral dosage form of nicotine for treating tobacco dependence, **Part 2:** See #2; S. Hursh, **Part 1:** I was reimbursed for travel expenses incurred as a participant in the Behavioral Economics Roundtable on Diabetes workshop supported by Sanofi US. I have no other professional Financial Involvements with any pharmaceutical or biotechnology companies, companies providing clinical assessment, scientific, or medical products, or companies doing business with or proposing to do business with ACNP; P. Roma, **Part 1:** I was reimbursed for travel expenses incurred as a participant in the Behavioral Economics Roundtable on Diabetes workshop supported by Sanofi US. I have no other professional Financial Involvements with any pharmaceutical or biotechnology companies, companies providing clinical assessment, scientific, or medical products, or companies doing business with or proposing to do business with ACNP; E. Cone, **Part 1:** Through my position at Pinney Associates, I provide consulting services on drug development, abuse liability assessment, *in vitro* drug formulation assessment, risk management/REMS, and FDA drug regulation to pharmaceutical firms that are developing and marketing new drugs and formulations. I also share a financial interest in patents for a new oral dosage form of nicotine for treating tobacco dependence, **Part 2:** Through my position at Pinney Associates, I provide consulting services on drug development, abuse liability assessment, *in vitro* drug formulation assessment, risk management/REMS, and FDA drug regulation to pharmaceutical firms that are developing and marketing new drugs and formulations. I also share a financial interest in patents for a new oral dosage form of nicotine for treating tobacco dependence; A. Buchhalter, **Part 1:** Through my position at Pinney Associates, I provide consulting services on drug development, abuse liability assessment, *in vitro* drug formulation assessment, risk management/REMS, and FDA drug regulation to pharmaceutical firms that are developing and marketing new drugs and formulations, **Part 2:** Through my position at Pinney Associates, I provide consulting services on drug development, abuse liability assessment, *in vitro* drug formulation assessment, risk management/REMS, and FDA drug regulation to pharmaceutical firms that are developing and marketing new drugs and formulations; R. Fant, **Part 1:** Through my position at Pinney Associates, I provide consulting services on drug development, abuse liability assessment, *in vitro* drug formulation assessment, risk management/REMS, and FDA drug regulation to pharmaceutical firms that are developing and marketing new drugs and formulations, **Part 2:** Through my position at Pinney Associates, I provide consulting services on drug development, abuse liability assessment, *in vitro* drug formulation assessment, risk management/REMS, and FDA drug regulation to pharmaceutical firms that are developing and marketing new drugs and formulations; S. Scholl, **Part 1:** Through my position at Pinney Associates, I provide consulting services on drug development, abuse liability assessment, *in vitro* drug formulation assessment, risk management/REMS, and FDA drug regulation to pharmaceutical firms that are developing and marketing new drugs and formulations, **Part 2:** Through my position at Pinney Associates, I provide consulting services on drug development, abuse liability assessment, *in vitro* drug formulation assessment, risk management/REMS, and FDA drug regulation to pharmaceutical firms that are developing and marketing new drugs and formulations.

W156. The Effect of Stereotype Threat, Perceived Discrimination, and Examiner-examinee Racial Discordance: Simple as Black and White?

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Background: Multiple factors impact the validity of neurocognitive assessments in clinical and research settings but only some of these factors are widely appreciated. This poses significant challenges to data interpretation, which is of particular concern in situations where cognition is a primary variable of interest (e.g., clinical trials investigations). Stereotype threat and perceived discrimination are both factors that have been found to disrupt cognitive processes, which may occur when an individual is part of a social group (e.g., African American, women) with an attached negative stereotype (e.g., intellectual inferiority). The purpose of the study was to examine the effects of stereotype threat, perceived discrimination, and examiner-examinee racial discordance on neurocognitive test performance.

Methods: Participants consisted of 92 adults including African-American ($n = 45$) and Caucasian ($n = 47$) adults who were recruited through fliers distributed around local college campuses. Participants were assigned to either the stereotype threat condition or non-threat condition using a quasi-random assignment. Within each study condition, participants were randomly assigned to either a Black or White examiner. All participants completed measures of perceived discrimination (Perceived Ethnic Discrimination Questionnaire; PED-Q) and were administered a brief neurocognitive test battery that included measures of premorbid intellectual ability, speed of information processing, attention/working memory, learning and memory, and executive functioning.

Results: Our results supported the negative effects of stereotype threat and perceived discrimination on general neurocognitive performance. There was a significant condition $\times$ examinee race interaction such that African Americans performed significantly more poorly in the stereotype threat condition than African Americans in the non-threat condition, $F\ (5,\ 87) = 4.25$, $p = .03$, partial $\eta^2 = .05$. African Americans who reported high levels of perceived discrimination performed significantly more poorly on neurocognitive assessment than African Americans who reported low levels of perceived discrimination, $F\ (1,\ 44) = 3.74$, $p = .04$, partial $\eta^2 = .05$. Examiner race mediated the relationship between perceived discrimination and performance on learning and memory, $F\ (2,\ 43) = 5.095$, $p = .03$, partial $\eta^2 = .11$, such that African Americans who reported high levels of perceived discrimination performed significantly more poorly on memory tests when tested by an examiner of a different race.

Conclusions: Overall, these results suggest that factors that are characteristic of the individual and the environment may impact the validity of neurocognitive test results. Although the present study was focused on ethnic group membership, stereotype threat

generalizes to a wide range of populations such as TBI, aging, psychiatric and neurological disease populations. The effects of such factors as stereotype threat and perceived discrimination are not subtle, and much work is needed to understand how this affects cognitive performance and other factors relevant to clinical research.
Keywords: Cognitive performance, ethnicity, stereotype threat, perceived discrimination, racial discordance
Disclosure: A. Thames, Nothing to Disclose; R. Bilder, Nothing to Disclose; D. Byrd, Nothing to Disclose; C. Hinkin, Nothing to Disclose; K. Duff, Nothing to Disclose.

W157. MicroRNA-206 Regulates Alcohol Consumption and Preference

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Background: microRNAs contribute to the control of transcript levels, and may be a mechanism behind the wide-ranging changes in gene expression associated with ethanol exposure and alcoholism. In a previous microarray study, we found microRNA-206 (miR-206) to be differentially regulated in the medial prefrontal cortex (mPFC) after chronic ethanol exposure. Here, we determined the functional role of miR-206 in alcohol dependence, consumption, and preference.
Methods: miRNAs were isolated using the mirVana miRNA Isolation kit. Quantitative real-time-PCR analysis of miRNA and mRNA expression levels was performed using TaqMan assays. Wistar rats were made alcohol-dependent (PD) by an established chronic alcohol vapor model. The same cohort of rats underwent cannulation surgeries in the mPFC, were injected with microRNA LNA inhibitors 3 times over 3 days, and alcohol consumption and preference were measured. miR-206 knockout (KO) and wildtype (WT) mice also underwent a standard chronic alcohol consumption model. Luciferase reporter assays to Brain Derived Neurotrophic Factor (BDNF) 3′UTR were performed to determine binding potential of miR-206.
Results: miR-206 was confirmed by PCR to be significantly upregulated in the mPFC, but not in the ventral tegmental area, amygdala, or nucleus accumbens. Inhibition of miR-206 in the mPFC of PD rats decreased drinking to the levels of non-dependent rats and significantly decreased ethanol preference in a two-bottle choice paradigm. Male miR-206 KO mice consumed significantly less ethanol than their WT counterparts at 10%, 13%, and 15% ethanol concentrations. Analysis using microRNA.org revealed 2 conserved target sites for miR-206 in the 3′UTR of BDNF. BDNF was downregulated in post-dependent rats by microarray analysis, and this was confirmed by rt-PCR. BDNF expression was repressed by miR-206 but not miR-9 in a 3′UTR reporter assay confirming that miR-206 is a functional binding target of BDNF.
Conclusions: In conclusion, we have identified persistent changes in the expression of miR-206 following alcohol dependence in the Wistar rat strain. Knockout animals established the importance of miR-206 in alcohol consumption and preference. Furthermore, inhibition of cortical miR-206 signaling decreased alcohol consumption and preference in post-dependent rats to the level of non-dependent rats. Moreover, we confirmed that miR-206 binds and inhibits the expression of BDNF. Overall, our findings indicate that miR-206 is a key modulator of escalated voluntary alcohol intake and preference following a history of alcohol dependence.
Keywords: microRNAs, alcoholism, BDNF, knock out animals, gene expression
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W158. Developmental Differences in the Neural Correlates of Trial-to-trial Variance in Response Time

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Background: Attentional deficits are core features of several pediatric psychiatric disorders, including bipolar disorder (BD) and attention-deficit/hyperactivity disorder (ADHD). One common measure of attentional regulatory deficits is increased intrasubject variability in response time (ISVRT) on motor response tasks. This increased trial-to-trial variance is hypothesized to reflect decreased efficiency of top-down attentional control processes (Bellgrove et al., 2004; Prado and Weissman, 2011). ISVRT is highly heritable in control populations (Kuntsi et al., 2006), suggesting a genetic component to the behavioral measure. Increased ISVRT has been suggested as a putative behavioral endophenotype of BD as it has been observed in both adults and children with the disorder, regardless of mood state, medication, or comorbidity (Bora et al., 2006; Brotman et al., 2009), and in unaffected, first-degree relatives of patients with BD (Brotman et al., 2009). Increased ISVRT has also been associated with ADHD (Kuntsi and Klein, 2012). Although some work has been done to elucidate the neural correlates of trial-to-trial variance in RT in adults (Weissman et al., 2006), to our knowledge, there have been no attempts to examine the neural correlates of ISVRT in children. A developmental examination of the neural correlates of ISVRT is the first step in understanding the role of ISVRT in pediatric psychiatric disorders.
Methods: Data were acquired from 14 healthy adults (3 male) ranging from 21-38 years of age (mean 25.9 y) and 13 healthy children (5 males) ranging from 9-17 years of age (mean 14.3 y). While functional imaging data was acquired on a 3T GE scanner, subjects performed a modified version of the global-local selective attention task originally employed by Weissman et al. (2006). The task was composed of 6 runs, three global runs interleaved with three local runs (order counterbalanced across subjects), of 96 trials each. We parametrically modeled BOLD-RT associations i.e., linear associations between trial-to-trial variance in the average BOLD response and trial-to-trial changes in RT. We modeled the 15 seconds following stimulus onset, using a finite impulse response (FIR) model to avoid making assumptions about the shape of the BOLD response. The FIR model allowed for estimation of the BOLD signal at 13 time points across the modeled 15 seconds. A linear mixed-effects model was employed in 3dLME in AFNI to identify clusters in which a group $\times$ time point interaction on BOLD-RT associations was present. Clusters that surpassed a height threshold of $p < 0.005$ uncorrected and an extent threshold of 20 voxels were identified as significant.
Results: Overall, standard deviation of RT was higher in children (215 ms) than adults (164 ms), however this difference did not reach significance ($p = 0.12$). A group $\times$ time point interaction on BOLD-RT associations was evident in four clusters: 1) left superior frontal gyrus (SFG), medial frontal gyrus, and cingulate; 2) right hippocampus; 3) left insula, inferior frontal gyrus (IFG); 4) right superior temporal gyrus, transverse temporal gyrus, and precentral gyrus. In these four clusters, the difference between groups appeared to be driven by a stronger association between BOLD response and RT in adults than children. In addition, in two clusters, children showed BOLD-RT associations that were in the opposite direction to those observed in adults. In the SFG cluster,

the children had a negative relationship between RT and activation, indicating that increased activation in this region was associated with faster (decreased) RT, while adults had a positive association, indicating that increased activation in this cluster was associated with greater (slower) RT. In the right hippocampus, adults had a negative relationship between RT and activation; again, the relationship in children was opposite (a positive association).

Conclusions: These results suggest developmental alterations in the association between modulation of brain activity and variation in RT. Compared to adults, children exhibited less modulation of cortical activation in association with RT variation. These lower RT-activity associations in children vs. adults may reflect the extended development seen in frontal cortical regions through adolescence. In adults, the robust relationship between variation in RT and frontal activation likely represents increased top-down control, perhaps to overcome attentional lapses, a process that may be less efficient in children. Consistent with our findings, one study in adults found that subjects with greater ISVRT across a task exhibited greater activation in frontal regions (Bellgrove et al., 2004). The present study shows that this relationship holds within adult subjects on a trial-to-trial basis, a phenomenon that is not completely developed in children. In addition, our results suggest that, in addition to frontal regions, the hippocampus and STG also show changes in activation on a trial-by-trial basis that is related to changes in RT. These findings help to define the normal development of the neural correlates of ISVRT, and lay the groundwork for future studies of pediatric psychopathology in which increased ISVRT is a symptom, such as ADHD and bipolar disorder.

Keywords: fMRI; intrasubject variability in response time; development; healthy

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W159. Differentiating Neural Networks with Interleaved TMS-BOLD Imaging: Insight into Addiction

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Background: Interleaved transcranial magnetic stimulation (TMS) and BOLD imaging in the MR environment provides us with a unique opportunity to probe neural circuitry. The purpose of the current study was to determine if, through the use of an optimized interleaved TMS-BOLD sequence in two cortical targets, we could differentially activate lateral and medial prefrontal cortex neural circuits.

Methods: Interleaved TMS/BOLD imaging data was acquired for a cohort of 15 healthy individuals and 15 cocaine users who received TMS in 2 runs with the coil positioned over the: 1) dorsolateral prefrontal cortex (DLPFC, EEG: F3), and 2) orbitofrontal/medial prefrontal cortex (OFC/MPFC, EEG: FP1)(Magstim MR-compatible coil). The TMS pulse started 100 ms before the onset of the next TR (100% motor threshold). BOLD data was analyzed using standard parametric techniques. Additionally 5 participants were scanned twice to evaluate test-retest reliability.

Results: Among healthy controls, DLPFC TMS was associated with a significant elevation of BOLD signal in multiple dorsal cortical areas. In contrast, OFC/MPFC TMS was associated with a significant elevation of BOLD signal in multiple ventral medial cortical regions as well as limbic subcortical areas. The cocaine users demonstrated a similar pattern of activity, but had selective dysregulation in the OFC/MPFC network.

Conclusions: These novel data demonstrate that it is possible to differentially activate known cortical-subcortical networks through an optimized TMS/BOLD sequence over the DLPFC and the OFC/MPFC. Test-retest reliability is high in healthy controls and among cocaine users there is a selective deficit in OFC/MPFC circuit function. These data have important implications for both basic neuroscience research and in patient populations that may have pathology differentially affecting mesolimbic versus mesocortical circuitry.

Keywords: addiction, brain stimulation, prefrontal cortex, striatum, neuroimaging

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W160. The Dopamine D1-D2 Receptor Heteromer Regulates Glycogen Synthase Kinase-3β Activity Independent of Akt in Rodent Prefrontal Cortex: Potential Relevance to Cognitive Function

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Background: The dopamine D1-D2 receptor heteromer is a receptor complex with unique pharmacological and functional properties, and which has been shown to induce brain derived neurotrophic factor (BDNF) expression in striatum upon activation. The D1-D2 heteromer has been recently shown to be expressed in prefrontal cortex (PFC), a region involved in cognitive functioning, but the role of the receptor complex in this region has not yet been elucidated. The phosphorylation status and activation state of glycogen synthase kinase-3β (GSK-3β), a protein kinase that has been implicated in cognitive dysfunction, is regulated by Akt and has been recently shown to be modulated in the PFC in response to mood stabilizers, antidepressants and antipsychotics. The activation of Akt is influenced by BDNF signaling through the tropomyosin receptor kinase B (TrkB). Given the ability of the D1-D2 receptor heteromer to influence BDNF expression, we therefore sought to elucidate a role for the D1-D2 receptor heteromer in the regulation of GSK-3β activation in PFC and begin to assess a potential role for this receptor complex in cognition.

Methods: Rats were administered a single injection of SKF 83959 (1.5 mg/kg s.c.), an atypical dopamine agonist that does not activate the Gs-coupled D1 receptor (D1R) or Gi-coupled D2 receptor, but induces Gq-linked intracellular calcium signaling mediated by the D1-D2 heteromer. The PFC was extracted from each animal 90 minutes following drug injection. Western Blot analysis was used to assess the expression levels of proteins involved in BDNF and Akt signaling and included: BDNF, TrkB (full and truncated isoform), GAD67, Akt, pAktSer473, pAktThr308, GSK-3α/β, pGSK-3α/β, inducible nitric oxide synthase (iNOS). As SKF 83959 also activates the dopamine D5 receptor (D5R), which is abundant in PFC, these experiments were repeated in mice gene-deleted for the D1R or the D5R. To begin to examine a role for the D1-D2

heteromer on cognitive function, we assessed the effect of SKF 83959 (0.4 mg/kg, s.c. daily or 1.5 mg/kg s.c. acute) on spatial memory in an egocentric task and attentional set shifting using the Morris water maze, two behavioral tests relevant to PFC function.
Results: Acute treatment with SKF 83959 in rats enhanced BDNF expression and signaling in PFC through its receptor TrkB. These changes were concomitant with increased expression of the GABA producing enzyme GAD67. Protein analysis in PFC of D1R and D5R gene-deleted mice revealed that these effects were mediated by the D5R, and not the D1-D2 receptor heteromer. SKF 83959 increased total and phosphorylated levels of Akt at the Ser473 site, consequently increasing phosphorylation, and decreasing the activity, of its substrate GSK-3β in rat PFC. These effects on GSK-3β were mediated by both the D1-D2 receptor heteromer and the D5R, albeit by different mechanisms. Activation of the D1-D2 heteromer appeared to mediate the inactivation of GSK-3β by a mechanism independent of Akt whereas D5R-induced GSK-3β phosphorylation was Akt-dependent. iNOS expression was elevated in the PFC of rats in each gene-deleted strain following SKF 83959 indicating that both the D1-D2 heteromer and D5R can regulate iNOS levels. In the Morris water maze, results showed improved spatial learning and memory in rats following SKF 83959 administration, and additionally, improved behavioral flexibility as demonstrated by a heightened ability to acquire a novel strategy during an attentional set shift.
Conclusions: The present findings highlight a novel physiological role for the dopamine D1-D2 receptor heteromer, linking activation of the receptor complex to the phosphorylation and inactivation of GSK-3β in PFC via a mechanism that is independent of BDNF-TrkB signaling and Akt activation. In addition, our studies demonstrated that SKF 83959 could improve cognitive performance in rats by inducing improvements in spatial learning and behavioural flexibility, behaviours dependent upon PFC functioning. Although further studies are required to link SKF 83959-induced improvements in cognitive performance to D1-D2 heteromer-mediated inactivation of GSK-3β, these studies may have important future implications to disorders characterized by cognitive dysfunction.
Keywords: GSK-3β, cognition, prefrontal cortex, dopamine D1-D2 receptor heteromer, D5 receptor
Disclosure: M. Perreault, Nothing to Disclose; J. Jones-Tabah, Nothing to Disclose; B. O'Dowd, Nothing to Disclose; S. George, Nothing to Disclose.

W161. Interleaved TMS/fMRI after rTMS: How to Make the Prefrontal Cortex Sing?

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Background: Transcranial magnetic stimulation (TMS) is both a therapeutic tool for depression and an investigational tool for probing neural circuitry and neurophysiology. Repetitive TMS (rTMS) of human motor cortex has been shown to alter cortical excitability as evidenced by changes in motor evoked potentials (MEPs). Assessing the neurophysiological effects of rTMS on non-motor areas is significantly more difficult because there are limited measurable outputs generated by these "silent" brain regions. Interleaving TMS with functional magnetic resonance imaging (fMRI) is a technique typically used to measure blood oxygenation-level dependent (BOLD) signal responses to discrete TMS pulses. What remains unexplored is how "offline" rTMS changes BOLD signal responses to "online" interleaved TMS/fMRI pulses.
Methods: Fourteen (14) healthy volunteers received 20 minutes of sham left prefrontal rTMS. Immediately following sham stimulation, participants were placed in a 3T MRI scanner for a series of interleaved TMS/fMRI pulses administered at 110% resting motor threshold (rMT). Next, participants were removed from the scanner for 20 minutes of real left prefrontal rTMS (10 Hz, 5 seconds on, 10 seconds off, 110% rMT). Finally, participants were returned to the scanner for another session of interleaved TMS/fMRI pulses. BOLD signal data were analyzed using standard parametric techniques.
Results: After sham rTMS, interleaved TMS/fMRI pulses produced significant BOLD signal increases in limbic and cognitive regions such as insula, cingulate, medial prefrontal cortex and dorsolateral prefrontal cortex. After real rTMS, BOLD signal responses to interleaved TMS/fMRI pulses were similar to baseline levels in ipsilateral regions but significantly augmented in contralateral regions such as insula, medial prefrontal cortex and dorsolateral prefrontal cortex.
Conclusions: Prefrontal rTMS may augment contralateral BOLD signal responses to interleaved prefrontal TMS/fMRI pulses. These data fit with previous neurophysiological studies that show enhanced contralateral MEP amplitude following excitatory 10 Hz motor cortex rTMS. This novel study provides insights into the neurophysiological changes induced by a single 20 minute session of 10 Hz prefrontal rTMS and suggests that BOLD signal evoked by interleaved TMS/fMRI can be used as an MEP proxy to investigate cortical excitability in non-motor areas.
Keywords: rTMS; interleaved TMS/fMRI; cortical excitability; prefrontal cortex; imaging;
Disclosure: J. Taylor, Nothing to Disclose; C. Hanlon, Nothing to Disclose; X. Li, Nothing to Disclose; M. George, Nothing to Disclose.

W162. Cognitive De-biasing Strategies Significantly Improve the Assessment of Pediatric Bipolar Disorder

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Background: Decades of research have demonstrated that relying solely on clinical judgment leaves one prone to a host of cognitive errorsthat compromise optimal decision-making (Garb, 1997; Gigerenzer, 2001; Meehl, 1951). Clinical judgment appears to be particularly vulnerable to faulty heuristics and biases when assessing for pediatric bipolar disorder, as evidenced by alarming rates of diagnostic disagreement and potential overdiagnosis (Moreno et al., 2007; Dubicka & Carlson, 2008). Despite abundant evidence documenting the problems associated with clinical judgment, little research to date has explored the effectiveness of targeted interventions, or cognitive de-biasing strategies, for improving clinical judgment in mental health practice (Croskerry, 2003; Galanter & Patel, 2005). The present project developed an intervention aimed at reducing cognitive-based error in the assessment of pediatric bipolar disorder addressing four cognitive heuristics likely to contribute to error (availability, overconfidence, race/ethnicity bias, and base rate neglect).
Methods: The study design was a randomized controlled trial, assigning participants to either a treatment condition teaching targeted debiasing strategies addressing four heuristics identified as probably contributing to errors evaluating pediatric bipolar disorder, or a control condition ("Diagnosis as Usual") that only received a brief tutorial (25 minutes) about pediatric bipolar disorder (also presented to the treatment group). Participants were mental health professionals ($N = 79$) currently treating pediatric populations. The treatment and control groups responded to four case vignettes. Primary outcome measures were clinicians' diagnoses and treatment decisions.
Results: Diagnosis as Usual overestimated the risk of bipolar disorder in the vignettes; whereas the debiasing treatment group produced significantly more accurate estimates, $F = 10.37$, R-squared $= .22$, $p < .0005$. The debiasing treatment group also made significantly fewer diagnostic errors across the vignettes, $F = 10.86$,

$p < .0005$, R-squared = .23. There was no evidence of race bias in either group, largest chi-squared (1 df) = 2.46, $p = .117$, $w = .18$, corresponding to a small effect.

Conclusions: A brief intervention (<30 minutes) demonstrated significant improvements in accuracy, and a large reduction in a tendency to overestimate the risk of pediatric bipolar disorder, in practicing mental health professionals. The effect sizes of the intervention were large. Interestingly, there was no evidence of race bias in the diagnosis of bipolar disorder across the four vignettes, with the largest observed effect size still in the small range. This contrasts with evidence of racially discrepant rates of clinical diagnoses and treatment selections (Strakowski et al., 1997; DelBello et al., 2001), but may be consistent with findings that there are culturaldifferences in how patients describe the presenting problem that interact with cognitive heuristics to create diagnostic error (Carpenter-Song, 2009). Overall, findings suggest that brief training interventions could have substantial impact on reducing diagnostic disagreement and error in diagnoses such as pediatric bipolar disorder.

Keywords: pediatric bipolar disorder, cognitive debiasing, training, diagnostic accuracy

Disclosure: M. Jenkins, Nothing to Disclose; E. Youngstrom, **Part 1:** Consulted with Lundbeck; travel support from Bristol-Myers Squibb.

W163. Economic Evaluation of Antipsychotic Treatment in Pediatric Disruptive Behavior Disorders: An example from the Metabolic Effects of Antipsychotics in Children (MEAC) Study

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Background: Economic evaluation is the science of rigorously measuring the balance between the cost of an intervention and its benefits.[1] The most common method of economic evaluation, decision analytic modeling, does not provide the same level of evidence as epidemiological studies, but provides investigators and policymakers a tool by which to identify key events or parameters which would influence the decision to adopt the new health program. Antipsychotic use is increasingly common among children[2], especially for treating disruptive and aggressive behavior. Antipsychotic treatment is associated with adverse changes in measures of cardiometabolic risk in this population, but can confer significant clinical benefits. However, there has been no substantive evaluation of the costs and benefits associated with antipsychotic treatment in children with disruptive behavior. Here, a cost-effectiveness analysis from the NIMH-funded Metabolic Effects of Antipsychotics in Children (MEAC, PI Newcomer, MH072912) study is presented, in which we describe the incremental cost-effectiveness of treatment of behavioral disorders in both the monetary cost and weight gained.

Methods: A decision analytic model was constructed based upon data from the MEAC study, consisting of a subset of the population (n = 87) for whom we had data on clinical effectiveness (measured by change in ABC irritability subscale score) and school suspensions during 12 weeks of initial antipsychotic treatment with aripiprazole, risperidone or olanzapine. The efficacy of treatment was considered in terms of clinical benefits; adverse outcomes were considered in terms of becoming obese (BMI percentile $\geqslant$ 95 for age and gender). A Monte Carlo microsimulation model was created, running 1,000 hypothetical patients through 4 cycles of 12-week data from the MEAC study to simulate 1 year of antipsychotic treatment. Primary results from the MEAC study reported no clinically or statistically important differences between treatment groups on clinical response; however there are important differences in adverse outcomes (weight gain) and drug acquisition cost. Therefore we report effectiveness as: 1) School suspension avoided and 2) incidence of obesity. We report the incremental cost-effectiveness ratio (ICER) as pounds per outcome avoided (or gained) and dollar cost.

Results: In our 1 year simulation, aripiprazole was associated with the least amount of weight gain of the three study drugs, with average gain of 15 lbs. Yearly weight gain for risperidone was 17 lbs, and for olanzapine was 58 lbs. In terms of dollar costs, risperidone was the least expensive, costing $120 per year. Yearly cost for aripiprazole and olanzapine were $1,712 and $1,810, respectively. Risperidone had fewer school suspensions per year (0.36) compared to aripiprazole (0.61), with each additional suspension avoided with risperidone costing 9 lbs. Olanzapine had the same number of suspensions as risperidone, but was associated with 161 lbs gained for every suspension prevented compared to aripiprazole. When considering the dollar cost per suspension prevented, risperidone dominated the other two drugs because it had lower dollar costs and fewer suspensions. Incidence of obesity was lowest in the aripiprazole group (0.28) compared to risperidone (0.43) and olanzapine (0.54). The difference in incidence of obesity between aripiprazole and risperidone (0.15) resulted in an ICER of $10,607 per point reduction in the incidence rate for aripiprazole compared to risperidone.

Conclusions: In the MEAC study, risperidone, aripiprazole and olanzapine had similar efficacy for treatment of disruptive behavior across a range of psychiatric diagnoses. To our knowledge, this is the first consideration of weight gain and dollar costs as metrics in evaluation of the cost-effectiveness of these drugs in treatment of children. We found that aripiprazole resulted in the least weight gain in disruptive children, but may be considered costly per case of obesity prevented by some policy makers. Risperidone offers a less expensive option, but may result in greater weight gain over aripiprazole. This approach to analysis provides clinicians and policy makers a systematic method for weighing costs, harms and benefits. However, we caution that users of this approach must recognize the limitations of simulation exercises.

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Keywords: Antipsychotic, obesity, cost effectiveness

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pediatric and adult metabolic monitoring forms, and has recieved honoraria from American Physician Institute, CME Outfitters, CMEology and the American Psychiatric Association., **Part 4:** Dr. Newcomer has recieved research support from NIMH, Bristol-Myers Squibb and Pfizer, Inc.

W164. Preference for Future Gains and Losses in Patients with Major Depression is Modulated by the Presence of Comorbid Posttraumatic Stress Disorder

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Background: Patients with major depressive disorder (MDD) demonstrate reduced sensitivity to reward and altered decision-making compared to healthy control subjects. Intertemporal choice is a ubiquitous form of decision-making about temporally delayed consequences that involve tradeoffs between immediate consumption and planning for a better outcome. Temporal discounting refers to the well-established tendency in animals and humans to place less value on a reward as the time to receipt of that reward moves further into the future. Whether patients with MDD differ from non-depressed controls in valuing immediate and delayed rewards and losses has received little attention to date, despite its potential relevance for real-world choices made by depressed patients. Moreover, it is unknown whether the presence of comorbid posttraumatic stress disorder (PTSD) in MDD patients has unique effects on future-based decision-making.
Methods: A case-control design was used to compare healthy, non-depressed control subjects (N = 15) versus untreatedMDD patients in a current major depressive episode (N = 20). MDD patients were subdivided into those with a comorbid diagnosis of post-traumatic stress disorder (P + MDD, N = 9) and those without (MDD-P, N-11). Severity of depression and anxiety was measured with the Hamilton Depression Rating Scale and Hamilton Anxiety Rating Scale, respectively. Participants completed two computer-based decision-making tasks, the Risky Gains Task and Temporal Discounting Task, with the aim of identifying differences in decision-making styles between MDD and controls, and within MDD subgroups. Quasi-hyperbolic temporal discounting functions were estimated for each patient group separately using nonlinear least squares estimation in combination with a representative agent model (Engelmann et al., 2012).
Results: The sample was well matched with no differences in demographic characteristics between groups. Depression severity was similar between MDD-P and P + MDD subjects, though the P + MDD patients had significantly greater anxiety. Under conditions of potential gain, both MDD patient groups demonstrated greater discounting for short-term (< 1 year) delayed rewards and losses compared to controls. For long-term (> 1 year) delayed rewards, MDD-P patients discounted more steeply than both control and P + MDD groups. Under conditions of potential loss, P + MDD patients demonstrated steeper discounting than both controls and MDD-P patients over all delay periods. The Risky Gains task showed no difference in risk-taking behaviors between control and depressed subjects, indicating that risk attitudes did not contribute to these differences in intertemporal choice.
Conclusions: Compared to healthy subjects, patients with MDD, regardless of comorbid PTSD, place greater value on immediate rewards as opposed to short-term delayed rewards. Compared to both controls and uncomplicated MDD patients, patients with PTSD comorbid with MDD show substantially greater preference to accept larger future losses over a smaller immediate loss. This unique characteristic of depressed PTSD patients may reflect a foreshortened sense of the future frequently present in PTSD patients. These results may inform areas warranting particular focus in psychotherapy treatment, and suggest potential directions for the investigation of neurological differences between these conditions.
Keywords: Major depression; Posttraumatic stress disorder; Neuroeconomics; Intertemporal choice; Discounting
Disclosure: B. Dunlop, **Part 1:** Consulting; BristolMyersSquibb, Medavante, Pfizer, Roche, **Part 2:** None, **Part 3:** None, **Part 4:** AstraZeneca, BristolMyersSquibb, Forest, Glaxo Smith Kline, Novartis, Pfizer, Transcept; B. Maciuba, Nothing to Disclose; J. Engelmann, Nothing to Disclose.

W165. Effect of Meta-chlorophenylpiperazine (mCPP) on Appetite and Satiety and on Emotional Processing and Mood in Healthy Volunteers

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Background: The 5-HT_{2C} receptoragonist meta-chlorophenylpiperazine (mCPP) has been reported to decrease food intake in lean and obese volunteers and to increase psychological and physiological symptoms of anxiety in healthy volunteers and in patients with panic disorder. However, the mechanisms underlying the decreased food intake and the specific emotional processes that mediate the anxiety response are unclear. The Sussex Ingestion Pattern Monitor (SIPM) uses a concealed weighing system and computer software to enable detailed collection and analysis of human eating behaviour and monitors intake volume in parallel with measures of appetite and satiety. The P1vital Oxford Emotional Test Battery (ETB) is a suite of emotion-related experimental paradigms that measure biases in cognitive processing that are thought to be core components of depression and anxiety. In this study, in healthy volunteers, we used the SIPM to investigate the effects of mCPP on eating microstructure and changes in appetite and satiety together with the ETB and questionnaires to investigate the effects of mCPP on emotional processing and mood.
Methods: The study was a between-subjects double blind placebo controlled design in which 24 male and 24 female participants were randomly assigned to placebo, 15 mg or 30 mg mCPP treatment groups (8 males and 8 females per group). Participants ate an ad libitum lunch of pasta and completed a battery of questionnaires (BDI/STAI/PANAS - pre and post drug) and appetite and mood ratings throughout the day, and were tested using the ETB post drug only.
Results: There was no significant effect of drug on amount eaten, number of forkfuls consumed, or eating rate. However, 30 mg mCPP significantly reduced appetite ratings and increased physical symptoms, including nausea, in both males and females. Calculation of meal satiation quotients (SQs: change in hunger ratings, divided by caloric intake) showed that, compared to placebo, females exhibited significantly higher SQs during the first two quartiles of the meal after 30 mg mCPP, and a higher SQ during the second quartile after 15 mg mCPP. Results from the ETB showed that during a surprise free recall task (of previously presented emotional words) participants were able to correctly recall a greater number of words after 15 mg and 30 mg mCPP compared to placebo. When shown previously presented emotional words (valid), and unseen distracter words (invalid) in an emotional recognition memory task, participants given 30 mg mCPP exhibited higher target sensitivity to valid words compared to placebo.
Conclusions: These data suggest that mCPP reduces appetite, and in females, enhances satiation with an earlier onset at the higher drug dose. The results are consistent with the hypothesis that activation of 5-HT_{2C} receptors enhances satiation and indicate that the SQ provides a powerful new approach to measure drug effects on satiation. mCPP enhanced memory for emotional words and this pattern of results differs from the effects of depression which

is characterised by impaired memory for positive stimuli. The effect of mCPP in this study is also distinct from the enhanced vigilance to threatening facial expressions that is associated with anxiety. The absence of anxiogenic-like effects in the present study may be accounted for by the use of low doses and oral administration as most previous reports of anxiogenic responses have used intravenous bolus infusion. The effects of mCPP contrast with the effects of tryptophan depletion which causes memory impairment and suggest that the effect of mCPP is serotonin mediated. Therefore, we conclude that the effects of 15 mg and 30 mg of mCPP on recognition and recall of emotional words is consistent with a serotonergic enhancement of memory.
Keywords: meta-chlorophenylpiperazine (mCPP), appetite, food intake, mood, memory, volunteers
Disclosure: C. Dourish, **Part 1:** P1vital Limited, **Part 2:** P1vital Limited, **Part 3:** P1vital Limited; J. Thomas, **Part 1:** P1vital Limited, **Part 4:** P1vital Limited.

W166. Current Treatment of Obsessive Compulsive Disorder (OCD): A Cross-sectional Analysis of OCD Treatment in 9 International Outpatient Settings

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Background: Obsessive Compulsive Disorder (OCD) has a lifetime prevalence of 0.8-2.0% and a one-year prevalence of 0.7-2.4% in the United States. OCD has a significant impact on the quality of life (QOL) of afflicted individuals, affecting social behaviour, family relationships, and the ability to study and work. First line pharmacological treatments for OCD are serotonin reuptake inhibitors (SRIs), with effect sizes ranging from 0.45 to 3.87. However, upwards of 40% to 60% of people with OCD treated with SRIs do not respond or only obtain a partial response. In cases of treatment resistance, OCD treatment guidelines, suggest continuing with the SRI for an extended period of time, raising the dose to the highest tolerated level, switching to another first-line treatment agent, or augmenting the SRI with an agent from a different drug class. Augmentation with antipsychotic medications has shown some benefit in treatment refractory OCD, however it is unknown what strategies is being used in clinical practice. The International College of Obsessive Compulsive Spectrum Disorders (ICOCS) is an organization which aims to advance, promote and facilitate research into the causes and consequences of OCD and OCD spectrum disorders. Members of ICOCS from 9 tertiary care centres around the world, including Mexico, Spain, Italy, Israel, Bulgaria, Canada, Turkey, South Africa and the United Kingdom participated in a cross-sectional study of OCD to obtain a "snap shot" view of the current status of pharmacological treatment of OCD around the globe.
Methods: Consecutive OCD patients at various stages of treatment in 9 international outpatient centres were evaluated. Participants were assessed in comprehensive clinical and structured interviews using an expanded version of the Structured Interview for DSM-IV (SCID) for OCD spectrum disorders. Participants were asked about their current treatment regimen, as well as a history all past treatments for OCD. In addition, clinicians evaluated study participants using the Dimensional Yale Brown Obsessive Compulsive Scale (D-YBOCS), the Yale Brown Obsessive Compulsive Scale (YBOCS), and the Montgomery Asberg Depression Rating Scale (MADRS). Response was evaluated by Clinical Global Impression – Improvement Scale Score $\leqslant$ 2 and/or by a YBOCS score $\leqslant$ 15. Patients completed a variety of self-report symptom severity measures. Participants were asked to identify which treatment agent was their primary or index OCD treatment and which were augmentation agents. Augmentation was defined as having an index OCD treatment agent as well as at least one additional agent. If more than one augmentation agent was being used, each drug was identified sequentially. All data was entered into an electronic database.
Results: Five hundred and three consecutive participants were entered into the database. Of these, 361 participants reported treatment information: n = 317 reported current use of at least one OCD medication, n = 44 were not currently taking medication for their OCD. No differences were found between those taking medication (N = 317) versus those who were not (N = 44) in terms of symptom severity (YBOCS, CGI-S), depressive symptoms (MADRS) or functional impairment (SDS). Most of the sample on medication was taking an SSRI (77.6%) as their primary OCD treatment. Current monotherapy was reported by 160 participants (44%), primarily with SSRIs (85%) or other antidepressants (13.5%). No significant differences were found in rates of response (CGI-I) or mean YBOCS scores between specific monotherapeutic agents. Current use of at least one augmentation agent was reported by 157 participants (49.5%), with 59% taking one augmentation agent; 29% taking 2 augmentation agents; 12% taking with 3 to 5 different augmentation agents. Antipsychotics (both typical and atypical) were the most frequently reported augmentation agents (33.8%) followed by antidepressants (28.6%) and benzodiazepines (18.5%). No significant differences were found in rates of response (CGI-I) or mean YBOCS scores between augmentation agent classes, with the exception of mood stabilizers: those augmented with mood stabilizers had significantly higher YBOCS scores (more severe) than those augmented with other agents. No significant differences were found in treatment response (as measured by YBOCS and CGI-I) when we compared monotherapy to 1 augmentation trial; 1 augmentation trials to two; and two trials to 3 or more. Using YBOCS $\leqslant$ 15 as the measure of response, those treated with a combination of SSRI plus a tricyclic antidepressant ($>$ 87% clomipramine) were more likely to be responders than those treated with an SSRI plus an antipsychotic ($p = .04$). No significant differences were found in rates of response between monotherapy or augmentation treatment strategies. Further analyses revealed that age of onset was significantly correlated with CGI-I scores: $r = -0.16$, $P = 0.05$, indicating that a earlier age of onset was associated with higher CGI-I scores (increased severity). Using YBOCS $\leqslant$ 15,, responders to either monotherapy or augmentation were significantly more likely than non-responders to be in remission for depression (MADRS $<$ 10) ($p < .05$).
Conclusions: No significant differences in OCD treatment response were found between monotherapy and augmentation or between different therapeutic agents. These results suggest that augmentation strategies impart little therapeutic benefit in those who do not respond to first-line treatments for OCD.
Keywords: Obsessive Compulsive Disorder, pharmcotherapy, treatment resistance, cross-sectional
Disclosure: M. Van Ameringen, **Part 1:** Speakers' Bureau: Valiant, Glaxo Smith Kline, Lundbeck, Pfizer Inc, Advisory Boards: Valiant, Eli Lilly, Janssen-Ortho Inc., Labo Pharm, Lundbeck, Pfizer Inc., Shire, **Part 4:** Janssen-Ortho Inc., NIH (National Institutes of Health), Pfizer Inc, ; W. Simpson, Nothing to Disclose; B. Patterson, Nothing to Disclose.

W167. Impact of Treatment Approach on Maternal and Neonatal Outcome in Pregnant Opioid-maintained Women

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Background: The objective of this study is to compare maternal and neonatal outcome of opioid-dependent women maintained on buprenorphine or methadone throughout pregnancy in a randomized double-blind double-dummy clinical trial (CT) with a

comparison group undergoing a structured standard protocol (SP) at the Medical University of Vienna, Austria.
Methods: One hundred and fourteen subjects were included in the analysis, with 77 in SP (n = 51 methadone, n = 26 buprenorphine), and 37 in CT (n = 19 methadone, n = 18 buprenorphine), comparing maternal concomitant consumption during third trimester, demographic birth data, duration of treatment for neonatal abstinence syndrome (NAS), morphine dose for NAS treatment and length of hospital stay (LOS).
Results: Both study groups yielded healthy neonates with no significant demographic differences and equivalently low rates of positive maternal urine toxicologies. However, NAS parameters were significantly better in CT regarding total medication dose administered to neonates ($p = 0.014$) and LOS ($p = 0.015$). Superior results were achieved in buprenorphine compared with methadone-exposed neonates regarding gestational age at birth ($p = 0.003$), birth weight ($p = 0.011$), total morphine dose administered ($p = 0.008$), NAS treatment duration ($p = 0.008$) and LOS ($p = 0.001$).
Conclusions: Comparably favorable outcome for mothers and infants and efficacy and safety of opioid medications were shown in both treatment approaches. Neonatal care could benefit from transferring successful CT procedures into clinical practice.
Keywords: addiction, treatment, maternal and neonatal outcome, pregnant opioid-maintained women
Disclosure: V. Metz, Nothing to Disclose; R. Jagsch, Nothing to Disclose; N. Ebner, Nothing to Disclose; J. Würzl, Nothing to Disclose; A. Pribasnig, Nothing to Disclose; C. Aschauer, Nothing to Disclose; G. Fischer, **Part 1:** Travel support & honorarium für presentations: Pfitzer, Reckitt Benckiser, Lumbeck.

W168. Discontinuations Following a Switch from Risperidone, Olanzapine, or Aripiprazole to Iloperidone in Patients with Schizophrenia: The i-FANS Study

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Background: Patients with schizophrenia often switch treatments due to efficacy and/or tolerability issues. In the **i**loperidone **F**lexible-dose Study **A**ssessing Efficacy and Safety and Tolerability of Two Switch Approaches i**N** **S**chizophrenia Patients (i-FANS) study, adults with schizophrenia exhibiting suboptimal efficacy and/or safety/tolerability were switched either immediately or gradually from their current antipsychotic treatment of risperidone, olanzapine, or aripiprazole to iloperidone 12–24 mg/d. The effects of both switch approach and pre-switch treatment on subsequent discontinuation rates are discussed.
Methods: Subjects in this 12-week, randomized, multicenter, open-label study were adult (18–64 years of age) outpatients with a DSM-IV-TR diagnosis of schizophrenia who were maintained on risperidone, olanzapine, or aripiprazole and were experiencing suboptimal efficacy and/or 1 or more predefined tolerability problems. Patients in each of these 3 cohorts were randomized 1:1 to switch immediately to iloperidone or to gradually taper their prior antipsychotic dose (to 50% on Day 1, 25% at Week 1, and 0% at Week 2) over the first 2 weeks of iloperidone use. For all patients, iloperidone was titrated to a target dose of 6 mg twice daily (bid) by Day 4, followed by increases (no more than 4 mg/d) up to 12 mg bid, based on investigator judgment. The number and percentage of patients who prematurely discontinued from the study treatment were summarized with reasons for premature discontinuation.
Results: Of the 500 randomized subjects (260 immediate switch and 240 gradual switch), 154 discontinued the study (82/260 [31.5%] in the immediate-switch and 72/240 [30.0%] in the gradual- switch groups). In the 3 cohorts combined, the most common reasons for discontinuation in the immediate- and gradual-switch groups were adverse events (AEs; 15.0% and 10.4%, respectively), lost to follow-up (6.5% and 6.3%), and patient withdrew consent (4.2% and 5.8%). Consistent with this combined analysis, discontinuation rates due to AEs for each cohort were higher for patients who underwent an immediate, rather than a gradual, switch (risperidone: 12.8% vs. 7.4%; olanzapine: 14.5% vs. 11.4%; aripiprazole: 17.8% vs. 12.5%, respectively). This difference in AE-related discontinuations between switch groups across the 12-week study is likely explained by discontinuations due to 'dizziness' (related to noradrenergic alpha-1 antagonism), as reported in both immediate- and gradual-switch groups: for the 3 cohorts combined (4.2% and 1.7% of the switch group, respectively), for risperidone (4.3% and 1.2%), olanzapine (2.6% and 3.8%), and aripiprazole (5.6% and 0%). Further, these reports of dizziness leading to discontinuation occurred predominantly during the first 2 weeks of treatment. For each switch group, the rate of discontinuation due to dizziness at Week 1 and Week 2, respectively, was: 3 cohorts combined: 2.7% and 0.8% (immediate) and 0.4% and 0% (gradual); risperidone: 1.1% and 2.2% (immediate) and 0.0% and 0.0% (gradual); olanzapine: 1.3% and 0% for both immediate and gradual switch; and aripiprazole: 5.6% and 0% (immediate) and 0% and 0% (gradual). As dizziness was the most frequently reported AE, a similar transient trend is observed when assessing the overall rates of dizziness. Rates of dizziness over the 12-week study were higher for patients who underwent an immediate, rather than a gradual, switch for the 3 cohorts combined (22.3% and 17.5%, respectively), as well as for each individual cohort (risperidone: 19.1% and 14.8%; olanzapine: 25.0% and 20.3%; aripiprazole: 23.3% and 17.5%, respectively). The difference in dizziness rates between switch groups was most pronounced during the first week of therapy and rates decreased from Week 1 to Week 2, respectively, for both immediate-switch and gradual-switch groups: 3 cohorts combined, 13.8% to 2.8% (immediate) and 8.3% to 1.3% (gradual); risperidone, 11.7% to 3.3% and 4.9% to 0%; olanzapine, 13.2% to 2.7% and 10.1% to 2.6%; aripiprazole, 16.7% to 2.4% and 10.0% to 1.3%, respectively.
Conclusions: In this 12-week study, AEs leading to discontinuation of iloperidone (10% to 15% of patients) were frequently captured as 'dizziness', occurred at a slightly higher rate in the immediate-switch group, and were confined to the first 1–2 weeks of initial treatment. These findings are aligned with the overall AE reports of dizziness that demonstrated predominance within the first week followed by a sharp decline at Week 2, and which are not meaningfully accounted for by those patients who had already discontinued due to dizziness after Week 1. The incidence of dizziness and resultant discontinuations in the gradual-switch group may have been lower than in the immediate-switch group due to alpha-1 receptor habituation from the pre-switch agent. Thus, both switch approaches are appropriate when switching to iloperidone from risperidone, olanzapine, or aripiprazole, although a gradual-switch approach may confer a slight advantage related to tolerability and adherence by minimizing the potential for exposure-related transient dizziness.
Keywords: schizophrenia, iloperidone, risperidone, olanzapine, aripiprazole, tolerability, efficacy
Disclosure: L. Citrome, **Part 1:** In the past 24 months I have engaged in collaborative research with, or received consulting or speaking fees, from: Alexza, Alkermes, AstraZeneca, Avanir, Bristol-Myers Squibb, Eli Lilly, Forest, Genentech, Janssen, Lundbeck, Merck, Novartis, Noven, Otsuka, Pfizer, Shire, Sunovion and Valeant; F. Kianifard, **Part 1:** Employee of Novartis Pharmaceuticals Corporation; X. Meng, **Part 1:** Employee of Novartis Pharmaceuticals Corporation ; A. Winseck, **Part 1:** Employee of Novartis Pharmaceuticals Corporation ; M. Hochfeld, **Part 1:** Employee of Pharmaceuticals Corporation ; S. Stahl, **Part 1:** Advent, Alkermes, Arbor Scientia, Arena, Astra Zeneca, Avanir,

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W169. The Reinforcing and Subjective Effects of Intravenous and Intranasal Buprenorphine in Heroin Users

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Background: Buprenorphine (BUP) initially was believed to have low abuse liability based on its partial agonist activity at μ opioid receptors. However, several clinical studies have revealed that when administered intravenously (IV) and intranasally (IN), the abuse liability of BUP is comparable to full μ opioid agonists. Consistent with these laboratory data, epidemiological studies from around the world have reported abuse and diversion of BUP for intravenous use. Increasingly, reports of BUP abuse by the intranasal route are emerging. However, relatively little is known about the pharmacodynamic effects of IN BUP, and no studies have directly compared the effects of BUP when it is administered by the IV and IN routes.
Methods: This investigation used unpublished data from two separate inpatient, double-blind, placebo-controlled studies to compare the reinforcing and subjective effects of IV and IN buprenorphine. During the first week after admission, participants were stabilized on 2 mg sublingual (SL) BUP. During the second week, while still being maintained on SL BUP, each participant was tested with each intranasal or intravenous buprenorphine test dose (0 mg, 2 mg, 4 mg, 8 mg, and 16 mg; one dose per day) in random order. During laboratory sessions, participants received sample doses of IN or IV BUP and money (US $20) and completed subjective effects questionnaires. Later that day, they completed a self-administration task to receive portions of the dose of drug or money they had sampled earlier in the day (0 to 100% in increments of 10%).
Results: Data from 25 participants were used in this analysis (13 IV, 12 IN). In general, positive subjective ratings such as drug "liking" and "I feel high" for both IV and IN BUP were significantly greater than placebo and the subjective effects of IV BUP were greater than IN BUP. However, ratings of "I feel a bad effect" were greater for IN compared to IV BUP. Specifically, participants frequently reported a burning sensation in the nose after IN BUP administration. Consistent with the positive subjective responses, all active BUP doses (IV and IN) maintained significantly higher progressive ratio break point values than placebo, and break point values for IV BUP were generally greater than for IN BUP. For both IV and IN BUP, the slopes of the dose-response curves were relatively flat.
Conclusions: Not surprisingly, the effects of IV BUP were more robust than IN BUP, and consistent with its partial agonist profile, the slopes of the dose-response curves were shallow. Adverse aspects of intranasal BUP administration may have blunted its positive subjective, as well as its reinforcing effects. Buprenorphine is an effective maintenance treatment for opioid dependence, particularly valued for its ability to reduce the positive subjective effects of other opioids and deter their abuse. However, the present data demonstrate that in participants maintained on a low dose of SL BUP, the medication itself has abuse liability when used by the IV and IN routes.
Keywords: Intranasal, Intravenous, Self administration, Buprenorphine, Abuse Liability
Disclosure: J. Jones, **Part 1:** I have previously received compensation (in the form of partial salary support) from investigator-initiated studies supported by Reckitt-Benckiser Pharmaceuticals; S. Comer, **Part 1:** I have received compensation (in the form of partial salary support) from investigator-initiated studies supported by Reckitt-Benckiser Pharmaceuticals, Schering-Plough Corporation, Johnson & Johnson Pharmaceutical Research & Development, Endo Pharmaceuticals, and MediciNova. In addition, I have served as a consultant to the following companies: Abbott, Alpharma, Analgesic Research, BioDelivery Sciences, Cephalon, Inflexxion, King, Neuromed, Purdue, and Shire, **Part 4:** Grants from Reckitt-Benckiser Pharmaceuticals, OMEROS, Johnson & Johnson Pharmaceutical Research & Development, Endo Pharmaceuticals and the Schering-Plough Corporation.

W170. MDMA Buffers Against Cues of Social Rejection

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Background: MDMA (±3,4-methylenedioxymethamphetamine, ecstasy) is used recreationally to increase feelings of empathy, sociability and interpersonal closeness, and has been used as an adjunct to psychotherapy for PTSD. However, it is unclear exactly how MDMA alters social cognitive processes to produce these "prosocial" effects. We previously reported that MDMA reduced identification of cues of social rejection, such as negative facial expressions. Here, we examine this possibility in greater depth by measuring effects of MDMA on both identification of and responses to emotional facial expressions and also on responses to "Cyberball", a simulated social acceptance and rejection task.
Methods: MDMA users (N = 20) participated in a three-session, within-participant, double-blind study in which they received oral MDMA 0.75 mg/kg, 1.5 mg/kg or placebo. At each session they identified dynamically developing emotional expressions of anger, fear, sadness and happiness while we measured their responses to these expressions in facial muscles sensitive to emotional state. Participants also played two virtual games of "catch", called "Cyberball", in which they were exposed to acceptance (>70% of tosses thrown to participant) and rejection (<30% of tosses thrown to participant) conditions. After each game we measured self-reports of self-esteem and mood. Typical subjective effects of MDMA were also assessed throughout the sessions.
Results: MDMA produced typical increases in self-reports of "prosocial" subjective feelings such as playful, loving, and friendly. MDMA slowed identification of angry facial expressions, suggesting blunted perception of negative social cues, but did not affect identification of other emotions. MDMA did not significantly alter facial emotional responses to correctly identified expressions of any type. MDMA buffered against reductions in self-esteem and positive mood after simulated social rejection, without affecting responses to social acceptance.
Conclusions: MDMA reduced the ability to identify cues of social rejection, i.e. angry facial expressions, and reduced the self-esteem and emotional effects of simulated social rejection without altering perception of positive emotions, or the effects of social acceptance. Thus, one way that MDMA increases feelings of interpersonal closeness or trust may be by blunting sensitivity to cues of social rejection. Further, our data suggest MDMA may particularly affect the perception or identification stage of processing, rather than responses to cues once they have been properly identified. Although our participants were all healthy normal adults, our

results suggest individuals highly sensitive to negative social cues at baseline (e.g. social phobics) might be particularly at risk for recreational use and abuse of this drug. Further, these effects suggest MDMA might be valuable as an adjunct to psychotherapy with social phobia. Future studies should examine the effect of MDMA on responses to cues of social rejection in individuals with social phobia.
Keywords: MDMA, ecstasy, emotional expression, social rejection, psychophysiology
Disclosure: M. Wardle, Nothing to Disclose; C. Frye, Nothing to Disclose; H. de Wit, **Part 1: Part 4:** One grant from Unilever for work not related to the current project.

W171. Neuroprotective Effects of Long-term Lithium Treatment on Amyloid Deposition in Older Adults with Bipolar Disorder

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Background: Lithium treatment has been associated with neurogenesis in the hippocampus, up-regulation of important neurotrophic factors such as B-cell lymphoma 2 (Bcl-2) and brain-derived neurotrophic factor (BDNF), and inhibition of glycogen synthase kinase 3 (GSK-3), a critical regulator of amyloid precursor protein involved in the development of neuritic plaques and neurofibrillary tangles associated with Alzheimer's disease (Schloesser 2012). Various lines of evidence point to the beneficial effects of this ion on brain health, including molecular and cellular data, mouse and human experiments, and epidemiological data (Young 2011). Investigators have also considered using lithium for neurodegenerative illnesses, such as Alzheimer's disease (Tariot 2009). To date there has been no examination of the relationship between long-term lithium exposure and levels of beta amyloid in patients with bipolar disorder (BD). The purpose of this pilot study was to examine whether long-term treatment with lithium ($>$ 10 years) is related to lower detected levels of fibrillar parenchymal amyloid beta as measured with Pittsburgh Compound-B (PiB) in older, non-demented adults with BD.
Methods: Seven older adult, non-demented subjects with BD were recruited for this study. These individuals have participated in a longitudinal (parent) study of cognitive function in older adults with BD. All subjects received structural MR brain scans as part of the parent study and subsequently agreed to participate in additional imaging at the University of Pittsburgh (UP) Positron Emission Tomography (PET) center to examine the relationship between long-term lithium treatment and amyloid deposition. All subjects provided written informed consent for study participation. [C-11]PIB PET imaging (HR + scanner, 10-15 mCi, 50-70 min post-injection scan) was performed for subjects who also underwent MR imaging for region (ROI) definition and CSF dilution correction of the PET data. After co-registration of the MR and PET image data, ROIs were defined on the MR images and transferred to the PET data for sampling over single and multiple image planes. ROIs included anterior cingulate cortex (ACG), antero-ventral striatum (AVS), frontal cortex (FRC), lateral temporal cortex (LTC), parietal cortex (PAR), and precuneus (PRC). A global (GBL6) mean was computed based on these ROIs. Additional ROIs were generated in subcortical white matter (SWM) to assess nonspecific PiB uptake and in cerebellum to estimate non-displaceable PiB uptake (reference region). The bilateral ROIs defined in both the right and left hemispheres were combined (averaged) to minimize the impact of noise and motion on the outcome measures. Positive PiB retention status (i.e., PiB +) was determined by applying PiB + retention thresholds that were established from a legacy UP PiB dataset by statistical clustering methods. The standardized uptake value (SUV) was determined for each ROI as the summed average PiB uptake over the 50-70 min post-injection period and each SUV was scaled by the individual's injected dose and body mass. The regional SUV measures were normalized to the cerebellar reference region SUV to generate SUV tissue ratio (SUVR) measures of PiB retention.
Results: Subjects were mean (SD) age of 66.5 (12.4) years. Four men, 3 women; Six of the 7 had BD I, 1 subject had BD II. Mean (SD) lithium treatment was 28 (9.5) years (min = 15, max = 43). Among the 7 subjects, the cerebellar SUV mean (SD) was 0.61 (0.10). SUVR mean (SD) among the ROIs: ACG, 1.45 (0.23); AVS, 1.24 (0.14); FRC, 1.50 (0.23); LTC, 1.39 (0.17); PAR, 1.39 (0.22); PRC, 1.49 (0.39). GBL6 was 1.41 (0.22). One subject was PiB + across all ROIs, another subjects was PiB + in one region (LTC); the remaining 5 subjects were PiB-.
Conclusions: This project is ongoing and will recruit a total of 10 older adults with BD on long-term lithium and 10 with minimal exposures to lithium. Results will be compared with mentally healthy comparators who have had PET-PiB imaging from other studies conducted at the PET Center. Results from the first 7 subjects reveal PiB binding consistent with studies in elderly control subjects (Rowe 2010). A limitation of this project is that lithium may have no effect on amyloid deposition, but could prevent amyloid-induced tau phosphorylation and neurofibrillary tangle formation. Thus, it is possible that individuals on long-term lithium are PiB + , yet have had a protective benefit of long-term lithium treatment.
Keywords: Bipolar Disorder, Amyloid, Lithium, Pittsburgh Compound B
Disclosure: A. Gildengers, Nothing to Disclose; J. Price, Nothing to Disclose; B. Meryl, Nothing to Disclose; J. Becker, Nothing to Disclose; T. Ibrahim, **Part 2:** Consulting for the University of Oklahoma, **Part 4:** Grants from Siemans; W. Klunk, **Part 1:** GE Healthcare, Neuroptix, Inc, **Part 2:** GE Healthcare, **Part 3:** GE Healthcare; C. Reynolds, **Part 4:** Pharmaceutical supplies for NIH sponsored work from BMS and Pfizer.

W172. Differences in the Magnitude of BOLD Response to Implicit Emotional Faces Predict Antidepressant Response to Scopolamine in Major Depressive Disorder

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Background: Pharmacological-fMRI studies have shown that activity in anterior cingulate cortex (ACC) predicts treatment response to ketamine (1) and that activity in middle occipital cortex predicts response to scopolamine (2) in patients with major depressive disorder (MDD). The cholinergic neurotransmitter system innervates the entire cerebral cortex (3), including ACC and visual cortex, and is involved in processing emotional information (4). Behavioral and functional evidence for emotional processing biases are evident in MDD, suggesting that emotional information in MDD is processed differently within the emotional circuitry of the brain (5). Here, we correlate antidepressant response to scopolamine with baseline differences in response magnitude to emotional faces during implicit and explicit processing.
Methods: Currently depressed MDD patients (n = 13;males = 2) participated in a fMRI attention study. Subsequently, patients participated in a double-blind, placebo-controlled crossover study that included a series of 3 i.v. infusions of scopolamine (4 ug/kg) and a series of 3 i.v. infusions of a placebo solution. Depression severity was assessed at baseline and at study end using the Montgomery-Asberg Depression Rating Scale (MADRS). BOLD signal was measures during the attention task, where two images of superimposed faces (happy or sad) and houses were presented. Participants attended to the face (AF) or house (AH) components

of the stimuli and performed a matching task; emotion was task-irrelevant. Multiple regression estimated BOLD response during AF and AH when expressions were sad (AFs, AHs) and happy (AFh, AHh). The difference in BOLD signal during explicit (AFh-AFs) and implicit (AHh-AHs) face processing was correlated with treatment response (percent change from baseline to study end) using the MADRS (voxel $p<0.01$; whole brain correction (WBC) $p<0.05$).

Results: Significant correlations were observed in ACC and in visual processing areas during implicit emotional processing. The difference in BOLD signal (AHh-AHs) correlated positively with treatment outcome in the ACC ($r=+0.81$, WBC $p<0.05$) and correlated negatively with treatment outcome in middle occipital cortex ($r=-0.76$, WBC $p<0.05$). No correlation occurred for BOLD differences during explicit processing of emotional faces.

Conclusions: Baseline differences in neural response magnitude to implicitly processed happy and sad emotional faces predict treatment response to scopolamine in patients with major depressive disorder. Patients who show the largest treatment response had larger baseline responses to implicitly processed happy emotional faces than to sad faces in the ACC and larger responses to implicitly processed sad than happy faces in visual processing areas. Poorer treatment responders showed the opposite pattern of BOLD response to happy vs sad faces. Importantly, these effects are specific to implicit processing of emotional faces, and thus are associated with automatic processing of unattended emotional stimuli. These findings indicate that the magnitude and direction of differential response to unattended emotional faces at baseline reflect the potential to respond to scopolamine, and suggest that relative differences in response magnitude to emotional stimuli at baseline in ACC and in visual processing areas may provide a biomarker of treatment response to the antimuscarinic agent, scopolamine.

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Keywords: biomarkers, mood disorders, scopolamine, emotional processing bias

Disclosure: M. Furey, **Part 1:** Dr. Furey is listed as a co-inventor on a patent application for the use of scopolamine and its metabolites in major depression. Dr. Frey has assigned his rights in the patent to the U.S. government but will share a percentage of any royalties that may be received by the government; W. Drevets, **Part 1:** Dr. Drevets is listed as a co-inventor on a patent application for the use of scopolamine and its metabolites in major depression. Dr. Drevets has assigned his rights in the patent to the U.S. government but will share a percentage of any royalties that may be received by the government., Myriad/ Rules Based Medicine, Inc., Johnson & Johnson, Inc., Esai Inc., **Part 2:** Johnson & Johnson, Inc., Esai Inc.; A. Khanna, Nothing to Disclose; C. Zarate, **Part 1:** Dr. Zarate is listed as a co-inventor on a patent application for the use of ketamine and its metabolites in major depression. Dr. Zarate has assigned his rights in the patent to the U.S. government but will share a percentage of any royalties that may be received by the government.

W173. ALKS 5461, a Novel Opioid Receptor Modulator, Normalizes Human EEG Responses in an Auditory Oddball Task after Cocaine Administration as Indicated by a Brain Network Activation Analysis

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Background: Cocaine abuse represents a major public health problem and a clear unmet medical need. Presently there are no FDA approved medications to treat cocaine abuse/dependence. Recent clinical studies have demonstrated a significant reduction in cocaine-positive urine samples in patients receiving buprenorphine (BUP), a partial opioid agonist, in combination with naltrexone, an opioid antagonist, compared to controls. It is hypothesized that pharmacologic activity at μ and/or κopioid receptors may be beneficial in the treatment of cocaine abuse. However, co-formulation of BUP and naltrexone is impractical due to pharmacokinetic, pharmacodynamic and physiochemical limitations. ALKS 5461 is a combination therapy of ALKS 33, a novel opioid receptor antagonist, and buprenorphine (BUP) co-formulated for sublingual administration. In a previous clinical study, a 1:1 dose ratio of ALKS 33:BUP blocked μ-opioid agonism of BUP as demonstrated by pupilometry and subjective responses. The primary objective of this DDI study was to determine the safety, tolerability and pharmacokinetics of ALKS 5461 and ALKS 33 during concurrent cocaine administration, as well as pharmacodynamic measures of subjective responses to cocaine. The purpose of this secondary analysis was to evaluate electrophysiological responses by employing an auditory oddball task in subjects receiving cocaine. A recently developed BNA (Brain Network Activation) analysis was used to assess changes compared to subjects receiving placebo.

Methods: A single-center, randomized, double-blind, placebo-controlled, multiple dose, parallel group study was conducted in 33 opioid-experienced non-treatment seeking cocaine users over a 14 Day (D) in-patient period. Subjects that tolerated baseline cocaine infusions (20 mg, D1; 40 mg D2) were randomized to ALKS 33 (8 mg), ALKS 5461 (8 mg ALKS 33 + 8 mg BUP, co-formulated), or PBO. Study drug was administered sublingually on D3-12 (AM); concurrent cocaine infusions (2 min) occurred at steady state of study drug on D11 (20 mg, IV) and D12 (40 mg, IV). EEG was recorded at 4 time-points for 24 subjects during the study as follows: At baseline (D0), preceding treatment; on screening (D2), when subjects received cocaine infusions (40 mg, IV); on D10, when subjects received study drug alone; and on D12 when subjects received both study drug and cocaine (40 mg, IV). Pharmacodynamic endpoints following cocaine infusion included Brief Substance Craving Scale (BSCS) and Visual Analog Scale (VAS) assessments. BNA, a newly developed event-related-potential (ERP)-based analysis, was employed to examine the changes in electrophysiological responses between D0 and D10 and between D2 and D12. The BNA intra-subject score was used to compare single subject network brain activity between two visits, and BNA measures were used to quantify the disparity or the similarity of the ERPs (BNA Wave analyses) between visits.

Results: 24 subjects completed all study assessments (ALKS 5461, $n=9$; ALKS 33, $n=6$; PBO, $n=9$). BNA qualitative analysis was performed on pooled ALKS 5461 and the ALKS 33 data sets ($n=15$) to provide sufficient statistical power. There was a larger change of the intra-subject and BNA Wave analysis scores from baseline to treatment (D0 vs. D10) in subjects given ALKS 5461 compared to both placebo and ALKS 33 alone. When co-administered with cocaine, there was still a larger change in subjects (D2 vs. D12) that received ALKS 5461 compared to subjects receiving ALKS 33 alone. There was also a high correlation between BNA measures and clinical craving assessments. In addition, using qualitative BNA analysis, treatment (ALKS 5461/ALKS 33) facilitated normalization in the response to a novel stimulus as was evident in the comparison between D0 and D10. Specifically, theta and delta responses were enhanced only for a novel stimulus but the response to target and frequent stimuli remained relatively similar between D0 and D10. In addition, *only* in the novel stimulus network, alpha activation observed at baseline (D0) was completely eliminated on D10.

Conclusions: Study results indicate that ALKS 5461 had a greater effect on BNA than ALKS 33 alone, both in the absence and in the presence of cocaine. These changes suggest a potential unique

therapeutic role for ALKS 5461 for the treatment of cocaine abuse/dependence. The normalization associated with the response to a novel stimulus is possibly related to the sensitivity of this response to abstinence-like effects, described in previous studies. Study design limitations may have limited the ability to detect qualitative BNA differences on cocaine infusion days. Finally, these data suggest that BNA analysis is a sensitive cost-effective method that allows for investigation of cocaine-dependence related drug effects on brain network activity in early stages of drug development.
Keywords: Cocaine, EEG, treatment, opioid
Disclosure: E. Sellers, **Part 1:** Dr. Ed Sellers is a Principal in DL Global Partners, a consulting firm that provides consultation to pharmaceutical and device companies. Alkermes Inc. has been a client of DL Global Partners.; R. Turncliff, **Part 1:** Employee of Alkermes, Inc.; A. Reches, Nothing to Disclose; D. Dickman, Nothing to Disclose; I. Laufer, Nothing to Disclose; K. Ziv, Nothing to Disclose; Y. Stern, Nothing to Disclose; Z. Halabi, Nothing to Disclose; B. Vince, **Part 1:** Consultant to Alkermes, Inc.

W174. Pharmacokinetic Modeling of ALKS 9070 (ALKS 9072), a Novel Once-monthly Prodrug of Aripiprazole

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Background: ALKS 9070 (ALKS 9072) is a linker lipid ester prodrug of aripiprazole (ARP) for extended-release intramuscular (IM) injection. A water-insoluble lauroyl prodrug approach was selected to chemically "mask" ARP following injection, minimizing the potential for injection site reactions and optimizing the ARP release profile for once-monthly dosing. The purpose of this study was to develop a multi-compartmental model capable of describing the pharmacokinetic (PK) profile of single dosing ALKS 9072 utilizing data obtained in a single dose PK, safety and tolerability study of ALKS 9072 following IM administration at 3 dose levels in patients with schizophrenia. The model was subsequently utilized to simulate dose levels and dosing paradigms of oral aripiprazole and ALKS 9072.
Methods: A randomized, double-blind, placebo-controlled, escalating single-dose study conducted at two sites in the US. Subjects (40; 28M/12F) with chronic, stable schizophrenia participated in the clinical study: mean age was 43 years old (range 21-55); 100% of subjects were Black. Subjects received oral (PO) ARP (Abilify 10 mg) daily for 5 days to assess tolerability and PK of ARP, followed by a 21-day washout period. Qualified subjects were randomized to ALKS 9072 or placebo (PBO) (4:1). Thirty-two subjects (23M/9F; BMI 18.8-38 mg/kg2) were randomized into 3 sequential cohorts of ALKS 9072: 150 mg (n = 10), 300 mg (n = 8), and 400 mg (n = 8) ARP free base equivalents or PBO (n = 2/cohort). PK samples were collected on Day 1 and on Day 27 (ALKS 9072 administration) pre-dose and at 1, 4, 8, and 12 hours post-dose. Single PK samples were collected Days 2-6, 24, 25, 28-48, and 51, 54, 57, 64, 71, 78, 85, and 115. PK samples were assayed for levels of ALKS 9072, ARP, and dehydroaripiprazole (dARP) by LC-MS/MS (LLOQ = 1 ng/mL). ARP and dARP Data from 22 subjects was used in the model development. Compartmental modeling was conducted using WinNonlin v5.3. A stepwise multiple-compartment PK modeling approach was employed to establish PK models for both oral ARP and ALKS 9072. A Weibull function best characterized the absorption profile of ARP following ALKS 9072 administration. In model predictability test, PK parameters from ALKS 9072 150 mg and 300 mg modeling were used to predict drug PK profile of the 400 mg dose level in comparison to observed data. The developed model was to simulate anticipated aripiprazole concentrations following monthly dosing ALKS 9072 administration in planned clinical studies.
Results: Tests of model fit and evaluation demonstrated that the model well predicted ARP and dARP concentration and exposure of following oral ARP and IM ALKS 9072 ($R^2 = 0.983$ and 0.984, respectively). In accordance with previously reported models, oral ARP PK was best characterized with 2-compartment model, with half-life of absorption and elimination of 0.3 hr and 3.3 days, respectively. A 5-compartment model was developed to describe ARP and dARP PK following ALKS 9072 IM administration. ARP exhibited a significantly longer absorption half-life (52 days) following ALKS 9072 administration, consistent with a once-monthly dose regimen. When PK parameters from the ALKS 9072 150 mg and 300 mg dose levels were used to predict ARP and dARP following 400 mg ALSK9072 PK, predicted values agreed well with the observed data ($R^2 = 0.97$), demonstrating the utility of the model for simulation. Using the resulted geometric mean of PK parameters, simulations of once-monthly dosing of ALKS 9072 300 mg, 450 mg and 600 mg will result in steady-state concentration levels of ARP comparable to daily oral ARP doses of 10 mg, 20 mg and 30 mg, respectively.
Conclusions: ALKS 9072 was well tolerated with few AEs and minimal reports of discomfort at the injection site. ALKS 9072 achieved therapeutic levels of ARP following single administration with a concentration-time profile consistent with once monthly administration and predicted minimal peak to trough ratio. Two multi-compartment PK models were successfully developed to describe the PK of ARP and dARP following administration of oral ARP and ALKS 9072. Simulated steady-state levels of ARP following ALKS 9072 administration are consistent with the current PO dose range of 10–30 mg/day for the treatment of schizophrenia.
Keywords: aripiprazole, pharmacokinetic modeling, depot, injectable
Disclosure: R. Turncliff, **Part 1:** Employee of Alkermes, Inc; W. Li, **Part 1:** Employee of Alkermes, Inc.; H. Pentikis, Nothing to Disclose.

W175. Long Acting Injectable vs. Oral Antipsychotics in Schizophrenia: A Systematic Review and Meta-analysis of Mirror-image Studies

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Background: As psychopathology and social functioning can worsen with repeated psychotic episodes in patients with schizophrenia, relapse prevention is critical. High non-adherence rates in this population can limit the efficacy of pharmacotherapy, therefore, the use of long-acting injectable antipsychotics (LAIs) is considered to be an important treatment option. However, new, large, randomized controlled trials (RCTs) showed no significant benefit of LAIs over oral antipsychotics (OAPs) (e.g., Rosenheck et al. 2011; Schooler et al. 2011). Moreover our latest meta-analysis of RCTs showed no superiority of LAIs over OAPs (Kishimoto et al. in submission: Studies = 21, $n = 4{,}950$, $RR = 0.93$, 95%CI: 0.80-1.08, $p = 0.35$). However, clinical trials might over-represent patients with better treatment adherence and lower illness severity. In addition, patients in clinical trials are likely to receive more and different types of attention than those in routine care, such as measures of adherence, reminders to attend clinical/research assessment sessions, etc. Therefore, the standard RCT might not be the best strategy to examine the efficacy of LAIs, and this possibility needs to be examined carefully. Mirror image studies, which compare the periods pre- and post-LAI introduction within subjects might be a more informative design to examine the effect of LAIs in the targeted population, even though mirror image studies have their own limitations.
Methods: A systematic review/meta-analysis was conducted of mirror image studies following patients at least 12 months (at least 6 months each on OAP and LAI). Co-primary outcomes were

hospitalization rate and number of hospitalizations. Pooled risk ratio or rate ratio together with their 95% confidence intervals (CIs) were calculated, using random-effects model. Number-needed-to-treat (NNT) was calculated where appropriate. With regard to the heterogeneity, τ^2, I^2, Q, p values were reported.
Results: We identified a total of 26 studies across 22 countries including 5,940 participants. LAIs showed strong superiority over OAPs in preventing a next hospitalization (18 studies, $n = 2722$, risk ratio = 0.44, 95%CI: 0.38-0.52, $p < 0.001$, $NNT = 3$; heterogeneity: $\tau^2 = 0.078$, $I^2 = 79\%$, $Q = 81.4$, df = 17, $p < 0.001$). LAIs also showed strong superiority over OAPs in decreasing the number of hospitalizations (19 studies, 7034 person years, rate ratio = 0.40, 95%CI: 0.31-0.51, $p < 0.0001$; heterogeneity: $\tau^2 = 0.266$, $I^2 = 93.8\%$, $Q = 288.2$, df = 18, $p < 0.001$) Although substantial heterogeneity was seen, all studies except one each consistently showed significant superiority regarding the rate and number of hospitalizations favoring of LAIs. This strong superiority remained across all of the following subgroups: first-generation antipsychotic-LAIs, second-generation antipsychotic-LAIs, studies published before 2000 and studies published after 2000, studies applying intention-to-treat analysis and those reporting observed cases. The extent to which publication bias might have contributed to these findings will be further discussed.
Conclusions: Result from mirror image studies in patients eligible for clinical use of LAIs showed strong superiority of LAIs compared to OAPs in preventing hospitalization. The results are in contrast with the meta-analysis of RCTs, which showed non-superiority of LAIs. However, given the possible biases in mirror image studies; i.e., expectation bias, time effect, etc., a cautious interpretation is required. Nevertheless, the population in mirror image studies better reflects the population receiving LAIs in clinical practice. Future RCTs may benefit from including patients at high-risk for relapse and those more closely reflecting routine clinical care.
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Keywords: schizophrenia, relapse, hospitalization, antipsychotics, long acting injection
Disclosure: T. Kishimoto, **Part 1:** Otsuka, Pfizer, Dainippon Sumitomo, Banyu, Eli Lilly, Dainippon Sumitomo, Janssen, Novartis, **Part 4:** Byoutaitaisyakenkyukai Fellowship (Fellowship of Astellas Foundation of Research on Metabolic Disorders) and Eli Lilly Fellowship for Clinical Psychopharmacology; M. Nitta, **Part 1:** Dainippon Sumitomo Pharama (employee of DSP), **Part 2:** Dainippon Sumitomo Pharama, **Part 3:** Dainippon Sumitomo Pharama, **Part 4:** NA; M. Borenstein, **Part 1:** Biostat, Inc (Founder of Biostat inc), **Part 2:** Biostat, Inc (Founder of Biostat inc); J. Kane, **Part 1:** Organon, Eli Lilly, BMS, Intracellular Therapeutics, Boehringer, Rules Based Medicine, Astra Zeneca, Otsuka, Novartis, Merck, Myriad, Esai, Pfizer, Lundbeck, J & J, Targacept, Shire, Amgen, Sunovion, Pierre Fabre, Janssen, Alkermes, Jazz, Forest Labs, **Part 2:** BMS, Otsuka, Merck, Novartis, Lilly, MedAvante; C. Correll, **Part 1:** Actelion, Alexza, AstraZeneca, Biotis, Bristol-Myers Squibb, Cephalon, Desitin, Eli Lilly, Gerson Lehrman Group, GSK, IntraCellular Therapies, Lundbeck, Medavante, Medscape, Merck, Novartis, Ortho-McNeill/Janssen/J&J, Otsuka, Pfizer, ProPhase, Sunovion, Takeda, Teva, and Vanda, **Part 2:** AstraZeneca, Bristol-Myers Squibb, Cephalon, GSK, Merck, Otsuka, Pfizer, ProPhase, **Part 3:** AstraZeneca, Bristol-Myers Squibb, Otsuka, Pfizer, ProPhase, **Part 4:** BMS, Janssen/J&J, Otsuka.

W176. Pharmacokinetic Profile of ITI-007, A Novel Approach for the Treatment of Schizophrenia and Other Psychiatric and Neurological Disorders

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Background: ITI-007 is an investigational new drug for the treatment of schizophrenia and other neuropsychiatric disorders. ITI-007 is a potent 5-HT_{2A} receptor antagonist with activity as a mesolimbic/mesocortical selective dopamine and glutamate phosphoprotein modulator and a serotonin reuptake inhibitor. This unique pharmacological profile is predicted to translate clinically to improved antipsychotic efficacy for the treatment of negative symptoms with improved cognition by glutamatergic modulation and the treatment of affective symptoms by serotonin reuptake inhibition, while improving positive symptoms via dopamine modulation. The potent 5-HT_{2A} receptor antagonism translates to improved sleep maintenance and enhanced antipsychotic and antidepressant efficacy. The pharmacokinetic, metabolic, and tolerability profile of orally administered ITI-007 was explored in patients with stable schizophrenia in a series of clinical studies.
Methods: Patients with schizophrenia or schizoaffective disorder, who were stable with regard to their psychotic symptoms, were washed off their previous antipsychotic medication for at least 4 days before randomization to ITI-007. In a double-blind, placebo-controlled study, patients were randomized to receive ITI-007 or placebo (N = 8/cohort; 6:2, drug:placebo) as an oral dose solution once daily in the morning for five days under fasted conditions. Doses were escalated in separate subject cohorts. Serial plasma samples were collected on Study Day 1 and Study Day 5 for pharmacokinetic analysis. In a separate study, the pharmacokinetic profile using a formulated capsule was evaluated. Serial plasma samples were collected for pharmacokinetic analysis. Safety and tolerability were assessed in both clinical studies. ITI-007 as the parent molecule and its metabolites were measured in plasma samples using a validated high performance liquid chromatography/tandem mass spectrometric (LC/MS/MS) assay. Pharmacokinetic parameters were calculated. Parent and metabolites were profiled for their receptor binding affinity using standard radioligand binding assays.
Results: ITI-007 was safe and generally well-tolerated with repeated administration in patients with stabilized schizophrenia. There were no drug-related serious adverse events. There were no safety concerns with respect to vital signs, 12-lead ECGs, or clinical chemistries. All adverse events were mild to moderate. Notably, there were no extrapyramidal side effects including no akathisia. ITI-007 plasma concentrations increased with increasing doses. Administration of ITI-007 as a formulated capsule improves its pharmacokinetic profile. Two metabolites were identified in human plasma and characterized. The metabolism of ITI-007 expands its pharmacological profile.
Conclusions: The present results demonstrate that ITI-007 is safe and well-tolerated across a wide range of doses in patients with stabilized schizophrenia. The lack of extrapyramidal side effects with ITI-007 is consistent with its mesolimbic/mesocortical selectivity. ITI-007 demonstrates a dose-related pharmacokinetic profile that supports once-a-day dosing. Administered as a formulated capsule, ITI-007 demonstrates excellent oral exposure. ITI-007 is metabolized into active metabolites that contribute to its unique pharmacological profile. Taken together, the data support continued clinical evaluation of ITI-007 for the treatment of psychiatric and neurological disorders. Previous data have shown

robust improvements in sleep maintenance at low doses of ITI-007 in patients with primary insomnia and rapid, long-lasting, dose-related engagement of brain targets using positron emission tomography in healthy volunteers. ITI-007 is currently in Phase 2 clinical development for the treatment of schizophrenia.
Keywords: ITI-007, Pharmacokinetic, Metabolism, Schizophrenia
Disclosure: K. Vanover, **Part 1:** Employee of Intra-Cellular Therapies, Inc., **Part 2:** Intra-Cellular Therapies, Inc., **Part 3:** Employee of Intra-Cellular Therapies, Inc.; R. Davis, **Part 1:** Consultant for Intra-Cellular Therapies, Inc., **Part 2:** Intra-Cellular Therapies, Inc., **Part 3:** Consultant for Intra-Cellular Therapies, Inc.; L. Wennogle, **Part 1:** Employee of Intra-Cellular Therapies, Inc., **Part 2:** Intra-Cellular Therapies, Inc., **Part 3:** Employee of Intra-Cellular Therapies, Inc.; P. Greengard, **Part 1:** Intra-Cellular Therapies, Inc., PsychoGenics, Neurologix, Envoy, Pfizer, Johnson & Johnson, **Part 2:** Intra-Cellular Therapies, Inc., PsychoGenics, Neurologix, Envoy, Pfizer, Johnson & Johnson, **Part 3:** None.; S. Mates, **Part 1:** Employee of Intra-Cellular Therapies, Inc., **Part 2:** Intra-Cellular Therapies, Inc., **Part 3:** Employee of Intra-Cellular Therapies, Inc.

W177. Nicotine Metabolism: Sex Differences in African American and Caucasian Smokers

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Background: Nicotine undergoes rapid biotransformation by the genetically variable liver enzyme CYP2A6 into its main metabolite, cotinine (COT), which is further metabolized exclusively by CYP2A6 to 3-hydroxycotinine (3HC). The ratio of 3HC/COT is highly correlated with CYP2A6 activity and with the rate of nicotine metabolism. Genetic and environmental variation in the rates of CYP2A6-mediated nicotine metabolism importantly alter numerous smoking behaviors, as tested primarily in heavy smoking Caucasians, including level of smoking, duration of smoking, ability to stop smoking, and health outcomes such as lung cancer. Previous studies in light smoking African American (AA) or heavy smoking Caucasians (C) have shown that the rate of nicotine metabolism, proxied by 3HC/COT, contributes to differences in response to smoking cessation treatments. Level of smoking, ethnicity and sex can all alter the rate of nicotine metabolism. Therefore a direct comparison of AA and C, in males and females, using one recruitment strategy for smokers of similar intensity, has not been performed.
Methods: This study directly compared levels of COT, 3HC, and their ratio among 254 treatment-seeking, heavy smoking AA and C enrolled in a smoking cessation trial. The AA ($n = 95$, 58% women) and C ($n = 159$, 51% women) smokers were enrolled concurrently in a cessation treatment trial and met the same inclusion eligibility, including smoking 12-40 cigarettes weekly for at least the past two years. During the week prior to the designated quit date they provided a saliva sample, assayed by LCMS at the University of Toronto labs.
Results: The AA and C smokers did not differ on number of cigarettes smoked per day (AA: 17.8 ± 6.0 SD; C: 18.5 ± 5.6). As African Americans were older, had higher BMI, smoked menthol at higher rates (84 vs 25%), and had higher nicotine dependence scores than C ($ps < 0.01$), these were included as covariates in all analyses. There was a main effect of sex for 3HC ($p < .001$) and the ratio of 3HC/COT ratio ($p < .001$) with women having higher levels than men. There was also a race effect on the 3HC/COT ratio with C higher than AA ($p < .05$). Race × sex interactions were observed for levels of COT ($p = .02$) and the sum of COT and 3HC ($p = .03$), with AA females having higher levels than all others ($ps < 0.05$). Consistent with what has been demonstrated in studies of these variables separately, and here examined directly, we found that: 1) women had higher 3HC/COT ratios than men, 2) C had higher ratios than AA, and 3) COT levels were higher among AA (particularly women) than C, despite similar smoking levels.
Conclusions: The results provide support for differences in nicotine metabolism by race and sex in heavy smokers with faster metabolism in C and in women. Despite similar levels of reported smoking, COT levels were higher in AA, particularly AA women. This may be a combination of greater nicotine intake (as usually interpreted) and reduced CYP2A6 activity. COT is both formed and removed by CYP2A6, and due to differential extraction ratios, being slower (i.e., in AA and/or men) will alter the second metabolic step (removal to 3HC) more than the first (formation from nicotine). This differential impact on COT's pharmacokinetics may lead to an accumulation of COT in those with slower CYP2A6 which may be reflective of differing rates of metabolism rather than differential nicotine intake. The difference in nicotine metabolism by race and sex, and the resulting effects on COT levels, may alter interpretation of epidemiological smoking exposure data (an overestimation of intake in AA and in males relative to C and to females for the same nicotine intake). Differential rates of nicotine metabolism may also alter levels of smoking and response to smoking cessation and thus may play a critical role in disease burden.
Keywords: nicotine metabolism, cotinine, 3-hydroxycotinine, sex differences, African American
Disclosure: A. King, **Part 1:** Consultant and advisor to Lundbeck in 2011, **Part 2:** Consultant, Respiratory Health Association of Metropolitan Chicago (non profit organization); L. Zhang, Nothing to Disclose; D. Roche, Nothing to Disclose; D. Cao, Nothing to Disclose; R. Tyndale, **Part 1:** Participated in one day advisory meetings for Novartis (2008) and McNeil (2011) respectively where travel costs and a stipend was provided. Receives honorarium as an associate editor for Clinical Pharmacology and Therapeutics.

W178. Impact on Hospitalization after Initiating Long-acting Injectable Antipsychotics for a Longer vs. Shorter Time Period among Medicaid Insured Patients with Schizophrenia

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Background: Continuous antipsychotic pharmacotherapy is important for the treatment success of patients with schizophrenia, with discontinuation of therapy associated with an increase in symptom severity and a greater risk for relapses. This study evaluated the impact of treatment with long-acting injectable (LAI) antipsychotics for a longer duration vs. a shorter duration on healthcare resource utilization among Medicaid insured patients with schizophrenia.
Methods: Schizophrenia patients $\geqslant 13$ years of age initiating LAI antipsychotics were identified from the *Thomson Reuters MarketScan Research* Medicaid database between 7/1/2005 and 6/30/2010. The study population was grouped into two study cohorts based on the duration of usage of LAI antipsychotic medication (Longer Usage Duration cohort: $\geqslant 180$ days of supply and Short Usage Duration cohort: < 180 days of supply). Patients were required to have at least 6 months of continuous medical and prescription drug insurance coverage prior to LAI initiation (baseline period) in order to assess patient clinical background. Baseline demographics and clinical characteristics were determined for both cohorts and compared. During the follow-up period, hospitalization related resource utilization was determined for each cohort and compared. A Cox regression model was used to determine the impact of the duration of LAI antipsychotic usage on the time to first hospitalization (all-cause and schizophrenia-related).
Results: Medicaid insured patients initiating LAI antipsychotics for $\geqslant 180$ days ($n = 2{,}838$) were slightly younger (38.91 vs. 39.96,

$p < 0.003$) and had a lower Charlson comorbidity index (0.57 vs. 0.65, $p = 0.012$) than those initiating LAI antipsychotics for a shorter time period ($n = 2,856$). A lesser proportion of patients in the Longer Usage Duration cohort had congestive heart failure (1.48% vs. 2.98, $p = 0.0001$), chronic pulmonary disease (12.26% vs. 15.02%, $p = 0.002$), rheumatic disease (0.39% vs. 0.84%, $p = 0.029$), and liver disease (1.59% vs. 2.77%, $p = 0.002$) and took concomitant medications (antidepressants: 44.29% vs. 48.91%, $p = 0.0005$; analgesics/antipyretics: 29.00% vs. 33.37%, $p = 0.0004$). The mean duration ($\pm$ standard deviation) of LAI usage among the Longer Usage Duration cohort was 604 ± 432 days vs. 86 ± 43 days for those who initiated LAI antipsychotics for a shorter time period. Schizophrenia patients who used LAI antipsychotics for a longer duration were hospitalized less for all causes (0.61 ± 1.41 vs. 0.79 ± 1.78, $p < 0.0001$) with a shorter length of stay (LOS) (4.93 ± 13.40 vs. 6.56 ± 18.63 days, $p = 0.0001$) and for schizophrenia (0.51 ± 1.26 vs. 0.63 ± 1.55, $p = 0.001$) with a shorter LOS (4.16 ± 11.94 vs. 5.18 ± 14.96 days, $p = 0.005$). Moreover, Cox-regression results showed that using LAI antipsychotics for a longer duration was correlated with longer time to the first hospitalization for any cause ($p < 0.0001$) or for a schizophrenia relapse ($p < 0.0001$).

Conclusions: Patients who are treated with LAI antipsychotics for a longer vs. shorter duration are less likely to have a hospitalization for any cause or a relapse. Patients with schizophrenia who used LAI antipsychotics for a shorter time period were sicker; however, in the regression analysis which controlled for general comborbidity the time to first hospitalization remained greater for those who used LAI antipsychotics for a longer time period vs. a short time period. The results of this study indicate that usage of LAI antipsychotics for a greater length of time may improve the treatment success of schizophrenia, although further study is warranted to evaluate the impact of long-term LAI antipsychotic usage on schizophrenia management.

Keywords: Long-acting injectable antipsychotic therapy, hospital resource utilization, schizophrenia

Disclosure: R. Bera, **Part 1:** Rimal Bera has received honoraria from Otsuka America Pharmaceutical, Inc. in connection with conducting this study and is on on the speakers bureau for Astra Zeneca, forest, Novartis and sunovian; C. Karson, **Part 1:** Craig Karson is an employee of CNK Consultants which has received research funds from Otsuka America Pharmaceutical, Inc. in connection with conducting this study; S. Offord, **Part 1:** Steve Offord is an employee of Otsuka America Pharmaceutical, Inc.; D. Zubek, **Part 1:** Donna Zubek is an employee of Otsuka America Pharmaceutical, Inc.; G. Lau, **Part 1:** Gina Lau is an employee of Otsuka America Pharmaceutical, Inc.; J. Lin, **Part 1:** Jay Lin is an employee of Novosys Health, which has received research funds from Otsuka America Pharmaceutical, Inc. in connection with conducting this study.

W179. Healthcare Impact of Initiating Long-acting Injectable Antipsychotic Therapy among Medicaid Insured Patients with Schizophrenia

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Background: Long-acting injectable (LAI) antipsychotics are recommended for treating patients with schizophrenia at any stage of the disease but are typically reserved for those who demonstrate recurrent nonadherence to oral antipsychotic therapy. We examined the healthcare impact of initiating LAI antipsychotics among patients with schizophrenia insured by Medicaid.

Methods: Patients with schizophrenia were identified from the *MarketScan Research* Medicaid database between 7/1/2005 and 6/30/2010. The index event was defined as the date patients initiated treatment with LAI antipsychotics. Patients were required to be $\geqslant$ 13 years at the index event and have 6 months of continuous medical/prescription drug coverage prior to (baseline) LAI initiation and during a variable follow-up period. Annualized healthcare utilization and costs (all cause and schizophrenia-related) for the baseline and follow-up periods were determined and compared.

Results: The study population consisted of 5,694 patients (Male: 55%, Female: 45%) with diagnosed schizophrenia with most between the ages of 18 and 55 (86%). The majority of patients had low comorbidity, as estimated by the Charlson Comorbidity Index (CCI) (CCI = 0: 67%, CCI = 1-2: 26%). The most prevalent comorbid conditions among the study population were diabetes (17%) and chronic pulmonary disease (14%). Nearly half of the study population took anticonvulsants and/or antidepressants. In comparison to the baseline period during the follow-up period in which the patients were taking LAIs, the mean number of all cause hospitalizations (1.52 ± 2.41 vs. 0.70 ± 1.61, $p < 0.0001$) and associated LOS declined (15 ± 29 vs. 6 ± 16, days $p < 0.0001$), as well as the number of schizophrenia-related hospitalizations (1.21 ± 2.04 vs. 0.57 ± 1.41, $p < 0.0001$) and associated LOS (12 ± 26 vs. 5 ± 14, days $p < 0.0001$), while the total number of outpatient claims remained similar for all causes and slightly higher for schizophrenia related claims. Total all cause annualized health care cost (i.e. sum of inpatient, outpatient and Rx) for patients taking LAIs was reduced by \$6,901 ($p < 0.0001$) with the main driver coming from a reduction in inpatient cost (−\$8,869, $p < 0.0001$).

Conclusions: The hospitalization burden and costs of schizophrenia is reduced after patients begin treatment with LAI antipsychotics, while the use of outpatient services for schizophrenia modestly increases, suggesting outpatient follow-up and monitoring is increased. The cost-offset that is attributed to a reduction in hospitalizations and LOS outweighs the cost increase from medications and outpatient claims. Further research is warranted on the outcomes of patients with schizophrenia treated with different types of LAI antipsychotics.

Keywords: Long-acting injectable antipsychotics, schizophrenia, healthcare resource utilization

Disclosure: C. Karson, **Part 1:** Craig Karson is a consultant of Otsuka America Pharmaceutical, Inc.; R. Bera, **Part 1:** Rimal Bera has received honoraria from Otsuka America Pharmaceutical, Inc. in connection with conducting this study and is on the speakers bureau for Astra Zeneca, forest, Novartis and sunovian.; S. Offord, **Part 1:** Steve Offord is an employee of Otsuka America Pharmaceutical, Inc.; D. Zubek, **Part 1:** Donna Zubek is an employee of Otsuka America Pharmaceutical, Inc.; G. Lau, **Part 1:** Gina Lau is an employee of Otsuka America Pharmaceutical, Inc.; J. Lin, **Part 1:** Jay Lin is an employee of Novosys Health which has received research funds from Otsuka America Pharmaceutical, Inc. in connection with conducting this study.

W180. Do Benzodiazepines Really Induce Negative Cognitive Effects in Elderly Psychiatric Patients?

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Background: Previous studies have reported that long term use of benzodiazepines may lead to cognitive impairment, such as memory reduction and difficulties in learning new material. A meta-analysis of 13 studies on middle aged long term benzodiazepine users demonstrated significant cognitive impairments compared to non-users. In the elderly, previous studies on the cognitive effects of benzodiazepine use have shown rather contradictory results, indicating that the cognitive impairment caused by

benzodiazepines may be small or absent in this age group. However, the majority of these studies included healthy, community dwelling subjects. Our knowledge about such effects in elderly psychiatric patients is therefore rather scarce. The aim of the present study was to investigate if there were any differences in cognitive performance in elderly psychiatric patients using or not using benzodiazepines at time of admittance to a psycho-geriatric hospital department.

Methods: A total of 241 elderly psychiatric patients, 168 benzodiazepine users and 73 non-users older than 60 years, were included in the study. We used a battery of standardized cognitive tests consisting of the Hopkins verbal learning test, the Stroop colour/word test and the Digit Vigilance test. All tests were performed within 48 hours after admission to hospital. Prescribed doses of all psychotropic medication including benzodiazepines were confirmed by serum concentration analyses.

Results: We found no significant differences in cognitive functioning between benzodiazepine users and non-users. Before correction for differences in baseline characteristics, nine out of 12 tests showed a non-significant trend of better cognitive function and three tests showed significant better function in the benzodiazepine group. The benzodiazepine group had significantly more years of education ($p = 0.006$), less dementia ($p = 0.026$) and more depression ($p < 0.001$) than the non-benzodiazepine group, otherwise patient characteristics were not significantly different. A multiple regression model was used to adjust for years of education, dementia and depression.

Conclusions: Our results showed that the use of benzodiazepines in our cohort of elderly psychiatric patients did not cause any cognitive impairment. There may be a number of reasons for this finding. The majority of our patients displayed both prescription data and serum concentrations corresponding to the recommended doses of benzodiazepines, and only a few patients displayed higher serum concentrations or signs of abuse. Elderly psychiatric patients in need of hospitalisation may be in a state of impaired cognitive function and marginal cognitive effects of benzodiazepine may be difficult to detect. Our data also corresponds with findings in healthy elderly benzodiazepine users where negative cognitive effects has been postulated to be small or absent. The strength of our study is the high number of patients included, serum concentration monitoring of all patients and statistical correction for differences in patients characteristics. Our study questions the perceived opinion that any long term use of benzodiazepines mediates negative cognitive effects in elderly psychiatric patients.

Keywords: benzodiazepines, elderly, cognitive function, neuropsychological tests

Disclosure: L. Tanum, Nothing to Disclose; G. Hoiseth, Nothing to Disclose; M. Tveito, Nothing to Disclose; K. Kristiansen, Nothing to Disclose; K. Kvande, Nothing to Disclose; B. Lorentzen, Nothing to Disclose; H. Refsum, Nothing to Disclose; J. Bramness, Nothing to Disclose.

W181. The Efficacy of the Glutamate NMDA Receptor Antagonist Memantine for Cognitive Deficits in Euthymic Subjects with Bipolar Disorder

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Background: Subjects with bipolar disorder experience significant cognitive and functional deficits, even when euthymic, but few studies have evaluated potential treatments for such deficits. Memantine is a glutamate NMDA receptor antagonist which has shown efficacy in cognitive dysfunction due to moderate to severe Alzheimer disease. We report here results from a three-site, randomized, controlled, parallel-arm clinical trial of adjuvant memantine versus placebo for cognitive deficits in euthymic subjects with bipolar disorder.

Methods: We randomized 72 euthymic subjects (mean age 46.6 + 9.7 years, 53% female) with bipolar disorder type I (55%) or type II (45%), who reported subjective cognitive deficits (scoring at baseline > 17 on the Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire, CPFQ). Subjects were assigned flexible doses (5-20 mg/day) of memantine or placebo (using a ratio 2:1 respectively) for a 12-week treatment study. At baseline and endpoint all subjects were administered neuropsychological tests, including tests of attention (the Rapid Visual Information Processing Task, RVIP of CANTAB), short-term/working memory (the Spatial Working Memory, SWM of the CANTAB), verbal and episodic memory (the California Verbal Learning Test, CVLT-II and the Delayed Matching to Sample, DMS of the CANTAB). We also administered the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), which includes five subscales (attention, immediate memory, visuospatial construction skills, delayed memory and language). The Social Adjustment Scale-Self Report (SAS-SR) was administered at baseline and endpoint to assess changes in social functioning. Mood scales and subjective cognitive questionnaires were administered monthly. We collected proton magnetic resonance spectroscopy (1H-MRS) data from $N = 11$ bipolar subjects before and after treatment. MRS data was acquired from two $15 \times 15 \times 15$ mm voxels centered on left and right hippocampus. 57 bipolar patients (79%) completed the 12 week study. 43 of the study completers enrolled in phase 2 and received open label treatment memantine (5-20 mg/day) for additional 12 weeks. 39 bipolar patients completed phase 2; neuropsychological tests and social functioning scales were again administered at the end of the follow-up.

Results: Over 12 weeks, the memantine group showed significant improvements over placebo in spatial and working memory (SWM: Between errors, Strategy, Total Errors), verbal and episodic memory (DMS: Percent correct and Total correct; CVLT: Trial 2; Trial 4; Recognition hits; Recognition of false positives), total RBANS score and three of five RBANS indexes (attention, language and delayed memory). There were no significant differences between treatment groups in changes in social functioning over the 12 weeks study. Adjuvant memantine was relatively well tolerated; retention in the study was 79% in the first 12 weeks of randomized treatment and 91% in the last 12 weeks of open treatment. $N = 9$ subjects undergoing magnetic resonance spectroscopy had adequate baseline and endpoint datasets for analysis. Compared to placebo ($N = 3$), memantine-treated subjects ($N = 6$) had increases in left hippocampus N-acetyl aspartate (NAA), a measure of neuronal viability, and in the right hippocampus choline (Cho). The initial improvements in neuropsychological tests during randomized treatment were maintained over 12 weeks of open follow-up.

Conclusions: Adjuvant memantine was associated with acute improvements on several cognitive domains in euthymic bipolar subjects over 12 weeks and such improvements persisted with ongoing treatment for an additional three months. Memantine treatment was also associated with measures of increased hippocampus neuronal viability.

Keywords: Bipolar disorder; Cognitive dysfunction; Memory; Memantine; Neuropsychology; Magnetic resonance spectroscopy

Disclosure: D. Iosifescu, **Part 1:** CNS Response, Inc - consultant, **Part 4:** This study was supported by Forest Laboratories. Since 2010 Dr. Iosifescu has received grant/research support through Mount Sinai School of Medicine from Brainsway, Euthymics Bioscience Inc., Neosync, and Shire. In the next 2 years, it is likely that he will receive grants from Hoffmann- La Roche Inc. and Astrazeneca Lp; W. Gilmer, **Part 1:** Consulting fees: Pfizer, Astra Zeneca, Eli Lilly, Speaking honoraria: Neuronetics; A. Fan, **Part 4:**

PI on a study funded by Sunovion; A. Gonenc, Nothing to Disclose; C. Moore, Nothing to Disclose; C. Randolph, Nothing to Disclose; M. Rapaport, Nothing to Disclose; T. Deckersbach, **Part 1:** Brain Cells. Inc - consultant, Systems Research and Applications Corporation (SRA) - consultant, Oxford University Press - royalties; A. Nierenberg, **Part 1:** Dr. Nierenberg has served as a consultant to: Appliance Computing Inc. (Mindsite), Brain Cells, Inc., Brandeis University, Bristol Myers Squibb, Clintara, Dianippon Sumitomo (Now Sunovion), Eli Lilly and Company, EpiQ, Forest, Novartis, PamLabs, PGx Health, Shire, Schering-Plough, Sunovion, Takeda Pharmaceuticals, Teva, and Targacept. He has consulted through the MGH Clinical Trials Network and Institute (CTNI): Astra Zeneca, Brain Cells, Inc, Dianippon Sumitomo/Sepracor, Johnson and Johnson, Labopharm, Merck, Methylation Science, Novartis, PGx Health, Shire, Schering-Plough, Targacept, and Takeda/Lundbeck Pharmaceuticals. Dr. Nierenberg received honoraria or travel expenses including CME activities from: APSARD, Belvoir Publishing, Boston Center for the Arts, University of Texas Southwestern Dallas, Hillside Hospital, American Drug Utilization Review, American Society for Clinical Psychopharmacology, Bayamon Region Psychiatric Society, San Juan, PR, Baystate Medical Center, Canadian Psychiatric Association, Columbia University, Douglas Hospital/McGill University, IMEDEX, International Society for Bipolar Disorders, Israel Society for Biological Psychiatry, John Hopkins University, MJ Consulting, New York State, Massachusetts Association of College Counselors, Medscape, MBL Publishing, Physicians Postgraduate Press, Ryan Licht Sang Foundation, Slack Publishing, SUNY Buffalo, University of Florida, University of Miami, University of Wisconsin, University of Pisa, and SciMed. Dr. Nierenberg is a presenter for the Massachusetts General Hospital Psychiatry Academy (MGHPA). The education programs conducted by the MGHPA were supported through Independent Medical Education (IME) grants from the following pharmaceutical companies in 2008: Astra Zeneca, Eli Lilly, and Janssen Pharmaceuticals; in 2009 Astra Zeneca, Eli Lilly, and Bristol-Myers Squibb. No speaker bureaus or boards since 2003. Dr. Nierenberg owns stock options in Appliance Computing, Inc. and Brain Cells, Inc. Additional income is possible from Infomedic.com depending on overall revenues of the company but no revenue has been received to date. Through MGH, Dr. Nierenberg is named for copyrights to: the Clinical Positive Affect Scale and the MGH Structured Clinical Interview for the Montgomery Asberg Depression Scale exclusively licensed to the MGH Clinical Trials Network and Institute (CTNI)., **Part 4:** Dr. Nierenberg has received grant/research support through MGH from AHRQ, Cephalon, Forest, Mylin, NIMH, PamLabs, Pfizer Pharmaceuticals, Takeda, and Shire. In the next 2 years, it is possible that he will receive grants from Dey Pharmaceuticals, Sunovion, and Targacept.

W182. Hydrocortisone and Intrusive Memories in Posttraumatic Stress Disorder

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Background: Posttraumatic stress disorder (PTSD) is characterized by automatic traumatic memory processing which can hardly be controlled by the patients. It is an ongoing debate whether reduced cortisol secretion in these patients might promote PTSD symptoms by a disinhibition of traumatic memory retrieval. Extensive evidence indicates that elevated glucocorticoid levels impair the retrieval of emotionally arousing information. Hence, the hypothesis was proposed that pharmacological elevation of cortisol levels might decrease risk and symptoms of PTSD by inhibiting excessive retrieval of traumatic memories. Several studies could support this hypothesis. However, all previous studies included small sample sizes and administered different doses of hydrocortisone.

Methods: We conducted a treatment study with two dosages of hydrocortisone (10 and 30 mg/d) within a double-blind, randomized, placebo-controlled, cross-over design. 30 female participants with PTSD were randomly assigned to either : 1.) 1 week placebo- 1 week hydrocortisone (10 mg/d)- 1 week placebo- 1 week hydrocortisone (30 mg/d) or 2.) 1 week hydrocortisone- 1 week placebo- 1 week hydrocortisone (10 mg/d) - 1 week placebo. For 20 participants administration took place at 9 am daily, for 10 participants at 12.30 pm. The primary outcomes were the frequency and the intensity of intrusions assessed three times per day (9 am, 13 pm and 19 pm). Secondary outcome was the overall-symptomatolgy of PTSD.

Results: We could not find any differences of the frequency and the intensity of intrusions between 10 mg hydrocortisone- 30 mg hydrocortisone- and placebo condition. Overall symptomatology also did not differ between the three conditions. Comparing different time points (9 am vs. 12.30 pm) of administration there were also no differences between the conditions at all.

Conclusions: For the first time we included a sample size of 30 participants with PTSD to test the hypothesis that the administration of hydrocortisone reduces automatic memory retrieval. However, we could not replicate previous findings showing a significant impact of hydrocortisone on automatic memory retrieval in participants with PTSD. Regarding the small sample sizes of previous studies the results of our study challenge the idea of a positive effect of hydrocortisone on automatic memory retrieval in PTSD.

Keywords: Posttraumatic Stress Disorder, Hydrocortisone, Intrusive Memories

Disclosure: P. Ludäscher, Nothing to Disclose; C. Schmahl, Nothing to Disclose; M. Bohus, Nothing to Disclose.

W183. Lurasidone Monotherapy for the Treatment of Bipolar Depression: Results of the 6-Week, Double-blind, Placebo-controlled PREVAIL-2 Study

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Background: Bipolar disorder is a chronic and often disabling illness with a lifetime prevalence of $\sim$4.4% (Merikangas et al, Arch Gen Psychiatry 2007;64:543-52). Major depressive episodes occurring in bipolar I disorder are particularly severe, with approximately 90% of individuals reporting severe impairment in functioning (Keck et al, J Psych Practice 2008;14 [Suppl 2]:31-38). Currently, few treatment options are available for the treatment of bipolar depression. The efficacy of antidepressants is not well-established, and may be associated with switch into mania, or an increased frequency of bipolar episodes i.e., rapid cycling (APA Practice Guidelines: Bipolar Disorder, April 2002; J Clin Psychiatry 2011;72:704-15; Gijsman et al, Am J Psychiatry 2004; 161:1537-47). The goal of this study was to evaluate the efficacy and safety of monotherapy with lurasidone in patients with bipolar I depression, without psychotic features.

Methods: In this multi-regional study, subjects ($n = 505$) meeting DSM-IV-TR criteria for bipolar I depression, with or without rapid cycling, with a Montgomery-Åsberg Depression Rating Scale (MADRS) score $\geqslant 20$ and a Young Mania Rating Scale score $\leqslant 12$, were randomized to 6 weeks of once-daily, double-blind treatment with either lurasidone 20-60 mg (LUR20-60), lurasidone 80-120 mg (LUR80-120) or placebo (PBO). Primary and key secondary outcomes were change from baseline to week 6 in MADRS and CGI-bipolar severity (CGI-BP-S) depression scores, respectively, analyzed using mixed model repeated measures (MMRM). Additional secondary outcome measures were analyzed

using analysis of covariance, last observation carried forward (ANCOVA-LOCF), or logistic regression.
Results: Study completion rates were 123/166 (74.1%) in the LUR20-60 group (mean modal dose, 34.6 mg/d), 124/169 (73.4%) in the LUR80-120 group (mean modal dose, 90.6 mg/d) and 127/170 (74.7%) in the PBO group. Lurasidone treatment resulted in significantly greater MADRS score reduction at Week 6 for both the LUR20-60 group (-15.4; $p<0.001$; effect size = 0.51) and the LUR80-120 group (-15.4; $p<0.001$, effect size = 0.51) vs. PBO (-10.7). Both LUR groups separated significantly from PBO from week 2 onward. Lurasidone treatment resulted in significantly greater Week 6 reduction in CGI-BP-S depression scores for both the LUR20-60 group (-1.8; $p<0.001$) and the LUR80-120 group (-1.7; $p<0.001$) compared with PBO (-1.1). Responder rates (reduction in MADRS $\geqslant$50% at Week 6) were significantly higher for LUR20-60 (53%) and LUR80-120 (51%) compared with PBO (30%; $p<0.001$ for both comparisons). Both LUR20-60 and LUR 80-120 groups showed significant improvement vs. PBO on the Hamilton Anxiety Rating scale ($p\leqslant0.05$), the Sheehan Disability Scale ($p\leqslant0.01$), the self-rated Quick Inventory of Depressive Symptomatology ($p\leqslant0.001$), and the Quality of Life, Enjoyment and Satisfaction Questionnaire ($p\leqslant0.001$). Discontinuation rates due to adverse events for LUR20-60 (7%) and LUR80-120 (6%) were similar to PBO (6%). For LUR20-60, LUR80-120, and PBO, respectively, the most frequently reported adverse events were nausea (10.4%, 17.4%, 7.7%), headache (14.0%, 9.0%, 11.9%), and akathisia (7.9%, 10.8%, 2.4%). Minimal changes in weight, lipids and measures of glycemic control were observed.
Conclusions: In this study, monotherapy with lurasidone, flexibly dosed at 20-60 mg/day or 80-120 mg/day, significantly reduced depressive symptoms in patients with bipolar I depression compared with placebo. The low discontinuation rate due to adverse events, the low incidence of adverse events, and the minimal effects on metabolic parameters suggest that lurasidone was well-tolerated as a monotherapy in this study.
Keywords: bipolar disorder, major depressive disorder, antipsychotic, lurasidone, randomized clinical trial
Disclosure: A. Loebel, **Part 1:** Full-time employee of Sunovion Pharmaceuticals, Inc, **Part 2:** Full-time employee of Sunovion Pharmaceuticals, Inc, **Part 3:** Full-time employee of Sunovion Pharmaceuticals, Inc; J. Cucchiaro, **Part 1:** Full-time employee of Sunovion Pharmaceuticals, Inc, **Part 2:** Full-time employee of Sunovion Pharmaceuticals, Inc, **Part 3:** Full-time employee of Sunovion Pharmaceuticals, Inc; R. Silva, **Part 1:** Full-time employee of Sunovion Pharmaceuticals, Inc, **Part 2:** Full-time employee of Sunovion Pharmaceuticals, Inc, **Part 3:** Full-time employee of Sunovion Pharmaceuticals, Inc; K. Sarma, **Part 1:** Full-time employee of Sunovion Pharmaceuticals, Inc, **Part 2:** Full-time employee of Sunovion Pharmaceuticals, Inc, **Part 3:** Full-time employee of Sunovion Pharmaceuticals, Inc; H. Kroger, **Part 1:** Full-time employee of Sunovion Pharmaceuticals, Inc, **Part 2:** Full-time employee of Sunovion Pharmaceuticals, Inc, **Part 3:** Full-time employee of Sunovion Pharmaceuticals, Inc; J. Hsu, Nothing to Disclose; J. Calabrese, **Part 1:** I have received federal funding or research support from, acted as a consultant to/served on advisory boards for, or provided CME lectures to the Department of Defense, Health Resources Services Administration, National Institute of Mental Health, Abbott, Adamed, AstraZeneca, Bristol-Myers Squibb, Cephalon, Cleveland Foundation, Dainippon Sumitomo, Eli Lilly, EPI-Q, Eisai, Elan, Forest, France Foundation, Genaissance, Glaxo Smith Kline, Janssen, Johnson & Johnson, Jazz, JDS, Lundbeck, Merck, Memory, NARSAD, Neurosearch, Novartis, Organon, OrthoMcNeil, Otsuka, Pfizer, Repligen, Sanofi Aventis, Schering-Plough, Servier, Solvay, Stanley Medical Research Institute, Supernus, Synosia, Takeda, Tikvah, and Wyeth; G. Sachs, **Part 1:** I have been a consultant for Otsuka, Johnson & Johnson, and Grunenthal, **Part 2:** I have stock/other financial relationship with Collaborative Care Initiative; and work as an employee of Bracket/Medco.

W184. Effect of Lurasidone Monotherapy or Adjunctive Therary on Anxiety Symptoms in Patients with Bipolar I Depression

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Background: Over half of patients diagnosed with bipolar disorder I (BP-I) depression are also burdended by clinically significant anxiety, and over one-third will be diagnosed with an anxiety disorder in their lifetime. The presence of clinically significant anxiety in patients with bipolar illness is associated with earlier onset and greater severity of bipolar illness, reduced treatment response, and worse overall outcome (Kessler et al, Arch Gen Psych, 2005; Simon et al, JAD, 2007). This analysis evaluated the effect of lurasidone as monotherapy or adjunctive to lithium (Li) or valproate (VPA) on symptoms of anxiety in patients with BP-I depression.
Methods: Patients meeting DSM-IV-TR criteria for BP-I depression, with or without rapid cycling, with a Montgomery Åsberg Depression Rating Scale (MADRS) score $\geqslant$20 and a Young Mania Rating Scale score $\leqslant$12, were randomized to 6 weeks of once-daily, double-blind treatment with lurasidone adjunctive to lithium (Li) or valproate (VPA) - PREVAIL 1, or lurasidine monotherapy - PREVAIL 2, or. Both were large, parallel-group multi-regional studies (combined n = 853). In PREVAIL 1, patients received either lurasidone 20-120 mg/day (LUR20-120) or PBO, in combination with either lithium (Li) or valproate (VPA). In PREVAIL 2, patients received either lurasidone 20-60 mg (LUR20-60), lurasidone 80-120 mg (LUR80-120) or placebo (PBO). In both studies, the primary outcome was change in depressive symptoms, assessed by the MADRS, from baseline (BL) to end of week 6, analyzed using mixed model repeated measures (MMRM). Symptom severity of anxiety was determined using the Hamilton Anxiety Scale (HAM-A). This present analysis reports study outcomes for depression (MADRS) and anxiety (Hamilton Anxiety Rating Scale - HAM-A by ANCOVA-LOCF) for both the overall study population, and for patients with moderate-to-severe anxiety (HAM-A $\geqslant$18 at BL).
Results: In PREVAIL 1, treatment with LUR20-120 adjunctive to Li or VPA, resulted in significantly greater reduction of depressive symptoms vs. PBO (plus Li/VPA), evidenced by greater MADRS score reduction from BL at Week 6 (-17.1 vs. -13.5; $p=0.005$; effect size = 0.34). Adjunctive treatment with LUR 20-120 mg/day also significantly reduced anxiety vs. PBO, indicated by greater HAM-A score reduction from BL at end of week 6 (-8.0 vs. -6.0; $p=0.003$; effect size = 0.34, all LOCF). One hundred and eight patients (31.8%) in this study met criteria for moderate-to-severe anxiety (HAMA $\geqslant$18) at baseline. General severity of illness was significantly higher in this subgroup compared with patients with lower anxiety burden (mean CGI-BP-S of 4.71 vs. 4.43; $p<0.001$). In the moderate-to-severely anxious subgroup, LUR20-120 mg/day also reduced depressive symptoms at end of week 6 vs. PBO (MADRS reduction -19.2 vs. -15.6; effect size = 0.30), but this did not achieve statistical significance ($p=0.127$). Significantly more patients with moderate-to-severe anxiety met anxiety treatment-responder criteria at study end ($\geqslant$50% reduction in HAM-A) on LUR20-120 vs. PBO (68.8% vs. 47.1%; $p=0.016$; LOCF). In PREVAIL 2, lurasidone monotherapy also significantly improved depressive symptoms vs. PBO, as demonstrated by significantly greater MADRS score reduction at Week 6, and this was true both for LUR 20-60 mg/day (-15.4; $p<0.001$; effect size = 0.51) and LUR 80-120 mg/day (-15.4; $p<0.001$, effect size = 0.51) vs. PBO (-10.7). Compared with PBO, both lurasidone dosing ranges also significantly reduced anxiety at end of week 6 (LOCF), reflected by HAM-A score reductions of -6.8 ($p=0.001$) with LUR 20-

60 mg/day and -6.3 ($p = 0.015$) for LUR 80-120 mg/day, vs. -4.6 for PBO. One hundred sixty five patients (34.0%) met criteria for moderate-to-severe anxiety (HAMA $\geqslant 18$) at baseline. Similar to findings in PREVAIL 1 (above), the reported general severity of illness of this subgroup in PREVAIL 2 was significantly higher compared to patients with lower anxiety at baseline (mean CGI-BP-S of 4.70 vs. 4.49; $p < 0.001$). In the moderate-severely anxious subgroup, lurasidone treatment reduced depressive symptoms at end of week 6 vs. PBO (MADRS reduction -15.2 for combined LUR treatment groups vs. -12.5 for PBO; effect size = 0.23), but this did not achieve statistical significance ($p = 0.204$). More lurasidone patients with moderate-to-severe anxiety at BL met anxiety treatment-responder criteria ($\geqslant 50\%$ reduction in HAM-A at LOCF endpoint) vs. PBO (52.0% vs. 37.3%; $p < 0.102$).
Conclusions: In this analysis, lurasidone, whether used adjunctive to lithium or valproate or as monotherapy in the treatment of BP-I depression, significantly improved symptoms of both depression and anxiety, reflected by reductions in MADRS and HAM-A scores. Lurasidone, used adjunctive to stable Li or VPA, resulted in a significantly greater rate of anxiety symptom responders; in depressed BP-I patients with moderate-to-severe anxiety at BL receiving monotherapy, the anxiety responder rate was numerically, but not statistically superior to PBO. Limitations of this analysis of anxiety- and related outcomes in these BP I depression studies include the secondary nature of these outcomes, and the restriction on pooling data across both studies imposed by the different treatment paradigms (adjunctive vs. monotherapy), which may have increased the statistical power of the analyses by subgroups. Sponsored by Sunovion Pharmaceuticals, Inc. The following information concerns a use of lurasidone that has not been approved by the U.S. Food and Drug Administration.
Keywords: lurasidone, bipolar depression, anxiety symptoms
Disclosure: R. Hirschfeld, **Part 1:** Health and Wellness Partners (Sunovian), Merck Manual Editorial Board, **Part 2:** The University of Texas Medical Branch; J. Cucchiaro, **Part 1:** Full-time employee of Sunonvion Pharmaceuticals, **Part 2:** Full-time employee of Sunonvion Pharmaceuticals, **Part 3:** Full-time employee of Sunonvion Pharmaceuticals, **Part 4:** Full-time employee of Sunonvion Pharmaceuticals; A. Pikalov, **Part 1:** Full-time employee of Sunonvion Pharmaceuticals, **Part 2:** Full-time employee of Sunonvion Pharmaceuticals, **Part 3:** Full-time employee of Sunonvion Pharmaceuticals, **Part 4:** Full-time employee of Sunonvion Pharmaceuticals; P. Warner, **Part 1:** Full-time employee of Sunonvion Pharmaceuticals, **Part 2:** Full-time employee of Sunonvion Pharmaceuticals, **Part 3:** Full-time employee of Sunonvion Pharmaceuticals, **Part 4:** Full-time employee of Sunonvion Pharmaceuticals; J. Hsu, **Part 1:** Full-time employee of Sunonvion Pharmaceuticals, **Part 2:** Full-time employee of Sunonvion Pharmaceuticals, **Part 3:** Full-time employee of Sunonvion Pharmaceuticals, **Part 4:** Full-time employee of Sunonvion Pharmaceuticals; H. Kroger, **Part 1:** Full-time employee of Sunonvion Pharmaceuticals, **Part 2:** Full-time employee of Sunonvion Pharmaceuticals, **Part 3:** Full-time employee of Sunonvion Pharmaceuticals, **Part 4:** Full-time employee of Sunonvion Pharmaceuticals; A. Loebel, **Part 1:** Full-time employee of Sunonvion Pharmaceuticals, **Part 2:** Full-time employee of Sunonvion Pharmaceuticals, **Part 3:** Full-time employee of Sunonvion Pharmaceuticals, **Part 4:** Full-time employee of Sunonvion Pharmaceuticals.

W185. Evaluation of Glycine Transporter Inhibitor Org 25935 for the Prevention of Relapse in Alcohol-dependent Patients: A Multisite, Randomized, Double-blind, Placebo-controlled Trial

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Background: Approved pharmacotherapies for alcohol dependence are currently limited to disulfiram, naltrexone, and acamprosate. Previous animal studies have shown that glycine modulates the release of ethanol-induced dopamine in nucleus accumbens, thus suggesting that the glycinergic system may be a potential drug target in the treatment of alcohol dependence. In animal models, Org 25935, a glycine transporter inhibitor that acts to increase synaptic glycine levels, was shown to have dose-dependent effects on ethanol intake, preference and relapse-like behavior without tolerance. In healthy human volunteers, Org 25935 easily crosses the blood cerebrospinal fluid (CSF) barrier. Glycine concentrations in CSF were approximately 2.5 fold higher compared with baseline values, thus corresponding to an increase of 150% after a single oral dose of 16 mg Org 25935. The current study aimed to translate these animal findings to humans by examining the effect of Org 25935 on relapse prevention in alcohol-dependent patients who had completed a detoxification program.
Methods: This was a randomized, double-blind, placebo-controlled, parallel-group clinical trial conducted at 18 centers in the Europe from April 2009-January 2010. Adult patients aged 18-65 years diagnosed with alcohol dependence were randomly assigned to receive Org 25935 12 mg BID or placebo for 84 days in a 1:1 ratio. Inclusion criteria comprised participation in an alcohol detoxification program prior to study entry, full abstinence from alcohol and benzodiazepines for at least 3 days, Clinical Institute Withdrawal Assessment score < 10, and breath alcohol concentration $< 0.02\%$ at screening and baseline. Exclusion criteria included major psychiatric comorbidity or recent recreational drug use, or use of prior medication (within 30 days) that could impact alcohol consumption such as naltrexone, acamprosate, or disulfiram. Assessment of daily alcohol consumption was conducted on days 3, 7, and weekly until day 28, and biweekly thereafter, using the interview-based Alcohol Timeline Follow-back method. The primary end point was percentage of heavy drinking days (defined as $\geqslant 5$ standard drinks per day for men and $\geqslant 4$ for women) and was calculated as number of heavy drinking days divided by the total number of days in the relevant 2-week interval. Secondary end points included other measures of relapse-related drinking behavior (drinks per day, time to relapse, and cumulative abstinence days). Efficacy analysis was conducted using the intent-to-treat (ITT) population (patients who received at least 1 dose of study medication and had at least 1 post-baseline efficacy assessment). A mixed-model repeated measurements (MMRM) analysis included fixed effects of treatment, biweekly periods, and (pooled) centers.
Results: The trial was stopped mid-way after a futility analysis showed that the likelihood of detecting a signal at study term was less than 40%. A total of 140 subjects were included in the modified ITT analysis (Org 25935: $n = 75$; placebo: $n = 65$). Subjects were predominantly male (74%), white (100%), and had a mean age of 49.3 ± 9.8 years. The mean $\pm$ SD percentage of days of relapse into heavy drinking was $15.3\% \pm 19.5$ for the Org 25935 group vs $13.6\% \pm 18.8$ for placebo. The least squares mean difference of 2.4 days (95% confidence interval: –3.4 to 8.2) was not statistically significant ($P = 0.41$). No statistically significant difference was observed for the percentage of days abstinent, number of drinks per day and per heavy drinking day, number of lapses and relapses, number of subjects with complete abstinence, or time to first drink and time to heavy drinking. The most frequent adverse events (AEs) with Org 25935 vs placebo, respectively, were fatigue (25% vs 14%), dizziness (20% vs 5%), and photophobia (12% vs 2%). Serious AEs were reported in 13% of subjects in the Org 25935 group and 18% in the placebo group; a majority of the events were substance-related (alcohol poisoning, drug withdrawal). There were no clinically relevant differences between groups in electrocardiographic evaluations. However, liver parameters showed a higher rate of subjects with at least one in-treatment value > 3xULN was observed in the Org 25935 groups vs. placebo for alanine aminotransferase (6.8% vs. 1.5%) and aspartate aminotransferase (10.8% vs. 3.1%).

Conclusions: In this study, Org 25935 failed to demonstrate benefit over placebo in alcohol relapse prevention.
Keywords: alcohol dependence, glycine transporter inhibitor, Org 25935, alcohol relapse prevention
Disclosure: A. Szegedi, **Part 1:** I am an employee and stockholder of Merck & Co., **Part 2:** see above, **Part 3:** see above; A. deBejczy, Nothing to Disclose; K. Nations, **Part 1:** Employed by Merck at the time of this research, held stock and stock options, Currently employed by INC Research, a Contract Research Organization, **Part 2:** As stated in #2, **Part 3:** As stated in #2; F. Ruwe, **Part 1:** I am an employee and stockholder of Merck & Co., **Part 2:** see question 2, **Part 3:** see question 2; B. Söderpalm, Nothing to Disclose; D. Michelson, **Part 1:** I am an employee and stockholder of Merck, **Part 2:** see above, **Part 3:** see above.

W186. Metabolism and Pharmacokinetics of the Antidepressant Amitifadine in Humans

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Background: Amitifadine is a serotonin-preferring triple reuptake inhibitor (TRI) that demonstrated robust antidepressant activity, significant improvement versus placebo on a MADRS-derived anhedonia factor score, and no significant weight gain or worsening of sexual dysfunction in a 6-week, phase 2 clinical trial (Trân et al., 2012). TRIs with their enhanced dopamine (DA) modulation may have broader efficacy across the heterogeneity of MDD patients, and theoretical advantages over SSRIs in domains of efficacy and tolerability such as anhedonia, cognition, fatigue, weight gain and sexual dysfunction. A phase 2B/3 trial is currently underway to explore these hypotheses further with amitifadine. Metabolic drug-drug interactions (DDI) either as substrate or inhibitor of cytochrome P450 (CYP-)-dependent hepatic metabolism are potential liabilities of antidepressants. CYPs are known to metabolize more than 75% of drugs, with CYP2D6, CYP2CP, CYP3A4, and CYP2C19 being the major CYP enzymes. Polymorphisms of CYP2D6 and CYP2C19 can result in highly variable metabolism of substrate antidepressants, raising concerns about adverse events and possibly efficacy. In addition, several antidepressants, e.g., fluoxetine, paroxetine and fluvoxamine, inhibit one or more of the key CYP isoforms. To assess the druggability of amitifadine, we evaluated the biopharmaceutics, *in-vitro* plasma protein binding, CYP metabolic phenotyping and CYP interaction potential, as well as *in-vivo* pharmacokinetics (PK) of amitifadine in humans.
Methods: Human plasma protein binding was determined using ultracentrifugation. Hepatic metabolism was measured in human hepatocytes by assessing metabolite formation rates. Parent/metabolite concentrations were quantitated by validated HPLC-MS/MS assay methods. Inhibition of CYP isoforms was determined in human liver microsome (HLM) incubations, using prototypical model substrates and inhibitors as positive and negative controls. Human plasma and urine PK of parent and major metabolite (EB10101) was determined after single- and multiple-escalating doses, and food effect was studied. PK was assessed by noncompartmental analysis of plasma and urine concentration-time profiles over 48 hours.
Results: Amitifadine (at 1 and 10 mM) was highly (99.4%) bound to human plasma, independent of concentration. After 4 h human hepatocytes incubation, 82% of amitifadine remained, suggesting low hepatic extraction. EB-10101, the major metabolite, was formed by two parallel metabolic pathways – a minor NADPH-dependent CYP pathway and a major monoamine-oxidase (MAO)-A-dependent pathway; a less prominent carbamate glucuronide metabolite was also found. The inhibitory DDI potential of amitifadine (0.05 – 100 mM) in HLM for CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 was evaluated. Amitifadine showed measurable inhibition, however, it was 19 to 198 times less potent than prototypical comparator inhibitors. Amitifadine was considered a potent inhibitor of CYP2B6 ($IC_{50} = 2\,\mu M$), a moderate inhibitor of the CYP1A2, CYP2C19, CYP2D6, CYP2C9, CYP3A4 activities (IC_{50} 10-22 μM), and a weak inhibitor of CYP2C8 ($IC_{50} > 100\,\mu M$). Single, oral doses of amitifadine (10-450 mg) showed reasonable dose-proportionality for c_{max} and AUC_{oo} up to 150 mg, with a low average coefficient of variation of 38%. The average t_{max} was 1.5 ± 0.7 hours and the average half-life ($t_{1/2}$) was 3.7 ± 0.4 hours. Oral clearance ranged from 21.2 L/hour (10 mg) to 13.2 L/hour (450 mg). At the 300 mg dose, the lactam metabolite (EB-10101) c_{max} was approx. 50% lower, and its AUC_{o-t} was >1.5-fold higher than those of amitifadine. The t_{max} for EB-10101 was 7.8 ± 4.3 hours (3.6 times > parent), and its $t_{1/2}$ was 14.3 hours. Urinary excretion of parent amitifadine and EB-10101 was negligible (<1% of dose). A concurrent high-fat meal with a single dose of 25 mg amitifadine did not affect its AUC_{oo} and $t_{1/2}$, but slightly decreased c_{max} and prolonged t_{max} by about 2.5-fold. In multiple dosing, c_{max} and AUC_{o-12} increased slightly by Day 10, with a drug accumulation ratio (AUC_{τ}) of 1.25 and 1.43, respectively, and no marked changes in t_{max} or $t_{1/2}$.
Conclusions: Amitifadine is highly plasma protein bound and undergoes primarily non-CYP, MAO-dependent hepatic metabolism to form its primary lactam metabolite, EB-10101. Although hepatic metabolism and urinary excretion were low, there is evidence of high extrahepatic, MAO-dependent metabolism, resulting in a short half-life and low accumulation of parent drug. Amitifadine is not expected to be sensitive to CYP-dependent DDI and genetic polymorphisms. Amitifadine showed only moderate *in-vitro* inhibition of the key CYPs, e.g., CYP2C9, CYP2C19, CYP2D6 and CYP3A4 isoforms, suggesting low likelihood of clinically relevant DDI; it was a potent inhibitor of only the relatively minor CYP2B6. Amitifadine is well-absorbed, and its PK is not significantly affected by food. Its PK is dose-proportional with little inter-subject variability. Overall, its biopharmaceutical characteristics, dual metabolic pathways, and predictable PK may be favorable for the pharmacotherapy of depression.
Keywords: Amitifadine depression metabolism phase 1 triple reuptake inhibitor
Disclosure: R. Marshall, **Part 1:** I am an employee of Euthymics Bioscience, Inc., **Part 2:** Euthymics Bioscience, Inc., **Part 3:** Euthymics Bioscience, Inc.; J. Venitz, **Part 1:** I am a clinical pharmacology consultant for Euthymics Bioscience, Inc, **Part 2:** Euthymics Bioscience, Inc, **Part 3:** Euthymics Bioscience, Inc; P. Tran, Nothing to Disclose; D. Wong, Nothing to Disclose; F. Bymaster, **Part 1:** I am an officer, shareholder and employee of Euthymics Bioscience, Inc, **Part 2:** Euthymics Bioscience, Inc, **Part 3:** Euthymics Bioscience, Inc.

W187. The Tryptophan-kynurenine Pathway in Major Depression: Neuroprotective Effects of Treatment

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Background: Major Depressive Disorder (MDD) is increasingly viewed as an inflammatory condition. Inflammatory biomarkers are elevated in patients with a depressive disorder possibly contributing to heart disease, stroke and dementia. Stress associated with MDD can induce shunts in the metabolic pathway of tryptophan shifting the balance between the kynurenine and serotonin pathways. A serotonergic deficit may thus ensue contibuting to at least some of the symptomts of depression. A toxic end product of the kynurenine pathway is quinolinic acid (QUIN) and 3-hydroxykynurenine (3-OHK); they impair neuronal function via NMDA agonism, excitotoxicity and apoptotic cell

death. These effects may account for some of the cognitive symptoms of depression, such as impaired concentration and declarative memory. Chronic untreated depression can predispose to dementia due to hippocampal cell death. We examined metabolites of the kynurenine pathway, tryptophan (T), kynurenine (K), kynurenic acid (KYNA), K/T ratio, 3-OHK and QUIN, in Healthy Control and MDD subjects at baseline (BL) and at weeks 8 (W8) and 12 (W12) following mono-therapeutic use of Escitalopram or Quetiapine. We sought correlations with depression severity and obtained blood levels of the therapeutic agents.

Methods: We conducted two consecutive studies with patients diagnosed with MDD using the MINI structured interview. The studies were of similar open-label design. In the first study 24 MDD patients were treated with ESC for 12 weeks; in the second study 31 MDD patients were treated with low doses of QTP for 12 weeks. Patients were evaluated at baseline (BL), and weeks 2, 4, 6, 8 and 12. Rating instruments included: Hamilton Depression and Anxiety Scales, and Beck Depression and Anxiety Inventories. Doses were flexibly adjusted depending on response and tolerability. The dose ranges were 10-40 mg daily for ESC and 25-250 mg daily for QTP. Follow-up evaluations included routine laboratory tests focusing on the metabolic syndrome, weight, liver and thyroid function, and blood concentrations of ESC and QTP. Blood samples were collected at BL, W8 and W12 of treatment. Statistical analyses were performed with SPSS software and the possible confounding effects of age, sex and BMI were taken into consideration.

Results: Both agents produced comparable antidepressant responses with 65% response rates. QTP was somewhat superior with respect to anxiety and insomnia. Overall both agents were tolerated well. Patients on QTP experienced daytime sedation if the dose titration was rapid. A number of these patients responded favorably to lower doses of QTP than recommended in previous studies. The biochemical analyses are summarized as follows: Escitalopram group: 1) Tryptophan levels increased from BL to W8 ($p<0.001$); 2) Kynurenine levels declined modestly from BL to W12 ($p<0.015$); 3) K/T ratio significantly declined from BL to W8 and remained significantly lower at W12 ($p<0.001$); 4) QUIN at W8 was reduced by a factor of 2 ($p<0.0005$) but significance was lost at W12; 5) 3-OHK levels were reduced by a factor of 2.23 $p<0.001$) at week 12. Quetiapine group: 1) Kynurenine levels trended downward from baseline to W8 ($p<0.07$) and to W12 ($p<0.084$); 2) 3-OHK levels were reduced by a factor of 3 ($p<0.004$). No significant differences were found between healthy controls and MDD patients at BL. None of the metabolites tested correlated significantly with depression severity or anxiety severity scores at BL. Blood level determinations of ESC and QTP corresponded to the doses the patients were receiving.

Conclusions: Depression has been associated with a pro-inflammatory state centrally and peripherally (Miller et al, 2009) It has also been established that there is an interaction between pro-inflammatory cytokines and serotonergic transmission involving the metabolism of tryptophan and modulation by the NMDA receptor. This interaction occurs in part through the enzyme, indoleamine 2,3-dioxygenase (IDO), that catabolizes tryptophan to kynurenine. Kynurenine metabolism has been implicated in the pathophysiology of depression, especially its chronicity (Myint and Kim, 2003). The up-regulation of the initiating step of the kynurenine pathway has been demonstrated in postmortem anterior cingulate cortex from individuals with schizophrenia and bipolar disorders (Miller et al, 2006; 2009). Our group (Myint et al, 2007a; Myint et al, 2007b)) has observed a lower plasma tryptophan index and neuroprotective kynurenic acid and higher tryptophan breakdown in depressed patients compared to controls. Our present data confirm that this pathway is abnormally regulated in depression. Additionally, we have demonstrated that this pathway responds differentially to ESC and QTP despite the fact that most patients responded favorably to both medications with more than 35% remitting in both groups. Since ESC and QTP have different psychodynamic profiles, it appears plausible that aspects of the Kynurenine pathway are differentially affected. Importantly, however, both medications exert neuroprotective action by reducing toxic metabolites, notably 3OHK with QTP and 3-OHK and QUIN with ESC. This apparent neuroprotective effect of two diverse psychotherapeutic agents, if confirmed in future studies, may have significant beneficial implications for the long-term management of depressive disorders.

Keywords: Depression, tryptophan, kynurenine, escitalopram, quetiapine, inflammation, IDO

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W188. Insulin Resistance as a Shared Pathophysiology between Mood and Cardiometabolic Disorders: Relevance of PPAR-γ Agonism

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Background: Longitudinal studies have shown a bidirectional relationship between metabolic illnesses and depression (Pan et al, 2012). Shared pathophysiology links mood disorders with cardiometabolic illnesses, including activated inflammatory signaling cascades, oxidative stress, dysregulation of the hypothalamic-pituitary-adrenal axis, and insulin resistance. Moreover, resistance to insulin signaling makes neurons energy deficient and vulnerable to oxidizing and other metabolic insults, resulting in impairment of synaptic plasticity. Given these associations, we have previously hypothesized that drugs with insulin sensitizing properties may also exhibit antidepressant efficacy. Pioglitazone is a PPAR-γ agonist that is an attractive potential candidate for testing this hypothesis and for treatment of depression, given its ability to improve insulin sensitivity, decrease inflammatory gene expression, and induce neuroprotection through mitigation of oxidative stress (Kemp et al., 2012).

Methods: Pioglitazone (15-45 mg/d) was administered (open-label) to 40 patients with major depressive disorder (MDD) and 34 patients with bipolar disorder (BD) over a 12- and 8-week duration, respectively. Patients with MDD additionally met criteria for metabolic syndrome or abdominal obesity (waist circumference $>$ 35 in. females, $>$ 40 in. males), and patients with BD met criteria for metabolic syndrome or insulin resistance. In MDD, pioglitazone was administered as monotherapy ($n=9$) or as an adjunct to conventional antidepressants ($n=31$). In BD, pioglitazone was administered in combination with a mood stabilizer ($n=34$). No change in concurrent antidepressant or mood stabilizer therapy was permitted for a minimum of 4 weeks prior to enrollment or during the trial. Diagnosis was confirmed by the Mini International Neuropsychiatric Interview. Symptoms were assessed by the Inventory of Depressive Symptoms (IDS), Quick Inventory of Depressive Symptoms (QIDS), and Hamilton Anxiety Scale (HAM-A). Data were pooled to assess the relationship between metabolic or inflammatory biomarkers and symptom improvement.

Results: In MDD, treatment with pioglitazone was associated with improvement in depressive symptoms as measured by change in IDS total scores (-19.1 ± 1.9; $p<.001$). Likewise, patients with BD experienced a significant decrease in baseline to endpoint IDS total scores (-16.5 ± 2.6; $p<.001$). Self-reported depressive symptoms also decreased in severity as measured by the QIDS in patients with MDD (-7.3 ± 1.0; $p<.001$) and BD (-7.2 ± 1.2; $p<.001$), respectively. A pooled analysis found that baseline levels of Interleukin-6 (IL-6) correlated with improvement on HAM-A and IDS total scores at

study endpoint ($r = -.28$, $p < .05$ and $r = -.35$, $p = .01$, respectively). The change in IL-6 also correlated with improvement on the HAM-A and IDS ($r = .37$, $p = .01$ and $r = .38$, $p < .01$, respectively). Decreases in HbA1c, a measure of blood glucose control, correlated with reduced depression severity measured by IDS scores ($r = .29$, $p = .03$). Decreases in insulin resistance measured by homeostasis model assessment (HOMA-IR) did not correlate with improvement in mood.

Conclusions: Change in IL-6 was significantly correlated with a reduction in depression severity, suggesting that anti-inflammatory actions may account for symptom improvement in patients undergoing pioglitazone treatment. In addition, a significant association was observed between higher baseline levels of IL-6 and greater depressive symptom reduction, suggesting that IL-6 may represent a pre-treatment predictor or moderator of antidepressant outcome. Lack of a correlation between HOMA-IR and mood outcomes indicates that mechanisms other than insulin sensitization may be responsible for the observed changes in depression severity. These findings are consistent with pre-clinical studies in which PPAR-γ agonism, NMDA receptor signaling, and anti-inflammatory activity accounted for the antidepressant-like and pro-cognitive effects of pioglitazone (Sauerbeck et al., 2011; Salehi-Sadaghiani et al., in press). Our results are consistent with results of a double-blind trial that found pioglitazone to be superior to placebo in the treatment of MDD even in the absence of metabolic syndrome or diabetes (Sepanjnia et al., 2012). Collectively, these data support the conduct of larger, placebo-controlled trials to fully delineate the role of PPAR-γ agonists as novel treatments for unipolar and bipolar depression.

Keywords: Depression; Insulin resistance; Pioglitazone; PPAR-gamma; Inflammation

Disclosure: D. Kemp, **Part 1:** Pfizer, AstraZeneca, Bristol-Myers Squibb, Corcept, Sanofi, Teva, Janssen, **Part 2:** AstraZeneca, Pfizer, **Part 3:** AstraZeneca, Pfizer, **Part 4:** NARSAD, Cleveland Foundation, Depressive and Bipolar Disorder Alternative Treatment Foundation; K. Gao, **Part 4:** NARSAD, Cleveland Foundation; T. Warneka, Nothing to Disclose; C. Conroy, Nothing to Disclose; S. Ganocy, **Part 1:** Eli Lilly, AstraZeneca, **Part 2:** Eli Lilly; F. Ismail-Beigi, **Part 1:** Eli Lilly; J. Calabrese, **Part 1:** Abbott, AstraZeneca, Bristol-Myers Squibb, Cephalon, Dainippon Sumitomo, EPI-Q, Inc., Forest, France Foundation, GlaxoSmithKline, Janssen, Johnson and Johnson, Lundbeck, Merck, Neurosearch, OrthoMcNeil, Otsuka, Pfizer, Repligen, Sanofi, Schering-Plough, Servier, Solvay, Supernus, Synosia, Takeda, and Wyeth., **Part 2:** AstraZeneca, Lundbeck, Merck, **Part 4:** Department of Defense, Health Resources Services Administration and National Institute of Mental Health, Abbott, AstraZeneca, Bristol-Myers Squibb, Cephalon, Cleveland Foundation, Eli Lilly, Glaxo Smith Kline, Janssen, NARSAD, Repligen, Stanley Medical Research Institute, Takeda, and Wyeth.

W189. The Space of Common Psychiatric Disorders

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Background: Clinical experience and factor analytic studies suggest that some psychiatric disorders may be more closely related to one another, as indicated by the frequency of their co-occurrence, which may have etiological and treatment implications. We sought toconstruct a virtual space of common psychiatric disorders, spanned by factors reflecting major psychopathological dimensions and locate psychiatric disorders in that space, and to examine whether location of disorders at baseline predicted prevalence and incidence of disorders at three year follow-up.

Methods: Data were drawn from individuals who participated in Waves 1 and 2 of the National Epidemiologic Survey on Alcohol and Related Conditions ($N = 34{,}653$). Exploratory factor analysis was used to identify the dimensions of this virtual space. Distance between disorders at Wave 1 was calculated using the loadings of the factors spanning the space of disorders as coordinates. This distance was correlated with the odds ratios adjusted for age, gender and race (AORs) of the prevalence and incidence of Axis I disorders in Wave 2, with the aim of determining if smaller distances between disorders at Wave 1 predicts higher disorder prevalence and incidence at Wave 2.

Results: A model with three correlated factors provided an excellent fit ($CFI = 0.99$, $TLI = 0.98$, $RMSEA = 0.008$) for the structure of common psychiatric disorders and was used to span the space of disorders. Distances between disorders ranged from 0.07 (between drug abuse and alcohol dependence) to 1.032 (between drug abuse and avoidant personality disorder). The correlation of distance between disorders in Wave 1 with AORs of prevalence in Wave 2 was -0.56. The correlation of distance in Wave 1 with AORs of incidence in Wave 2 was -0.57. Use of alternatives measures of distance (e.g., derived from loadings on models based on confirmatory factor analyses or as function of odds ratios at Wave 1) had substantially poorer predictive power.

Conclusions: Mapping psychiatric disorders can be used to quantify the distance among disorders. Proximity in turn can be used to predict prospectively the incidence and prevalence of Axis I disorders. These findings have implications for the classification, differential diagnoses, etiology and treatment of psychiatric disorders.

Keywords: Virtual space, comorbidity, structure of psychiatric disorders, distance

Disclosure: C. Blanco, Nothing to Disclose; R. Krueger, Nothing to Disclose; D. Hasin, Nothing to Disclose; S. Wang, Nothing to Disclose; M. Olfson, Nothing to Disclose.

W190. Levomilnacipran SR 40 mg and 80 mg in Major Depressive Disorder: A Phase III, Randomized, Double-blind, Fixed-dose, Placebo-controlled Study

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Background: Major depressive disorder (MDD) is a serious and chronic disorder associated with functional impairment, high rates of relapse, recurrence, and resistance to therapy. Levomilnacipran (1*S*, 2*R*-milnacipran), a potent and selective serotonin and norepinephrine reuptake inhibitor (SNRI), has 2-fold greater potency for norepinephrine relative to serotonin reuptake inhibition and over 10-fold higher selectivity for norepinephrine reuptake inhibition compared with duloxetine, venlafaxine, and desvenlafaxine; the sustained release formulation (SR) allows for once-daily dosing. This Phase III study (NCT01377194) evaluated the efficacy, safety, and tolerability of levomilnacipran SR 40 and 80 mg versus placebo in patients with recurrent MDD.

Methods: A double-blind, placebo-controlled, multicenter, randomized (1:1:1), fixed-dose study compared levomilnacipran SR 40 mg/day or 80 mg/day with placebo in patients with MDD. Outpatients from US and Canadian study centers were 18-75 years of age and met the DSM-IV-TR criteria for recurrent MDD with a current major depressive episode of at least 6 weeks but not longer than 12 months in duration, and $\leqslant 5$ major depressive episodes within the previous 5 years. Scores $\geqslant 26$ on the Montgomery-Asberg Depression Rating Scale (MADRS) and $\geqslant 4$ on the Clinical Global Impressions-Severity (CGI-S) scale were also required. The study comprised a 1-week, single-blind placebo run-in period, 8-weeks of double-blind treatment, and 1-week, double-blind down-taper period. Patients were randomized by computer-generated

schedule. Levomilnacipran SR patients received 20 mg/day on Days 1 and 2, and 40 mg/day on Days 3-5; on Day 6 and thereafter, patients in the 80-mg/day group were up-titrated to 80 mg, while patients in the 40-mg/day group remained at 40 mg. The primary efficacy measure was the MADRS; total score change from baseline to Week 8 was analyzed using a mixed-effects model for repeated measures (MMRM) on the Intent-to-Treat Population (ITT) with a Hochberg procedure to control for multiple comparisons. Sensitivity analyses using the last observation carried forward (LOCF) and pattern-mixture model (PMM) approaches were also conducted. The secondary efficacy measure was change from baseline to Week 8 in the Sheehan Disability Scale (SDS) total score. Additional efficacy measures included the 17-item Hamilton Rating Scale for Depression ($HAMD_{17}$), SDS subscales, MADRS response ($\geqslant$50% total score reduction) and remission (total score $\leqslant$10) rates at Week 8, and $HAMD_{17}$ response ($\geqslant$50% total score reduction) and remission (total score $\leqslant$7) at Week 8. Safety was evaluated by adverse events (AEs), clinical laboratory tests, vital signs, and physical findings.

Results: Of 562 patients who were randomized and received treatment (Safety Population: placebo = 186; levomilnacipran SR 40 mg = 188; levomilnacipran SR 80 mg = 188), 83% of placebo and 77% and 76% of levomilnacipran SR 40-mg and 80-mg patients, respectively, completed the study. Demographic characteristics were similar among treatment groups. The least squares mean difference (LSMD) with 95% confidence interval (CI) for MADRS total score change from baseline to Week 8 was significantly superior for levomilnacipran SR versus placebo (40 mg: -3.303 [-5.457, -1.148], $P = .0027$; 80 mg: -3.141 [-5.293, -0.988], $P = .0043$; MMRM); improvement for levomilnacipran SR was significant from Week 4 onward for both doses. Analyses using LOCF (LSMD [95% CI] = 40 mg: -2.415 [-4.521, -0.309], $P = .0247$; 80 mg: -2.380 [-4.451, -0.308], $P = .0244$) and PMM approaches supported the primary results. LSMD (95% CI) for SDS total score change at Week 8 was also significant for both doses of levomilnacipran SR versus placebo (40 mg: -1.827 [-3.620, -0.033], $P = .0459$; 80 mg: -2.720 [-4.494, -0.946], $P = .0028$; MMRM). Significant improvement relative to placebo was also seen for both dose groups on $HAMD_{17}$ and CGI-S. MADRS response rates were significantly greater in both the levomilnacipran 40-mg (49% [$P = .0035$]) and 80-mg groups (47% [$P = .0095$]) than placebo (34%). Significantly more levomilnacipran SR 40-mg and 80-mg patients than placebo patients achieved MADRS remission (30% [$P = .0117$], 32% [$P = .0020$], and 18%, respectively). AEs led to the discontinuation of more levomilnacipran SR 40-mg (6%, $P = .0317$) and 80-mg (10%, $P = .0006$) patients than placebo (2%); 55% of placebo and 68% and 79% of levomilnacipran SR 40-mg and 80-mg patients had double-blind treatment-emergent AEs (TEAEs). Common TEAEs reported in $\geqslant$5% of patients in both levomilnacipran SR groups and at least twice the rate of placebo were heart rate increased, erectile dysfunction, nausea, dry mouth, and constipation. Serious AEs were reported in 1 placebo (facial bone fracture/road traffic accident) and 3 levomilnacipran SR 40 mg (noncardiac chest pain in 1 patient; intussusception in 1 patient; asthma in 1 patient) patients during double-blind treatment.

Conclusions: Treatment with levomilnacipran SR 40 mg and 80 mg for 8 weeks produced significant improvement in MDD symptoms relative to placebo; significant improvement in functional impairment was also demonstrated. Treatment benefits were similar at both doses, occurred as early as 4 weeks, and persisted throughout the study. Levomilnacipran SR was generally well tolerated.

Keywords: levomilnacipran, major depressive disorder, serotonin, SNRI, norepinephrine

Disclosure: D. Bakish, **Part 1:** principal investigator for Forest Laboratories, Pfizer's speakers bureau, **Part 3:** Pfizer speakers bureau, **Part 4:** Forest Laboratories, Inc; C. Gommoll, **Part 1:** Employee of Forest Research Institute, **Part 2:** Employee of Forest Research Institute, **Part 3:** Employee of Forest Research Institute, **Part 4:** Employee of Forest Research Institute; C. Chen, **Part 1:** Employee of Forest Research Institute, **Part 2:** Employee of Forest Research Institute, **Part 3:** Employee of Forest Research Institute, **Part 4:** Employee of Forest Research Institute; W. Greenberg, **Part 1:** Employee of Forest Research Institute, **Part 2:** Employee of Forest Research Institute, **Part 3:** Employee of Forest Research Institute, **Part 4:** Employee of Forest Research Institute; R. Nunez, **Part 1:** Employee of Forest Research Institute, **Part 2:** Employee of Forest Research Institute, **Part 3:** Employee of Forest Research Institute, **Part 4:** Employee of Forest Research Institute; M. Liebowitz, **Part 1:** received an investigatory initiatied research study grant from Pfizer, stock options in Pherin Pharmaceuticals; A. Khan, **Part 1:** principal investigator of over 340 clinical trials sponsored by over 65 pharmaceutical companies and 30 CROs, **Part 2:** Rhine Pharmaceuticals.

W191. The Efficacy of Vilazodone on Anxiety Symptoms in Patients with Major Depressive Disorder: A *Post Hoc* Analysis of Two Randomized Controlled Trials

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Background: Major depressive disorder (MDD) is a common and debilitating illness. Anxiety is a common comorbid symptom, with higher levels associated with more severe depression, greater functional impairment, greater chronicity of illness, and greater suicidality. Following an adequate course of treatment, residual anxiety symptoms are associated with greater risk of depression relapse and recurrence. Vilazodone, a serotonin reuptake inhibitor and 5-HT_{1A} receptor partial agonist, is approved by the US Food and Drug Administration for the treatment of MDD. The efficacy and safety of vilazodone in MDD were established in 2 positive placebo-controlled Phase III trials. Data from both studies were pooled and *post hoc* analyses were performed to evaluate the efficacy of vilazodone on anxiety symptoms in patients with MDD.

Methods: Data from 2 Phase III 8-week, double-blind, randomized, placebo-controlled trials (NCT00285376, NCT00683592) were pooled to analyze the effects of vilazodone on different anxiety measures. Patients were 18-70 years of age with DSM-IV-TR–defined MDD and a minimum score $\geqslant$22 on the 17-item Hamilton Depression Scale ($HAMD_{17}$). Study designs were similar in both trials, with a 1-week screening period followed by 8-weeks double-blind treatment. Patients randomized to vilazodone were titrated to a target dose of 40 mg once daily over a 2-week period according to a fixed-titration schedule. The primary efficacy outcome, mean change from baseline in Montgomery-Asberg Depression Rating Scale (MADRS) at end of treatment [EOT], was assessed using an analysis of covariance (ANCOVA) model based on the intent-to-treat (ITT) population (patients who received study medication and postbaseline MADRS evaluation). Additional outcome measures included the $HAMD_{17}$, the Hamilton Anxiety Rating Scale (HAMA), and the Clinical Global Impressions-Severity (CGI-S) and -Improvement (CGI-I) scales. *Post hoc* analyses evaluated the effects of vilazodone relative to placebo on several measures of anxiety including the $HAMD_{17}$ anxiety/somatization subscale, HAMA psychic anxiety subscale, and MADRS and HAMD anxiety-related single items. To more fully investigate the effects of vilazodone, different patient subgroups were also analyzed, including patients with anxious depression (defined as $HAMD_{17}$ anxiety/somatization subscale $\geqslant$7 at baseline) and patients stratified by baseline depression severity (moderate depression = MADRS < 30, moderately severe depression = 30 $\leqslant$ MADRS < 35, and severe depression = MADRS $\geqslant$ 35).

Results: Of 863 patients in the ITT population (placebo, n = 432; vilazodone, n = 431), 357 (82.6%) placebo and 351 (81.4%) vilazodone patients had anxious depression at baseline; according

to MADRS baseline scores, 31% of patients had moderate (placebo, n = 143; vilazodone, n = 128), 49% had moderately severe (placebo, n = 204; vilazodone, n = 217), and 20% had severe (placebo, n = 85; vilazodone, n = 86) depression. For the overall population, least squares mean difference (LSMD) for change in $HAMD_{17}$ anxiety/somatization subscale at Week 8 was significantly greater for vilazodone versus placebo (LSMD = -0.62 [95% CI = -1.00, -0.25]; $P < .01$). Vilazodone also showed significant improvement versus placebo at Week 8 on the HAMA psychic anxiety subscale (LSMD = -1.18 [-1.74, -0.63]; $P < .0001$). Significant differences in favor of vilazodone-treatment relative to placebo were seen as early as Week 2 on the $HAMD_{17}$ anxiety/somatization subscale and Week 4 on the HAMA psychic anxiety subscale and continued until the end of the study. In patients with anxious depression, significantly greater improvements were seen for vilazodone relative to placebo at Week 8 on both the $HAMD_{17}$ anxiety/somatization subscale (LSMD = -0.75 [-1.17, -0.32]; $P < .001$) and HAMA psychic anxiety subscale (LSMD = -1.32 [-1.92,-0.71]; $P < .0001$). On both of these measures, vilazodone showed statistical separation from placebo starting at Week 2 and continuing until the end of the study. Changes on the $HAMD_{17}$ anxiety/somatization subscale were significantly larger for vilazodone relative to placebo for both the moderately severe (LSMD = -0.59 [-1.15, -0.03]; $P = .039$) and severe (LSMD = -1.05 [-2.02, -0.07]; $P = .036$) depression subgroups. Similarly, significant improvements versus placebo were seen on the HAMA psychic anxiety subscale in patients with moderately severe (LSMD = -1.27 [-2.09, -0.45]; $P < .010$) and severe depression (LSMD = -1.60 [-2.96, -0.25]; $P = .020$). In patients with moderate depression, differences versus placebo did not reach significance on either measure ($HAMD_{17}$ anxiety/somatization subscale: LSMD = -0.50 [-1.09, 0.08]; $P = .090$; HAMA psychic anxiety subscale: LSMD = -0.77 [-1.69, 0.15]; $P = .100$).

Conclusions: In these *post hoc* pooled analyses, vilazodone compared with placebo showed significantly greater improvement of anxiety symptoms as determined by several measures of anxiety. Relative to the overall population, larger treatment effects were seen in patients with more severe depression and greater anxiety levels at baseline. These *post hoc* results suggest that vilazodone is effective at treating anxiety symptoms associated with MDD.

Keywords: MDD

Disclosure: M. Thase, **Part 1:** Alkermes, AstaZeneca, Bristol-Myers Squibb Company, Eli Lilly & Co., Dey Pharma, LP, Forest Laboratories, Inc.(includes PGx, Inc.), Gerson Lehman Group, Guidepoint Global, Lundbeck, MedAvante, Inc., Merck and Co., Inc., Mylan Laboratories (formerly Dey Pharmaceuticals), Neuronetics, Inc., Otsuka, Ortho-McNeil Pharmaceuticals (includes Jannsen and Johnson&Johnson), Pamlab, LLC, Pfizer (includes Wyeth Ayerst Pharmaceuticals), Roche, Shire US, Inc., Sunovion, Supernus Pharmaceuticals, Takeda, Teva Pharmaceuticals, and Transcept Pharmaceuticals, **Part 2:** Spouse's employment at Embryon (formerly Advogent), which did business with BMS and Pfizer/Wyeth, ended in 2011. Spouse's current employment with Peloton Advantage, which does business with Pfizer and Sunovion, **Part 3:** Spouse's former employment at Embryon (formerly Advogent), which did business with BMS and Pfizer/Wyeth, which ended in 2011. Spouse's current employment with Peloton Advantage, which does business with Pfizer and Sunovion, **Part 4:** Agency for Healthcare Research and Quality, Alkermes, AstraZeneca, Eli Lilly and Co., Forest Laboratories, Inc., Glaxo Smith Kline, National Institute of Mental Health, Otsuka Pharmaceuticals, PharmaNeuroboost, Roche; J. Edwards, **Part 1:** Full time employee of Forest Research Institute, **Part 2:** Full time employee of Forest Research Institute, **Part 3:** Full time employee of Forest Research Institute; D. Chen, **Part 1:** Full time employee of Forest Research Institute, **Part 2:** Full time employee of Forest Research Institute, **Part 3:** Full time employee of Forest Research Institute; A. Ruth, **Part 1:** Adam Ruth is a full time employee of Prescott Medical Communications Group, a Forest Research Institute contractor, **Part 2:** Adam Ruth is a full time employee of Prescott Medical Communications Group, a Forest Research Institute contractor, **Part 3:** Adam Ruth is a full time employee of Prescott Medical Communications Group, a Forest Research Institute contractor.

W192. Predictive Deficits Underlie Auditory Verbal Hallucinations in Schizophrenia: A Model-based fMRI Study

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Background: Active psychosis in schizophrenia is among the most severe and burdensome medical conditions worldwide. Nevertheless, the mechanisms of auditory verbal hallucinations (AVH) and other positive symptoms of psychosis are not well understood. Previous research suggests that deficits in prediction and learning mechanisms, such as prediction-error signaling, may underlie the generation of positive symptoms, although a direct link between such deficits and the generation of symptoms remains to be established. The present study used fMRI to identify (1) neural activations related to AVH and (2) sensory prediction-error signals in the auditory cortex in patients with schizophrenia. We hypothesized that patients would show a deficit in prediction-error signaling and that this deficit would correlate with increased resting activation in the auditory cortex, a neural phenotype of AVH.

Methods: Ten patients with schizophrenia who reported experiencing frequent AVH and 10 sociodemographically and neuropsychologically matched controls participated in this study. We used a sparse-sampling fMRI paradigm that manipulated participant's expectations to hear speech by varying the probability of speech stimuli (versus blank stimuli) at different periods of the task. Participants were asked to press a button immediately following each trial if they heard speech during that trial. We operationalized AVH as trials in which no stimulus was presented but in which a speech percept was signaled. Based on a predictive-coding algorithm, we computed a trial-by-trial estimate of speech prediction errors and regressed this estimate against BOLD signal for each participant. Group-level regression analyses in SPM8 included a within-patient t-test of AVH versus blank trials and a group-by-stimulus ANOVA for testing between-group differences in prediction-error effects, as well as region-of-interest-based Pearson correlations.

Results: Patients had an average of 20 AVH episodes in the scanner. In patients, AVH trials had increased activation in the left superior temporal sulcus compared to blank trials ($p = 0.001$, uncorrected). All 20 participants showed prominent prediction-error signals in the auditory cortex, but patients had abnormally decreased prediction-error signals in the right superior-middle temporal cortex ($p < 0.05$, corrected). The magnitude of activation during blank trials in the auditory region associated with AVH correlated strongly with the magnitude of the deficit in prediction-error signaling across participants ($r = 0.51$, $p = 0.02$). Patients receiving higher doses of antipsychotic treatment exhibited less prediction-error deficits ($p = 0.04$, one-tailed).

Conclusions: We replicated the previously reported finding that increased activation in the auditory cortex accompanies the experience of AVH in patients with schizophrenia, and we further showed that these patients had a concomitant deficit in sensory prediction-error signals in a similar region of the auditory cortex. Importantly, our findings tie deficits in prediction-error signaling to the degree of auditory activation in the absence of a stimulus, thereby establishing for the first time a direct link between deficits in sensory predictive-coding and the neural phenotype of AVH,

and highlighting the importance of prediction and learning mechanisms in schizophrenia.
Keywords: schizophrenia, hallucinations, psychosis, model-based fMRI, predictive-coding
Disclosure: G. Horga, Nothing to Disclose; K. Schatz, Nothing to Disclose; A. Abi-Dargham, Nothing to Disclose; B. Peterson, Nothing to Disclose.

W193. Effect of Paternal Age on Schizophrenia-related Endophenotypes: Examination of Data from the Consortuim on the Genetics of Schizophrenia (COGS)

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Background: Multiple studies have documented that children of older fathers have increased risks of developing schizophrenia spectrum disorders, and that among those offspring who develop such disorders, those with older fathers present with more severe clinical symptoms. This effect seems to begin among offspring of fathers in their mid thirties and the effect increases at least until the fathers are in their fifties. The magnitude of the effect of paternal age may be small and the mechanism by which it is exerted is unknown. The influence of advanced paternal age on neurophysiological abnormalities related to schizophrenia is also unknown. Examination of the relationship between paternal age and endophenotypes will help guide research efforts to clarify the mechanisms by which advanced paternal age increases the risk of schizophrenia.
Methods: We examined the associations between paternal age and endophenotypic deficits in the well-characterized family-based sample from the Consortium on the Genetics of Schizophrenia (COGS). All families included at least one affected subject and one unaffected sibling. Subjects underwent standardized clinical assessments and met criteria for schizophrenia (probands; n = 293) or were unaffected first-degree siblings of those probands (n = 382). All subjects had information on paternal age available and completed a comprehensive endophenotype battery, which included prepulse inhibition, antisaccade performance, the continuous performance task, the letter-number span task, the California Verbal Learning Task, and the Pennsylvania Computerized Neurocognitive Battery (an assessment of abstraction and mental flexibility, verbal memory, face memory, spatial memory, spatial processing, sensorimotor dexterity, and emotion processing). After controlling for covariates, potential paternal age–endophenotype associations were analyzed in probands alone and then analyzed in both probands and unaffected siblings. We employed simple models as well as models with interactions that accounted for gender and multiplex (vs. sporadic) families. We examined the data using both paternal age at birth as a continuous variable as well as dichotomizing subjects by those whose fathers were older or younger or than 40 years old when they were born.
Results: Preliminary analysis of 16 endophenotypes showed that the Continuous Performance Test–Identical Pairs (both 3-digit and 4-digit versions), Verbal Memory, Spatial ability, abstraction, and sensorimotor dexterity were associated with paternal age. However, the association of the CPT-IP tasks and spatial ability with advanced paternal age was in the positive (i.e., the opposite of predicted) direction, and the other endophenotypes showed interaction effects with positive and negative directions (e.g., abstraction positive for probands and negative for siblings). After appropriate statistical corrections for multiple tests, no significant associations between paternal age and endophenotype performance were present. Quantifying paternal age as a dichotomous versus a continuous variable did not qualitatively change the results.
Conclusions: Given the literature indicating that paternal age is positively correlated with schizophrenia risk, we predicted that older paternal age would be associated with worse endophenotype performance However, in the COGS data set there was no association between paternal age and performance on any endophenotype. One possible explanation for this lack of an association may be that paternal age influences neurobiological processes that are independent of the neurobiological processes reflected by endophenotype performance. Another explanation may be that the COGS sample differed from the general population of schizophrenia patients in that, by design, non-ill family members were available to complete an extensive neurocognitive battery. Analysis of data from larger samples that include patients from families that are not intact will be necessary to definitively explore the effect of paternal age on schizophrenia-related endophenotype performance.
Keywords: Genetics, Schizophrenia, Paternal Age, Endophenotypes
Disclosure: A. Radant, Nothing to Disclose; S. Millard, Nothing to Disclose; D. Tsuang, Nothing to Disclose; M. Esterberg, Nothing to Disclose; D. Braff, Nothing to Disclose; N. Swerdlow, Nothing to Disclose; M. Green, **Part 1:** Dr. Green has been a consultant for Abbott, Cypress, Dainippon Sumitomo, Lundbeck, Otsuka, Sanofi-Aventis, Takeda, and Teva, and he has been a speaker for Janssen, Cilag, Otsuka, and Sunovion; K. Nuechterlein, **Part 4:** Dr. Nuechterlein, reports an investigator-initiated research grant from Ortho-McNeil Janssen Scientific Affairs and consultation to Merck and Wyeth; L. Siever, Nothing to Disclose; J. Silverman, Nothing to Disclose; B. Turetsky, **Part 1:** Dr. Turetsky has received unrelated research support from AstraZeneca and Pfizer and is a consultant to Roche; L. Lazzeroni, Nothing to Disclose; M. Calkins, Nothing to Disclose; L. Seidman, Nothing to Disclose; A. Olincy, **Part 1:** Dr. Olincy has received unrelated research support from Lundbeck.

W194 Brain Structural Community Abnormalities Revealed using PLACE (Path Length Associated Community Estimation)

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Background: We investigated node-level community structure abnormalities in bipolar I disorder. Community structures were extracted using top-down hierarchical trees via the maximization of a novel metric ψ^{PL}. Additionally, a complete statistical framework (PLACE) was developed to detect changes in community on the nodal level.
Methods: We scanned 25 bipolar I subjects (14 male/11 female; age: 41.7 ± 12.6) and 25 gender/age matched healthy subjects (13 male/12 female; age: 42.2 ± 10.8) on a Siemens 3T Trio scanner. T1 weighted images were acquired with MPRAGE sequence (FOV = 250 × 250 mm; TR/TE = 1900/2.26 ms; flip angle = 9°; voxel size = 1 × 1 × 1 mm). Diffusion weighted (DW) images were acquired using SS-SE-EPI sequences (FOV = 190 × 190 mm; resolution 2 × 2 × 2 mm; TR/TE = 8400/93 ms; 64 gradient, b = 1000 s/mm^2 and one bo image). Structural brain networks were generated using a pipeline consisting of eddy current correction followed by the computation of diffusion tensors and then deterministic tractography. MPRAGE images were used to generate label maps using the Freesurfer software. Brain networks formed by the 68 cortical regions were generated by counting the number of fibers connecting each pair of nodes. We propose to extract community structure by finding groups of nodes that are highly integrated. Our method is based on ψ^{PL}, defined as the difference between the mean inter- and the mean intra- modular path lengths ($inter_{PL}$/$intra_{PL}$). For two communities C_i and C_j the $inter_{PL}$ and $intra_{PL}$ are

defined as: $\text{inter}_{PL}^{Ci \leftrightarrow Cj} = \Sigma_{n \text{ in } Ci,\, m \text{ in } Cj} \{d_{nm} / (N_i N_j)\}$, $\text{intra}_{PL}^{Ci} = \Sigma_{n,\, m \text{ in } Ci;\, n>m} \{d_{nm} / (N_i^2 - N_i)/2\}$ where N_i denotes the number of nodes in a community C_i, d_{nm} denotes the shortest path length connecting nodes n and m. In the case of two modules, for example, ψ^{PL} is defined as: $\psi^{PL} = \text{inter}_{PL}^{C1 \leftrightarrow C2} - 0.5*(\text{intra}_{PL}^{C1} + \text{intra}_{PL}^{C2})$. To partition the 68 cortical regions into modules, we conducted hierarchical clustering. At the first level, brain regions were randomly assigned to one of two modules, and optimal assignment was determined using simulated annealing. This process is repeated at each level until a 4-level binary tree is reached (a total of 16 modules). To assess group-level community structure differences between a test tree and a *reference* tree, we propose a node-level consistency measure (Z) for each node k as follows: $Z(k) = (N_c)^2/(N_p N_q)$; $k = 1 \ldots 68$where N_c denotes the number of common nodes between the two communities C_p and C_q, that contain this node k in the *test* and *reference* trees. In order to examine group differences in community structures at the nodal level, we first construct the group mean trees (for control and bipolar group) by extracting the community structure corresponding to the group mean connectivity matrices. Next, all individual subjects' trees are compared to the mean control tree (i.e., *reference* tree), thus yielding 25 Z vectors in the healthy group, and 25 in the bipolar group. To detect group differences in local community structures, node-wise 2-sample T-tests for Z were conducted. Alternatively, a more powerful test can be constructed, for each community in the 4th level binary tree of the mean normal group, by concatenating the Z vectors of all nodes in this community, on which 2-sample Hotelling's T-squared tests are conducted.

Results: Results showed a significant group difference ($p = 0.0059$, uncorrected) in bipolar versus control for the community containing the bilateral paracentral gyrus and posterior cingulate (figure). On a node level, T-tests on Z revealed similar findings. In particular, the right paracentral gyrus exhibited the lowest node-level consistency ($p = 0.0005$, passing Bonferroni correction). Qualitative comparison between the two mean community structures reveals that the right and left paracentral gyri, while belonging to the same community in the healthy group, are assigned to different communities in the bipolar group. Additionally the right isthmus and posterior cingulate, paracentral gyrus and precuneus are assigned to one community while the same regions in the left hemisphere are assigned to another community.

Conclusions: Results revealed a relative left-right decoupling in the community structure of bipolar subjects, adding to a growing body of literature implicating deficits in inter-hemispheric communication. Of note, in one of our previous studies using a similar sample, global deficits were found across all regions of corpus callosum, although more prominent deficits were noted in the anterior section. By contrast, using PLACE here the left-right decoupling is most prominent in the posterior part of the brain involving regions of the default mode network (DMN). While it is unclear why anterior DMN regions were not found to exhibit group difference in this current study, it is likely that investigating community structure using PLACE may reveal configurational abnormalities, instead of localized white matter integrity changes as investigated in previous studies. Lastly, as all subjects were euthymic, this decoupling effect indicates persistent community structural abnormalities in the absence of a mood episode. Part of the DMN, especially the bilateral precuneus, has been theorized to be responsible for reflective self-awareness. Our findings thus further support the role of DMN in affective disorders. Future studies may be needed to further investigate the dependence of such decoupling on mood states.

Keywords: Brain Community Structure, Bipolar disorder, DTI, Connectome

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W195. Testing Glutamatergic Strategies in Early Psychosis: Longitudinal Rodent Pharmacological MRI Studies and a Randomized, Double-blind, Placebo-controlled Proof-of-concept Trial in Patients at Clinical Risk for Psychosis

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Background: Our recent studies using a coordinated brain imaging and animal models approach have implicated hippocampal hypermetabolism as a biomarker of acute psychosis and psychosis risk. Here, we have extended this work in patients and rodents by longitudinally testing glutamate-lowering therapeutic strategies on hippocampal structural and functional MRI imaging endpoints. First, we have studied the subchronic NMDA antagonist rodent model of psychosis and the role of glutamatergic pre-treatment in preventing hippocampal abnormalities and second we have completed a randomized, double-blind, placebo controlled proof-of-concept trial in patients at clinical risk for psychosis. The longitudinal rodent study builds upon previous work which suggests that hippocampal hypermetabolism in schizophrenia and related disorders is driven by increases in extracellular glutamate efflux, and that increases in extracellular glutamate are a pathophysiologic mechanism underlying functional and structural progressive brain abnormalities in psychotic disorders. Reduction of excess, potentially neurotoxic glutamatergic activity through a range of pharmacologic strategies, including gabapentin pre-treatment, may reduce abnormal hypermetabolism in hippocampal subregions and prevent hippocampal volume reduction. The clinical intervention tested is informed by prior clinical studies which suggest that gabapentin is effective as an add-on therapy to reduce psychotic symptoms in patients with schizophrenia and related disorders.

Methods: We first performed a longitudinal pharmacological MRI imaging study of C57b6 mice ($n = 8$ per group) exposed to intermittent ketamine S.Q. (8 mg, 16m/kg, 32 mg/kg) vs. saline three times weekly over one month (total $n = 12$ doses) and measured chronic changes in basal hippocampal metabolism and structure at one month 48 hours after last drug dose. We next pre-treated a second cohort of rodents with a glutamate limiting strategy (gabapentin 150 mg/kg or LY379268 10 mg/kg) vs. saline 30 min prior to intermittent ketamine 16 mg/kg in the same paradigm to determine the effects of this pre-treatment strategy on hippocampal functional and structural imaging endpoints at one month 48 hours after the last drug dose. Finally, to see if a glutamate-limiting strategy would lower hippocampal CBV and reduce early psychotic symptoms *in-vivo*, we performed a three week, randomized, double-blind, placebo-controlled trial comparing gabapentin (3200 mg/d) vs. placebo, with patient tolerability and safety; longitudinal changes in hippocampal subregional CBV; and longitudinal changes in symptoms as assessed by the Structured Interview for Prodromal Syndromes (SIPS) as outcomes. We further tested the association between subthreshold psychotic symptom changes and changes in hippocampal metabolism in trial subjects.

Results: In mice exposed to sub-chronic ketamine, hippocampal hypermetabolism and hippocampal atrophy were evident by one month in the 16 mg/kg and 32 mg/kg groups. These abnormalities were prevented by a glutamate-lowering pre-treatment strategy. Clinically, a total of $n = 5$ subjects received gabapentin (3200 mg/d) and $n = 4$ subjects received placebo, with $n = 9$ subjects enrolled and completed, with no drop outs. Randomization to high-dose

gabapentin was well-tolerated and safe in this clinical population with no adverse events reported. Subthreshold positive psychotic symptoms ($t_7 = 2.2$, $p = .06$) and hippocampal CA1 CBV ($t_7 = 1.9$, $p = .09$) were reduced at a trend level in subjects randomized to gabapentin. Reduction in CA1 subfield CBV was associated with improvement in subthreshold positive psychotic symptoms across groups ($r = .73$, $p = .025$, $n = 9$). There was no apparent trend for gabapentin to reduce general or disorganized symptoms, though negative symptoms were nominally reduced on the SIPS/SOPS ($t_7 = 1.3$, $p = .21$). Improvement in positive symptoms was associated with improvement in negative symptoms across groups ($r = .75$, $p = .021$).

Conclusions: These preliminary results suggest the utility of glutamate-limiting drugs in patients meeting both clinical and brain biomarker criteria to delay, attenuate, or prevent onset of psychosis-related phenotypes, including lowering of abnormal hippocampal hypermetabolism, protection of hippocampal structure, and reduction of subthreshold symptoms of psychosis. Future clinical research will extend this study period to test the effects of a glutamate-limiting therapeutic strategy on hippocampal structure longitudinally in patients at clinical risk for psychosis and to test the efficacy of this strategy in early psychosis including the possibility of clinical prevention.

Keywords: hippocampus, psychosis, glutamate, ketamine, MRI

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W196. Transient Ziprasidone's Dopamine D2/3 Receptor Occupancy - A Clinical 24-hour [11C]-Raclopride PET Study

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Background: Ziprasidone is an atypical antipsychotic with relatively short peripheral half-life (6-7 hours). Thus, it is currently recommended to be taken in divided dosage – typically twice a day. However, previous studies suggest that once a day dosing may sustain striatal dopamine $D_{2/3}$ receptor occupancy within the 60-70% therapeutic range at peripheral trough levels. The purpose of this study was to investigate if ziprasidone's occupancy to the dopamine $D_{2/3}$ receptors is maintained across a day employing a within subject design.

Methods: Positron Emission Tomography (PET) scans with [^{11}C]-Raclopride were performed in 12 patients with schizophrenia and 44 healthy controls. Each patient completed [^{11}C]-Raclopride PET scans at 5, 13 and 23 hours after the last dose of ziprasidone 60 mg. Previous to the PET scan, patients were maintained on oral ziprasidone monotherapy at 120 mg/day divided in two doses for at least 1 week. PET scans were performed on a high-resolution neuro-PET camera system CPS-HRRT. Binding potential non-displaceable (BP_{nd}) from patients and controls was estimated with the simplified reference tissue model using the cerebellum as reference region. The patient's $D_{2/3}$ receptor occupancies were estimated with reference to BP_{nd} data of controls in the caudate, putamen and ventral striatum. Nonlinear regression analysis was applied to correlate the plasma level of ziprasidone with receptor occupancy. The data was fitted to a rectangular hyperbola (one-site occupancy model) to estimate ED_{50} (serum level of ziprasidone associated with 50% receptor occupancy). The time-course of receptor occupancy across the regions of interest, indicating a central receptor occupancy half-life, was estimated by a 1-phase exponential decay equation.

Results: The mean occupancies in the putamen at 5, 13 and 23-hour were 66%, 39% and 2% (5 h vs. 13h: $Z = -2.191$, $p = 0.028$; 13 h vs. 23h: $Z = -2.701$, $p = 0.007$); in the caudate were 62%, 35% and -6% (5 h vs. 13h: $Z = -2.497$, $p = 0.013$; 13 h vs. 23h: $Z = -2.701$, $p = 0.007$); and in the ventral striatum were 68%, 47% and 11% (5 h vs. 13h: $Z = -2.497$, $p = 0.013$; 13 h vs. 23h: $Z = -2.497$, $p = 0.013$). The time-course of receptor occupancy across regions indicated an occupancy half-life of 8.3-hour (CI 95%: 4.6-39-hr; $R^2 = 0.56$). The ED_{50} across regions was estimated to be 204 nmol/L (84 ng/ml) (CI 95%: 177-231 nmol/L; $R^2 = 0.68$). Prolactin levels were higher at 5 hours than 13 hours ($Z = -2.934$, $p = 0.003$), and higher at 13 hours than 23 hours ($Z = -1.994$, $p = 0.046$).

Conclusions: This is the first study to assess ziprasidone's central occupancy at 3 time points using a within-subject design. Our results indicate that ziprasidone has a mean occupancy of 66% in the putamen 5 hours after administration, which then declines to 39% at 13 hours and 2% at 23 hours, corresponding to an estimated central half-life of ziprasidone of 8.3 hours. Thus, the time-course of the ziprasidone's central dopamine binding mirrors its known peripheral pharmacokinetics. Our results bear closer resemblance to those with quetiapine and clozapine for which no occupancy has been shown one day after the last dose. They also stand in a sharp contrast to the longer central than peripheral pharmacokinetics reported with olanzapine and risperidone as well as aripiprazole. However, ziprasidone, which has a dissociation constant (K) between 2.7 nM and to 6 nM, exhibits *in vitro* more than 20-fold higher affinity for the dopamine D_2 receptors in comparison to clozapine (K = 76 to 180 nM) and quetiapine (K = 140 to 680 nM). The rapid central decrease in $D_{2/3}$ receptor occupancy we observed with ziprasidone may entirely be associated with a short central half-life that mirrors the peripheral half-life. This is in contrast to the combination of fast dissociation and short central half-life described with quetiapine and clozapine. In addition, the short central occupancy half-life may contribute to its relatively low incidence of EPS at clinical doses. The time-course of striatal occupancy also was mirrored by a similar rate of decline in plasma prolactin levels, lending further support to our main finding. The results indicate that ziprasidone 60 mg should be administered twice daily to sustain therapeutic central dopamine D2 receptor occupancy (i.e. 60%).

Keywords: Antipsychotic, PET, Ziprasidone, Dopamine, D2

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W197. Modafinil Modulates Activation and Functional Coupling of the Prefrontal Cortex During Working Memory in Patients with Schizophrenia

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Background: Schizophrenia has been associated with altered functional coupling within cortical circuits. Consistent with this, recent studies have shown abnormal connectivity between the dorsolateral prefrontal cortex (DLPFC) and other brain regions underlying working memory in patients with schizophrenia (PTs) compared to healthy volunteers, especially hippocampus formation (HF) (Rasetti et al, 2011). Evidence also indicates monoaminergic drugs modulate neural circuits including those underlying working memory (Mattay et al, 2003; Apud et al, 2007; Rasetti et al. 2010). In the current study, we explore the effect of Modafinil, a wake-promoting agent that works through adrenergic, dopaminergic, histaminergic and GABAergic mechanisms, on the activity and connectivity of brain regions underlying working memory in patients with schizophrenia and healthy volunteers. Based on evidence that monoamines spatially tune the neuronal signal during information processing, we hypothesized that modafinil would enhance cortical efficiency and DLPFC-HF coupling during working memory task.
Methods: We performed a double-blind, placebo-controlled, cross-over study. Coded modafinil (100 mg/day) or placebo was administered orally for 7 days and fMRI was performed two hours after medication administration on the seventh day. The second arm of the study was performed after a one-week wash-out period following the first arm. Forty-five HVs (30 males, 15 females; Mean age = 31.7 years) and 11 PTs (7 males, 4 females; Mean age = 25.9) underwent BOLD fMRI (3T) while performing the 2-back working memory task. Gender, race and handedness were similar across the groups. First level processing and second level analysis (factorial ANCOVA with drug and diagnosis as factors and age, IQ and 2-back accuracy as covariates of no interest) were conducted in SPM5. Coupling between the right DLPFC (rDLPFC), a region showing abnormal functional coupling in PTs (Rasetti et al, 2011), and other brain regions involved in working memory was measured in each subject using psycho-physiological interaction (PPI) model in SPM5.
Results: There was a main effect of diagnosis on left middle frontal gyrus activity (x y z = -27 0 69, Z = 3.27, $p_{uncorr} = 0.001$), with PTs showing greater activation than HVs. There was a main effect of drug ($p_{FWE} = 0.09$ within BA46/middle frontal gyrus ROI), with modafinil decreasing DLPFC activation, both in PTs and in HVs. PPI analysis revealed a main effect of drug with increased rDLPFC-HF coupling (x y z = -27 -21 -15, Z = 4.24, pFWE = 0.005) on modafinil when compared to placebo. This latter effect was due to an increase in the coupling in the sample of PTs, while no significant differences were observed in HVs. This was confirmed by the analysis of drug*diagnosis interaction (x y z = -30, -21, -15, Z = 3.38, pFWE = 0.050). Specifically, in PTs only, coupling between the right DLPFC and hippocampus shifted from negative during placebo to positive during modafinil, mimicking the positive coupling observed in HVs. Similar results of an effect of modafinil on right DLPFC-hippocampus coupling in PTS were observed in the analysis of a smaller sample (NCs = 11, PTs = 11) in which the groups were matched for gender, race, handedness and 2-back accuracy and age was used as a covariate of no interest.
Conclusions: The results suggest that modafinil not only modulates DLPFC activity during working memory as previously reported (Rasetti et al, 2010), but also modulates the functional coupling of the right DLPFC with hippocampus. Interestingly, the connectivity modulating effects of modafinil between the right DLPFC and hippocampus, were much more predominant in PTs. Overall, these results indicate that monoaminergic drugs including Modafinil differentially modulate the neural circuitry underlying working memory in patients with schizophrenia compared to healthy volunteers.
Keywords: Modafinil, Working Memory, DLPFC, fMRI, Schizophrenia
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W198. Neural Correlates of the Discrepancy between Verbal and Performance IQ

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Background: Many psychiatric disorders are characterized by large discrepancies between verbal and perceptual abilities. Children with language delay or autism, for example, have low verbal relative to perceptual ability (1), whereas children with nonverbal learning disability have high verbal relative to perceptual abilities (2). The underlying neural correlates of the VIQ-PIQ discrepancy have not yet been examined.
Methods: Using surface-based deformations to analyze brain morphology, we examined the neural correlates of the VIQ-PIQ discrepancy in two independent samples (n = 62, 83) collected on two scanners of differing field strengths (1.5Tesla and 3Tesla) of healthy control participants (age 5-54 years). We correlated the VIQ-PIQ discrepancy with cortical thickness (CT) and with the difference between the CT of the right and left hemispheres, at each voxel on the cerebral surface. **Cortical Gray Matter Segmentation.** We sampled gray-scale values of "pure" representations of cortical gray and white matter bilaterally in the frontal, temporal, occipital, parietal lobes. We averaged these 4 values for each tissue type, and computed a threshold value halfway between the mean gray and white matter values; these threshold values on a slice-by-slice basis provided an initial rough classification of cortical gray and white matter that were then manually edited. The intraclass correlation coefficient measuring reliability of cortical gray matter volumes using a 2-way random effects model was 0.98. **Cortical Thickness.** Isolated brains were coregistered to a selected template brain (3) using a similarity transformation, followed by a high-dimensional, nonrigid warping algorithm based on the dynamics of fluid-flow. We subtracted the coregistered brain of each participant from its cortical mantle and used a three-dimensional morphological operator to distance-transform the white matter surface to the nearest point on the inner surface of the cortical gray matter of the same participant (4, 5) to calculate CT. Because the brain and its local features, such as CT, were scaled during the similarity transformation of that brain to the template brain, these thicknesses values, measured in template space, inherently

accounted for generalized scaling effects within the cerebrum.
Analyses. We used multiple linear regression at each point on the reference surface to examine associations of VIQ-PIQ with CT. We used False Discovery Rate to account for the multiple correlations computed across the cortical surface (6). We computed the correlation between CT and VIQ-PIQ, and evaluated the *p*-value of this correlation using a Student's *t*-test. Statistical maps displayed color-coded *p*-values across the surface of the cortex.
Results: In both samples, we detected significant cortical thinning associated with an increasing discrepancy between verbal and spatial abilities in bilateral anterior and posterior cortex. In both samples, significant cortical thinning is observed in both right and left hemispheres in the medial aspect of the prefrontal cortex, and in the lateral aspect of the occipital lobes, including the inferior and middle occipital gyri. We further detected thickening of cortex in right hemisphere relative to the left associated with better verbal than spatial ability, and cortical thickening in the left relative to right associated with better spatial than verbal ability, in the superior temporal gyrus, lateral front-orbital gyrus, and the middle frontal gyrus in the 1.5T sample, and in the same regions but also including the middle temporal gyrus and middle and inferior occipital gyri in the 3T sample.
Conclusions: We have identified neural correlates that explain one aspect of variability in normal intelligence that has not been explored previously. The brain regions associated with the VIQ-PIQ discrepancy support specific aspects of information processing, and variation in cortical anatomy in these regions may underlie dysfunction in information processing that would specifically affect performance on IQ tasks. Posterior regions support object recognition (7), the integration of multisensory data (7), word recognition (8), and receptive language (9), functions that contribute to both VIQ and PIQ. Anterior regions support coordination of multiple cognitive systems (10), behavioral inhibition (11), crystallized knowledge (12) and verbal fluency (13, 14), all functions that contribute to VIQ and PIQ. The study provides the first examination of the neural correlates of the VIQ-PIQ discrepancy in healthy people. We demonstrated that the VIQ-PIQ discrepancy is associated with CT and is represented bilaterally in the brain. Further, thickening in right hemisphere CT relative to left was associated with poor spatial relative to verbal skill, and thickening in left hemisphere CT relative to right was associated with poor verbal relative to spatial performance. This finding supports theories that propose variation in cortical anatomy, such as cerebral asymmetry, underlies differences cognitive competencies within individuals.
Keywords: Verbal IQ, Performance IQ, Cortical thickness, Morphometry, MRI, Cerebral Asymmetry.
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W199. Role of Hypocretin-dynorphin Co-transmission in Motivated Behavior

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Background: Hypocretin (orexin) is a hypothalamic peptide implicated in arousal and reward seeking. Genetic or pharmacological reduction of hypocretin signaling attenuates the reinforcing effects of natural rewards like reproductive behavior as well as those of many drugs of abuse (e.g. nicotine, cocaine). These effects resemble those produced by activation of the kappa opioid receptor (KOR) which binds the endogenous opioid peptide dynorphin that is implicated in dysphoria and depressive-like states. Hypocretin and dynorphin may exert opposing effects on brain reward systems, with hypocretin enhancing and dynorphin reducing reward sensitivity. Despite their opposing actions, both peptides are known to be expressed by the same population of neurons in the hypothalamus that projects to areas of the midbrain (i.e. ventral tegmental area, VTA) that are critical for the expression of motivated behavior. We sought to determine whether hypocretin and dynorphin systems interact in a manner that influences motivated behavior.
Methods: The ultrastructural localization of hypocretin and dynorphin immunoreactivity in mouse hypothalamus was visualized with electron microscopy. To measure sensitivity of brain reward circuitry after treatment with hypocretin- or KOR-antagonists, mice were implanted with lateral hypothalamic stimulating electrodes and trained in a rate-frequency variant of the intracranial self-stimulation (ICSS) procedure. Attention, motor impulsivity, and operant responding for food reward in drug-treated rats were measured using the 5-choice serial reaction time task (5CSRTT). Likewise, drug taking was assessed using operant intravenous self-administration of cocaine by mice lacking the hypocretin-1 receptor ($HcrtR1^{-/-}$) or wildtype controls ($HcrtR1^{+/+}$). The effects of a KOR antagonist on cocaine taking were then measured in both lines of transgenic mice. To identify the locus of action for the effects of drugs or genetic manipulations on the behaviors tested, whole cell current-clamp recordings were made from mouse brain slices containing the VTA. The effects of bath-applied hypocretin and dynorphin on spontaneous firing rate of identified dopamine (DA) neurons were measured. To test whether VTA DA neurons mediate the effects of hypocretin-dynorphin transmission on drug taking, rats were implanted with intra-VTA cannulae for delivery of antagonists and trained to self-administer cocaine intravenously.
Results: Hypocretin and dynorphin were colocalized in cellular compartments, including axonal vesicles, in nearly all instances where immunolabeling was detected. The HcrtR1 antagonist SB334867 produced dose-dependent increases in ICSS thresholds that were abolished by pretreatment with the KOR antagonist norbinaltorphimine (norBNI). Likewise, impulsivity (as reflected by premature responses) in the 5CSRTT was attenuated by SB334867, and this effect was blocked by norBNI pretreatment. Similarly, cocaine-induced increases in impulsivity were abolished by SB334867 pretreatment. Intravenous cocaine self-administration was significantly reduced in $HcrtR1^{-/-}$ mice and this effect was reversed with norBNI treatment. *In vitro* recordings of VTA DA neurons showed that hypocretin and dynorphin caused the predicted effects on spontaneous firing rate, exciting or inhibiting these cells, respectively. Concurrent application of both peptides, however, yielded no net effect on firing rate. In rats trained to self-administer cocaine intravenously, intra-VTA infusion of SB334867 reduced cocaine intake and this effect was blocked by norBNI pretreatment.
Conclusions: The close anatomical association of hypocretin and dynorphin in VTA-projecting hypothalamic neurons raises the possibility that both peptides are co-released under conditions of intense depolarization and function as co-neuromodulators. Impaired hypocretin function attenuates the rewarding effects of lateral hypothalamic stimulation, abolishes cocaine-induced impulsivity, and markedly reduces cocaine self-administration. Concurrent impairment of dynorphin function reverses these behavioral effects. These observations can be explained in part by the opposing actions of hypocretin and dynorphin on the firing rate of VTA DA neurons. This idea is substantiated by the ability of intra-VTA HcrtR1 blockade to decrease cocaine taking and for KOR blockade to reverse this effect. While the actions of both peptides appear to be modulatory (i.e. disruption of HcrtR1 and KOR signaling reduced but never completely abolished the behaviors tested), our findings suggest a novel cellular mechanism for adjusting the sensitivity of brain reward systems, with

hypocretin enhancing, and dynorphin reducing reward sensitivity by their actions in the VTA.
Keywords: Reward motivation addiction neuropeptide dopamine
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W200. Functional Capacity Assessment in Older Adult Populations

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Background: Existing research on aging and cognition has shown that many cognitive abilities such as processing speed, working memory and spatial cognition decline with age. Declines are especially apparent under conditions of complexity; when a task represents an unfamiliar cognitive domain; and for populations with cognitive impairments such as MCI, dementia or persistent mental illness. Recently much attention has been given to the identification of both pharmacological and non-pharmacological strategies to prevent or remediate cognitive declines. Clearly the development of efficacious remediation strategies must be dependent on a clear understanding of the relationship of declines in cognitive abilities to the performance of routine everyday activities. Currently much of the assessment of functional performance is based on standardized neuropsychological measures of abilities or paper and pencil based tests of functional performance. Unfortunately these measures do not capture the complexities of everyday tasks and are not deliverable remotely. We have developed an innovative approach to functional assessment which involves technology-based simulations of routine everyday activities. Data will also be presented regarding the performance of these tasks from diverse samples of adults and on the relationships between component cognitive abilities and task performance.
Methods: The samples included male and female adults ranging in age from 18 to 91 years of age from a variety of educational and ethnic backgrounds who lived independently in the community and varied in cognitive status. All of the participants were recruited for participation in research projects examining aging, cognition and functional performance conducted at the NIH funded Center for Research and Education on Aging and Technology Enhancement. All participants in each of the studies completed a battery of standardized neuropsychological measures of component cognitive abilities. In addition, performance data was collected on a variety of routine everyday activities including money management, health information seeking, medication management, health benefits decisions, and basic work activities using computer-based task simulations. The simulations included using an ATM to perform banking transactions and a telephone menu system to refill prescriptions and manage basic home utility tasks. The simulations are unique in that they present current technology-based versions of these tasks, which is important given the ubiquitous requirements for use of technology across all domains important to independent functioning.
Results: The task performance data included real time measures of accuracy, types of difficulties encountered by the participants and response times. Overall, the data showed that younger adults typically out perform older adults on these basic routine activities. Importantly however, the tasks were also sensitive to detecting within age cohort performance differences even among the non-impaired samples of older adults. In general in addition to wide inter-cohort performance differences there were also wide intra-cohort performance differences. As expected there were also differences in performance between the impaired and non-impaired samples of elderly. The data also indicated that component cognitive abilities were strong predictors of performance and variability in ability performance mappings. These relationships were found after controlling for differences in other potential moderating factors such as level of education.
Conclusions: Overall, the data from this series of studies indicate that a computer-based task assessment battery may be a useful tool for assessing functional performance in a variety of patient populations. Technology offers a flexible format that allows for easy tailoring of the assessment protocols to meet the needs of unique populations or settings and the possibility of administering assessments and delivery interventions remotely outside of clinical settings such as the home, residential facilities or outpatient treatment centers. The battery may also be used for assessment of the effects of cognitive remediation or pharmacological interventions.
Keywords: functional assessment; cognition, aging, technology-based simulations
Disclosure: S. Czaja, Nothing to Disclose; P. Harvey, **Part 2:** Abbot Labs, Amgen, Boeheringer Ingelheim, Bristol-Myers-Squibb, Forest Labs, Genetech, Johnson and Johnson, Pharma Neuorboost, Roche Pharma, Shire Pharma, Sunovion Pharma, Takeda Pharma, **Part 4:** Astra-Zeneca; D. Loewenstein, Nothing to Disclose.

W201. Differences in Amphetamine-evoked Dopamine Release in Cortex and Striatum

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Background: In addition to its abuse potential, amphetamine (AMPH) is a widely prescribed treatment for attention deficit hyperactivity disorder (ADHD). Extensive rodent studies suggest that the behavioral effects of therapeutic doses of amphetamine and other psychostimulants are preferentially mediated by the cortical catecholamines, norepinephrine and dopamine compared to subcortical regions. Given differences in the effects of psychostimulants on cerebral metabolic rate between rodents and primates, it is important to compare the effects of amphetamine on extracellular dopamine levels between cortex and striatum in non-human primates. As part of combined microdialysis/PET imaging studies to measure cortical DA release with the radiotracer [11C]FLB 457, we compared the effect of multiple doses of AMPH on cortical and sub-cortical DA levels using *in vivo* microdialysis in 5 adult rhesus macaques.
Methods: On the day prior to the dialysis experiment, microdialysis probes were implanted at bilateral target locations in the anterior cingulate cortex and the caudate based on co-registered MRI and CT images. Samples were collected every 10 min for 1 h prior and 2 hours following intravenous injection of a single dose of AMPH.
Results: Average baseline DA levels in the anterior cingulate cortex were 0.31 ± 0.03 nM ($n = 31$ observations). Upon injection of AMPH (0.15, 0.3, 0.5, or 1.0 mg/kg), cortical DA levels increased to 593 ± 36, 965 ± 130, 1385 ± 213, or 2067 ± 393 % of baseline levels. In the cortex, peak levels were achieved after 30-40 min followed by a slow decline. Nevertheless, DA levels remained elevated for the remainder of the experiment (2 hrs). Average baseline levels in the caudate were 12.9 ± 2.9 nM ($n = 12$ observations). Injection of AMPH (0.3, 0.5, or 1.0 mg/kg) increased DA to 1834 ± 282, 2670 ± 809, or 5807 ± 235 % of baseline levels, respectively. In the caudate, this peak increase was achieved after approximately 20 min and followed by an apparent biphasic decline. Following an initial rapid decline (50-70 min post AMPH), DA levels continued to decrease much more slowly and remained elevated at relative levels (% baseline) similar to those in the cortex.
Conclusions: These data are the first report demonstrating a regionally different temporal profile of AMPH-induced increases

in extracellular DA levels in the NHP. The AMPH-induced increase in DA was more profound in the caudate, and DA levels declined slowly in the anterior cingulate cortex. The slow decline of AMPH-evoked DA levels is consistent with the long lasting radiotracer displacement observed in PET studies.
Supported by RO1 DA026472, RO1 AA0188330, and a VA Merit Award
Keywords: amphetamine dopamine prefrontal cortex non-human primate
Disclosure: H. Jedema, Nothing to Disclose; R. Narendran, Nothing to Disclose; C. Bradberry, Nothing to Disclose.

W202 Remission During 12 Months of Double-blind Treatment with Lurasidone vs. Quetiapine XR in Patients with Schizophrenia

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Background: Remission is a key treatment goal in schizophrenia for physician and patient alike. Remission is highly correlated with favorable functional and occupational outcomes (Cassidy et al, Schiz Bull 2010;36:1001-8; Boden et al, Br J Psych 2009;107:232-7), and a lower risk of relapse (Lipkovich et al, J Psych Res 2007;41:305-10). The goal of the current post-hoc analysis was to evaluate the effectiveness of lurasidone and quetiapine XR in achieving remission in a patient population who had been recently hospitalized with an acute exacerbation of schizophrenia.
Methods: This double-blind, parallel-group study utilized a previously randomized study population and a noninferiority design to evaluate long-term maintenance of antipsychotic efficacy during 12 months of flexible dose treatment with lurasidone (40-160 mg/day), compared with quetiapine XR (200-800 mg/day). Subjects were outpatients with prior acute exacerbation of chronic schizophrenia who had recently completed 6 weeks of randomized, double-blind, placebo-controlled, fixed dose treatment with either lurasidone (80 mg/day or 160 mg/day) or quetiapine XR (600 mg/day). The primary endpoint, time-to-relapse, was analyzed using a Cox proportional hazards model with a prespecified noninferiority margin of 1.93. Here, we determined remission rates using the Remission in Schizophrenia Working Group (RSWG) criteria for symptomatic remission (Andreasen et al, 2005), which require a score of 3 (mild) or better for all of the following 8 PANSS items (G5 - mannerisms and posturing, G9 - unusual thought content, N1 - blunted affect, N4 - social withdrawal, N6 - lack of spontaneity, P1 - delusions, P2 - conceptual disorganization, P3 - hallucinatory behavior). Remission rates were analyzed both with (sustained remission) and without (symptomatic remission) the $\geqslant$6 month duration criteria. A logistic regression analysis (using both observed case [OC] and last observation carried forward [LOCF] samples) was performed with the remission, based on RSWG criteria, as the dependent variable, treatment as a categorical factor, and baseline PANSS total score as a covariate.
Results: Twelve months of treatment with lurasidone was associated with a lower risk of relapse compared with quetiapine XR, with a hazard ratio [95% CI] of 0.728 [0.410, 1.295], indicating a 27.2% reduction in relapse risk. Noninferiority of lurasidone was successfully demonstrated versus quetiapine XR. Subjects treated with lurasidone were significantly more likely, compared with quetiapine XR, to meet sustained remission criteria at 12 months (61.9% vs. 46.3%; $p = 0.043$; LOCF analysis). Among 12 month study completers, higher attrition due to insufficient clinical response in the quetiapine XR group (21.2% vs. 9.3%) resulted in similar sustained remission rates at 12 months for lurasidone vs. quetiapine XR (71.8% vs. 69.7%; $p = 0.741$). Subjects treated with lurasidone were significantly more likely, compared with quetiapine XR, to achieve symptomatic remission at Month 6 (60.6% vs. 41.7%; $p = 0.001$; OC analysis); numerical separation was maintained for study completers (Month 12; OC) (70.7% vs. 55.3%; $p = 0.055$; OC analysis).
Conclusions: In this study, a significantly higher proportion of subjects met RSWG criteria for symptomatic remission at 6 months, and sustained remission during 12 months of treatment with lurasidone compared with quetiapine XR. Both symptomatic and sustained remission are attainable goals in the long-term treatment of schizophrenia.
Keywords: Schizophrenia, remission, relapse, lurasidone, quetiapine XR
Disclosure: A. Loebel, **Part 1:** Full-time employee of Sunovion Pharmaceuticals, Inc., **Part 2:** Full-time employee of Sunovion Pharmaceuticals, Inc., **Part 3:** Full-time employee of Sunovion Pharmaceuticals, Inc.; J. Cucchiaro, **Part 1:** Full-time employee of Sunovion Pharmaceuticals, Inc., **Part 2:** Full-time employee of Sunovion Pharmaceuticals, Inc., **Part 3:** Full-time employee of Sunovion Pharmaceuticals, Inc.; J. Xu, **Part 1:** Full-time employee of Sunovion Pharmaceuticals, Inc., **Part 2:** Full-time employee of Sunovion Pharmaceuticals, Inc., **Part 3:** Full-time employee of Sunovion Pharmaceuticals, Inc.; J. Hsu, **Part 1:** Full-time employee of Sunovion Pharmaceuticals, Inc., **Part 2:** Full-time employee of Sunovion Pharmaceuticals, Inc., **Part 3:** Full-time employee of Sunovion Pharmaceuticals, Inc.; K. Sarma, **Part 1:** Full-time employee of Sunovion Pharmaceuticals, Inc., **Part 2:** Full-time employee of Sunovion Pharmaceuticals, Inc., **Part 3:** Full-time employee of Sunovion Pharmaceuticals, Inc.; P. Warner, **Part 1:** Full-time employee of Sunovion Pharmaceuticals, Inc., **Part 2:** Full-time employee of Sunovion Pharmaceuticals, Inc., **Part 3:** Full-time employee of Sunovion Pharmaceuticals, Inc.; A. Pikalov, **Part 1:** Full-time employee of Sunovion Pharmaceuticals, Inc., **Part 2:** Full-time employee of Sunovion Pharmaceuticals, Inc., **Part 3:** Full-time employee of Sunovion Pharmaceuticals, Inc.; J. Kane, **Part 1:** I have received honoraria for lectures and/or consulting from Alkermes, Amgen, Bristol-Myers Squibb, Cephalon, Eisai, Boehringer Ingelheim, Eli Lilly, Intracellular Therapeutics, Janssen, Johnson & Johnson, Lundbeck, Merck, Novartis, Otsuka, Pfizer, Pierre Fabre, Proteus, Roche, Sunovion, and Targacept, **Part 2:** I have received honoraria for lectures and/or consulting from Alkermes, Amgen, Bristol-Myers Squibb, Cephalon, Eisai, Boehringer Ingelheim, Eli Lilly, Intracellular Therapeutics, Janssen, Johnson & Johnson, Lundbeck, Merck, Novartis, Otsuka, Pfizer, Pierre Fabre, Proteus, Roche, Sunovion, and Targacept, **Part 3:** I am a shareholder of MedAvante

W203. Antidepressant-like Effects of Buprenorphine and Kappa Receptor Antagonists in Rodent Behavioral Tests

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Background: Buprenorphine is a drug with a mixed pharmacology, but is predominately a high affinity partial agonist at mu-opioid receptors (m-OR) and antagonist at kappa-opioid (k-OR) receptors. The pharmacological effects of buprenorphine, especially k-OR antagonist effects, are consistent with other opioid compounds that produce antidepressant and antianxiety effects in rodent models. This study examined the behavioral effects of buprenorphine in rodent behavioral screening tests that have good predictive validity for clinical antidepressant and anxiolytic effects. The WKY rat is a rodent genetic model for depression based on their exaggerated physiological and behavioral responses to stress. In contrast to Sprague-Dawley rats, WKY rats respond to systemic administration of k-OR antagonists. The effects of buprenorphine were compared in the forced swim test in WKY and SD rats. In addition, C57BL/6J mice were examined for the effects of buprenorphine in the forced swim test and tail suspension test.

Methods: The modified rat forced swim test was conducted in WKY and Sprague-Dawley rats (Taconic, Germantown NY) as described previously (Detke et al., 1995; Lopez-Rubalcava and Lucki, 2000). Briefly, rats were administered two swim sessions 24 h apart in a glass cylinder filled with water (21-23°C) 30 cm deep. After the first swim session, rats were injected with buprenorphine (0.25 mg/kg) 23, 5 and 1 h prior to the second 5 min test. The second swim session was videotaped and the frequency of immobility, swimming and climbing behaviors were scored. C57BL/6J mice (Jackson Laboratories) were injected with doses of buprenorphine (0.5-2.0 mg/kg) 30 min prior to the forced swim test and the tail suspension test. Tests were conducted and scored as previously described (Crowley et al. 2004).
Results: WKY rats, but not SD rats, responded to systemic buprenorphine administration of buprenorphine (0.25 mg/kg) in the FST. Immobility was reduced and swimming increased. This pattern of response is similar to that produced by the k-OR antagonists, nor-BNI and DIPPA in WKY rats (Carr et al., 2010). Acute administration of buprenorphine to C57BL/6 mice produced a significant reduction of immobility (0.25-1.0 mg/kg) in the forced swim test and the tail suspension test. The effects of buprenorphine were not due to increased locomotor activity.
Conclusions: Buprenorphine produced a significant reduction of immobility in WKY rats using the modified rat forced swim test and in the mouse forced swim test and tail suspension tests. The positive responses to buprenorphine in these rodent screening tests for antidepressant drugs provide behavior models for determining their relevant pharmacological mechanisms of action. The behavioral effects of buprenorphine in WKY rats were obtained in a strain of rats that are resistant to the antidepressant and anxiolytic effects of SSRIs. These responses in rodents agree with previous reports that buprenorphine may be effective for treatment resistant depression in humans (Bodkin et al., 1995; Nyhuis et al. 2008) and are supportive of further clinical testing for buprenorphine in depression.
Keywords: Buprenorphine, depression, kappa opioid receptor, antidepressant, animal models
Disclosure: I. Lucki, Nothing to Disclose; G. Carr, Nothing to Disclose; B. Brookshire, Nothing to Disclose; D. Bracco, Nothing to Disclose; E. Falcon-Morales, Nothing to Disclose.

W204. Effect of L-methylfolate on Core Symptoms of Major Depression from a Randomized Clinical Trial

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Background: Patients with major depressive disorder (MDD) often present with metabolic dysregulation, which in turn, has been associated with poor antidepressant response. This analysis assessed the effect of L-methylfolate 15 mg as an adjunct to SSRIs on core symptoms of depression and examined correlations of symptom improvement with metabolic and inflammatory biomarkers.
Methods: 75 inadequate responders to SSRIs were enrolled in a 60-day, multi-center, double-blind, placebo-controlled trial. Patients received L-methylfolate 15 mg/day for 60 days, placebo for 30 days followed by L-methylfolate 15 mg/day for 30 days, or placebo for 60 days. In a sub-analysis study of the effects on core symptoms of depression, mean change from baseline to endpoint was evaluated for the Maier subscale (HDRS items 1, 2, 7-10, and 13) for L-methylfolate and placebo. In addition, correlations between BMI and other biomarkers were examined.
Results: 74 patients were enrolled. For pooled data, mean change on the Maier subscale was -3.3 ± 3.7 for L-methylfolate vs. -1.5 ± 3.2 for placebo ($p = 0.016$). Mean improvement in core symptoms of depression was significantly greater with L-methylfolate vs. placebo among patients with a BMI $\geqslant 30\,kg/m^2$ (phase-pooled difference in mean change: -2.637; 95% CI: -4.410, -0.864, $p = 0.004$). Average mean change from baseline with L-methylfolate vs. placebo for the HDRS-28 was significantly correlated ($p \leqslant 0.05$) with the presence of biomarkers alone, biomarkers combined with genomic markers, and combinations of genomic markers.
Conclusions: A robust response in core symptoms of depression on the Maier subscale was observed with L-methylfolate as an adjunct to SSRIs. Improvement in core symptoms of depression was associated with the presence of metabolic/ inflammatory markers that were examined.
Keywords: major depression, L-methylfolate, biomarkers, genotype
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W205. BDNF Val66Met Modulates BOLD Response to Affective Instrumental Learning in Humans

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Background: Preclinical models implicate the BDNF Val66Met polymorphism in impaired fear extinction and anxiety phenotypes (Chen et al., 2006; Lipsky and Marini 2007), but the role of this genotype in human adaptive learning requiring both avoidance of adverse circumstances as well as attainment of rewarding experiences remains largely unknown. Here, we assessed this SNP's influence on the amygdala and hippocampus, two key regions involved in emotional regulation and learning (Ledoux 2000; Farinelli et al., 2006; Herry et al., 2008) during higher-order reinforcement learning whereby videos of fearful and happy expressions predicted choice-related monetary loss and gain respectively.
Methods: Thirty-three healthy participants (12 met carriers, 21 val homozygotes) underwent fMRI (at 3T; 16 channel head coil) while passively viewing dynamic happy, fearful, and neutral facial expressions. In addition, 61 participants including the 33 passive viewing cohort (21 met carriers, 40 val homozygote) underwent reinforcementlearning during fMRI (3T, 16 channel head coil), while they *1)* watched a cue video of emotional or neutral expression; *2)* made a choice between two non-face pictures simultaneously presented, with one of the pictures portraying emotional content concordant with the preceding video; and *3)* saw an outcome cue delineating monetary reward if the concordant picture was correctly chosen, or loss if the non-concordant picture was chosen. Preprocessing (8 mm smoothing), first-level analysis with SPM5, and random-effects ANOVAs were performed to assess BOLD response to passive viewing and during establishment of cue-outcome association. We tested for regional specificity of Val66Met influence on BOLD response to higher-order emotional cues in amygdala and hippocampus, given their intimate inter-connectivity and collective mediation of learning and LTP and their role in regulation of emotions (Ledoux 2000; Dolan 2002; Farinelli et al., 2006; Herry et al., 2008). To this aim, we extracted percentage BOLD signal change from manually segmented whole amygdala and hippocampal regions of interest (ROI) for each emotional viewing condition separately for each of the 33 individuals who participated in passive viewing, and while they underwent affective reinforcement learning.
Results: Using a 2 *by 2 by* 3 repeated measures ANOVA (task ['passive viewing vs. higher-order emotional conditioning'] *by* region ['whole amygdala and hippocampus'] *by* valence) with Val66Met genotype as the between-subjects factor, we found a task *by* region *by* BDNF interaction ($F_{2,\ 30} = 3.71$, $p = 0.032$). Whereas the hippocampal response was not affected by genotype, there was a decreased BOLD response to reinforced emotional cues in the amygdala of met carriers. To further assess valence-specific BDNF influence on neural coding of predictive emotional cues during reinforcement learning, we extracted BOLD signals measured during viewing of loss and gain predictive fear and happy cues from left and right amygdala and hippocampal ROIs in all 61 reinforcement learning participants. Using a 2 *by* 2 *by* 3 repeated measures ANOVA (region *by* hemisphere 'left vs. right' *by* valence) with BDNF Val66Met genotype as the between subjects factor, we found an interaction between region and hemisphere at $F_{2,58} = 18.21$, $p = 10^{-}4$, driven by a marked reduction in left amygdala BOLD signals. Importantly, no main effects of BDNFgenotype and no interaction between genotype and valence was found on neural coding of predictive emotional cues, supporting aVal66Met influence on these regions that is not fear specific. The observed BOLD response pattern was in line with previous research (Soliman et al., 2010; Andero et al., 2012), in that met carriers showed a consistent overall decrease in BOLD response to reinforced emotional cues. To assess the behavioral utility of the Val66Met genotype, we used a 3 *by* 2 (valence *by* conditioning) repeated-measures ANOVA on choice-related performance scores, with BDNF as between-subjects factor. We found main effects of genotype ($F_{1,\ 59} = 4.392$, $p = 0.040$) and valence ($F_{2,\ 58} = 100.59$, $p < 10^{-5}$), with choice accuracy during affectively-relevant instrumental choice behavior surpassing chance-level for the aversive and rewarding conditions only, and more so for the met carriers.
Conclusions: Here, we demonstrated that met carriers performed better by gaining more money while avoiding losses in the subsequent choice behavior. This behavioral pattern was associated with an overall decrease in amygdala BOLD response to facial cues, and this neural response pattern was shown to be specific to emotional cues carrying loss/gain predictive value. Together, these findings suggest an adaptive utility of the pronounced decrement in amygdala BOLD response found in the met carriers. By demonstrating that the BDNF Val66Met polymorphism mediates flexible adaptive behavior in both reward and aversive learning, these data may demonstrate a neurogenetic mechanism underlying emotionally meaningful adaptive behavior,

and thereby provide a possible framework for understanding the neurogenetic correlates of mood and anxiety disorders.
Keywords: Emotion, Learning, genetics, BDNF, Aversive, Appetitive, behavior
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W206. Reduced Default Mode Functional Connectivity Between Medial Prefrontal and Superior Temporal Gyrus Regions in Youths with Bipolar Disorder

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Background: The default mode network (DMN) has received increased attention and has been implicated in neuropsychiatric disorders including bipolar disorder (BD). The DMN is believed to include anterior brain regions such as the medial prefrontal cortex (mPFC), anterior cingulate (ACC), and posterior and lateral regions such as the precuneus, posterior cingulate cortex (PCC), hippocampus/parahippocampal gyrus, lateral temporal cortex, and lateral parietal cortex. (Greicius et al., 2003). Several of these cortical regions undergo significant maturational changes in adolescence and have been found to be abnormal in BD. The aim of this study was to measure the functional connectivity of the DMN in youths with BD and compare it to that of healthy adolescent controls (HC).
Methods: Fourteen adolescents (aged 15.8 ± 2.4 years; females: $n = 9$ (35.7%), with DSM-IV bipolar disorder, currently euthymic and 5 unmedicated, and 23 HCs (14.7 ± 2.6 years; females $n = 11$ (56.5%), had an MRI scan on a 3T magnet, which included an eight-minute BOLD EPI recording in the resting state. The functional connectivity toolbox *Conn* (www.nitrc.org/projects/conn) (Whitfield-Gabrieli et al., 2012) was utilized in SPM 8 for this analysis. *Conn* implements the component-based noise correction method for physiological and other noise source reduction. In addition *Conn* involves removal of movement, temporal covariates, temporal filtering and windowing of the residual blood oxygen level-dependent (BOLD) contrast signal. Next, first-level estimation of multiple standard functional connectivity measures are computed, and then second-level random-effect analysis for resting state data is performed. Two source regions of interest within the DMN, the mPFC (MNI coordinates $x = 0$, $y = 54$, $z = -8$), and the precuneus/posterior cingulate (MNI coordinates $x = 0$, $y = -56$, $z = 28$) regions were evaluated. Target ROIs included other regions within the DMN such as bilateral cingulate, inferior parietal, superior temporal and parahippocampal regions. Differences between functional connectivity between source and target ROIs within the DMN were contrasted between youths with BD and HC, correcting for multiple comparisons (FDR).
Results: Reduced functional connectivity in youths with BD was found between the mPFC and the right posterior superior temporal gyrus ($t(34) = 2.98$, $p = 0.04$, FDR corrected; (MNI coordinates $x = 60$, $y = -30$, $z = 24$) and between the mPFC and the cingulate ($t(34) = 2.95$, $p = 0.04$, FDR corrected; (MNI coordinates $x = 0$, $y = 6$, $z = 40$) compared to HC. In addition, there was a trend for HC to have greater functional connectivity between the precuneus and the right posterior superior temporal gyrus ($t(34) = 2.07$, $p = 0.09$, FDR corrected).
Conclusions: We found reduced functional connectivity between the mPFC and the right posterior superior temporal gyrus and cingulate and a trend toward reduced connectivity between the precuneus and the right posterior superior temporal gyrus in youths with BD as compared to HC. These findings are consistent with structural and task-based fMRI studies in youths with BD, which have also reported abnormalities in regions of the mPFC (Pavuluri et al., 2007; Wilke et al., 2004), PCC/Precuneus (Kaur et al., 2005), and temporal cortex (Frazier et al., 2005; Pavuluri et al., 2007). The DMN is thought to integrate cognitive and emotional processing (Greicius et al., 2003) and may play a role in top-down attentional control (Sonuga-Barke et al., 2007). While the functions of the DMN are still being clarified, individual regions associated with the DMN, such as the mPFC and PCC have been linked to a variety of functions including emotion modulation and executive function (working memory, and attention). Furthermore, the superior temporal gyrus has also been implicated in emotional and social processing, two deficits frequently encountered in BD (Pavuluri et al., 2007). Overall our findings suggest DMN impairments exist in youths with BD and further evaluation of this network is warranted. References Frazier, J. A., et al. (2005). Cortical gray matter differences identified by structural magnetic resonance imaging in pediatric bipolar disorder. *Bipolar Disord, 7*, 555-569. Greicius, M. D., et al. (2003). Functional connectivity in the resting brain: a network analysis of the default mode hypothesis. *Proc Natl Acad Sci U S A, 100*(1), 253-258. Kaur, S., et al. (2005). Cingulate cortex anatomical abnormalities in children and adolescents with bipolar disorder. *Am J Psychiatry, 162*(9), 1637-1643. Pavuluri, M. N., et al. (2007). Affective neural circuitry during facial emotion processing in pediatric bipolar disorder. *Biol Psychiatry, 62*(2), 158-167. Sonuga-Barke, E. J., et al. (2007). Spontaneous attentional fluctuations in impaired states and pathological conditions: a neurobiological hypothesis. *Neurosci Biobehav Rev, 31*(7), 977-986. Whitfield-Gabrieli, S., et al. (2012). Conn: a functional connectivity toolbox for correlated and anticorrelated brain networks. *Brain Connect, 2*(3), 125-141. Wilke, M., et al. (2004). Voxel-based morphometry in adolescents with bipolar disorder: first results. *Psychiatry Res, 131*(1), 57-69.
Keywords: Bipolar Disorder, functional connectivity, adolescents
Disclosure: M. Lopez-Larson, Nothing to Disclose; D. Yurgelun-Todd, **Part 1:** D. Yurgelun-Todd is a consultant to Kyowa Hakko, Eli Lilly, and Janssen.

W207. Heritability and Linkage Analysis of Personality in Bipolar Disorder

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Background: The many attempts that have been made to identify genes for bipolar disorder have met with limited success, which has generally been attributed to genetic heterogeneity and small gene effects. However, it is also possible that the categorical phenotypes used in genetic studies of bipolar disorder are not the most informative or biologically relevant. We have explored aspects of personality as quantitative phenotypes for bipolar disorder through the use of the Temperament and Character Inventory (TCI), a self-administered questionnaire that assesses personality in seven dimensions according to Cloninger's psychobiological model. Four temperament scales are included: novelty seeking (NS), harm avoidance (HA), reward dependence (RD), and persistence (PS). Three character scales are also included: self-directedness (SD), cooperativeness (CO), and self-transcendence (ST).
Methods: We first evaluated the extent of group differences between bipolar subjects and their first-degree relatives in 101 families collected for genetic studies of bipolar disorder. We also compared these groups with 53 independent controls. We then assessed the heritability of these five personality domains in the 101 bipolar families and subsequently performed a genome-wide

linkage study in the subset of 51 families for which genetic data was available using pedigree-wide regression methods.
Results: NS, CO, and ST all clearly distinguished bipolar subjects from their first-degree relatives and controls. For these, relatives with major depressive disorder (MDD) did not differ from their unaffected relatives, nor did unaffected relatives differ from controls, but subjects with MDD did show differences from controls for ST only. SD successfully discriminated between all groups, except for unaffected relatives and controls, and HA discriminated between all groups. RD and PS did not show group differences. Five of the seven domains were found to be significantly heritable in this sample. For the temperaments, heritabilities were 19% for NS, 25% for PS, and not significant for HA and RD. For the character domains, heritabilities were 38% for SD, 32% for CO, and 17% for ST. Linkage analysis of the five heritable domains revealed suggestive evidence for linkage with LOD scores >2.2 to chromosomes 5 (SD), 6 (PS), 10 (NS), 11 (CO), 12 (PS), 16 ST), and 19 (PS), with a significant peak on chromosome 8 for SD (LOD $= 3.7$).
Conclusions: These results suggest that aspects of personality may define subtypes of bipolar disorder that are more genetically homogenous, which may aid in the identification of predisposing genetic variants.
Keywords: bipolar disorder, personality, TCI, heritability, genetic linkage
Disclosure: T. Greenwood, Nothing to Disclose; J. Badner, Nothing to Disclose; W. Byerley, Nothing to Disclose; B. Consortium, Nothing to Disclose.

W208. Effects of Aromatase Inhibition and Androgen Activity on Serotonin and Behavior in Male Macaques

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Background: Aggression in humans and animals has been linked to androgens and serotonin function. However, there is not much evidence to support treatment of aggressive disorders with serotonergic agents. To further our understanding of the role of androgens in the regulation of serotonin in male macaques, we manipulated circulating androgens and the activity of aromatase; and then determined the availability of serotonin using a fenfluramine challenge paradigm with prolactin measurement as an indicator of serotonin availability. Correlations between prolactin/serotonin, aromatase activity and androgen activity were sought.
Methods: Male Japanese macaques (*Macaca fuscata*) were castrated for 5 months and then treated with placebo, testosterone (T), T + Dutasteride (5a reductase inhibitor; Avodart^{TM}), or T + Letrozole (non-steroidal aromatase inhibitor; Femera^{TM}) for 3 months ($n = 5$/group). Afterwards, two groups were rested without treatment for 7 months, and then treated with Flutamide + ATD (androgen antagonist plus steroidal aromatase inhibitor) or dihydrotestosterone (DHT) + ATD for 3 months ($n = 5$/group). Behavioral observations were made during treatments. At the end of each 3-month treatment period, every animal was sedated with propofol and administered a bolus of fenfluramine (5 mg/kg). Serum was collected for 1 h before and 2 hours after fenfluramine injection. Prolactin, T, DHT, and estradiol concentrations were determined by RIA. ANOVA and linear regression analysis were applied to the data.
Results: Fenfluramine significantly increased prolactin in all groups ($p < 0.0001$). Fenfluramine-induced prolactin secretion in the T-treated group was significantly higher than the other groups ($p < 0.0001$). Complete block of aromatase with ATD significantly reduced the prolactin/serotonin response in the presence or absence of DHT. Androgen administration did not correlate with serotonin availability suggesting that serotonin is not regulated by androgens in macaques. Serotonin correlated with aromatase activity and presumed production of neural estradiol ($p < 0.0008$; r squared $= 0.95$). In the presence of high, medium or low serotonin, androgen treatment significantly increased aggressive behavior and yawning compared to pre-treatment ($p = 0.0006$ and 0.0016, respectively). Yawning strongly reflects androgen activity and it was the best predictor of aggression ($p = 0.058$; r squared $= 0.63$). There was no correlation between aggression or yawning and prolactin/serotonin.
Conclusions: Together, the data suggest that aromatase activity and the production of neural estradiol support serotonin production and that androgens increase aggression by another mechanism in macaques.
Keywords: serotonin; aggression; androgen; fenfluramine; aromatase
Disclosure: C. Bethea, Nothing to Disclose; A. Reddy, Nothing to Disclose; N. Robertson, Nothing to Disclose; K. Coleman, Nothing to Disclose.

W209. Multiple Obesity-related Genes are Associated with Antipsychotic-induced Weight Gain in Drug Naïve Pediatric Patients

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Background: Weight gain is a common and serious side effect of second-generation antipsychotic drugs (SGA). Recent work from our group found that variants near the melanocortin 4 receptor (*MC4R*) gene significantly predicted antipsychotic-induced weight gain (Malhotra et al. 2012), and *MC4R* is a known risk gene for obesity in the general population. We hypothesized that the risk genes in the general population may also be risk genes for antipsychotic-induced weight gain. We used the single nucleotide polymorphisms (SNPs) that are associated with obesity in the general population as candidate SNPs, and examined whether they are significantly associated with antipsychotic-induced weight gain in a drug-naïve pediatric sample. The statistical power may be enhanced in detecting significant genetic signals in pharmacogenetic studies.
Methods: Review of the published genome-wide association studies (GWAS) of obesity or body mass index (BMI) in the general population revealed that 69 SNPs from 44 genes/regions reached genome-wide significance ($p < 5 \times 10$^-8). Our sample consisted of 139 drug-naïve pediatric patients undergoing treatment with SGAs (risperidone, quetiapine, and aripiprazole) for 12 weeks (58.3% male, 77% Caucasian, mean age $= 13.38 \pm 3.75$ years). Patients were genotyped using the Illumina Omni-1Quad platform. 65 out of the 69 candidate SNPs were either directly genotyped or had proxy SNPs in our dataset. Separate association studies were performed on each of the 65 SNPs in additive, recessive, and dominant models. Change in BMI from baseline to 12 weeks was the phenotype. Significance level was set at $p < 0.05$.
Results: Out of 195 association tests (65 SNPs in additive, dominant, and recessive models, i.e., $65 \times 3 = 195$), 23 were significant at $p < 0.05$ level ($23/195 = 11.8\%$). Out of 65 SNPs, 14 (21.5%) had at least one significant association test in any of the models. The 65 SNPs were from 44 independent genes or genomic regions, of which 10 (22.7%) were associated with BMI changes in at least one of the three models. These were significantly more than what is expected by chance, p's < 0.0001.
Conclusions: Some risk genes of obesity in the general population appear also to be risk genes of antipsychotic-induced weight gain. Due to its within-subject design in pharmacogenetic studies, enhanced statistical power resulted in significant genetic findings in relatively small samples. Pharmacogenetics may be at a

particular advantage of identifing genes for complex traits with considerable and variable environmental contributions. Further studies are needed to elucidate the biological mechanisms of antipsychotic-induced weight gain.
Keywords: Pharmacogenetics; Antipsychotics; Weight Gain; Obesity; GWAS
Disclosure: J. Zhang, Nothing to Disclose; T. Lencz, **Part 1:** As a consultant for Eli Lilly; C. Correll, **Part 1:** Actelion, Alexza, AstraZeneca, Biotis, Bristol-Myers Squibb, Cephalon, Desitin, Eli Lilly, Gerson Lehrman Group, GSK, IntraCellular Therapies, Lundbeck, Medavante, Medscape, Merck, Novartis, Ortho-McNeill/Janssen/J&J, Otsuka, Pfizer, ProPhase, Sunovion, Takeda, Teva, and Vanda, **Part 2:** AstraZeneca, Bristol-Myers Squibb, Cephalon, GSK, Merck, Otsuka, Pfizer, ProPhase, **Part 3:** AstraZeneca, Bristol-Myers Squibb, Otsuka, Pfizer, ProPhase, **Part 4:** BMS, Janssen/J&J, Otsuka; A. Malhotra, **Part 1:** Genomind, Shire, Eli Lilly, Sunovion, Abbott, **Part 2:** Genomind, **Part 4:** Abbott.

W210. Reduced Risk of Neurological Disorders in Patients Receiving Lithium Treatment

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Background: Lithium has been a standard treatment for Bipolar Disorder for more than 50 years. A variety of studies have examined the medical consequences of long-term Lithium treatment. There has been some evidence that long-term Lithium treatment is associated with a reduced risk of heart disease and cerebrovascular disease. This study compares the incidence of cerebrovascular disease in psychiatric patients receiving and not receiving Lithium.
Methods: This study is a retrospective chart review of adult psychiatric outpatients treated at the New York State psychiatric Institute Lithium Clinic, and two affiliate lithium clincs at the Columbia University Medical Center and the Foundation for Mood disorders. Patients at the clincis were primarily being treated for Major Depression or Bipolar Disorders. All patient diagnoses were made by a board-certified psychiatrist, and patients were assigned to Lithium treatment as appropriate for their individual diagnoses. All patients underwent yearly physical exams and blood chemistries performed by a separate medical practice. The chart review included patient demographic information, diagnosis, treatment information, and any reported medical complications. Odds ratios were calculated to assess the risk of having a disorder for patients receiving Lithium compared to patients not receiving Lithium.
Results: To date, 732 patients have been entered in the database (55.3% female, 44.6% male), ranging in age from 16 to 88 years old. Of these, 378 patients (51.6%) received Lithium treatment, with the duration of Lithium treatment ranging from 0.1 – 30.0 years (mean 3.19 yrs; SD 5.72 yrs.). The frequency of any neurological disease in this group was very low: 91 patients (12.4%) had some neurological condition, ranging in frequency of 28 patients with Migraine Headache to one patient each with Dementia, Multiple Sclerosis, or ALS. Odds ratios were calculated to assess the risk of having a disorder for patients receiving Lithium compared to patients not receiving Lithium. For Parkinson's Disorder, the OR was 1.2; for Cerebrovascular Disease, the OR was 0.24; for Optic Nerve Atropy/Neuritis, the OR was 0.19, for Migraine Headache, the OR was 2.88, for "Stroke", the OR was 1.15. Lastly, though not a neurological condition, the OR for Myocardial Infarction was 0.32.
Conclusions: Patients receiving long-term Lithium treatment for psychiatric illness have a significantly lower likelihood of cerebrovascular disease, optic nerve atrophy/neuritis, and myocardial infarction, compared to psychiatric patients not receiving Lithium. Patients receiving Lithium have a significantly greater likelihood of Migraine Headache. These results suggest that long-term Lithium treatment may protect against myocardial infarction and some neurological disorders.
Keywords: lithium, mood disorders, neurological disorder, cardiovascular disease
Disclosure: J. Prosser, Nothing to Disclose; M. Gilbert, Nothing to Disclose; R. Fieve, Nothing to Disclose.

W211. Double-blind, Placebo-controlled Trial of Pramipexole Augmentation in Treatment-resistent Major Depressive Disorder

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Background: Multiple next-step strategies for treatment of major depressive disorder have demonstrated efficacy, but up to 1/3 of individuals do not achieve symptomatic remission despite multiple interventions. Existing next-step strategies also have substantial safety concerns which may limit their application.
Methods: This study investigated the antidepressant efficacy of a flexible dose of the dopamine agonist pramipexole as an adjunct to standard antidepressant treatment in an 8-week randomized, double-blind, placebo-controlled trial conducted in a tertiary-level depression center. We randomized 60 outpatients with treatment–resistant nonpsychotic major depression, who remained depressed (defined as Montgomery-Asberg Depression Rating Scale (MADRS) score >18), despite treatment with at least one prior antidepressant in the current depressive episode. Primary outcome measure was the MADRS score
Results: The analysis using a mixed effects model indicated a modest but statistically significant benefit for pramipexole ($p<0.05$). Overall, 40% and 33% of patients randomized to augmentation with pramipexole achieved response and remission, respectively, compared to 27% and 23% with placebo, however those differences were not statistically significant. Augmentation with pramipexole was well tolerated, with no serious adverse effects identified.
Conclusions: For patients who have failed to respond to standard antidepressant therapies, pramipexole is a safe and potentially efficacious augmentation strategy. ClinicalTrials.gov: http://www.clinicaltrials.gov/ NCT00231959
Keywords: Placebo, Pramipexole, Major Depressive Disorder, Treatment-resistent Disorder, Augmentation
Disclosure: M. Fava, **Part 1:** Advisory/Consulting/Lifetime, Abbott Laboratories; Affectis Pharmaceuticals AG; Alkermes, Inc.; Amarin Pharma Inc.; Aspect Medical Systems; AstraZeneca; Auspex Pharmaceuticals; Bayer AG; Best Practice Project Management, Inc.; BioMarin Pharmaceuticals, Inc.; Biovail Corporation; BrainCells Inc; Bristol-Myers Squibb; CeNeRx BioPharma; Cephalon, Inc.; Clinical Trials Solutions, LLC; CNS Response, Inc.; Compellis Pharmaceuticals; Cypress Pharmaceutical, Inc.; DiagnoSearch Life Sciences (P) Ltd.; Dinippon Sumitomo Pharma Co. Inc.; Dov Pharmaceuticals, Inc.; Edgemont Pharmaceuticals, Inc.; Eisai Inc.; Eli Lilly and Company; EnVivo Pharmaceuticals, Inc.; ePharmaSolutions; EPIX Pharmaceuticals, Inc.; Euthymics Bioscience, Inc.; Fabre-Kramer Pharmaceuticals, Inc.; Forest Pharmaceuticals, Inc.; GenOmind, LLC; Glaxo Smith Kline; Grunenthal GmbH; i3 Innovus/Ingenis; Janssen Pharmaceutica; Jazz Pharmaceuticals, Inc.; Johnson & Johnson Pharmaceutical Research & Development, LLC; Knoll Pharmaceuticals Corp.; Labopharm Inc.; Lorex Pharmaceuticals; Lundbeck Inc.; MedAvante, Inc.; Merck & Co., Inc.; MSI Methylation Sciences, Inc.; Naurex, Inc.; Neuronetics, Inc.; NextWave Pharmaceuticals; Novartis AG; Nutrition 21; Orexigen Therapeutics, Inc.; Organon Pharmaceuticals; Otsuka Pharmaceuticals; PamLab, LLC.; Pfizer Inc.; PharmaStar; Pharmavite LLC.; PharmoRx Therapeutics; Precision Human Biolaboratory; Prexa Pharmaceuticals, Inc.; Puretech Ventures; PsychoGenics; Psylin Neurosciences, Inc.; Rexahn Pharmaceuti-

cals, Inc.; Ridge Diagnostics, Inc.; Roche; RCT Logic, LLC; Sanofi-Aventis US LLC.; Sepracor Inc.; Servier Laboratories; Schering-Plough Corporation; Solvay Pharmaceuticals, Inc.; Somaxon Pharmaceuticals, Inc.; Somerset Pharmaceuticals, Inc.; Sunovion Pharmaceuticals; Supernus Pharmaceuticals, Inc.; Synthelabo; Takeda Pharmaceutical Company Limited; Tal Medical, Inc.; Tetragenex Pharmaceuticals, Inc.; TransForm Pharmaceuticals, Inc.; Transcept Pharmaceuticals, Inc.; Vanda Pharmaceuticals, Inc., Speaking/Publishing:, Adamed, Co; Advanced Meeting Partners; American Psychiatric Association; American Society of Clinical Psychopharmacology; AstraZeneca; Belvoir Media Group; Boehringer Ingelheim GmbH; Bristol-Myers Squibb; Cephalon, Inc.; CME Institute/Physicians Postgraduate Press, Inc.; Eli Lilly and Company; Forest Pharmaceuticals, Inc.; GlaxoSmithKline; Imedex, LLC; MGH Psychiatry Academy/Primedia; MGH Psychiatry Academy/Reed Elsevier; Novartis AG; Organon Pharmaceuticals; Pfizer Inc.; PharmaStar; United BioSource, Corp.; Wyeth-Ayerst Laboratories, Equity Holdings: Compellis, Patent for Sequential Parallel Comparison Design (SPCD) and patent application for a combination of azapirones and bupropion in Major Depressive Disorder (MDD); for research and licensing of SPCD with RCT Logic., Copyright for the MGH Cognitive & Physical Functioning Questionnaire (CPFQ), Sexual Functioning Inventory (SFI), Antidepressant Treatment Response Questionnaire (ATRQ), Discontinuation-Emergent Signs & Symptoms (DESS), and SAFER; Lippincott, Williams & Wilkins; Wolkers Kluwer; World Scientific Publishing Co. 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Cusin, Nothing to Disclose; A. Nierenberg, **Part 1:** Received honoraria from: Belvoir Publishing, University of Texas Southwestern Dallas, Hillside Hospital, American Drug Utilization Review, American Society for Clinical Psychopharmacology, Baystate Medical Center, Columbia University, IMEDEX, MJ Consulting, New York State, Medscape, MBL Publishing, Physicians Postgraduate Press, SUNY Buffalo, University of Wisconsin, University of Pisa. APSARD, ISBD, SciMed, In the past 36 months he has served as a consultant to: American Psychiatric Association (only travel expenses paid), Appliance Computing Inc. (Mindsite), Basliea, Brain Cells, Inc., Brandeis University, Bristol Myers Squibb, Dainippon Sumitomo, Eli Lilly and Company, EpiQ, Novartis, PGx Health, Shire, Schering-Plough, Takeda PharmaceuticalsTargacept consulted for through the MGH Clinical Trials Network and Institute (CTNI): Astra Zeneca, Brain Cells, Inc, Dianippon Sumitomo/Sepracor, Johnson and Johnson, Labopharm, Merck, Methylation Science, Novartis, PGx Health, Shire, Schering-Plough, Targacept, and Takeda/Lundbeck Pharmaceuticals, Dr. Nierenberg is a presenter for the Massachusetts General Hospital Psychiatry Academy (MGHPA). The education programs conducted by the MGHPA were supported through Independent Medical Education (IME) grants from the following pharmaceutical companies in 2008: Astra Zeneca, Eli Lilly, and Janssen Pharmaceuticals; in 2009 Astra Zeneca, Eli Lilly, and Bristol-Myers Squibb, No speaker bureaus or boards since 2003, **Part 2:** Full time employee of the Massachusetts General Hospital (MGH), **Part 4:** Received grant/research support through: MGH from NIMH, PamLabs, Pfizer, Shire; D. Iosifescu, **Part 1:** CNS Response, **Part 4:** Dr. Isofescu has received research suppor through Mount Sinai School of Medicine from Brainsway, EIthymics, Neosync, and Shire; N. Iovieno, Nothing to Disclose; A. Rush, **Part 1:** Dr. A. Rush has received consulting fees from Otsuka Pharmaceutical Co, Ltd, University of Michigan, and Brain Resource Ltd; speaker fees from Singapore College of Family Physicians; royalties from Guilford Publications and the University of Texas Southwestern Medical Center, **Part 4:** travel grant from CINP and research support from the National Institute of Mental Health and Duke-NUS; R. Perlis, **Part 1:** Dr. Perlis has received consulting fees from RIDVentures, Proteus, Biomedical, and Pamlab. He serves on the scientific advisory board of, Genomind., **Part 4:** He has received royalties from Concordant Rater Systems (now a Medco subsidiary). This study was sponsored by NIMH, award K23-MH67060,.

W212. Experience Integrating Ketamine Into the Healthcare System: Outpatient and Inpatient Treatment of Post-Partum Depression, Suicidal Ideation and Comorbid Chronic Pain-Mood Disorders

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Background: Ketamine is increasingly being used in clinical settings in an off-label fashion for treatment of major depression and chronic pain. Recent studies showing improvement in suicidal ideation has further increased the interest in its clinical use because when it works, it does so within hours, possibly reducing the risk of suicidal behavior. However, many issues need to be addressed before widespread clinical use can be recommended and definitive controlled trials can be designed. This includes the need for: a) a better developed conceptual framework for the mechanisms underlying Ketamine's antidepressant and nocioceptive properties; b) a clinical algorithm guiding appropriate selection of patients (e.g., first episode vs. treatment resistant depressed patients; presence of suicidal ideation; or patients with co-occurring chronic pain); c) the identification of dosing strategies or adjunct agents that can extend the therapeutic effect; d) optimization of Ketamine administration protocols (i.e., intramuscular vs. intravenous route of administration and bolus vs. infusion, maximally effective dose, and consequences of concurrent benzodiazepines administration); e) larger placebo-controlled studies demonstrating the effectiveness of Ketamine in the treatment of suicidal ideation; f) knowledge regarding the psychiatric medications that patients can be taking prior to receiving the treatment; and g) identification of predictive biomarkers and/or illness subtypes more likely to benefit from Ketamine treatment.
Methods: Clinical cases of Ketamine administration for depression, suicidal ideation, and pain at the UT Health Science Center in San Antonio are being reviewed for this presentation. Clinical chart data and available rating scales will be summarized. When used for treatment of depression, Ketamine is largely administered as in the previously published depression trials (0.5 mg/kg) in 40-minute IV infusion. For the treatment of chronic pain and in few cases of depression, much higher doses of Ketamine (up to 2 mg/kg) are administered as IV bolus along with concurrent benzodiazepines (most often midazolam). Ketamine administration is largely conducted in outpatient settings under direct physician supervision by an anesthesiologist with constant monitoring of vital signs (heart rate, blood pressure, respiratory rate, temperature, and oxygen saturation). Full psychiatric

evaluations were conducted before the treatment and psychiatric follow was done within 1-3 days after Ketamine administration. For most depressed patients, mood ratings were collected using the HAMD-17, HAMD-7, QIDS-SR16 and Bipolar Inventory of Symptoms Scale (BISS). Assessment of pain severity was based on ratings severity from 0 = No pain to 10 = Extreme pain.
Results: In agreement with published literature a single Ketamine infusion rapidly alleviated depressive symptomatology (response) in more than half of our patients. The treatment is well tolerated without major side effects. In some patients with comorbid pain, pain also decreased. Most patients first noticed improvement in mood the day after infusion. Although in a patient with severe MDD and residual suicidal ideation after a suicide attempt of high lethality, a sustained clinical response (including resolution of suicidality) was noted as soon as 120 minutes after the infusion began. In one case of severe post-partum depression, a single bolus infusion of Ketamine (with concurrent use of midazolam) led to a sustained complete remission of symptoms (leading to patient discontinuing her SSRI) that was maintained for 2 months (date of last follow up).
Conclusions: A growing body of clinical and research data suggest Ketamine may have clinical utility in some cases of depression and chronic pain. Clinical trials are required to identify the conditions that would maximize Ketamine acute effectiveness, possibly sustain its benefit and ensure the safety of long-term, regular use.
Keywords: Ketamine, NMDA-Receptors, Depression, Suicide, Pain, post-partum, antidepressants
Disclosure: M. Quinones, Nothing to Disclose; N. Diazgranados, Nothing to Disclose; M. Eckmann, Nothing to Disclose; S. Ramamurthy, Nothing to Disclose; C. Bowden, Nothing to Disclose; P. Delgado, Nothing to Disclose.

W213. Tissue Specific Effects of Psychological Stress on the Development of Acute Insulin Resistance

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Background: Epidemiologic studies report an increased risk of developing type 2 diabetes in depressed individuals. In addition, population-based surveys have found that the prevalence of depression is 8-25% in diabetic patients, and 40-80% in diabetic patients with complications. However, the specific mechanisms linking depression and diabetes are not understood. We hypothesized that psychological stress may cause the development of insulin resistance, which is a risk factor in developing type 2 diabetes.
Methods: We tested the hypothesis in an animal model of psychological stress referred to as a learned-helplessness procedure consisting of 180 times of inescapable foot shocks (IES) followed by an escape test. In this study, mice that received IES were tested for acute insulin resistance by measuring glucose metabolism and insulin signaling in the liver, skeletal muscle, adipose tissue and brain.
Results: When compared to normal and sham mice, IES mice displayed elevated blood glucose levels in both glucose tolerance and insulin tolerance tests. Furthermore, IES exposure impaired hepatic insulin signaling via the insulin-induced insulin receptor / insulin receptor substrate 1 / Akt pathway, without affecting similar pathways in skeletal muscle, adipose tissue and brain. Additionally, a rise in murine growth-related oncogene KC/GRO, a homolog to human interleukin-8, was associated with impaired glucose metabolism in IES mice, indicating a mechanism by which psychological stress by IES may influence glucose metabolism.
Conclusions: The present results indicate that insulin action is compromised in the liver, but not in other tested tissues, in a model of psychological stress induced by IES.
Keywords: Psychological stress, Inescapable foot shocks, Learned-helplessness phenotype, Insulin sensitivity,
Disclosure: L. Li, Nothing to Disclose; J. Messina, Nothing to Disclose; X. Li, Nothing to Disclose.

W214. Serotonergic Modulation of Neuronal Excitability in the BNST: Effects of Chronic Alcohol

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Background: Anxiety is a core symptom of alcohol withdrawal that can lead to relapse and alcohol dependence. Several lines of evidence suggest that the serotonin 2c receptor (5HT2c-R) plays a key role in anxiety and may be altered following ethanol exposure. Previous data from our lab indicates that chronic intermittent ethanol (CIE) promotes anxiety-like behavior in mice, which is occluded by 5HT2c-R antagonists. The mechanism of CIE-induced anxiogensis is unknown, but our preliminary data indicates that CIE increases neuronal excitability in the bed nucleus of stria terminalis (BNST), an important neural substrate of withdrawal-induced anxiety and relapse. Recent data from our lab also indicates that serotonin (5HT) has both excitatory and inhibitory postsynaptic effects in the BNST that are receptor-dependent, suggesting that serotonergic systems may serve to fine tune the neural output of the BNST. These studies were designed to test the hypothesis that CIE exposure induces a shift in the net effect of 5HT on neuronal excitability in the BNST, which may reflect changes in 5HT receptor expression or intracellular signaling cascades that mediate their effects.
Methods: For these studies, male DBA/2J mice were pretreated with pyrazole (1 mmol/kg, i.p.) and exposed to ethanol vapor or room air for 5 days using a 16 hr on, 8 hrs off schedule. All experimental manipulations were performed following a 24 hr withdrawal period. Experiment 1: Coronal sections of the BNST from control and CIE mice were processed for immunohistochemistry and probed with FOS antibodies. The number of FOS + were counted as a proxy measure of neuronal activity within the BNST. Experiment 2: Coronal sections of the BNST from control and CIE mice were prepared for *ex vivo* electrophysiology. The magnitude of changes membrane potential following bath application of 5HT (10 μM) or mCPP (20 μM) in the presence of TTX were measured in current clamp. Experiment 3: Tissue punches of the BNST were stored in RNAlater and processed for RT-PCR. Fold changes in 5HT1a- and 5HT2c-R mRNA expression were quantified in CIE mice relative to control mice.
Results: CIE induced a significant increase in FOS + cells in the BNST, suggesting an increase in neuronal activity that is consistent with our preliminary electrophysiological data. We also found that the hyperpolarization response to 5HT was reduced in CIE mice, which exhibited a shift toward excitation in the presence of 5HT. Furthermore, 5HT2c/b agonist mCPP induced depolarization or no response in control mice, with a shift toward greater and more frequent depolarization responses in CIE mice, supporting the idea that 5HT2c-Rs mediate excitatory postsynaptic responses in the BNST. In order to investigate the mechanism of this CIE-induced shift toward excitation in the BNST, we examined expression of 5HT1a and 5HT2c receptors in the BNST following CIE and found a robust downregulation of both receptors subtypes. Given that these receptors have opposing actions on excitability in the BNST, reducing expression of both would not account for the effects of CIE on excitability, suggesting that downstream signaling modalities may be involved or that there is some alteration in 5HT2c-R mRNA splicing. We intend to follow up these results with Western blots.
Conclusions: Chronic ethanol exposure induces plasticity in 5HT receptor signaling in the BNST that enhances excitatory post-

synaptic responses to serotonin, which in turn may cause anxiety-like behavior. Our results indicate that downregulation of 5HT1a receptor mRNA in the BNST is a potential substrate for this plasticity, which we intend to follow up with Western blots. However, given that 5HT2c receptor mRNA was also down-regulated after CIE, we will look at the effects of CIE on downstream signaling as well.

Keywords: Alcohol, withdrawal, serotonin, BNST, anxiety

Disclosure: C. Marcinkiewcz, Nothing to Disclose; N. McCall, Nothing to Disclose; J. Jennings, Nothing to Disclose; T. Kash, Nothing to Disclose.

W215. A Six Month Randomized Controlled Trial of Long Acting Injectable Risperdone 50 and 100 mg in Treatment Resistant Schizophrenia

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Background: Patients with persistent delusions and/or hallucinations (treatment resistant schizophrenia [TRS]) despite at least two usually adequate trials of typical or atypical antipsychotic drugs (APDs) comprise about 30 % of schizophrenia patients. Clozapine is the only APD approved for TRS. We have postulated that the multireceptor chemistry of clozapine coupled with the relatively higher dose and longer duration of treatment used in TRS clozapine compared to NTR schizophrenia contributes to its reported superiority TRS. Higher doses of olanzapine have been reported to be efficacious in TRS. The usual dose of long acting injectable risperidone (Risperdal Consta) in non-TRS patients is 25 or 37.5 mg IM q 2 weeks, with no difference in efficacy noted. It was therefore of interest to study higher doses of Risperdal Consta in TRS with its assured parenteral administration

Methods: This was a double blind, randomized, multicenter investigator-initiated, Janssen-sponsored study to assess the efficacy for psychopathology and cognition, safety and tolerability study of two doses of Risperdal Consta: 50 mg and 100 mg biweekly, for six months in 160 TRS patients; 78 randomized to the 100 mg group and 82 to the 50 mg group. All patients were required to have a score $\geqslant 4$ on at least one of the following three PANSS positive symptom items P2 Conceptual Disorganization, P3 Hallucinatory Behavior, or P6, Suspiciousness/Persecution. Treatment effects over time were analyzed by repeated measured analysis of variance (ANOVA) with time as within subjects factor and treatment group as the between subjects factor using a mixed model ANOVA. Other measures included CGI, GAF, PSP and a full cognitive battery administered at baseline, 6, 12, 18 and 24 weeks. MRI scans were obtained at baseline and 24 weeks in 38 subjects.

Results: The mean PANSS Total score at baseline for the combined group of subjects was 89.4 + /-SD13.8 with no group differences. In the high dose group, 55 or 70.5% of patients in the 100 mg dose completed the study compared to 50 or 71.9% in the low dose group. Both doses of Consta were effective to reduce positive and negative symptoms. The percentage of patients with $\geqslant$20% improvement in PANSS Total at 6, 12 and 24 weeks for the two groups were not significantly different: 22.1%, 36.8% and 45.5% for the 100-mg group and 22.2%, 36.9% and 45.8% for the 50-mg group, respectively. There were statistically significant time effects for the CGI, GAF and PSP, indicating non-significantly different improvements in both groups over time. The improvement in CGI Severity of $\sim$0.6 for both groups would be considered clinically significant. The improvement in PSP between baseline and 24 weeks was robust in both groups, with an $\sim$11 point increase from 40 to 51 in both groups, effect size 1.0. There was a 10 point improvement in GAF-Score for both groups, representing a mean change of $\sim$25%. Working memory and declarative memory significantly improved with both treatments. Nine of the 78 (11.5%) 100 mg dose and 5/82 (6.1%) 50 mg dose patients were briefly hospitalized during the 6 month period, a non-significant difference. No significant differences were observed between the two treatment groups with some measure of safety, e.g. prolactin elevations and extrapyramidal symptoms.

Conclusions: The TRS patients in this study were significantly improved compared to baseline. The extent of improvement was comparable to that previously observed in another multicenter trial conducted by the PI with clozapine vs high dose olanzapine in TRS. (Meltzer et al. J Clin Psychiatry 2008; 69(2):274-285). The limitation of this study was that it did not include comparison with 25 mg Risperdal Consta which, had it been less effective than the two doses in this study, would have supported the conclusion that both of the higher doses of Risperdal Consta were required to achieve the improvement noted. Better adherence due to long acting injectable formulation may have contributed to the efficacy noted here. The longer duration of treatment was demonstrated to be clinically useful as was the tolerability of long acting injectable medication. Further study of longer term treatment with Risperdal Consta in comparison with clozapine for TRS would be of interest.

Keywords: Risperdone, long acting injectable, schizophrenia, treatment resistance, cognition

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W216. A Clinical Laboratory Model of Allostasis of the Brain Reward System Diurnal Cortisol and Sleep in Recently Detoxified Opioid Dependent Patients, Normal Control Subjects & Patients Drug Free for 60-90 Days

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Background: The high rate of relapse in the early months of drug-free treatment for opiate dependence has been linked theoretically to a persistent, albeit loosely defined, state of physiological dysregulation consequent to opiate withdrawal. Koob and Kreek have applied the term allostasis to describe changes in the HPA axis and brain reward system that may persist following detoxification from opiates: 1) the normal homeostasis of the HPA axis is disturbed; 2) responses to natural rewards (e.g., food, sex, etc.) are dampened; 3) the response to drug-related stimuli is

markedly enhanced; and, 4) patients complain of anhedonia & sleep disturbance. The duration of the various elements of dysregulation after detoxification is uncertain; as is the question of how & whether findings on allostasis in the rodent can be translated into clinically meaningful data, especially in the growing population of patients addicted to prescription opioids. In this study, clinical measures hypothesized to mirror elements of allostatic dysregulation were assessed in patients dependent on prescription opioids, compared with normal control subjects. The study included assessments of: 1) prefrontal cortical and psychophysiological responses to images of drug cues and natural rewards; 2) objective and subjective measures of sleep; and, 3) diurnal cortisol. Postulated changes in CNS responses to drug cues and naturally rewarding stimuli were examined using a novel, cost-effective neuroimaging technology, functional near-infrared spectroscopy (fNIRs), which allowed on-site neuroimaging that was not disruptive to the patients' treatment schedule. Hedonic responses to these stimuli were assessed in an acoustic startle paradigm, as well as subjective reports of craving.

Methods: Three groups were recruited into this study: recently detoxified patients dependent on prescription opioids ($n = 7$; 3 female), patients dependent on prescription opioids who had been in supervised, drug-free residential care for 60-90 days ($n = 7$; 4 female) and non-addicted control subjects ($n = 7$; 1 female). Following demographic and behavioral assessments, participants completed a cued-response task while being monitored with fNIR, followed by an affect-modulated startle response task. They then completed 8 consecutive days of sleep actigraphy, and subjective sleep quality ratings. Salivary cortisol was sampled 5x daily on days 4 and 5 of the 8-day period.

Results: In the cued-response paradigm, both patient groups reported pre-to-post test increases in craving in response to drug cues ($p < .001$), coupled with decreases in perceived capacity to control urges ($p < .03$), indicating the effectiveness of stimuli. Recently detoxified patients showed greater response to drug cues than extended care patients in right PFC (middle frontal gyrus; $p < .05$). The 3-way ANOVA failed to reach significance ($F(2,18) = 2.29$, $p = .130$; partial $eta^2 = .20$). For the patients, there was a trend for the magnitude of the fNIR responses to pill images to correlate with the number of days since last drug use (Pearson's $r = -.41$, $p = .11$). Results from the startle response task revealed that recently detoxified patients showed increased startle in response to natural reward stimuli (suggesting a negative hedonic evaluation) relative to the extended care group ($p = .004$), whereas extended care patients & controls showed inhibited startle (suggesting positive hedonic evaluation of natural rewards The patients' startle response to natural rewards was strongly correlated with the days since last drug use. Pearson's $r = -.69$, $p = .006$. Actigraphy and sleep diary data over 8 days revealed that recently detoxified patients tended to spend less time in bed ($p = .05$) and less time asleep ($P = .04$) in spite of residing in a structured sleep environment; extended care patient's sleep was similar to normal controls. Average cortisol levels were highest overall among recently detoxified patients ($p = .005$), and intermediate for extended care compared to normal controls. The circadian pattern of the average evening cortisol levels appeared to be elevated in the recently detoxified patients ($p = .03$) and elevated to an intermediate level in extended care patients. Within the extended care group, those with lower overall cortisol spent more time asleep ($p = .03$) than those with higher overall cortisol.

Conclusion: These results suggest possible re-regulation of dysregulated brain reward systems and HPA axis in prescription opiate-dependent patients in association with the duration of the drug free period. Impaired capacity to derive pleasure from natural rewards, hedonic responses to drug cues, HPA axis dysregulation and sleep disturbances may all contribute to the heightened risk of relapse early in the drug-free period following detoxification. Individual differences within the patient groups raise heuristic questions with regard to: 1) whether efforts to sustain the opiate-free period (as with naltrexone or long term residential care) may have greater utility for selected patients; and, 2) whether these measures might have prognostic significance, leading to more effective individualized treatment strategies. These assessments could be explored as possible biomarkers in clinical translational addiction research.

Keywords: dependence, allostasis, fNIR, startle, diurnal

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W217. Neuropeptide Y Signaling in the Bed Nucleus of the Stria Terminalis Regulates Binge-Like Alcohol Drinking

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Background: Endogenous anti-stress systems, including neuropeptide Y (NPY) signaling, protect against the deleterious effects of alcohol and stress by acting in key brain regions involved in the regulation of anxiety and drinking behaviors, including the bed nucleus of the stria terminalis (BNST) in the extended amygdala. Previous research has shown that NPY generally exerts anti-anxiety and anti-drinking effects by acting through the NPY Y1 receptor (Y1R), while the opposite behavioral effects occur when the Y2R is activated. The focus of this study was two-fold: 1) Examine the role of NPY signaling in the BNST in the regulation of binge-drinking and anxiety. 2) Determine if repeated binge-drinking alters NPY systems in the BNST.

Methods: We first examined the effects of compounds that act at Y1R and Y2R in the BNST of male C57BL/6J mice during binge-like ethanol drinking in the drinking-in-the-dark (DID) paradigm. We then utilized whole-cell patch-clamp electrophysiology to study the effects of selective activation of Y1R and Y2R on synaptic transmission in the BNST. Finally, we examined the impact of one or three cycles of binge-like exposure on NPY systems in the BNST using immunohistochemistry and electrophysiology.

Results: We found that Y1R agonists, but not Y2R antagonists, injected in to the BNST reduced alcohol consumption in the DID paradigm but did not alter locomotion or measures of anxiety-like behavior in the open field. Additionally, we found that Y1R agonists led to increases in GABA release onto neurons in the BNST, whereas Y2R agonists had the opposing effect. After three cycles of DID, basal GABAergic transmission was increased and the ability of NPY to modulate GABAergic transmission via Y2R was significantly blunted. In addition, both Y1R and Y2R protein expression in the BNST were increased. Interestingly, no altera-

tions in synaptic transmission or NPY signaling were observed after a single cycle of DID.
Conclusion: Together, these results led to the hypothesis that the anxiogenic and pro-drinking effects of chronic ethanol exposure may be due to dysregulation of NPY signaling via alterations of Y1R and/or Y2R function.
Keywords: amygdala, physiology, neuropeptide, anxiety, neural circuits
Disclosure: T. Kash, Nothing to Disclose; K. Pleil, Nothing to Disclose; E. Lowery, Nothing to Disclose, T. Thiele, Nothing to Disclose.

W218. Association between Microstructural Integrity of the Frontostriatal Tracts and School Functions: Inattention Symptoms and Sustained Attention as Mediators

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Background: Although our prior research demonstrated an association between disturbed frontostriatal circuitry integrity and a wide range of executive dysfunctions in youth with attention-deficit hyperactivity disorder (ADHD) and typically developing youth, its functional significance on school adjustment has not been examined. The goal of this study is to assess links between microstructural integrity of frontostriatal circuitry and school functioning, perhaps the most important functional domain influenced by ADHD diagnosis/symptoms, and to identify the mediating role of specific executive functions and ADHD symptoms on such links.
Methods: We assessed 32 youth with ADHD (mean age = 11.4 ± 2.3, Full-scale IQ = 109.1 ± 12.2, 29 males) and 32 age-, sex-, IQ-, and handedness-matched typically developing youth by using the Kiddie epidemiologic version of the Schedule for Affective Disorders and Schizophrenia for psychiatric diagnosis, the Social Adjustment Instrument for Children and Adolescents for four domains of school functioning (academic performance, attitude toward school, school social relationship, and school behavioral problems) and the SNAP-IV for inattention and hyperactivity-impulsivity symptoms. The participants received the tasks involving executive functions in the Cambridge Neuropsychological Test Automated Battery: Intra-dimensional/Extra-dimensional Shifts, Spatial Working Memory, Rapid Visual Information Processing (RVP), and Stocking of Cambridge. The frontostriatal tracts were reconstructed by diffusion spectrum imaging tractography and were subdivided into four functionally distinct segments, including dorsolateral, medial prefrontal, orbitofrontal, and ventrolateral tracts. Tract-specific analysis was used and generalized fractional anisotropy values were computed along individual targeted fiber tracts to investigate alterations in microstructure integrity. All the analyses were controlled for the participants' sex and age.
Results: Youth with ADHD had lower generalized fractional anisotropy of all the bilateral frontostriatal fiber tracts; poorer academic performance, more negative attitude, less social interactions, and more behavioral problems at school; and worse performance in set-shifting, sustained attention, attention control, and spatial planning than typically developing youth. Due to small sample size and no group difference in the correlations between frontostriatal tracts and four domains of school functions, we did not stratify our analysis for the two groups. We found that bilateral orbitofrontal tracts integrity was positively correlated with all four domains of school functioning and the eight frontostriatal tracts were significantly associated with school behavioral problems. Mediator analyses of the associations between bilateral orbitofrontal tracts and school functioning revealed that these associations were mediated by sustained attention as measured by the RVP and by inattentive symptoms; however, these associations were not mediated by other executive functions such as set-shifting, working memory, and spatial planning or hyperactivity-impulsivity symptoms.
Conclusion: Our findings demonstrate a direct association of the frontostriatal circuitry, particularly bilateral orbitofrontal tracts, with attention and functional impact on academic performance and school behaviors. The links, supported by our findings, are mediated by inattention symptoms as observed by the parents and sustained attention as measured by the CANTAB. The similarity of these associations in youth with and without ADHD suggests that ADHD may be a severe manifestation of a common pathway of attentional functioning in youth rather than emerging from a distinct pathological mechanism.
Keywords: ADHD, Frontostriatal circuitry, Orbitofrontal tract, school functioning, attention, mediators
Disclosure: S. Shur-Fen Gau, Nothing to Disclose; K. Merikangas, Nothing to Disclose; W.I. Tseng, Nothing to Disclose.