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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

J Craig. Nelson*, Thomas D. Stewart, Ainslie Hatch, Kimberly Largay, Elizabeth E. Bellochio, Sabrina V. Marler, Ross A. Baker, John Sheehan, Robert M. Berman

University of California, San Francisco, California

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.
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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

Helen Lavretsky*, Ascia Eskin, Stanley Nelson, Steve Cole

UCLA, Los Angeles, California

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

James Joseph. Mahoney*, Ari Kalechstein, Thomas Newton, Ryan Bennett, Nicholas Arnoudse, Richard De La Garza

Baylor College of Medicine, Pearland, Texas

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, ~41 years old, had ~12 years of education, used cocaine for ~16 years and ~17 out of the last 30 days, and used ~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 ± 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
Disclosure: J. Mahoney, Nothing to Disclose; A. Kalechstein, Nothing to Disclose; T. Newton, Nothing to Disclose; R. Bennett, Nothing to Disclose; N. Arnoudse, 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. There is no potential interest affected with regard to the data presented in this abstract, **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. There is no potential interest affected with regard to the data presented in this abstract.

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

Eric Finzi*, Norman Rosenthal

Chevy Chase Cosmetic Center, Chevy Chase, Maryland

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

Daniel E. Casey*, Kimberly Laubmeier, Eudicone James, Ronald N. Marcus, Ross A. Baker, John Sheehan, Robert M. Berman

Oregon Health and Science University, Portland, Oregon

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 ⩾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

Carolyn I. Rodriguez*, Lawrence S. Kegeles, Amanda Levinson, Sue Marcus, Helen Blair. Simpson

Columbia University, Bronx, New York

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

Himanshu P. Upadhyaya*, Angelo Camporeale, J. Antoni Ramos-Quiroga, David Williams, Yoko Tanaka, Jeannine Lane, Robert R. Conley, Rodrigo Escobar, Paula Trzepacz, Albert J. Allen

Eli Lilly and Company, Indianapolis, Indiana

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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