The University of Texas Southwestern Medical Center at Dallas Institutional Review Board

Protocol Title: Ondansetron for Bipolar and Alcohol Use Disorders

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AIMS

Primary Mood Aim: *Determine if ondansetron as an add-on therapy is associated with a greater reduction in depressive symptoms than placebo therapy in outpatients with bipolar disorder (BPD) and alcohol use disorder.*

Primary Alcohol Aim: *Determine if ondansetron as an add-on therapy is associated with a greater reduction in alcohol use than placebo therapy in outpatients with BPD and alcohol use disorder.*

Secondary Aims: 1) *Determine if ondansetron as an add-on therapy is associated with a greater reduction in manic symptoms than placebo therapy in outpatients with BPD and alcohol use disorder.* ***2)*** *Determine if ondansetron as an add-on therapy is associated with a greater reduction in alcohol craving than placebo therapy in outpatients with BPD and alcohol use disorder.* ***3)*** *Examine genotype as a baseline predictor of ondansetron response.*

Exploratory Analyses: ***1)*** *Determine if ondansetron as an add-on therapy is associated with a greater improvement in cognition than placebo therapy in outpatients with BPD and alcohol use disorder.* ***2)*** *Determine if reduction in alcohol use and alcohol craving is associated with reduction in manic and depressive symptoms in outpatients with BPD and alcohol use disorder.*

BACKGROUND

BPD is a severe and persistent psychiatric illness affecting 1.3-3.5% of the population.[1-3] Drug and alcohol abuse are common in persons with BPD.[4] Regier et al.[1] found a 61% lifetime prevalence of substance abuse in bipolar I and 48% prevalence in bipolar II patients. This prevalence is substantially greater than the 6% prevalence reported in the general population (odds ratio 8) and more than twice that of people with major depressive disorder (unipolar depression). ***Thus, patients with BPD and substance-related disorders represent a significant public health concern.***

Alcohol is the most commonly abused substance in BPD. Numerous studies have reported high rates of alcohol-related disorders in BPD.[5-7] Persons with bipolar I disorder have a 46% lifetime prevalence of alcohol-related disorders compared to 14% in the population as a whole.[1] ***Odds ratio of alcohol dependence is 5.5 for bipolar I disorder and 3.1 for bipolar II disorder***.

Substance abuse adversely affects the course of BPD. The negative impact of substance abuse on BPD is well documented. Studies report increased hospitalization[8-12] and lower rates of recovery during hospitalization in BPD patients with substance abuse.[13] Aggression and violence are also significantly greater in BPD patients with comorbid substance abuse.[14, 15] In addition, substance abuse is associated with medication nonadherence in BPD.[4, 16-19] Thus, substance-related disorders have a significant adverse impact on the course of BPD.

Cognition in BPD and Alcohol Dependence. Cognition is an important symptom domain in alcohol dependence. The severe and generally irreversible memory changes associated with the Wernicke-Korsakoff syndrome are a dramatic example of the effects of alcohol on cognition.[20] Less severe, but still clinically significant, memory impairment is more common.[21] Some data suggest that memory impairment improves with cessation of alcohol use[22] but persisting cognitive deficits have also been reported.[21] BPD is also associated with impairment in memory and executive functioning[23] even following resolution of mood symptoms.[24, 25] The combination of alcohol dependence and BPD appears to be associated with an additive, detrimental effect on memory.[26-28] Thus, BPD and alcohol dependence are associated with poorer memory and executive functioning than BPD or alcohol dependence alone, that persists long after cessation of alcohol use.[27, 28] Therefore, a medication with a favorable safety profile that decreases alcohol use, and improves mood and memory would be very useful in this dual diagnosis population.

Limited data are available on the pharmacotherapy of BPD with comorbid alcohol dependence. However, the studies, to date, have been promising. Literature on the treatment of alcohol dependence in BPD is quite limited. Salloum et al. reported that 24 weeks of valproate therapy was associated with a significant reduction in heavy drinking days in 59 patients with BPD I and alcohol dependence.[29] Our group reported reduction in depressive symptoms, but no significant between-group differences in alcohol use, in 115 outpatients with BPD I or II disorder and alcohol abuse or

dependence given 12 weeks of quetiapine.[30] However, a subgroup of patients with higher levels of alcohol consumption at baseline showed a much more favorable response to quetiapine as compared to placebo. We also reported a reduction in alcohol use and improvement in depressive symptoms in patients with BPD given naltrexone as compared to placebo.[31]

Ondansetron May be Useful for Reducing Alcohol Consumption and Improving Mood

A. Alcohol Use: Ondansetron is a serotonin (5-HT_3) receptor antagonist that is FDA-approved as an antiemetic at doses ranging from 8 to 24 mg. The patent has expired. The 5-HT_3 receptor appears to mediate, in part, the CNS effects of alcohol.[32] Alcohol potentiates 5-HT_3 receptor-mediated ion currents.[33] This effect is blocked by 5-HT_3 receptor antagonists.[34] Dopaminergic mesocorticolimbic dopamine pathways, in part, mediate the rewarding of alcohol and other substances of abuse.[35-39] The 5-HT_3 receptors in this

pathway regulate dopamine release from neurons.[40] Blockade of the 5-HT_3 receptor reduces alcohol use in animal models, possibly through a decrease in dopamine release.[41] Consistent with these pre-clinical findings, ondansetron appears to reduce alcohol consumption in humans. Johnson et al. randomized 271 outpatients with alcohol dependence to ondansetron (1, 4 or 16 μg/kg BID) or placebo for 11 weeks. Interestingly, differences in response were observed based on whether the participants had an early or late onset of alcohol dependence.[42] All ondansetron doses were superior to placebo in reducing drinks per day and drinks per drinking day in those with early onset alcohol dependence (≤ 25 years). The 4 μg/kg ondansetron dose was also superior to placebo on days abstinent and total days abstinent per week. A significant difference from placebo on carbohydrate deficient transferrin (CDT, a biomarker of alcohol use) was observed with the 1 and 4 μg/kg doses. Later research determined that people with the LL genotype for the serotonin transporter (5-HTT) gene had a greater reduction in alcohol use with ondansetron than those with the LL/SS genotype.[43] Thus, ondansetron is a potential treatment for alcohol dependence in which both a clinical characteristic (age on onset) and a biomarker (genotype) have been associated with clinical response.

B. Mood Symptoms: Ondansetron may also be useful for psychiatric symptoms. Johnson et al. examined scores on the Profile of Mood States (POMS) in patients with alcohol dependence receiving ondansetron (1, 4 or 16 μg/kg BID) or placebo.[44] The 16 μg/kg dose showed the greatest separation from placebo on the POMS. However, even the lower dosages were associated with significant improvement on many of the subscales in those with early-onset alcohol dependence. Ondansetron, at a much higher dose than used in the alcohol dependence studies (4 mg BID), was associated with improvement in depression and fatigue, as compared to placebo, in patients with hepatitis C. Two 12-week, randomized, double-blind trials have reported improvement with ondansetron (8mg/day) in patients with schizophrenia on negative symptoms of the Positive and Negative Syndrome Scale (PANSS) and visual memory.[45, 46] Given these data we will assess mood and cognition in the proposed study.

PILOT STUDIES

As mentioned above, our group has conducted prior treatment trials in patients with BPD and substance use over the past 15 years including some of the largest trials in this area published to date (n=90,115, 120, 130)[30] and two of the three were published, randomized, controlled trials in BPD and alcohol dependence. Our staff members have extensive experience conducting research in this population. We have previously utilized all of the procedures and outcomes measures proposed in the current proposal.

EXPERIMENTAL APPROACH

Study Overview: A 12-week, randomized, double-blind, parallel-group, placebo-controlled study of ondansetron in 70 persons with early-onset alcohol use disorder and features of BPD, is proposed. Changes in alcohol use and mood will be assessed. Flexible dosing, based on depressive symptoms and alcohol use, will be utilized beginning at the low doses used for alcohol dependence and upwardly titrating, if needed, to the higher doses used for schizophrenia. A timeline for the study is provided in Figure 1.

Details of Proposed Experiment: A 12-week, randomized, double-blind, parallel-group, flexible-dose, placebo-controlled trial of ondansetron in 70 outpatients with features of BPD and early-onset alcohol use disorder with active alcohol use is proposed. Potential participants will be identified through physician referral and through flyers and brochures at clinics that treat the population needed for this study. In most cases, the potential participant will call our clinic. At this time an appointment will be arranged, where informed consent will be obtained and assessment procedures, including a review of inclusion and exclusion criteria, will be performed. A structured clinical interview for DSM-V (SCID) will be performed to establish the diagnoses of bipolar I or II disorder and alcohol use disorder. The Clinical Institute Withdrawal Assessment of Alcohol Use-Revised[47] (CIWA-Ar) will be administered. Eligible participants will then be given the Hamilton Rating Scale for Depression[48] 17-item version ($HRSD_{17}$), Inventory of Depressive Symptomatology–Self-Report[49-52] 30-item version ($IDS\text{-}SR_{30}$), Young Mania Rating Scale[53] (YMRS), Penn Alcohol Craving Scale[54] (PACS), Psychobiology of Recovery in Depression III - Somatic Symptom Scale[55] (PRD-III), a cognitive assessment, and a urine drug screen. Recent alcohol use (and if present, other substance use) will be assessed using the Timeline Followback (TLFB) method.[56, 57] The length of problem alcohol use will be assessed by asking “When did alcohol first start causing you problems?” Blood will be drawn for routine laboratory analyses including a complete blood count (CBC), SMA-20 (includes a liver panel with AST, ALT, and GGT), and CDT level at baseline (week 0) and weeks 4, 8, and 12. Mood stabilizer levels will also be tested, if possible, to assure the participant’s medication adherence. Cognitive assessments will be performed at baseline and week 12. See Table 1 for a summary of the assessment schedule. Women of childbearing potential will receive a urine pregnancy test at baseline and weeks 4, 8, and 12 and will be counseled about effective contraceptive methods. A psychiatrist (PI or co-I) will assess participants at baseline and weekly follow-up visits and will participate in the informed consent process. Participants will be randomized (1:1) to receive ondansetron (0.5

mg BID) or placebo. Study participants will begin study medication at 0.5 mg BID. Participants who are tolerating the study medication well will have the opportunity to have a medication titration in a dose-response manner to 1.0 mg, 2.0 mg, or 4.0 mg BID at weeks 4, 8 and 10. At week 4 participants with < 30% reduction in drinks per week and/or 30% reduction in the $HRSD_{17}$, who are tolerating the medication well, will have a dose increase to 1.0 mg BID. At week 8, participants who are tolerating the medication well and have <50% reduction in drinks per week and/or the HRSD17 will titrate to the next higher dose (i.e., a patient who did not titrate up at week 4, but fails to meet criteria at week 8 will titrate to 1.0 mg BID). If they still have not achieved a 50% reduction in drinks per week and/or $HRSD_{17}$ at week 10 they will again titrate to the next higher dose, 1.0 mg, 2.0 mg or 4.0 mg BID. At weekly visits the $HRSD_{17}$, $IDS\text{-}SR_{30}$, YMRS, and assessment of alcohol will again be evaluated. Participants will be paid for their time and inconvenience: $10 at baseline I, $60 at baseline II and week 12, $30 at weeks 1, 2, 3, 5, 6, 7, 9, 10, and 11 and $50 at weeks 4 and 8 (based on length of assessments), as well as an additional $5 for each visit on Weeks 1-12 if they bring back their study medication bottle(s) to the appointment. Participants will also receive a $2 cash payment that increases by $2 each time an appointment is attended and resets back to $2 if an appointment is missed. Bus passes ($2.50) will be provided when needed. After completing the study, participants will be provided standard psychiatric care until an outside referral is arranged.

Inclusion/Exclusion Criteria

Inclusion

- Outpatient men and women age 18-70 years old with bipolar I, II or NOS disorder, or schizoaffective disorder (bipolar type), or cyclothymic disorder, or major depressive disorder (MDD) with mixed features.
- Current diagnosis of alcohol use disorder (DSM V terminology) with onset ≤ age 25.
- Alcohol use (by self-report) of at least 15 drinks in the 7 days prior to intake.
- If diagnosis of: bipolar I, II, or NOS, or cyclothymic disorder: Patient on a stable dose of a mood stabilizer therapy (lithium, anticonvulsant, atypical antipsychotic) for at least 14 days prior to randomization.
- If diagnosis of schizoaffective disorder (bipolar type): Patient on a stable dose of an atypical antipsychotic for at least 14 days prior to randomization. An atypical antipsychotic (Risperidone) will be prescribed to participants who meet criteria for schizoaffective disorder, but are not on a stable dose of an atypical antipsychotic at the time of screening.
- If diagnosis of major depressive disorder (MDD) with mixed features: Patient on a stable dose of an antidepressant for at least 14 days prior to randomization. Patients who meet criteria for MDD with mixed features, but are not on an antidepressant at the time of screening, will be prescribed either Sertraline (50mg daily) or Escitalopram (5mg daily) prior to randomization. The doses may be titrated up by a study physician to achieve a therapeutic level.

Exclusion

- Baseline YMRS or $HRSD_{17}$ scores ≥ 35 to exclude those with very severe mood symptoms.
- Evidence of clinically significant alcohol withdrawal symptoms defined as a CIWA-Ar score of ≥ 10.
- Therapy in past 14 days with naltrexone, acamprosate, disulfiram, or topiramate.
- Vulnerable populations (e.g. pregnant, breastfeeding, cognitively impaired (e.g. dementia, mentally challenged), incarcerated).
- High risk for suicide defined as > 1 attempt in past 12 months that required medical attention, any attempt in the past 3 months or current suicidal ideation with plan and intent such that outpatient care is precluded.
- Intensive outpatient treatment (defined as ≥ 3 visits each week) for substance abuse (AA, NA meetings, or less intensive counseling at baseline will be allowed).
- Severe or life-threatening medical condition (e.g., hepatic cirrhosis) or laboratory or physical examination findings consistent with serious medical illness (e.g., dangerously abnormal electrolytes).
- AST or ALT > 3 times the upper limit of normal.
- History of severe side effects or allergic reaction with prior ondansetron therapy (e.g. for emesis) or use of medications with significant drug-drug interactions with ondansetron (phenytoin, carbamazepine, and rifampicin, apomorphine, tramodol).

Discontinuation Criteria

- Change in diagnosis to any disorder other than those allowed for inclusion.
- Development of active suicidal or homicidal ideation with plan and intent.
- Pregnancy.
- Development of severe or life-threatening medical condition.
- Involuntary psychiatric hospitalization or incarceration.
- Significant alcohol withdrawal (e.g. delirium tremens) based on clinical judgment. Increases in CIWA-Ar scores will initiate a careful clinical assessment of possible worsening of withdrawal symptoms.

Recruitment and Patient Flow at Referral Sources: For over 15 years, we have conducted clinical trials in BPD and substance abuse. We have conducted some of the largest trials in BPD and substance dependence including a trial of quetiapine in 115 patients with BPD and alcohol dependence in slightly over 2 years. Given these data and the inclusion and exclusion criteria (e.g. only those with early onset alcohol dependence, baseline medications, baseline mood state, minimum baseline amount of drinking, early onset of drinking) of the proposed study, we anticipate enrolling 70 participants in approximately 2.5 years. We enroll participants through referrals from treatment providers in the community and advertisements.

Assessments: The clinician version of the SCID is a brief structured interview for major Axis I disorders in DSM including major depressive disorder, BPDs, psychotic disorders, and substance abuse/dependence.[58] CIWA-Ar is a 10-item, clinician-rated scale with a range from 0-67 that assesses alcohol withdrawal symptoms.[47] $HRSD_{17}$ is an observer-rated measure of depressive symptomatology.[48] $IDS\text{-}SR_{30}$ is a 30-item self-report scale of depressive symptom severity.[49-52] YMRS is an 11-item, observer-rated measure of manic symptoms. PACS is a 5-item, self-report measure that includes questions about alcohol craving.[54]

PRD-III - Somatic Symptom Scale[59] is a 24-item side effects rating scale that covers a wide range of common medication side effects. TLFB[56, 57] is a method for assessing recent drinking, in which participants retrospectively estimate daily alcohol consumption over a period of time ranging from 7 days to 24 months. Brief Visuospatial Memory Test-Revised (BVMT-R)[60] is a measure of visuospatial memory that has been standardized and normed for use with adults ages 18-79 years. Rey Auditory Verbal Learning Test (RAVLT) measures verbal or declarative learning and memory.[61] Stroop Test measures the ease with which a person can shift perceptual sets to conform to changing demands and suppress a habitual response in favor of a nondominant one.[62] The Treatment Impressions Inventory (TII) is a scale generated by the PI and statistician in an effort to detect placebo effects in study participants. The assessment consists of 40 statements and requires the participant to respond based on how much he/she agrees with each statement on a 5 degree Likert scale. This assessment will be piloted in this study and given only at the baseline visit. The Pill Box Test will be given at baseline and week 12. The test is a neurocognitive measure for executive functioning that also has implications for gauging medication adherence.[63]

Management of concomitant psychotropic medications: Treatment of patients with the concurrent diagnosis of a major mental illness in addition to alcohol use disorder requires the ability to change dosages, or add and subtract concomitant medications in the interest of participant safety, retention, and generalizability. We elected to allow changes in concomitant medications for psychiatric symptoms when clinically needed. To provide consistency to the medication management, the study physicians will take over the management of these medications and use a modification of a treatment guideline we used in prior studies. Changes in concomitant medications will also be used as a covariate in the data analysis.

Ondansetron: Both IV and oral formulations are available. Generic equivalents have been available since 2006. Typical doses for nausea and vomiting are 8-24 mg. The oral formulation will be used in this study. **Ondansetron dosing in current proposal:** Lower ondansetron doses have been used for alcohol dependence than for nausea or psychiatric symptoms. In this study we plan to target both mood and alcohol use. Therefore, we propose beginning at a low dose, consistent with prior alcoholism studies, and titrating up (in a double-blind fashion) to doses used for other psychiatric disorders (e.g. schizophrenia) based on tolerability and response (alcohol use, depressive symptoms).

Genetic analysis: Blood samples will be sent for genotyping to UT Southwestern McDermott Center for Human Growth and Development (site of much of the genetic analysis at our institution). The 5-HTT gene [LL/LS/SS (associated with ondansetron response)] will be examined, and other analyses, based on available literature on BPD and alcohol dependence, BPD or ondansetron available at the end of the study, will be considered.

There has been a recent increase in interest in inflammatory and immune aspects of schizophrenia and bipolar disorder. This has been accompanied by the use of anti-inflammatory drugs to treat these diseases. In a preliminary study, one protein marker (C-reactive protein) was identified that appeared to predict the response to anti-inflammatory drugs. Although pharmaceutical companies have looked for genetic markers of drug response, little work has been done looking at blood proteins and other non-genetic markers. For this reason SMRI is beginning to collect sera on the patients in many SMRI-funded treatment trials. The sera is collected on patients at the beginning and at the end of the trial, and then sent to the Stanley Laboratory of Developmental Neurovirology at Johns Hopkins University (under the direction of Dr. Robert Yolken) for analysis of protein markers of inflammation, such as C-reactive protein, cytokines, and antibodies to common infectious agents such as *Toxoplasma gondii* and herpes viruses. All sera will be sent to SMRI laboratory labeled with numbers; thus no patient identifying information will be sent to SMRI. This data is shared with the PI of the treatment trial who then assesses the data and results of the trial to determine whether the protein markers are predictive of the responders to this drug. The PI is of course then free to publish the results.

STATISTICAL ANALYSES PLAN

Randomization: Dr. Jeon-Slaughter, a statistician, will randomize patients using a random number program. We will stratify the randomization based on > 4 or ≤ 4 drinking days per week at baseline (selected based on anticipated mean drinking patterns informed by data from our prior research).

Primary Aim: Determine if ondansetron as an add-on therapy is associated with a greater reduction in depressive symptoms than placebo therapy in outpatients with bipolar disorder (BPD) and alcohol use disorder. Determine if ondansetron as an add-on therapy is associated with a greater reduction in alcohol use than placebo therapy in outpatients with BPD and alcohol use disorder. Participants completing baseline and at least one post baseline assessment will be used in the analysis (intent-to-treat [ITT] sample). In the spirit of an ITT analysis, data will be collected even on participants who miss assessments or discontinue medication. Data on participants who do not complete the study will be analyzed up to the point of study discontinuation. A random regression that includes all data will be conducted with treatment group as the between-subjects factor; time as the within-subjects factor; and a group by time interaction with mood (e.g.

HRSD17) and alcohol-related outcomes (e.g. alcohol use, CDT level) as the dependent variables. The model will allow for random slopes and intercepts while all other factors will be fixed effects. SAS Proc Mixed will be used. The baseline value of the outcome will always be used as a covariate. The need for additional covariates or transformations of variables as well as goodness of fit of the final model will be investigated. The following covariates will be considered: age, gender, baseline use of substances other than alcohol, presence of anxiety disorders, baseline use of psychotropic medications, and change in use of psychotropic medications. Covariates will be included if they significantly improve the fit of the final model. An *a priori* alpha of 0.05 will be used for all other analyses. Other outcome measures will be assessed using similar methods. ***Examine genotype as a baseline predictor of ondansetron response.*** The purpose of this analysis is to identify moderators of treatment effect. Treatment effect is determined by treatment group main effect and treatment group by time interaction effect estimated from the random regression model described for the primary aim. Genotype will be included in the random regression model for the alcohol-related outcomes along with genotype by treatment group interaction and genotype by treatment group by time interaction. Significance for either interaction term would indicate that genotype is a moderator of the treatment effect. ***Determine if reduction in alcohol use and alcohol craving is associated with reduction in manic and depressive symptoms in outpatients with BPD and alcohol use disorder.*** We will explore correlations between baseline to exit changes in mood (e.g. HRSD17) and alcohol use/craving assessments using a Pearson's correlation coefficient in ondansestron and placebo groups.

Sample Size: A sample of n=70 provides 80% power for a two-sample t-test to compare groups with alpha=.05 on outcomes with a medium to large effect size (Cohen's d ≥ 0.7).

Data and Safety Monitoring: In addition to data and safety monitoring by the PI and staff, a DSMB will be formed consisting of Alicia Meuret, Ph.D. (Chair) (Southern Methodist University), Carroll Hughes, Ph.D. (UT Southwestern, statistical expertise), and Arthur Westover, M.D. (Psychiatrist, UT Southwestern). The meeting will be conducted using the guidelines provided by the SMRI.

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