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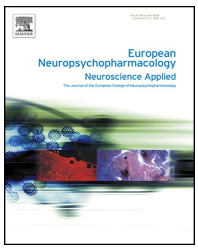

A randomized, double-blind, placebo-controlled proof-of-concept study of ondansetron for bipolar and related disorders and alcohol use disorder

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Abstract
Bipolar disorder is associated with high rates of alcohol use disorder. However, little is known about the treatment of this dual diagnosis population. Previous studies suggest that ondansetron decreases alcohol use, particularly in people with specific single nucleotide polymorphism (SNP) alleles. A 12-week, randomized, double-blind, placebo-controlled trial of ondansetron was conducted in 70 outpatients with bipolar spectrum disorders and early onset alcohol use disorder. Outcome measures included alcohol use, assessed with the Timeline Followback method, Penn Alcohol Craving Scale (PACS), Hamilton Rating Scale for Depression (HRSD), Inventory of Depressive Symptomatology-Self-report, and Young Mania Rating Scale. SNPs rs1042173, rs1176713 and rs1150226 were explored as predictors of response. Participants had a mean age of 44.9 $\pm$ 9.4 years, were mostly men (60.0%), and African American (51.4%). Mean ondansetron exit dose was 3.23 $\pm$ 2.64 mg. No significant between-group differences in alcohol use measures were observed. However, a significant reduction in HRSD scores was observed ($p = 0.045$). Inclusion of SNPs increased effect sizes for some alcohol-related outcomes and the HRSD. Ondansetron was well tolerated. This proof-of-concept study is the first report on ondansetron in bipolar people with bipolar disorders and alcohol use disorder.

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Alcohol use did not demonstrate a significant between-group difference. However, the findings suggest that ondansetron may be associated with reduction in depressive symptom severity in persons with bipolar illnesses and alcohol use disorder. A larger trial is needed to examine the effects of ondansetron on bipolar depression.

1. Introduction

Bipolar disorder (BPD) is a severe and persistent psychiatric illness affecting 1.3–3.5% of the population (Kessler et al., 1996; Merikangas et al., 2007; Regier et al., 1990). Drug and alcohol abuse are common in persons with BPD (Brown et al., 2001). Regier et al. found a 61% lifetime prevalence of substance abuse in bipolar I and 48% prevalence in bipolar II patients (Regier et al., 1990). Similarly, Grant et al. observed a 61% lifetime prevalence of an SUD in people with bipolar I disorder in the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) study (Grant et al., 2005). 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.

The negative impact of substance abuse on BPD is well documented. Studies report increased hospitalization (Haywood et al., 1995; Himmelhoch and Garfinkel, 1986; O'Connell et al., 1991; Sonne et al., 1994; Tohen et al., 1990) and lower rates of recovery during hospitalization in BPD patients with substance abuse (Goldberg et al., 1999). Aggression and violence are also significantly greater in BPD patients with comorbid substance abuse (Saxon et al., 1994; Scott et al., 1998). In addition, substance abuse is associated with medication nonadherence in BPD (Baldessarini et al., 2008; Brown et al., 2001; Manwani et al., 2007; Perlis et al., 2010; Sajatovic et al., 2009). Numerous studies have reported high rates of alcohol-related disorders in BPD (Dunner et al., 1979; Mendlewicz et al., 1972; Morrison, 1974). Persons with bipolar I disorder have a 46% lifetime prevalence of alcohol-related disorders compared to 14% in the population as a whole (Regier et al., 1990). Odds ratio of alcohol dependence is 5.5 for bipolar I disorder and 3.1 for bipolar II disorder.

Limited data are available on the pharmacotherapy of BPD with comorbid alcohol use disorder (AUD) (Naglich et al., 2017). Seven randomized, double-blind, placebo-controlled medication trials in people with bipolar disorder and alcohol-use disorder have been reported to date (Salloum and Brown, 2017). Only one of these demonstrated statistically significant differences in alcohol consumption with medication as compared to placebo. In this study, 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 (Salloum et al., 2005). Psychotherapeutic approaches have also been explored in this dual diagnosis population. Weiss et al. reported that an integrated group therapy that addressed both BPD and substance use was associated with fewer days of substance use than group drug counseling focusing on substance use (Weiss et al., 2007). Schmitz et al. observed that an individual cognitive behavioral therapy specific for BPD and substance use improved attendance and tended to improve medication adherence and mood but did not decrease substance use (Schmitz et al., 2002). The limited available literature suggests that this dual diagnosis population may be quite challenging to treat with available medications. Therefore, additional pharmacotherapeutic treatments are needed.

Ondansetron is a serotonin (5-HT_3) receptor antagonist that is US Food and Drug Administration-approved as an antiemetic. The 5-HT_3 receptor appears to mediate, in part, the brain effects of alcohol (Lovinger, 1999). Alcohol potentiates 5-HT_3 receptor-mediated ion currents (Lovinger, 1991). This effect is blocked by 5-HT_3 receptor antagonists (Zhou and Lovinger, 1996). Dopaminergic mesocorticolimbic dopamine pathways, in part, mediate the rewarding of alcohol and other substances of abuse (Bloom and Morales, 1998; Di Chiara and Imperato, 1988; Koob, 1992; Soderpalm and Ericson, 2011; Wise and Bozarth, 1987). The 5-HT_3 receptors in this pathway regulate dopamine release from neurons (Engleman et al., 2008). Blockade of the 5-HT_3 receptor reduces alcohol use in animal models, possibly through a decrease in dopamine release (Kilpatrick et al., 1987). Consistent with these preclinical 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 (Johnson et al., 2000). All ondansetron doses were superior to placebo in reducing drinks per day and drinks per drinking day in those with early onset alcohol dependence ($\leq$ 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 revealed 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 (Johnson et al., 2011). Thus, ondansetron is a potential treatment for alcohol dependence in which both a clinical characteristic (age of onset) and a biomarker (genotype) have been associated with clinical response.

A very limited literature suggests that ondansetron may also be useful for mood 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 (Johnson et al., 2003; Vaughan et al., 2012). 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 some subscales in those with early-onset alcohol dependence. Furthermore, ondansetron at 4 mg BID was associated with improvement in depression and fatigue, as compared to placebo, in patients with hepatitis C (Piche et al., 2005). Given these literature findings, we conducted a proof-of-concept study of ondansetron in people with bipolar disorder and related disorders and AUD. The aims were to determine if ondansetron decreased alcohol use and improved mood symptoms in people with bipolar disorders and AUD.

2. Experimental procedures

2.1. Study design

A 12-week, randomized, double-blind, flexible-dose, placebo-controlled, parallel-group, study of ondansetron was conducted in 70 outpatients with bipolar disorders and early-onset AUD (onset at age 25 or before selected based on prior published ondansetron research suggesting a more favorable response in this subpopulation (Johnson et al., 2000) with active alcohol use. Included were 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, a current diagnosis of AUD with onset $\leq$ age 25 and alcohol use (by self-report) of at least 15 drinks in the 7 days prior to intake. Excluded were those with a baseline Young Mania Rating Scale (YMRS) or Hamilton Rating Scale for Depression (HRSD) scores $\geq$ 35 to exclude those with very severe mood symptoms, evidence of clinically significant alcohol withdrawal symptoms defined as a Clinical Institute Withdrawal Assessment for Alcohol, revised (CIWA-Ar) score of $\geq$ 10, therapy in past 14 days with naltrexone, acamprosate, disulfiram, or topiramate, vulnerable populations (e.g. pregnant, breastfeeding, cognitively impaired (e.g. dementia), incarcerate, 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 $\geq$ 3 visits each week) for substance abuse (Alcoholics Anonymous 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)., aspartate transaminase (AST) or alanine transaminase (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). All participants signed written informed consents approved by The University of Texas Southwestern Medical Center Institutional Review Board. The first assessment was conducted on April 24, 2014 and the final on May 2, 2018. Participants were randomized (1:1), using a random number sequence and stratification based on based on $>$ 4 or $\leq$ 4 drinking days per week at baseline, to receive ondansetron (0.5 mg BID) or placebo (see Supplementary Figure S1 for Consort Diagram). At week 4, participants with $<$ 30% reduction in both drinks per week and score on the HRSD, who tolerated the medication well had a dose increase to 1.0 mg BID, with an additional increase to 2.0 mg BID in those with $<$ 50% reduction in drinks per week and the HRSD at week 8. If they still had not achieved a 50% reduction in drinks per week and HRSD at week 10, they had a dose increase to 4.0 mg BID. These cutoffs were selected to allow for a dose increase for participants who were not responding. Participant demographic information is presented in Table 1. The study was conducted at The University of Texas Southwestern Medical Center in Dallas, TX. This trial was registered at ClinicalTrials.gov (NCT02082678).

2.2. Measures

At weekly visits, the HRSD, Inventory of Depressive Symptomatology-Self-report (IDS-SR), YMRS, and assessment of alcohol were evaluated. Outcome measures included alcohol use as assessed with the Timeline Followback method, and carbohydrate deficient transferrin (CDT) and γ-glutamyltransferase (GGT) levels. Craving was assessed using the Penn Alcohol Craving Scale (PACS). Mood was assessed with the HRSD, IDS-SR, and YMRS. Relationships between changes in alcohol use and changes in mood were explored. Side effects were assessed using the PRD-III Somatic Symptom Scale, a 24-item side effects rating scale that covers a wide range of common medication side effects (Thase et al., 1996).

2.2.1. Genotyping

At baseline, 55 participants supplied a blood sample from which genomic DNA was extracted using the Applied Biosystem TaqMan Universal PCR Master mix along with TaqMan SNP Genotyping Probes. Three SNPs were selected based on previous reported findings and genotyped: rs1042173, rs1176713, and rs1150226 (Johnson et al., 2013). Analysis of genotypes was completed using Applied Biosystems Sequence Detection System (AB SDS) v2.4. Prior to continuing with primary analyses, genotype frequencies were checked for deviation from the Hardy-Weinberg equilibrium (HWE). Observed genotypes were compared against expected genotypes using a chi-squared goodness-of-fit test. Statistical significance was evaluated at $p < 0.001$. HWE departure was observed for rs1150226 ($p = 0.001$) with an excess of the AG genotype and paucity of the GG genotype. Complete results are presented in Supplementary Table S1.

Previous research on ondansetron treatment responses suggest that individuals carrying the genotypes rs1150226-AG and rs1176713-GG have a statistically significant positive? effect on a variety of alcohol use outcomes (Johnson et al., 2013). As such, genotypes were combined based on the proposed inheritance pattern of the trait, in which genotypes reported to have a positive effect on alcohol use outcomes were combined and compared against the genotype without an effect on alcohol use (e.g., Johnson et al., 2013):

(1) Combination 1: For rs1150226, genotype AG was combined with genotype AA to be compared against homozygous GG (recessive pattern). For rs1176713, genotype AG was combined with genotype AA to be compared against genotype GG (recessive pattern). For rs1042173, genotype AC was combined with genotype CC to be compared against genotype AA (dominant pattern). This combination produced three genotype factors, each with two levels.
(2) Combination 2: Those with genotypes found to be predictive of alcohol measures (i.e., rs1150226-AG or rs1176713-GG) were combined into a single group to be compared against all other genotypes across the three SNPs. This combination produced one genotype factor with two levels.

As a preliminary analysis, SNP genotypes were examined for group differences using a chi-squared test. No statistically significant group differences in genotype frequencies were found. These genotype combinations, along with sample frequencies, are presented in Supplementary Table S2.

Table 1 Demographic descriptive statistics.

	Whole Sample		Placebo		Ondansetron	
	Mean	SD	Mean	SD	Mean	SD
Age	44.91	9.41	43.29	10.01	46.54	8.60
Education	12.74	2.20	12.79	2.55	12.70	1.82
	Frequency	Percent	Frequency	Percent	Frequency	Percent
Sex						
Female	28	40.0	17	48.6	11	31.4
Male	42	60.0	18	51.4	24	68.6
Race						
African American	36	51.4	18	51.4	18	51.4
Asian/Pacific	6	8.6	3	8.6	3	8.6
Caucasian	18	25.7	9	25.7	9	25.7
Hispanic	9	12.9	4	11.4	5	14.3
Native American	1	1.4	1	2.9	0	0
Marital Status						
Married/Live-in	14	20.0	7	20.0	7	20.0
Widowed	2	2.9	1	2.9	1	2.9
Divorced	16	22.9	7	20.0	9	25.7
Separated	4	5.7	3	8.6	1	2.9
Never Married	34	48.6	17	48.6	17	48.6
Annual Income						
< $15K	46	65.7	19	54.3	27	77.1
$15K-$34K	13	18.6	9	25.7	4	11.5
$35K-$49K	5	7.2	3	8.6	2	5.7
$50K-$99K	4	5.7	3	8.6	1	2.9
> $100K	1	1.4	1	2.9	0	0
Missing	1	1.4	0	0	1	2.9
AUD						
Mild	3	4.3	2	5.7	1	2.9
Moderate	8	11.4	1	2.9	7	20.0
Severe	58	82.9	32	91.4	26	74.3
Severity unknown	1	1.4	0	0	1	2.9
Mood						
Bipolar I	30	42.9	13	37.1	17	48.6
Bipolar II	20	28.6	11	31.4	9	25.7
NOS	14	20.0	9	25.7	5	14.3
MDD mixed	2	2.9	1	2.9	1	2.9
Schizoaffective	4	5.7	1	2.9	3	8.6
Concomitant Medications						
Anxiolytic	16	22.9	9	25.7	7	20.0
Antidepressant	38	54.3	20	57.1	18	51.4
Antipsychotic	34	48.6	13	37.1	21	60.0
Hypnotic	2	2.9	2	5.7	0	0.0
Mood stabilizer	49	70.0	28	80.0	21	60.0
Stimulant	1	1.4	1	2.9	0	0.0
Total *n*	70		35		35	

Note. There were no statistically significant differences between placebo and ondansetron on demographic variables. NOS: Bipolar disorder not otherwise specified; MDD: Major depressive disorder with mixed features.

2.3. Statistical analysis

The primary outcomes of this study were drinks per week for alcohol assessment and the HRSD for depressive symptom severity. Additional alcohol assessments included the number of alcohol days, the number of standard drinks, the number of heavy alcohol days, and CDT and GGT levels. A sample of $n = 70$ was selected to provide 80% power to compare groups with outcomes with a Cohen's $d \geq 0.7$. Prior to conducting analyses, the number of alcohol days, standard drinks, and heavy alcohol days were corrected for "days covered." As a result, the number of alcohol days and the number of heavy alcohol days are presented as proportions. Additionally, both GGT and CDT variables contained a small number of outlier cases. These were deleted prior to performing analyses. Secondary outcomes included mood measures (i.e., IDS-SR, HRSD, and YMRS), PACS total score, and tolerability. Treatment groups were compared on baseline measures to determine group equivalency prior to examining the outcome measures of interest. For continuous baseline measures, including age, education, and the outcomes of interest, independent samples *t*-tests were conducted. For categorical mea-

Table 2 Descriptive statistics for outcome measures at baseline.

	Whole Sample			Placebo			Ondansetron			Comparisons	
	Mean	SD	*n*	Mean	SD	*n*	Mean	SD	*n*	*t*	*p*
YMRS	8.49	6.21	70	7.46	5.37	35	9.51	6.88	35	−1.40	.168
HRSD	14.00	6.35	70	14.23	7.25	35	13.77	5.39	35	0.30	.766
IDS-SR	29.34	16.50	64	29.53	16.52	30	29.18	16.73	34	0.09	.932
PACS	16.90	7.94	63	17.53	7.40	30	16.33	8.48	33	0.60	.553
PRD	7.75	5.95	65	7.41	5.68	32	8.09	6.28	33	−0.46	.647
Drinking Days[a]	0.58	0.34	70	0.67	0.33	35	0.48	0.33	35	2.43	.018
Standard Drinks	4.49	4.07	70	4.92	4.09	35	4.06	4.07	35	0.88	.381
Heavy Drinking Days[a]	0.40	0.35	70	0.45	0.37	35	0.34	0.33	35	1.39	.171
GGT	51.08	51.27	48	59.05	49.02	21	44.89	53.02	27	0.95	.348
CDT	50.27	23.23	47	51.93	31.64	21	48.92	13.72	26	0.44	.664

Note. [a]Drinking days per days covered, represented as percentages. YMRS: Young Mania Rating Scale; HRSD: Hamilton rating scale for depression; IDS-SR: Inventory of Depressive Symptomatology – Self Report; PACS: Penn Alcohol Craving Scale; PRD: PRD-III Somatic Symptom Scale; GGT: γ-glutamyltransferase; CDT: carbohydrate deficient transferrin.

sures, including sex, race, marital status, and annual income, chi-squared analyses were conducted.

Participants with at least two valid measurement points were included in the primary analyses. To examine the effect of treatment group and genotypes on the eight outcomes of interest, a series of linear mixed-effects regression models with random intercepts were conducted. An autoregressive covariance structure was used to account for the relatedness in within-subject measures over time. Additionally, the restricted maximum likelihood (REML) method was used to estimate model parameters. This method allows for use of information available for each case (without listwise deleting those cases with missing data on one or more measurement occasions) and does not require data imputation prior to parameter estimation. For each outcome, three models were analyzed:

(1) The exclusion of genotype factors, in which the fixed effects were time, treatment group, a time × group interaction, and two covariates: age and sex;
(2) The inclusion of genotype combination 1, in which the fixed effects were time, treatment group, a time × group interaction, and five covariates: age, sex, rs1150226 (with two levels: GG and AG + AA combined), rs1176713 (with two levels: GG and AG + AA combined), and rs1042173 (with two levels: AA and AC + CC combined);
(3) The inclusion of genotype combination 2 in which the fixed effects were time, treatment group, a time × group interaction, and three covariates: age, sex, and one SNPs factor with two levels (rs1150226-AG + rs1176713-GG combined and all other genotypes combined).

In each case, the treatment × time interaction term was used to examine whether change over time for a particular outcome varied by treatment group. Finally, Cohen's *d* effect sizes were calculated for each treatment group comparison and genotype comparison. All analyses were performed using IBM SPSS Statistics version 25.0 (Armonk, NY: IBM Corp.). Results were deemed statistically significant at $p < 0.05$.

3. Results

3.1. Outcome measures at baseline

Of the 70 included participants, 35 were randomized to receive ondansetron and 35 were randomized to placebo. During the double-blind phase, 11 participants (31.4%) withdrew or discontinued from the ondansetron group (five participants lost to follow-up) and 13 participants (37.1%) withdrew or discontinued from the placebo group (six participants lost to follow-up). The primary reason for discontinuation was hospitalization or other medical complications. Participants had a mean age of about 45 years, were primarily male (60%), African American (51.4%) and with income less than $15,000 per year. Participants generally had severe AUD (82.9%) and were largely bipolar I (43%), bipolar II (29%), and bipolar NOS (20%) (Table 1). Descriptive statistics for clinical measures at baseline are presented in Table 2. There were no statistically significant group differences in alcohol and mood diagnoses. Treatment groups were well matched at baseline with the exception of the number of drinking days ($Mean_{treatment} = 0.48$, $Mean_{placebo} = 0.67$; $t(68) = 2.43$, $p = 0.018$). The mean ondansetron dose at exit was 3.24 ± 2.64 mg/day and the mean week 12 dose was 3.82 ± 2.84 mg/day.

3.2. Analysis of models excluding SNPs

For models in which SNP factors were not included, a statistically significant treatment group effect was found for HRSD [$F(1, 64.84) = 4.166$, $p = 0.045$, $d = -0.53$] in favor of ondansetron. The treatment group effect for IDS-SR was non-significant but the effect size was medium ($d = -0.43$) and favored ondansetron. The treatment group effect was statistically non-significant for all primary alcohol outcomes. Results can be found in Table 3. Additionally, the alcohol-related Cohen's *d* effect sizes were small but favored ondansetron: alcohol days ($d = -0.24$), standard drinks ($d = -0.10$), and heavy drinking days ($d = -0.15$). For secondary alcohol measures (i.e., GGT and CDT) the treatment group effect was also statistically non-significant. Cohen's *d* effect sizes are presented in Table 4.

Because of the statistically significant findings related to HRSD scores, an additional post hoc analysis was done to further examine its magnitude of change. On average, HRSD scores in the treatment group decreased by 37.42%, compared to 22.53% in the placebo group, from baseline to exit. Additionally, 42.9% of the ondansetron group experienced

Table 3 Results from linear mixed effects models.

No SNPs

	YMRS			HRSD			IDS-SR			PACS			PRD		
	F	*p*	β	*F*	*p*	β	*F*	*p*	β	*F*	*p*	β	*F*	*p*	β
Time	2.349	**.007**	-	5.811	**< 0.001**	-	13.535	**< 0.001**	-	8.820	**< 0.001**	-	6.220	**< 0.001**	-
Group	0.232	.632	−1.87	4.166	**.045**	1.22	2.718	.104	4.69	0.001	.977	−0.48	4.380	**.040**	2.15
Time × Group	1.325	.202	-	1.266	.237	-	1.677	.071	-	1.379	.175	-	2.123	**.016**	-

	Drinking Days			Standard Drinks			Heavy Drinking Days			GGT			CDT		
	F	*p*	β	*F*	*p*	β	*F*	*p*	β	*F*	*p*	β	*F*	*p*	β
Time	5.197	**< 0.001**	-	5.043	**< 0.001**	-	7.211	**< 0.001**	-	0.092	.912	-	1.957	.149	-
Group	0.823	.368	0.03	0.146	.704	0.06	0.317	.575	0.02	3.839	.056	11.05	1.125	.294	4.62
Time × Group	1.559	.102	-	1.515	.117	-	1.005	.444	-	3.700	**.031**	-	0.341	.712	-

SNP Combination 1

	YMRS			HRSD			IDS-SR			PACS			PRD		
	F	*p*	β	*F*	*p*	β	*F*	*p*	β	*F*	*p*	β	*F*	*p*	β
Time	1.861	**.039**	-	4.553	**< 0.001**	-	10.148	**< 0.001**	-	6.195	**< 0.001**	-	4.995	**< 0.001**	-
Group	0.099	.754	−1.43	4.460	**.040**	1.84	2.080	.156	4.99	1.005	.321	1.39	3.628	.063	2.82
Time × Group	1.400	.165	-	0.944	.504	-	1.115	.348	-	1.380	.176	-	3.088	**< 0.001**	-
rs1150226	0.663	.420	-	0.303	.584	-	0.130	.720	-	0.373	.545	-	0.138	.712	-
rs1176713	1.228	.274	-	0.419	.521	-	0.632	.431	-	0.613	.438	-	0.052	.820	-
rs1042173	0.020	.888	-	0.332	.567	-	0.805	.375	-	0.617	.436	-	1.410	.242	-

	Drinking Days			Standard Drinks			Heavy Drinking Days			GGT			CDT		
	F	*p*	β	*F*	*p*	β	*F*	*p*	β	*F*	*p*	β	*F*	*p*	β
Time	4.616	**< 0.001**	-	3.994	**< 0.001**	-	5.928	**< 0.001**	-	0.386	.682	-	2.971	.059	-
Group	0.282	.598	−0.01	0.156	.694	0.27	0.130	.721	0.02	3.074	.088	15.26	0.369	.547	3.48
Time × Group	1.627	.085	-	1.272	.235	-	0.993	.456	-	2.581	.088	-	0.076	.927	-
rs1150226	0.580	.450	-	0.064	.802	-	0.052	.821	-	0.145	.705	-	0.791	.380	-
rs1176713	0.603	.441	-	1.361	.250	-	1.325	.256	-	1.369	.250	-	2.552	.119	-
rs1042173	1.834	.182	-	0.766	.386	-	1.262	.267	-	0.087	.770	-	2.687	.110	-

SNP Combination 2

	YMRS			HRSD			IDS-SR			PACS			PRD		
	F	*p*	β	*F*	*p*	β	*F*	*p*	β	*F*	*p*	β	*F*	*p*	β
Time	2.010	**.023**	-	4.808	**< 0.001**	-	10.759	**< 0.001**	-	6.713	**< 0.001**	-	4.814	**< 0.001**	-
Group	0.066	.798	−1.55	5.558	**.022**	1.97	2.476	.122	5.32	1.007	.320	1.45	4.835	**.033**	2.77
Time × Group	1.286	.226	-	0.997	.452	-	1.161	.312	-	1.448	.145	-	2.959	**.001**	-
SNP	2.017	.162	-	2.203	.144	-	1.587	.214	-	1.255	.268	-	1.059	.309	-

	Drinking Days			Standard Drinks			Heavy Drinking Days			GGT			CDT		
	F	*p*	β	*F*	*p*	β	*F*	*p*	β	*F*	*p*	β	*F*	*p*	β
Time	4.760	**< 0.001**	-	4.352	**< 0.001**	-	6.501	**< 0.001**	-	0.259	.773	-	2.939	.061	-
Group	0.560	.458	0.01	0.196	.660	0.24	0.310	.580	0.04	3.165	.083	14.20	0.637	.430	4.69
Time × Group	1.719	.063	-	1.266	.239	-	0.948	.499	-	3.116	.055	-	0.086	.917	-
SNP	0.861	.358	-	0.571	.454	-	0.091	.764	-	0.120	.731	-	0.046	.831	-

Note. Estimates of fixed effects are presented for treatment group only to conserve space. Reference treatment group is Ondansetron. Reference for SNP combination 1 is AG + AA genotype (rs1150226), AG + AA genotype (rs1176713), and AC + CC genotype (rs1042173). Reference for SNP combination 2 is rs1150226AG + rs1176713GG. Statistically significant *p*-values are presented in bold. YMRS: Young Mania Rating Scale; HRSD: Hamilton rating scale for depression; IDS-SR: Inventory of Depressive Symptomatology – Self Report; PACS: Penn Alcohol Craving Scale; PRD: PRD-III Somatic Symptom Scale; GGT: γ-glutamyltransferase; CDT: carbohydrate deficient transferrin.

Table 4 Cohen's d values for comparisons among SNP combinations.

	No SNP	Combination 1				Combination 2	
	Group	Group	rs1150226	rs1176713	rs1042173	Group	SNP
YMRS	0.12	−0.10	−0.25	0.90	−0.04	−0.04	0.40
HRSD	−0.53	−0.67	−0.17	0.52	−0.18	−0.67	0.49
IDS-SR	−0.43	−0.46	−0.11	0.64	−0.27	−0.51	0.39
PACS	0.01	−0.32	−0.19	0.63	−0.24	−0.32	0.32
PRD	−0.55	−0.62	0.12	0.19	−0.37	−0.63	0.33
Drinking Days[a]	−0.29	−0.17	0.24	−0.64	0.41	−0.30	−0.32
Standard Drinks	−0.10	−0.13	0.08	−0.95	0.27	−0.28	−0.25
Heavy Drinking Days	−0.15	−0.11	−0.07	−0.92	0.34	−0.46	0.18
GGT	−0.60	−0.63	−0.14	−0.97	0.10	−0.62	−0.12
CDT	−0.33	−0.22	−0.32	−1.35	0.57	−0.28	−0.07

Note. [a]Drinking days per days covered, represented as percentages. Negative Cohen's *d* values represent lower average scores for the treatment group, genotypes AG + AA on rs1150226, genotypes AG + AA on rs1176713, genotypes AC + CC on rs1042173, and the "all else" genotype group for SNP combination 2. YMRS: Young Mania Rating Scale; HRSD: Hamilton rating scale for depression; IDS-SR: Inventory of Depressive Symptomatology - Self Report; PACS: Penn Alcohol Craving Scale; PRD: PRD-III Somatic Symptom Scale; GGT: γ-glutamyltransferase; CDT: carbohydrate deficient transferrin.

a response, defined as a decrease of 50% or more in HRSD scores, compared to only 22.9% in the placebo group.

3.3. Analysis of models including genotype combination 1

For models in which genotype combination 1 [rs1150226 (with two levels: GG and AG + AA combined), rs1176713 (with two levels: GG and AG + AA combined), and rs1042173 (with two levels: AA and AC + CC combined)] was included, the statistically significant treatment group effect for HRSD remained [$F(1, 47.39) = 4.460$, $p = 0.040$, $d = -0.67$], and was in favor of ondansetron (Table 3). Treatment group and SNP effects were statistically non-significant for all other outcomes. However, for the primary alcohol outcomes, the standardized mean differences between treatment and placebo groups were relatively similar to those calculated when excluding SNP information. For alcohol days ($d = -0.17$), standard drinks ($d = -0.13$), and heavy drinking days ($d = -0.11$), the ondansetron group reported lower alcohol use (Table 4). A similar effect emerged for GGT ($d = -0.63$) and CDT ($d = -0.22$). Cohen's *d* effect sizes were also calculated for group differences in the three SNP factors included in genotype combination 1 (i.e., three SNP factors each with two levels) and can be found in Table 4.

3.4. Analysis of models including genotype combination 2

For models in which genotype combination 2 (i.e., rs1150226-AG + rs1176713-GG combined vs. all other genotypes combined) was included, the statistically significant treatment effect for HRSD remained [$F(1, 50.62) = 5.558$, $p = 0.022$, $d = -0.67$], again in favor of ondansetron (Table 3). Treatment group and SNP effects were statistically non-significant for all other outcomes, including the primary alcohol outcomes. However, for the primary alcohol outcomes, the standardized mean differences between treatment and placebo groups were somewhat larger compared to those calculated when excluding SNP information or including SNP combination 1 (Table 4). For alcohol days ($d = -0.30$), standard drinks ($d = -0.28$), and heavy drinking days ($d = -0.46$), the ondansetron group demonstrated lower alcohol use. A similar effect emerged for GGT ($d = -0.62$) and CDT ($d = -0.28$). For the IDS-SR, the standardized mean difference was medium ($d = -0.50$). Additionally, Cohen's *d* effect sizes were calculated for group differences in SNP combination 2 and can be found in Table 4.

3.5. Tolerability/Adverse events

Ondansetron was well tolerated as indicated by the statistically significant treatment group effect on the PRD outcome [$F(1, 62.28) = 4.380$, $p = 0.040$, $d = -0.55$] with a greater decrease in overall somatic complaints with ondansetron than with placebo. A total of 41 adverse events across 20 participants were noted during the study. Thirteen of the 20 participants with adverse events were in ondansetron group, however the difference in the occurrence of events between the placebo and treatment group was statistically non-significant [$\chi^2(1) = 2.52$, $p = 0.112$]. The most common events for the placebo group were gastrointestinal (27%), suicide attempt/ideation (13%), hyperglycemia (13%), and auditory hallucinations (13%). For the ondansetron group, the most frequent events were gastrointestinal (23%), neurological (i.e., headache, dizziness, paresthesia, blurry vision; 19%), and cardiovascular [i.e., atrial fibrillation (prolonged QTc interval), high blood pressure; 11%].

4. Discussion

This proof-of-concept study, is, to our knowledge, the first to examine the use of ondansetron in people with both bipolar disorder and AUD. Statistically significant reductions in

alcohol use were not observed in the overall sample. This is in contrast to prior ondansetron reports that have observed a reduction in alcohol use in people who have AUD without bipolar disorder. However, ondansetron did not appear to be as effective in reducing alcohol use in this dual diagnosis population as in people in the studies in the literature with AUD but without bipolar disorder (Johnson et al., 2011, 2000). Only one randomized, double-blind, placebo-controlled trial has demonstrated a significant difference between active medication and placebo in people with bipolar disorder and an AUD (Salloum et al., 2005). These negative findings may suggest that this population has a relatively treatment resistant AUD. Alternatively, the negative findings could be due to poor medication adherence that is reported in people with bipolar disorder who have an AUD (Perlis et al., 2010). Many of the prior clinical trials in BPD and AUD have focused on alcohol use as the outcome. For example, three of the studies examined drugs, such as naltrexone, topiramate and acamprosate, that are primarily used for AUD (Brown et al., 2009; Sylvia et al., 2016; Tolliver et al., 2012). The valproate study that demonstrated a reduction in alcohol consumption used a design whereby study drug was added following lithium stabilization and included the use of antidepressants for depression (Salloum et al., 2005). One of our clinical trials of quetiapine in BPD and AUD demonstrated a significant reduction in depressive symptoms but not on alcohol use measures (Brown et al., 2008). Although speculative, it is possible that alcohol use is more challenging to treat in people with BPD and AUD than is depression. In addition, the difference in response in our report compared to other ondansetron studies might be explained, in part, by the modest sample size of the current study which limited the statistical power.

In addition, our dosing strategy was not the same as that used by Johnson et al. (Johnson et al., 2000). We started at 1 mg/day and, based on response, increased the dose up to 8 mg/day. In contrast, Johnson et al. based the dosing on weight (2–32 mcg/kg/day) so if one assumes a 70 kg weight then the dosing ranged from 0.14 mg/day to 2.24 mg/day and the most effect dose was the equivalent to 0.56 mg/day. Thus, it is possible that the current study dosed too high to see the optimum effect of alcohol use. Of note, Johnson et al. found that the higher 16 mcg/kg/day (2.24 mg/day for a 70 mg person) was most effect in improving POMS scores (Johnson et al., 2003; Vaughan et al., 2012). Furthermore, an 8 mg/day dose of ondansetron demonstrated efficacy for depression in hepatitis C (Piche et al., 2005). These findings suggest that different doses may be needed for alcohol use than for depression.

The favorable effect on ondansetron on depressive symptoms is of interest. We started at 1 mg/day and based on mood and alcohol use response increased the dose as high as Vaughn et al., in an analysis of pooled data from clinical trials of ondansetron for AUD, observed an increase in positive affect and decrease in negative affect as assessed by the POMS (Vaughan et al., 2012). A study in patients with hepatitis C reported that ondansetron was associated with less fatigue and lower Beck Depression Inventory (BDI) scores than placebo (Piche et al., 2005). In addition, several studies in animal models of depression suggest that ondansetron(Gupta et al., 2014a; Li et al., 2013; Ramamoorthy et al., 2008) and other 5-HT_3 antagonists(Gupta et al., 2015, 2014b) may have antidepressant properties. To our knowledge, the current report is the first suggesting improvement in depressive symptoms in people with bipolar disorder given ondansetron. No changes in manic symptoms were observed with ondansetron as compared to placebo. People with bipolar disorder, on average, spend much more time depressed than manic or hypomanic (Kupka et al., 2007). However, the safety and efficacy of antidepressants for bipolar depression remains controversial (Gitlin, 2018). Thus, additional options for the treatment of bipolar depression are needed and the findings may be of much clinical importance.

Prior studies have reported specific genotypes that are related to a favorable response to ondansetron in reducing alcohol consumption. Therefore, we explored SNP combinations that, in prior research, increased the effect size of ondansetron response. In general, genotype combination 2 (i.e., rs1150226-AG and rs1176713-GG vs. all other genotypes) but not combination 1 [i.e., rs1042173 (GG vs. AG + AA), rs1176713 (GG vs. AG + AA), and rs1150226 (AA vs. AC + CC)] increased the effect sizes of the alcohol-related outcomes.

Ondansetron was well tolerated. The somatic symptom scale used to track medication side effects decreased more with ondansetron than with placebo. Although highly speculative, this finding might suggest enhanced feelings of well-being with ondansetron as compared to placebo. The good tolerability suggests that higher doses, which might enhance the treatment effects, could be explored in future studies in this population.

The study had several limitations. The sample size was modest which limited the statistical power to detect between-group differences. In particular, unbalanced cell frequencies for the rs1176713 SNP (2 GG genotype, 2.9%; 53 AG + AA genotype, 75.7%) is likely to threaten the internal validity of results for this factor. Astatistically significant discrepancy between the sample genotype frequencies and population genotype frequencies emerged for rs1150226; the AG genotype was overrepresented and the GG genotype underrepresented in our sample. In addition, because the primary outcome of the study was alcohol use, the sample was heterogeneous in terms of bipolar spectrum diagnosis and mood state. The study did not include a psychosocial intervention for AUD for all of the participants. Thus, the design was that of a monotherapy study for AUD rather than an add-on design where the pharmacotherapy or placebo is added to a psychosocial platform. The study medication was, however, added to baseline stable pharmacotherapy. The sample consisted primarily of dual diagnosis patients with low income levels. It is not known is the findings are generalizable to higher functioning and higher income populations. Finally, the assessment period was only 12 weeks. Thus, changes in alcohol use and mood over a longer period of time could not be assessed.

In conclusion, ondansetron was associated with a significant improvement in depressive symptoms in people with bipolar disorder and AUD. Alcohol use outcomes favored ondansetron but were not statistically significant. Ondansetron appeared to be well tolerated in this population. Although speculative, ondansetron may serve as a model drug to explore the relationship between the 5-HT3 receptor and depression. It is possible that 5-HT3 receptor

antagonists, such as ondansetron, have potential in treating depression. Therefore, clinical trials focusing on the use of ondansetron for bipolar depression or even MDD seem warranted.

Conflict of interest

Dr. Brown reports research current or recent grants from NIH and the Stanley Medical Research Institute. All other authors have no conflicts of interest to declare.

Contributors

Dr. Brown designed the study and wrote much of the manuscript. Ms. McArdle and Ms. Bice collected much of the data and edited the manuscript. Dr. Palka performed the statistical analyses and wrote part of the manuscript. Drs. Ivleva and Nakamura and Ms. Patel and Mr. Tipton assessed the participants for eligibility and for safety throughout the study and edited the manuscript. Dr. McNutt provided valuable consultation about the genetics analysis and reviewed and edited multiple versions of the manuscript. Ms. Holmes was involved in randomization procedures and blinded dispensing of study drug and edited the manuscript.

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Supplementary materials

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