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Addictive Behaviors

A pilot study of full-dose ondansetron to treat heavy-drinking men withdrawing from alcohol in Brazil

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HIGHLIGHTS

- Ondansetron has emerged as a promising medication for the treatment of alcoholism.
- Ondansetron had a favorable side-effect profile.
- An ondansetron dose of 16 mg/day was not effective to treat alcoholics.
- The optimal dosage to treat alcoholism has yet to be determined.

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ABSTRACT

Ondansetron has emerged as a promising medication for the treatment of alcohol dependence, mainly among early-onset alcoholics. This research primarily aimed to evaluate the efficacy and safety of ondansetron at a 16 mg/day dosage to treat alcohol-dependent outpatients. A double-blind, placebo-controlled, 12-week study was carried out at the University of São Paulo, Brazil. The total sample comprised 102 men, 18—60 years of age, with an International Classification of Diseases (ICD-10) diagnosis of alcohol dependence. Half of our sample discontinued the treatment and the main outcome measures (proportion of abstinent days and proportion of heavy drinking days) were analyzed using the treatment adherents as well as with an imputed sample. The main factors associated with treatment retention were older age and smoking status. Although there were no significant differences between the main outcome measures of both medication groups in the adherents, ondansetron demonstrated a slight but significant superiority over the placebo regarding the proportion of heavy drinking days in the imputed sample (7.8% versus 11.7%, respectively). It appears that the optimal dosage to treat alcoholism has yet to be determined. Further, ondansetron may only be useful in treating some types of alcoholics. Ondansetron was well tolerated and no serious adverse events were registered.

Pourquoi pas Johnson

1. Introduction

To date, the US Food and Drug Administration has approved the following medications for alcohol dependence: disulfiram, acamprosate, and oral/extended-release naltrexone. Several other medications are under active study, such as ondansetron, topiramate, baclofen, and some antidepressants (Castro & Baltieri, 2004; Garbutt, Kampov-Polevoy, Gallop, Kalka-Juhl, & Flannery, 2010; Mann & Hermann, 2010; Rosner et al., 2010). Of these non-approved drugs, ondansetron has emerged as a promising medication for the treatment of alcohol dependence, mainly among early-onset alcoholics (Johnson, Roache, Ait-Daoud, Zanca, & Velazquez, 2002; Johnson et al., 2000; Kranzler, Pierucci-Lagha, Feinn, & Hernandez-Avila, 2003).

Studies have shown that the 5-HT_3 antagonist ondansetron reduces alcohol-induced positive subjective effects and alcohol preference (Dyr & Kostowski, 1995; McBride et al., 2004; Myrick, Anton, Li, Henderson, Randall & Voronin, 2008). In fact, 5-HT_3 receptors are densely distributed in the mesocorticolimbic neuronal terminals, regulating dopamine release. Ondansetron blocks the peripheral and central 5-HT_3 receptors, and through central antagonism, it inhibits dopamine-release cell firing in the nucleus accumbens (Swift, Davidson, Whelihan, & Kuznetsov, 1996; Ye, Ponnudurai, & Schaefer, 2001). In addition, ondansetron appears to have activity at the 5-HT_{1A}, 5-HT_{1B}, α-1-adrenergic, and μ-opioid receptors (McNulty, 2007).

Differing from studies that have evaluated ondansetron efficacy at dosages ranging from 12 to 24 mg daily for the treatment of other psychiatric and neurological disturbances, such as depression in bulimic patients (Faris et al., 2006), hallucinations and delusions in Parkinson's psychosis (Friedberg, Zoldan, Weizman, & Melamed, 1998; Zoldan, Friedberg, Livneh, & Melamed, 1995), and tardive dyskinesia in schizophrenic patients (Sirota, Mosheva, Shabtay, Giladi, &

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Korczyn, 2000), alcoholism clinical trials have tested relatively low doses of ondansetron (between 1 and 16 μg/kg bid). Notwithstanding these low doses used to treat alcoholism, one study has investigated the efficacy of a higher dose of this medication (up to 0.45 mg/kg tid) for smoking cessation (Cropp & Gora-Harper, 1995).

Considering the high safety and low toxicity of ondansetron in the treatment of different medical problems (Fabi et al., 2008; Salvucci et al., 2011; Ye et al., 2001), as well as its presumed efficacy at doses above 12 mg per day for other neuropsychiatric disorders, we decided to test this drug among alcohol-dependent outpatients at a dosage usually prescribed to manage chemotherapy-induced nausea and vomiting, in the same way as has been carried out in studies on its efficacy for treating other neuropsychiatric illnesses.

2. Method

2.1. Design

A randomized, double-blind, placebo-controlled clinical trial was performed to determine the efficacy of ondansetron in reducing drinking, promoting alcohol abstinence, and decreasing cravings in alcohol-dependent individuals. The treatment lasted 12 weeks.

2.2. Participants

Male patients, aged 18–60 years, and with an International Classification of Diseases (ICD-10; World Health Organization, 1992) diagnosis of alcohol dependence that enrolled as outpatients in the Assistance Sector of the Interdisciplinary Group of Studies on Alcohol and Drugs at the University of São Paulo (PROGREA), Brazil, were assessed for trial. This service (PROGREA) is exclusively dedicated to the treatment of men with alcohol and/or any other type of drug abuse or dependence.

Exclusion criteria were: (a) <18 years or ≥60 years of age; (b) clinically significant medical disease that might have interfered with the evaluation of the study medication, or presence of a safety concern (e.g., cirrhosis, kidney impairment, unstable hypertension, diabetes mellitus, seizure disorder, cardiac failure); (c) positive screen for other types of drug abuse except nicotine, verified through the application of the DAST (Drug Abuse Screening Test, when cut-off ≥5) (Skinner, 1982); (d) clinically significant psychiatric illness, including any psychotic disorder, bipolar disorder, or severe depression as evaluated with the Mini International Neuropsychiatric Interview (MINI version 5.0) (Amorim, 2000); (e) previous treatment with ondansetron within 6 months of randomization; (f) current use of disulfiram, naltrexone or acamprosate; (g) current use of any psychotropic medication including antidepressants, mood stabilizers, antipsychotics, anxiolytics, stimulants, or hypnotics; (h) inability to give full informed consent, and (i) clinical history of mental retardation, as it would reduce the accuracy of the information provided.

All subjects provided written informed consent, were assured of the confidentiality of the data, and were informed that they were free to withdraw their consent and discontinue participation in the study at any time without prejudice to their continued medical care. The Ethics Committee of the Clinical Hospital of the University of São Paulo, approved this study.

2.3. Measures

Before initiating the double-blind treatment, all patients were evaluated with the revised Clinical Institute Withdrawal Assessment for Alcohol (CIWA-Ar; Sullivan, Sykora, Schneiderman, Naranjo, & Sellers, 1989), the Short Alcohol Dependence Data (SADD; Raistrick, Dunbar, & Davidson, 1983), and the Alcohol Use Identification Test (AUDIT; Bohn, Babor, & Kranzler, 1995), and underwent 2-week detoxification period. This pre-study phase was conducted on an outpatient basis and the patients were given medications with reference to their CIWA-Ar scores, such as up to 6 mg/day lorazepam and 300 mg/day vitamin B1, in case they manifested withdrawal symptoms. The patients included in this study manifested minimal to moderate withdrawal symptoms, which allowed them to be treated on an outpatient basis. Mean cellular volume (MCV), laboratory tests to screen for liver disorders – γ-glutamyl-transpeptidase (GGT), aspartate aminotransferase (AST), alanine aminotransferase (ALT), bilirubin, and prothrombin time – and a clinical evaluation of heart function – electrocardiography (ECG), observation, palpation, and auscultation – were performed in this pre-study phase.

Before randomization, subjects were distinguished as being either early (EOA) or late onset alcoholics (LOA) by applying a single question — "At what age did drinking become a problem for you? ". EOA had an age of onset of alcoholism between the ages of 13–25 years, and LOA had an age of onset of alcoholism greater than 25 years of age.

Subsequently, following a breathalyzer (that had to be 0.00%) and a full history and clinical examination, patients who fulfilled the inclusion criteria initiated the study. Socio-demographic data and lifetime drinking history, such as daily intake of alcohol in grams, drinking onset age, problem drinking onset age, and duration of problem drinking (in years) were obtained in a standardized, semi-structured interview commonly used in the therapeutic setting of the PROGREA. Alcohol consumption was assessed at each visit using the timeline follow-back method (Annis et al., 1996). The Hamilton Depression Rating Scale (HDRS; Hamilton, 1960), and the Obsessive-Compulsive Drinking Scale (OCDS; Anton, Moak, & Latham, 1995) were applied at weeks 1, 6, and 12 of the study. After week 1, the UKU Side Effect Rating Scale (UKU; Lingjaerde, Ahlfors, Bech, Dencker & Elgen, 1987) was applied at each visit.

Patients were assessed 12 times during the study. Major variables recorded at each visit included the patients' self-reported quantity, frequency of alcohol consumption, and drug side effects. For all participants, abstinence from alcohol was evaluated based on the patient's self-report at each appointment, by measuring alcohol abuse hepatic indices — GGT, ALT, AST, and MCV at week 6 and 12, and by interviewing a family member at each patient's appointment. Cardiac exam (observation, palpation and auscultation), and abstinence symptoms of all participants were evaluated at each appointment. Patients with a history of substance-related disorders in treatment programs can develop an understanding of the detection parameters for alcohol by urine or breath testing, and some attempt to circumvent monitoring by timing their drinking. It is known that some patients drink during weekends or other times when testing is unlikely to occur. Therefore, we preferred evaluating the levels of alcohol abuse hepatic indices across the study, verifying if these indices were decreasing, and investigating if changes in these measures were in line with patients' self-report.

In addition, medication compliance was evaluated at each appointment by asking patients the following questions: (a) Have you already forgotten to take your medications? (b) Are you sometimes neglectful in regard to your medicine time? (c) Do you skip your medicine time when you are feeling well? (d) When you feel bad (sick, feeling side effects) due to the medicine, do you skip it? Those that answered in the negative to the 4 questions were considered adherent to this study. Furthermore, the capsules in the returned packages were counted (capsules taken subtracted from capsules given) at every appointment. We coded an individual as adherent if they took 80% or more of the total prescribed pills on a particular week.

2.4. Outcome criteria

The primary outcome measures were:

a) Percentage of abstinent days (%ABS);
b) Percentage of heavy drinking days (%HDD; a heavy drinking day was defined as the consumption of more than 70 g ethanol or more than 5 standard drinking units).

The secondary outcome measures were:

a) Mean drinks per day (1 drink = 14 g of ethanol);
b) Subjective reports of side effects;
c) Reasons for dropouts;
d) Factors associated with discontinuation of the treatment.

Patients who did not attend follow-up, who did not take 80% or more of the total prescribed pills on a particular week, and whose outcomes were unknown were considered to have dropped out of the research. Three reasons for dropping out from this research were categorized: (a) "refuse to continue" (the patient affirmed that he wanted to stop that type of treatment and to try others, e.g., psychotherapy only); (b) "protocol violation" (the patient used other pharmacologic drugs during the study and/or stopped taking the study medication); and (c) "lost to follow-up" (the patient gave up following the study and did not manifest any desire to be treated differently).

In addition, the principle of this double-blind procedure was verified by obtaining a prediction from each patient with reference to his allocated treatment and a prediction from the researcher (active medication or placebo).

2.5. Procedure

Between 2008 and 2010, 172 patients were screened. As shown in Fig. 1, 49 declined to participate in this study and 21 were excluded because of coexisting diseases, leaving a sample of 102 individuals. All the selected patients were encouraged to participate in AA groups, but this was not an obligatory condition of participation in this study. The same doctor who collected the data carried out the clinical evaluations, and this fact could have generated issues regarding the integrity of this study. Thus, we also tested this hypothesis.

The participants were randomly divided into 2 groups, through computer-generated random numbers. All participants were instructed to take 1 capsule in the morning and one at night. Once a week, the patients received an envelope with 2 packages containing 7 capsules. One package was designated for morning dosing and the other for night-time.

One group received 2 capsules each containing 8 mg ondansetron, and the other group received 2 placebo capsules every day during the 12 weeks. All capsules in each treatment group were identical in appearance and size and had been manufactured and distributed by the Pharmacy Sector at the Psychiatric Institute of the Clinical Hospital of São Paulo University. This study was not sponsored by a pharmaceutical company.

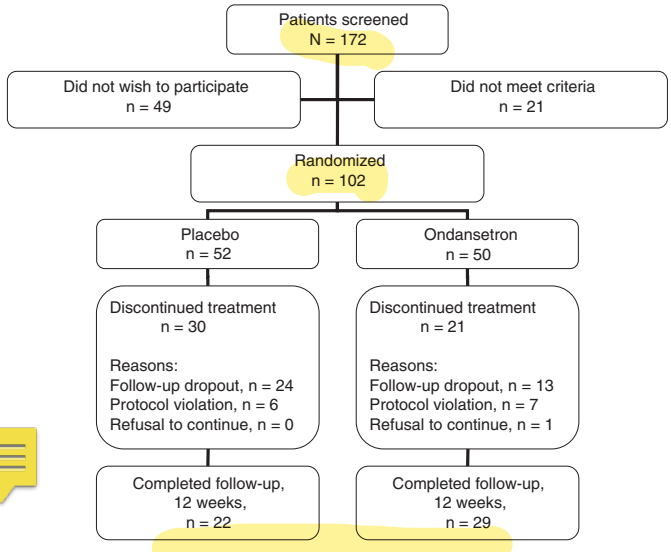

Fig. 1. Consort flow chart, randomization, and retention study.

At each appointment, all patients received standardized brief cognitive behavioral interventions. The overall goal of these interventions was to increase the person's ability to cope with high-risk situations that could precipitate relapses. The drinking behavior of the patients was reviewed in each visit, and the medication compliance and motivation for change were improved using motivational interviewing strategies. It was recommended that patients monitor good and bad daily situations during all treatment, and this was discussed with their doctors, and, when possible, related to drinking behavior. The following topics were standardized and applied to each patient during this treatment: management of negative mood, assertiveness, drink refusal skills, enhancement of social support networks, and relapse prevention.

The codes referent to the medications used were revealed to the researchers only after all patients had completed the study. Only 2 pharmacists from the Pharmacy Sector at the Psychiatric Institute of the Clinical Hospital of the University of São Paulo knew what medication corresponded to which specific code. The packages containing the capsules were distributed to patients by 2 trained research assistants, who had also been blinded to the study and who assessed the outcome of each patient throughout the study period.

2.6. Statistical Analysis

We used the generalized estimating equations (GEE, Hedeker & Gibbons, 1997) approach, which accommodated the repeated measures data and accounted for within-subject correlations. Non-normally distributed variables were log-transformed.

As half of our sample discontinued the treatment, we first used GEE to analyze the data of those who completed it. Little's test was used to verify the missing-data mechanism. Subsequently, we performed a multiple-imputation analysis with Markov Chain Monte Carlo (MCMC, Horton & Lipsitz, 2001; Gilks, Richardson & Spiegelhalter, 1996) approaches and then used the GEE in SPSS-18. Maintaining the original variability of the missing data was achieved by creating imputed values based on variables associated with the causes of missing data.

In order to evaluate the predicting factors of dropouts, we analyzed the effect of multiple baseline variables, group membership, and typology on treatment retention by applying a longitudinal logistic regression model with GEE featuring an autoregressive correlation structure. We recoded the data into a dichotomous variable with either "observed" or "missing" as the outcome for this analysis.

The proportion of abstinence (%ABS), and the proportion of heavy drinking days (%HDD) were analyzed using the GEE model featuring autoregressive correlation structure in both models (complete case and multiple imputed data set). Mean drinks per day and biomarkers were analyzed only for completers using the GEE model.

Log-rank test was also used to evaluate differences in retention by assignment condition. Finally, we assessed the power of our sample to detect differences between both medication groups using G*Power 3.1 (Faul, Erdfelder, Lang, & Buchner, 2007).

For all statistical tests performed, differences between the 2 groups were accepted as significant if they achieved the .05 level with two-tailed tests. Data were analyzed using SPSS 18, and Stata 9.

3. Results

3.1. Sample characteristics

As shown in Table 1, all 102 selected participants were randomly assigned to 2 groups: 50 (49.02%) in the ondansetron group, and 52 (50.98%) in the placebo group. There were no significant differences between both groups, in terms of socio-demographic data, baseline biochemical tests, preferential beverages, and psychometric measures.

Table 1
Baseline characteristics of overall sample.

Characteristic	Placebo (n = 52)	Ondansetron (n = 50)	p
Age, mean (SD)	42.19 (9.02)	43.66 (10.14)	t = −.77, 100df, p = .44
Marital status, n (%)			
Married	37 (71.15)	27 (54)	χ^2 = 4.83, 2 df, p = .09
Single	4 (7.69)	11 (22)	
Separated / Widowed	11 (21.16)	12 (24)	
Race, n (%)			
White	14 (26.92)	20 (40)	χ^2 = 2.41, 2 df, p = .30
Black	11 (21.16)	11 (22)	
Mixed	27 (51.92)	19 (38)	
Education, n (%)			
Grade 12 or less	32 (61.54)	24 (48)	χ^2 = 1.89, 1 df, p = .17
High school or more	20 (38.46)	26 (52)	
Quantity of ethanol per day (in grams), mean (SD)*	285.07 (171.42)	300.15 (200.45)	t = -.41, 100 df, p = .68
Years since alcohol-related problems occurred, mean (SD)	13.11 (8.41)	14.06 (11.33)	t = −.48, 100 df, p = .63
Early onset alcoholics, n (%)	25 (48.06)	25 (50)	χ^2 = .04, 1 df, p = .85
Alcoholic smokers, n (%)	33 (63.46)	32 (64)	χ^2 < .01, 1 df, p > .99
Cigarettes per day, mean (SD)[a]	15 (12.78)	17.34 (8.37)	t = −.87, 63 df, p = .39
Alcoholic smokers by typological groups, n (%)			
EOA	14 (26.92)	14 (28)	χ^2 = 2.55, 3df, p = .47
LOA	19 (36.54)	18 (36)	
Family history of alcoholism, n (%)	42 (80.77)	36 (72)	χ^2 = 1.09, 1 df, p = .30
Previous treatments for alcoholism, n (%)	28 (53.85)	29 (58)	χ^2 = .18, 1 df, p = .67
Preferential beverage, n (%)			
Spirits	39 (75)	38 (76)	χ^2 = .93, 2 df, p > .99
Beer	12 (23.08)	12 (24)	
Wine	1 (1.92)	0	
Monthly income (in R$, the Brazilian currency), mean (SD)	1418.19 (890.99)	1479.01 (1232.13)	t = −.29, 100 df, p = .77
Plasma GGT, U/L; mean (SD) (reference range 8–61)	255.75 (446.91)	147.88 (269.46)	U = 1198, p = .49
Plasma ALT, U/L; mean (SD) (reference range<41)	41.40 (32.55)	39.18 (35.29)	t = .33, 100 df, p = .74
Plasma AST, U/L; mean (SD) (reference range<37)	49.90 (44.56)	34.16 (22.27)	U = 1140, p = .67
Plasma MCV, f/L; mean (SD) (reference range 80–100)	94.09 (6.94)	93.90 (8.43)	t = .13, 100 df, p = .90
Total bilirubin, mg/dL; mean (SD)[b] (reference range 0.20–1.00)	0.61 (0.29)	0.56 (0.30)	t = 1.47, 100 df, p = .32
Indirect bilirubin, mg/dL; mean (SD)[b] (reference range 0.10–0.60)	0.48 (0.41)	0.37 (0.22)	t = 1.55, 100 df, p = .12
Prothrombin/INR; mean (SD)[b] (reference range 0.95–1.20)	0.99 (0.04)	0.98 (0.04)	t = 1.27, 100 df, p = .21
CIWA-Ar, mean (SD)[b]	13.83 (8.93)	13.08 (7.97)	t = .44, 100 df, p = .66
SADD, mean (SD)[b]	24.67 (6.97)	26.76 (8.11)	t = −1.39, 100 df, p = .17
AUDIT, mean (SD)[b]	28.42 (5.91)	29.90 (6.11)	t = −1.24, 100 df, p = .22
OCDS, mean (SD)	44.33 (10.19)	46 (9.59)	t = −.85, 100,df, p = .40
HDRS, mean (SD)	9.56 (5.49)	8.46 (5.02)	t = 1.05, 100 df, p = .29

* Indicates alcohol usage during the last 3 months preceding the study.
[a] Indicates mean cigarettes by day for all alcoholic smokers.
[b] Indicates biological markers that were measured and instruments that were applied over 2 weeks before the beginning of double-blind study; GGT, γ-glutamyl transferase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; MCV, mean cellular volume; CIWA-Ar, Clinical Institute Withdrawal Assessment; SADD, Short Alcohol Dependence Data; AUDIT, The Alcohol Use Disorders Identification Test; OCDS, Obsessive–Compulsive Drinking Scale; HDRS, Hamilton Depression Rating Scale.

3.2. Treatment retention

Overall, 51 patients dropped out of the trial. Reasons for dropout were classified as refusal to continue (2%), protocol violation (26%) or lost to follow-up (72%). Dropout rates among participants randomized to placebo were 57.7%, and 42% among those randomized to ondansetron. This overall difference between both groups was not significant (χ^2 = 2.56, 1 df, p = .11, log-rank test).

3.3. Predicting factors of treatment retention

The following variables were included in a longitudinal logistic regression model with GEE: age, marital status, race, educational level, years since alcohol-related problems occurred, alcoholism typology, previous treatment for alcoholism, preferential beverage, smoking status, family history of alcoholism, medication group, and mean scores on HDRS, CIWA-Ar, SADD, and OCDS. Of these variables, only younger age and nonsmoking status were significantly associated with early discontinuation of treatment, as it is shown in Table 2. Neither medication group nor alcoholism typology predicted treatment retention.

3.4. Percent abstinent days and percent heavy drinking days

All baseline variables (shown in Table 1) and those related to alcohol consumption at each appointment were included in the analysis of missing mechanism (Little's test), showing that the mechanism was not missing completely at random [χ^2 (200) = 431.57, p < .01]. Thus, we first decided to analyze the data from completers only. Subsequently, we used the 2 variables (age and smoking status) that predicted missingness to carry out multiple-imputation analysis and to perform GEE on the total sample.

Considering only the sample composed of adherents, GEE analysis did not indicate a significant difference between ondansetron and placebo for the %ABS [χ^2(12) = 12.59, p = .40], where on-average, there was 76.1% occurrence of abstinence in the placebo group compared with 88.6% for ondansetron across the medication period, illustrated in Fig. 2. In addition, neither alcoholism typologies [χ^2(12) = 13.44,

Table 2
Baseline variables associated with discontinuation of treatment.

Variables	Wald	Df	p	OR	CI (95%)
Age	6.99	1	<.01**	.93	.88–.98
Marital status					
Married (reference)					
Single	2.87	1	.09	.49	.21–1.12
Separated/widowed	.08	1	.78	.91	.45–1.82
Race					
White (reference)					
Black	1.77	1	.18	.51	.19–1.37
Mixed	1.20	1	.27	1.47	.74–2.92
Education					
Grade 12 or less (reference)					
High school or more	1.01	1	.32	1.40	.73–2.68
Years since alcohol-related problems occurred	1.02	1	.31	1.03	.97–1.09
Typology					
Early onset alcoholic (reference)					
Late onset alcoholic	.03	1	.86	1.09	.43–2.72
Previous treatment for alcoholism	.85	1	.36	.74	.39–1.40
Preferential beverage					
Spirits (reference)					
Beer	.37	1	.54	1.24	.62–2.50
Alcoholic smokers	4.93	1	.03*	.51	.28–.92
Medication group					
Placebo (reference)					
Ondansetron	1.23	1	.27	.73	.42–1.27
Family history of alcoholism	.51	1	.47	2.25	.24–20.58
HDRS	<.01	1	.94	.99	.93–1.06
CIWA-Ar	.36	1	.55	.99	.94–1.03
SADD	.73	1	.39	1.03	.96–1.10
OCDS	.49	1	.48	.99	.95–1.03

HDRS, Hamilton Depression Rating Scale; CIWA-Ar, Clinical Institute Withdrawal Assessment; SADD, Short Alcohol Dependence Data; OCDS, Obsessive–Compulsive Drinking Scale.
* p<.05.
** p<.01.

p = .34] nor the interaction effect between medication groups and typology [$\chi^2(1) = 2.80$, p = .09] demonstrated statistical significance during the treatment. Similarly, the GEE analysis did not demonstrate a significant effect of ondansetron over placebo for the %HDD [$\chi^2(12) = 15.52$, p = .16], where on-average, there was 9.5% occurrence of heavy consumption in the placebo group compared with 5.9%

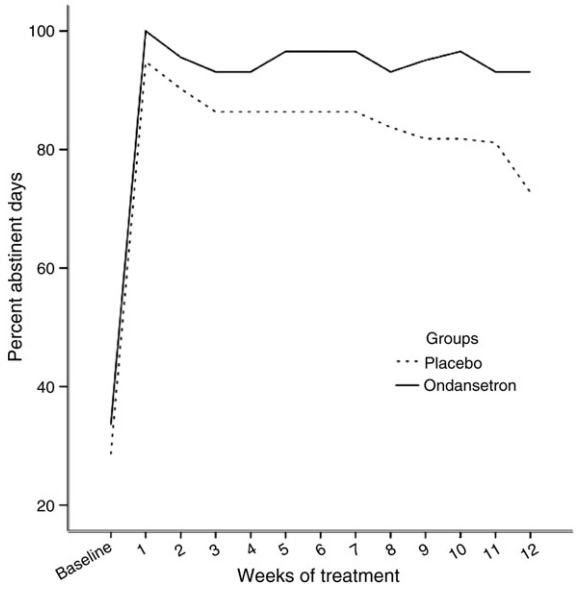

Fig. 2. Percent abstinent days at baseline and during trial by medication group among adherent subjects.

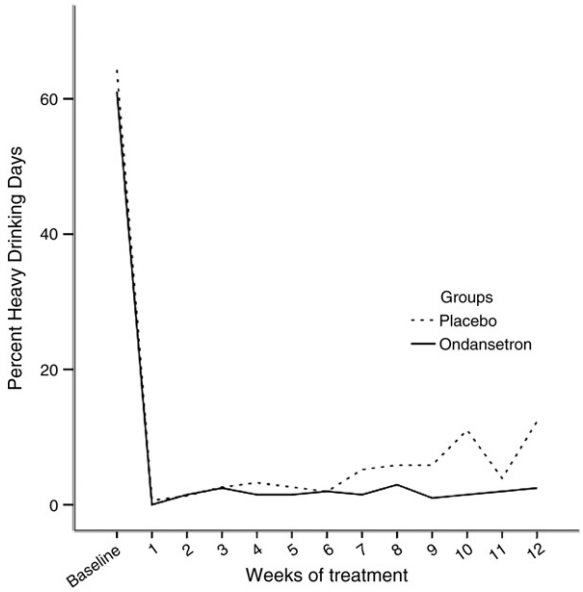

Fig. 3. Percent heavy drinking days at baseline and during trial by medication group among adherent subjects.

for ondansetron across the medication period, illustrated in Fig. 3. In addition, neither alcoholism typologies [$\chi^2(12) = 17.41$, p = .09] nor the interaction effect between medication groups and typology [$\chi^2(1) = 2.65$, p = .10] indicated statistical significance across the medication period.

When we consider the imputed sample (total sample), the GEE analysis did not reveal a significant difference between ondansetron and placebo regarding the %ABS [$\chi^2(12) = 7.92$, p = .79], where on-average, there was 66.6% occurrence of abstinence in the placebo group compared with 77.9% for ondansetron across the medication period. In addition, neither alcoholism typologies [$\chi^2(12) = 11.92$, p = .45] nor the interaction effect between medication groups and typology [$\chi^2(1) = 0.06$, p = .81] indicated statistical significance during the treatment. Conversely, the GEE analysis demonstrated a significant effect of ondansetron over placebo regarding the %HDD [$\chi^2(12) = 23.35$, p = .02], where on-average, there was 11.7% occurrence of heavy consumption in the placebo group to the 7.8% occurrence in the ondansetron group across the medication period. In addition, alcoholism typologies revealed differences during the treatment [$\chi^2(12) = 24.52$, p = .02], where on-average, there was12.9% occurrence of heavy consumption in EOA compared with 7.1% occurrence in LOA. The interaction effect between medication groups and typology [$\chi^2(1) = .73$, p = .39] did not indicate statistical significance across the medication period.

3.5. Drinks per day, biomarkers, and psychometric variables

Considering only the sample composed of adherents, GEE analysis did not indicate a significant difference between ondansetron and placebo with regard to mean drinks per day [$\chi^2(12) = 15.49$, p = .22], where on-average, the placebo group consumed 1.09 (SD = .26) drinks, and the ondansetron group consumed .66 (SD = .18) drinks per day, as it is illustrated in Fig. 4. In addition, neither alcoholism typologies [$\chi^2(12) = 13.16$, p = .36] nor the interaction effect between medication groups and typology [$\chi^2(1) = .91$, p = .34] demonstrated statistical significance during the treatment.

As shown in Table 3, considering only adherents (for whom all variables measured during the treatment were known), there were no significant differences between both medication groups throughout this study in terms of biomarkers and psychometric measures.

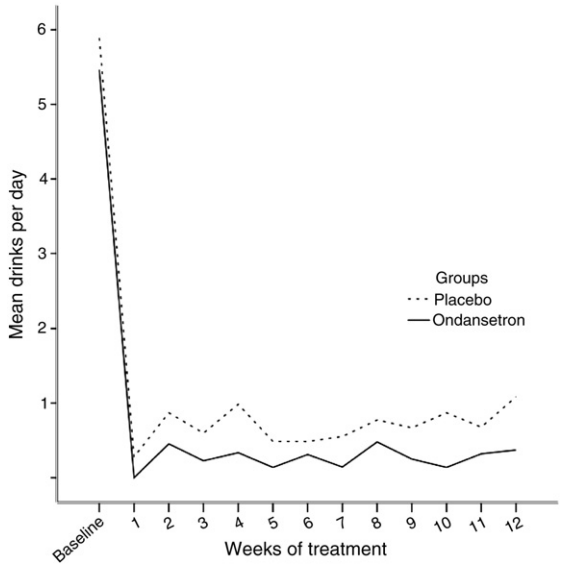

Fig. 4. Mean drinks (in units) per day at baseline and during trial by medication group among adherent subjects.

3.6. Safety and tolerability

The profile of side effects by group is shown in Table 4. There were no statistically significant differences between both groups. Although patients in the ondansetron group more frequently reported constipation, it was not significantly different from the placebo group.

3.7. Integrity of the double-blind trial

Researchers were queried regarding what treatment they thought the patients were receiving. In addition, the subjects were questioned at each study visit about the probable type of pharmacological treatment they were receiving. Overall, researchers were able to correctly differentiate active treatment from placebo in 56.9% of cases ($\chi^2 = 2.21$, 1 df, $p = .14$), and 53.9% of the patients were able to differentiate active treatment correctly from placebo ($\chi^2 = .74$, 1 df, $p = .39$).

3.8. Sample power

The G*Power statistical program was used in a MANOVA for repeated measures with tests of between–within interaction effects. The significance criterion was set at .05, and the test used was two-tailed. In order to calculate the sample power, we considered the completers sample only.

Table 4
Side-effect profile of subjects receiving placebo or ondansetron.

Clinical event	Placebo (n = 52) n (%)	Ondansetron (n = 50) n (%)	p (1df)
Nothing reported	26 (50)	24 (48)	$\chi^2 = .04$, $p = .84$
Somnolence	2 (3.85)	1 (2)	$\chi^2 = .30$, $p > .99$
Headache	9 (17.31)	7 (14)	$\chi^2 = .21$, $p = .65$
Dyspepsia	7 (13.46)	9 (18)	$\chi^2 = .39$, $p = .53$
Diarrhea	3 (5.77)	1 (2)	$\chi^2 = .96$, $p = .62$
Constipation	6 (11.54)	11 (22)	$\chi^2 = 2.01$, $p = .16$
Genitourinary symptoms	5 (9.61)	4 (8)	$\chi^2 = .08$, $p = .77$
Pruritus	3 (5.77)	3 (6)	$\chi^2 < .01$, $p > .09$

With regards to the variable %ABS evaluated across the study, the sample comprising 51 subjects achieved 33% power to detect differences between the 2 treatment groups versus the hypothesis of equality between both conditions. Theoretically, a sample of 289 adherents would be necessary to achieve 80% power with an effect size fixed at 25%, [Pillai's V = .05, Wilks' λ = 18.06, F (12, 276) = 1.79]. Considering that half the sample could drop out of a study with a similar design and components, a total sample of 578 adherent subjects would be necessary to produce significant results, at least from a theoretical point of view.

4. Discussion

An ondansetron dose of 16 mg/day was not significantly more effective than a placebo in increasing the proportion of abstinence during this 12-week randomized efficacy evaluation. Fifty percent of selected participants completed the study and the main factors associated with treatment retention were older age and smoking status. After multiple-imputation analysis, ondansetron was slightly but significantly more effective than placebo in terms of decreasing the proportion of heavy drinking days.

High rates of discontinuation have been observed in other pharmacological trials for alcoholism (Baltieri, Daro, Ribeiro, & Andrade, 2008; Johnson et al., 2007; Kranzler, Escobar, Lee, & Meza, 1996). However, it is possible to affirm that neither ondansetron nor placebo was linked to dropouts. There is some evidence that some factors, such as older age and proactive participation of family members are related to better treatment retention (Graff et al., 2009; Oslin, Pettinati, & Volpicelli, 2002). The literature reveals mixed results regarding the effect of smoking on alcoholism treatment retention. Nevertheless, smoking may possess some capacity to help alcoholics cope with urges to drink (Schmidt & Smolka, 2007), and consequently increase adherence to alcoholism treatment. Some clinical and experimental studies have suggested that alcoholic smokers could be interested in smoking cessation but prefer to address alcohol dependence

Table 3
Psychometric variables and laboratory tests of adherents.

Variables	Baseline		At week 6th		At week 12th		p (Wald's χ^2, 2 df)
	Ondansetron (n = 29)	Placebo (n = 22)	Ondansetron (n = 29)	Placebo (n = 22)	Ondansetron (n = 29)	Placebo (n = 22)	
OCDS, mean (SD)	44.97 (9.04)	46.45 (9.20)	20.59 (7.66)	24.04 (9.47)	17.93 (6.59)	21.91 (9.92)	$\chi^2 = 2.26$, $p = .32$
HDRS, mean (SD)	7.35 (4.58)	10.91 (6.35)	3.72 (3.22)	6.27 (5.29)	2.79 (3.32)	5.73 (5.44)	$\chi^2 = 1.55$, $p = .46$
Plasma GGT, U/L; mean (SD) (reference range 8-61)	92.83 (109.28)	362.91 (589.99)	39.72 (22.58)	141.50 (257.84)	33.52 (14.41)	152.18 (263.64)	$\chi^2 = 3.73$, $p = .15$
Plasma ALT, U/L; mean (SD) (reference range<41)	39.14 (42.16)	39.36 (30.82)	26.52 (13.70)	22 (10.72)	26.41 (14.86)	23.50 (11.72)	$\chi^2 = 1.17$, $p = .56$
Plasma AST, U/L; mean (SD) (reference range<37)	31.14 (16.44)	55.95 (54.01)	24.66 (6.31)	31.81 (29.91)	25.48 (8.76)	39.23 (36.08)	$\chi^2 = 2.65$, $p = .27$
Plasma MCV, f/L; mean (SD) (reference range 80–100)	93.32 (6.34)	95.45 (6.35)	90.67 (6.01)	92.54 (6.79)	89.66 (5.18)	91.44 (7.79)	$\chi^2 = .07$, $p = .97$

OCDS, Obsessive–Compulsive Drinking Scale; HDRS, Hamilton Depression Rating Scale; GGT, γ-glutamyl transferase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; MCV, mean cellular volume.

prior to embarking on quitting smoking, given the difficulty in stopping both drugs at the same time (Baltieri, Daro, Ribeiro, & Andrade, 2009; Ellingstad, Sobell, Sobell, Cleland, & Agrawal, 1999; Joseph, Willenbring, Nugent, & Nelson, 2004).

Ondansetron had a favorable side-effect profile. In this study, although the most common adverse effects of ondansetron were dyspepsia and constipation, there were no differences between both medication groups. One could presume that the full-dose ondansetron could have contributed to the high dropout rates in this study. Despite this, the reported side-effects between the placebo and ondansetron groups were not different. In addition, other studies on ondansetron efficacy in treating depressive and anxiety symptoms (concomitant to or even derived from other illnesses) have successfully tested daily doses between 8 and 24 mg, reporting a reduction in depressive symptoms (Faris et al., 2006; Harmer, Reid, Ray, Goodwin, & Cowen, 2006; Piche et al., 2005), decrease of anxiety in subjects with obsessive–compulsive disorder (Soltani et al., 2010), and even improvement of cognitive impairments among schizophrenics (Akhondzadeh et al., 2009; Bennett & Vila, 2010). In addition, 8 mg ondansetron (but not 4 mg) was shown to be useful for decreasing signs of opiate withdrawal (Chu et al., 2009; Sell, Cowen, & Robson, 1995).

There are some explanations for the inefficacy of ondansetron at a dosage of 16 mg/day in this study. First, this study was under-powered and of insufficient sample size. It can be true that ondansetron has some effect at a "full" dose, but this was only seen after imputation for dropouts. Second, previous studies have suggested that high ondansetron doses do not work very well. In fact, a U-shaped non-monotonic dose-response has been observed for EOA, with a 4 μg/Kg bid dose working better than a higher (16 μg/Kg bid) or a lower dose (1 μg/Kg bid) (Johnson et al., 2000; Kranzler et al., 2003). Third, our sample mostly comprised severely alcohol-dependent individuals. According to Sellers et al. (1994), ondansetron appears to be less effective for treating heavy drinkers than light drinkers. Fourth, studies have shown ondansetron is significantly more efficacious in reducing drinking severity in alcohol-dependent individuals carrying the LL genotype of the serotonin transporter-linked polymorphic region (5′-HTTLPR) compared with the LS or SS genotype (Kenna et al., 2009). Hence, only those alcohol-dependent individuals with a specific allelic constitution of the serotonin transporter gene (5-HTT) could be treated successfully, independently of the age of onset of problem drinking (Johnson et al., 2011). Interestingly, studies using samples of the Brazilian population have showed a higher frequency of S allele, even when ethnic groups are separated (Meira-Lima et al., 2005; Mendes de Oliveira et al., 1998). This might be attributed to the great admixture of races occurring in Brazil, as the majority of the population are relatively recent immigrants (Parra et al., 2003).

Participants showed high GGT levels at baseline. One explanation for this is that our sample comprised mainly spirits drinkers, and some studies have reported higher incidence of liver damage among spirits drinkers than beer or wine drinkers (Gronbaek et al., 2004; Kerr et al., 2000). In addition, spirits can contain high levels of higher alcohols, mainly in illicit or home-produced beverages (Lachenmeier et al., 2008).

Our study shows that high doses can be safely used. Though further research comparing high doses with the much smaller doses used previously would be interesting, the study design would clearly need to be sufficiently powered to compare different doses against a third placebo arm, and further adjusting for the L/S genotype effect, as well as any possible age-of-onset effects.

We must cite several weaknesses in our study design:

(1) There were no other psychotherapeutic procedures associated with the pharmacological treatment and behavioral management that could increase the compliance of the patients and the effectiveness of the treatment;
(2) The number of dropouts in this study was high, probably due to the design, which allowed patients to follow the standard community-based treatment programs, without norms to increase patient retention. Although this approach to trial design, which allows normal life events to influence trial outcome, probably enhances external validity, it can lead to considerable difficulties in interpreting data, such as motives for relapse and premature discontinuation of follow-up;
(3) Our service is exclusively dedicated to the treatment of men with alcohol and/or other drug problems. Therefore, our findings cannot be extended to women;
(4) A larger sample size would have been required to provide higher power for this comparison;
(5) Although we used ECG and clinical evaluation of our patients through anamnesis and cardiac auscultation at screening, only clinical evaluation, but not ECG was conducted at each appointment during the study;
(6) Although we tested alcohol breath concentration at baseline, we did not analyze breath alcohol levels across the study to confirm self-report;
(7) There was no follow-up of participants after medication ceases at 12 weeks. This can be disappointing as the outcomes in Figs. 2 and 3 seem to show a trend toward increasing benefit for the active group toward the end of the study. Although the dropout rate is likely to increase once participants are no longer receiving medication, longer-term relapse data could have significantly improved the trial.

In summary, our study was not able to show the efficacy of ondansetron at a 16 mg/day dosage to treat alcohol dependent outpatients, using only the treatment adherents. With an imputed sample, ondansetron was significantly effective in decreasing the proportion of heavy drinking days. Although multiple imputation is a valuable technique that allows the use of complete-data statistics on data sets with missing data, the true missing data mechanism will always be elusive and untestable from the data, and no amount of complex modeling can overcome this. Thus, the superiority of ondansetron over the placebo regarding the proportion of heavy drinking days in the imputed sample must be carefully considered in the interpretation of the data. Nevertheless, our study showed full-dose ondansetron was clinically safe, and no serious side effects were registered. In addition, our study highlights the need of combining medication and more intensive psychosocial treatments early in treatment in order to increase treatment retention (Baltieri & Correa Filho, 2012).

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Contributors

João Maria Corrêa Filho was involved in all aspects of the manuscript writing and interpretation of the results. Danilo Antonio Baltieri conceived of the manuscript idea and the study design, helped with the manuscript writing and the interpretation of the results.

Conflict of interest

There is not any conflict of interest.

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