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Effects of Ondansetron in Early- Versus Late-Onset Alcoholics: A Prospective, Open-Label Study

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Background: Early-onset alcoholics (EOAs) have a greater familial loading for alcoholism, more severe progression of the disorder, a greater severity of comorbid psychopathology, and a poorer response to treatment than late-onset alcoholics (LOAs). Ondansetron, a 5-hydroxytryptamine-3 antagonist, was found to be superior to placebo in the treatment of EOAs, but not of LOAs. This study compared the tolerability and potential efficacy of an oral solution of ondansetron in EOAs versus LOAs.

Methods: Forty outpatients with alcohol dependence (67.5% male; 87.5% European American; 20 EOAs; 20 LOAs) received an oral solution of ondansetron at a dosage of 4 μg/kg twice daily for 8 weeks, together with weekly relapse-prevention therapy.

Results: EOAs had a significantly greater decrease in drinks per day, drinks per drinking day, and alcohol-related problems than LOAs. Changes in the level of carbohydrate-deficient transferrin were consistent with changes in self-reported drinking behavior.

Conclusions: An oral solution of ondansetron seems suitable for the treatment of alcohol dependence, yielding findings consistent with evidence from a placebo-controlled trial that ondansetron, at a dosage of 4 μg/kg twice daily, is of value in the treatment of EOAs.

Key Words: Ondansetron, 5-HT_3 Antagonist, Alcoholism Subtype, Serotonin Function, Alcoholism Treatment.

SEROTONERGIC MEDICATIONS, PARTICULARLY the selective serotonin reuptake inhibitors (SSRIs) fluoxetine and citalopram, have been extensively evaluated for the treatment of alcoholism [see Kranzler (2000) for a review]. The effects of ondansetron, a 5-hydroxytryptamine-3 (5-HT_3) antagonist, have also been studied in relation to human drinking and alcohol dependence. Ondansetron reduced alcohol-induced positive subjective effects (Johnson et al., 1993a) and augmented certain stimulant, sedative, and discriminant effects of alcohol without affecting psychomotor performance or alcohol pharmacokinetics (Johnson et al., 1993b; Swift et al., 1996; cf Doty et al., 1994). In a clinical trial, Sellers et al. (1994) found that ondansetron 0.5 mg (but not 4 mg) given twice a day reduced alcohol consumption more than placebo among a subgroup of heavy drinkers (Sellers et al., 1994). Johnson et al. (2000b) studied ondansetron as an adjunct to relapse-prevention therapy in alcoholic subtypes based on the age of the onset of problem drinking. They found that, at the optimal dosage (i.e., 4 μg/kg twice daily), ondansetron was superior to placebo in reducing both self-reported alcohol consumption and the plasma concentration of carbohydrate-deficient transferrin (CDT), although the effect was evident only among early-onset alcoholics (EOAs).

EOAs (i.e., those with the onset of problem drinking before age 25) have a greater familial loading for alcoholism, more severe progression of the disorder, and a greater severity of comorbid psychiatric disorders, particularly antisocial personality disorder (Babor et al., 1992; Cloninger, 1987). Such patients generally have a poorer response to alcoholism treatment than do late-onset alcoholics (LOAs; i.e., those with the onset of problem drinking at age 25 or later). Together with two studies that showed differential effects of SSRIs among subgroups of alcoholics (Kranzler et al., 1996; Pettinati et al., 2000), the study by Johnson et al. (2000b) supports the clinical utility of matching serotonergic pharmacotherapy to alcoholic subtypes.

Although there is a growing literature that supports a dichotomous approach to subtyping alcoholics, a variety of specific methods have been used to differentiate subtypes. These methods include the use of genetic epidemiological data from an adoption study (Cloninger et al., 1981), application of cluster analysis to detailed empirical data from a sample of alcoholics (Babor et al., 1992), and use of a single item from a questionnaire administered to alcoholics in treatment (Johnson et al., 2000a). Given the complexities in the application of the first two approaches (Epstein et al., 2002), the use of a single measure (age of onset) to

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differentiate EOAs from LOAs seems to be the most suitable for clinical application (Johnson et al., 2000a).

This 8-week, open-label study was conducted to examine the feasibility of using an oral solution of ondansetron to treat alcohol dependence and to compare the effects of ondansetron on drinking behavior among EOAs and LOAs. The protocol and consent form were approved by the Institutional Review Board of the University of Connecticut Health Center.

METHODS

Assessments

At screening, subjects underwent a medical history, a physical examination, and laboratory testing. The Structured Clinical Interview for DSM-IV (First et al., 1995) was used to evaluate DSM-IV criteria for alcohol dependence (American Psychiatric Association, 1994), to determine the age of onset of the disorder [i.e., EOA (age <25 years) or LOA (age ≥25 years)], and to screen for other substance use and major psychiatric disorders. We chose this criterion for age of onset because it can be readily applied in the clinical setting and is presumably more reliable than group assignment made on the basis of a single question.

The following assessments were administered at study entry and at each weekly visit: timeline follow-back (Sobell and Sobell, 1992), Beck Depression Inventory (Beck et al., 1961), Alcohol Urge Questionnaire (AUQ; Bohn et al., 1995), and a checklist of adverse events. The Drinker Inventory of Consequences (DrInC; Miller et al., 1995) was administered at study entry and at the end of the study. Blood was obtained at baseline, at the end of week 4 of treatment, and at the end of the study. Because CDT is the most specific marker of chronic heavy drinking (Arndt, 2001), we used the Bio-Rad (Hercules, CA) %CDT TIA assay for CDT content, expressed as a percentage of total transferrin (Myrick et al., 2001), as an objective marker of heavy drinking.

Subjects

Forty alcohol-dependent outpatients (20 EOAs and 20 LOAs) were enrolled in the study. Inclusion criteria included age 18 to 65 years, ability to read English at an eighth grade or higher level, and willingness and ability to provide written, informed consent to participate. Although abstinence at enrollment was not required, subjects were selected on the basis of their reported desire to stop drinking. Subjects were excluded if, on the basis of history, physical examination, or routine laboratory evaluation, they had a current, clinically significant physical disease, serious psychiatric illness, or DSM-IV diagnosis of drug (other than nicotine) dependence. Women of childbearing potential were excluded if they were pregnant, lactating, or not practicing a reliable and effective method of birth control. The sample was predominantly male (67.5%), European American (87.5%), middle-aged (mean, 43.7 years), and well educated (mean, 14.7 years).

Treatments

All subjects received weekly individual or group psychotherapy based on a treatment manual that focused on coping-skills training (Kadden et al., 1992; Marlatt and Gordon, 1985); the psychotherapy was delivered by a master's-level therapist experienced in coping-skills training. Medication was dispensed as an oral solution of the injectable form of the medication (2 mg/ml). A research pharmacist used artificially sweetened cherry syrup to dilute the concentration to a dosage of 4 μg/kg/ml. At each study visit, subjects were given a 10-day supply of the solution, along with an oral syringe, and they were trained to measure 1 ml for administration twice daily. Medication compliance was assessed by measuring the unused solution returned at each visit and by patient reports of medication use.

Statistical Analysis

The proportion of subjects in each age-of-onset group with adverse effects was evaluated with χ^2 and Fisher's exact tests. The choice of a criterion for determining age of onset (i.e., the age at which DSM-IV criteria for alcohol dependence were met) was made *a priori*. Heavy drinking was defined as five or more drinks in a day for men and four or more drinks in a day for women. A repeated-measures analysis of covariance was used to evaluate the main effects of time (pretreatment/treatment) and age of onset (EOA/LOA). In addition to the F and p values, we report the effect size (η^2) for the analysis of alcohol-related outcomes. An η^2 value of 0.01 reflects a small effect, whereas 0.06 is a medium effect and 0.14 is a large effect (Green et al., 2000). The CDT data were analyzed by using the log of the ratio of the two time points during treatment (i.e., weeks 4 and 8), with the baseline level as a referent, similar to the approach used by Johnson et al. (2000b). The number of days of study participation was used as a covariate in these analyses. For the AUQ and the adverse effects measure, multilevel modeling was performed with HLM software (version 5.04, Scientific Software International, Chicago, IL; Raudenbush et al., 2001). In these analyses, the within-person measure (time) is a level 1 factor, and the between-persons measure (age-of-onset group) is a level 2 factor.

RESULTS

Subjects

As shown in Table 1, most subjects were male and European American. However, LOAs were older, more educated, more likely to be employed, and more likely ever to have married than EOAs. EOAs had a greater intensity of drinking and severity of alcohol-related consequences, whereas LOAs had significantly fewer abstinent days.

Study Adherence, Medication Compliance, and Adverse Events

A total of 28 subjects (70%) completed the study (65% of EOAs and 75% of LOAs); EOAs completed a mean of 6.1 weeks (SD, 2.2 weeks), and LOAs completed a mean of 6.3 weeks (SD, 2.4 weeks) of treatment ($p > 0.10$). The groups were also comparable on medication compliance, as measured by weekly monitoring of the volume of medication ingested [EOAs, 75.4% (SD, 15.1%) of doses; LOAs, 66.3% (SD, 18.3%) of doses; $p > 0.10$].

Table 2 shows the adverse effects reported by both groups. All adverse events were mild to moderate in severity. However, three subjects [two LOAs (one due to chest pain and one due to irritability and constipation) and one EOA (due to sexual dysfunction and constipation)] discontinued the study due to adverse effects, which also resolved spontaneously. More LOAs experienced symptoms of anxiety [80 vs. 50%; $\chi^2(1) = 3.96$; $p = 0.047$] and nausea [45 vs. 15%; $\chi^2(1) = 4.29$; $p = 0.038$].

Effects of Ondansetron on Drinking and Alcohol-Related Consequences

As shown in Table 3, all self-reported measures of alcohol consumption and alcohol-related consequences declined significantly in both groups over the course of the 8-week treatment period. As can be seen in Table 3 and in

Table 1. Demographic and Clinical Features By Age-of-Onset Group[a]

Variable	Early-onset alcoholics (n = 20)	Late-onset alcoholics (n = 20)	Test statistic	p Value
Demographics				
Sex (% male)	75	60	$\chi^2(1) = 1.03$	0.31
Race (% European American)	90	85	FET[b]	0.50
Age (years)	40.5 (6.7)	46.9 (7.1)	$F = 8.52$	<0.001
Education (years)	14.0 (2.2)	15.4 (2.4)	$F = 5.26$	0.027
Ever married (%)	70	100	FET	0.010
Employed (%)	80	100	FET	0.053
Clinical features				
Days abstinent (%)	31.2 (25.1)	14.1 (18.0)	$F = 6.11$	0.018
Drinks/day	6.5 (4.2)	5.4 (2.3)	$F = 1.04$	0.31
Drinks/drinking day	10.5 (8.4)	6.2 (2.1)	$F = 4.78$	0.035
Heavy-drinking days (%)	56.5 (26.4)	60.5 (25.2)	$F = 0.24$	0.63
DrInC total score[c]	46.6 (21.8)	24.6 (13.4)	$F = 14.79$	<0.001
DSM-IV criteria[d]	5.10 (1.5)	4.70 (1.2)	$F = 0.89$	0.35
AUQ score[e]	15.2 (8.1)	15.3 (6.2)	$F = 0.00$	0.97
BDI score[f]	11.1 (6.0)	8.3 (6.9)	$F = 1.94$	0.17
Symptom count[g]	3.4 (1.8)	2.2 (2.3)	$F = 3.45$	0.071

[a] Data are mean (SD) unless otherwise indicated.
[b] FET = Fisher's exact test, used in place of the χ^2 test when cell expectancy was <5.
[c] Drinker Inventory of Consequences (Miller et al., 1995).
[d] Alcohol dependence (American Psychiatric Association, 1994).
[e] Alcohol Urge Questionnaire (Bohn et al., 1995).
[f] Beck Depression Inventory (Beck et al., 1961).
[g] Symptom Checklist.

Table 2. Number of Patients Experiencing Specific Adverse Events

Adverse event	Early-onset alcoholics (n = 20)	Late-onset alcoholics (n = 20)	Statistic	p Value
Anxiety	16	10	$\chi^2(1) = 3.96$	0.047
Fatigue	13	11	$\chi^2(1) = 0.42$	0.52
Difficulty sleeping	13	9	$\chi^2(1) = 1.62$	0.20
Headache	12	10	$\chi^2(1) = 0.40$	0.53
Drowsiness	11	6	$\chi^2(1) = 2.56$	0.11
Muscle aches	11	6	$\chi^2(1) = 2.56$	0.11
Stomach discomfort	11	6	$\chi^2(1) = 2.56$	0.11
Diarrhea	8	6	$\chi^2(1) = 0.44$	0.51
Nausea	9	3	$\chi^2(1) = 4.29$	0.038
Constipation	6	2	FET	0.12
Fever	4	1	FET	0.17
Any of the above events	20	16	FET	0.053

FET, Fisher's exact test (used when cell expectancy was <5).

Figs. 1 through 3, EOAs had a significantly greater reduction than LOAs of drinks per day ($\eta^2 = 0.177$), drinks per drinking day ($\eta^2 = 0.139$), and the DrInC total score ($\eta^2 = 0.177$). The groups showed comparable improvement on the percentage of both days abstinent ($\eta^2 = 0.025$) and days of heavy drinking ($\eta^2 = 0.067$).

CDT levels are shown in Fig. 4. Although the group differences were not statistically significant, EOAs had a greater decrease in the log CDT ratio than LOAs at week 4 [$F(1,27) = 2.35$; $p = 0.14$; $\eta^2 = 0.080$] and at week 8 [$F(1,32) = 0.56$; $p = 0.46$; $\eta^2 = 0.017$].

With respect to the multilevel analyses, alcohol urge did not decrease significantly during treatment, showing neither a linear nor a quadratic trend, nor did age of onset have an effect on either the linear or the quadratic trajectory ($p > 0.10$). The number of reported symptoms reflective of adverse events showed a significant quadratic time effect [$\gamma 20 = 0.0018$; $t(38) = 4.50$; $p < 0.001$], with symptoms decreasing from baseline to week 6 and subsequently increasing. This quadratic trend was evident in both EOAs and LOAs, but the trend was significantly more pronounced in the EOAs [$\gamma 21 = -0.0012$; $t(38) = -2.29$; $p = 0.028$].

DISCUSSION

This study provided support for both the feasibility of using an oral solution of ondansetron and its differential effects among alcoholics grouped by age of onset of alcohol dependence. Compliance with the oral solution was acceptable; approximately 70% of doses were consumed. With respect to drinking outcomes, the study yielded consistent evidence of a greater treatment response among EOAs compared with LOAs, although on some measures the difference did not reach statistical significance, possibly due to low statistical power. Only effects that were in the large range of effect sizes were statistically significant. Other measures, such as heavy drinking days and the CDT level at week 4, which were in the medium range of effect sizes, did not reach significance. As would be expected given the effects on drinking, we also observed a greater reduction of DrInC total scores among EOAs than among LOAs. Furthermore, among EOAs, the correlation between declines during treatment in the mean number of drinks consumed and the DrInC score ($r = 0.80$) was significantly greater than it was among LOAs ($r = 0.31$; $z = 2.08$; $p = 0.038$). Decreases over time in the CDT ratio were also consistent with reported reductions in the drinking measures.

We found that the urge to drink was not affected by ondansetron treatment in either age-of-onset group. One possible explanation for the discrepancy between these

Table 3. Changes From Before Treatment in Alcohol-Related Measures During Treatment by Age-of-Onset Group

	Early-onset alcoholics			Late-onset alcoholics			Between groups[b]	
Alcohol-related measure	Change[a]	*t*	*p*	Change[a]	*t*	*p*	*F*	*p*
Days abstinent (%)	30.2 (29.4)	4.60	0.000	24.8 (21.2)	5.11	0.000	0.82	0.373
Drinks/day	4.53 (4.5)	4.51	0.000	1.98 (2.1)	4.07	0.001	6.90	0.013
Drinks/drinking day	5.78 (8.9)	2.92	0.009	1.55 (2.0)	3.35	0.004	5.08	0.032
Heavy-drinking days (%)	35.1 (24.7)	6.36	0.000	26.7 (27.4)	4.24	0.000	2.30	0.139
DrInC total score[c]	30.3 (27.7)	4.50	0.000	11.4 (11.2)	4.31	0.000	6.88	0.013

[a] Mean (SD).
[b] The between-groups tests included days between baseline and study end as a covariate.
[c] Drinker Inventory of Consequences (Miller et al., 1995).

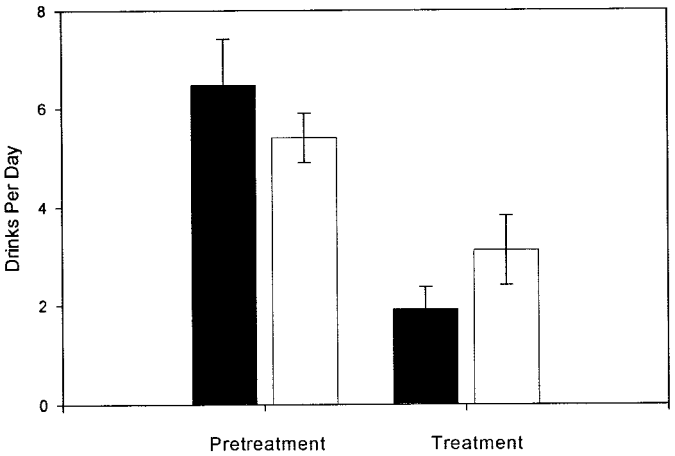

Fig. 1. Mean (SEM) values for drinks per day during the pretreatment and treatment periods. EOA, early-onset alcoholic group ($n = 20$); LOA, late-onset alcoholic group ($n = 20$). The within-groups decrease was significant ($p < 0.01$) for both groups but was greater ($p < 0.05$) in the EOAs. ■, EOA; □, LOA.

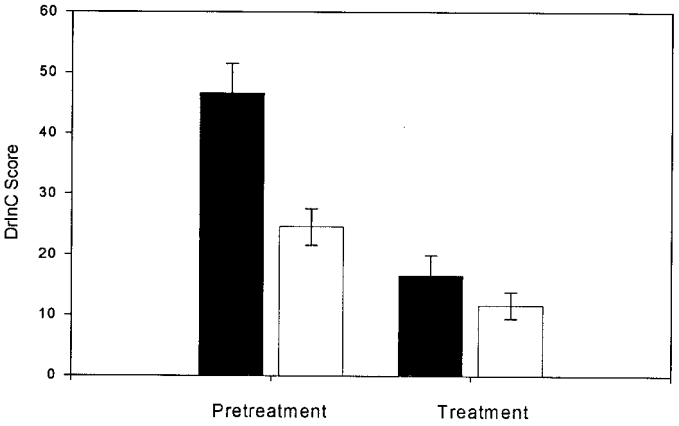

Fig. 3. Mean (SEM) values for the Drinker Inventory of Consequences (DrInC) total score during the pretreatment and treatment periods. EOA, early-onset alcoholic group ($n = 20$); LOA, late-onset alcoholic group ($n = 20$). The within-groups decrease was significant ($p < 0.001$) for both groups but was greater ($p < 0.05$) in the EOAs. ■, EOA; □, LOA

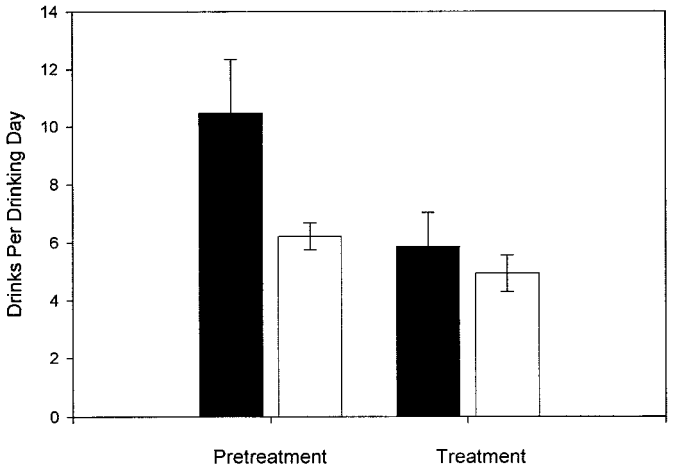

Fig. 2. Mean (SEM) values for drinks per drinking day during the pretreatment and treatment periods. EOA, early-onset alcoholic group ($n = 20$); LOA, late-onset alcoholic group ($n = 20$). The within-groups decrease was significant ($p < 0.01$) for both groups but was greater ($p < 0.05$) in the EOAs. ■, EOA; □, LOA

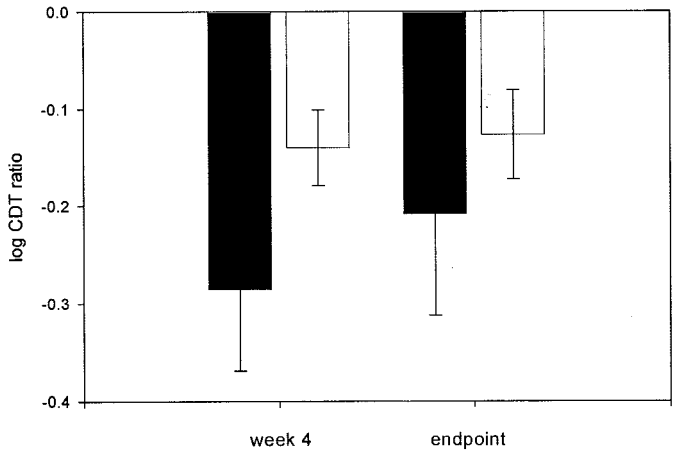

Fig. 4. Decline from baseline in mean (SEM) values for the log of carbohydrate-deficient transferrin (CDT) concentration at 4 and 8 weeks of treatment. EOA, early-onset alcoholic group ($n = 20$); LOA, late-onset alcoholic group ($n = 20$). The between-groups difference was not significant ($p > 0.10$). ■, EOA; □, LOA

findings and those reported recently by Johnson et al. (2002) is that we used the AUQ (Bohn et al., 1995) to measure the urge to drink, whereas Johnson et al. (2002) used an analog scale to measure craving.

Although studies in both animals and humans have shown that 5-HT_3 antagonists reduce alcohol intake (Fadda et al., 1991; Johnson et al., 2000b; Knapp and Pohorecky, 1992; Sellers et al., 1994; Tomkins et al., 1995), the mechanism of this effect is not well understood. Several lines of research suggest that 5-HT_3 receptor antagonists modify the reinforcing properties of alcohol. Because the alcohol-induced release of dopamine in the nucleus accumbens may play a major role in ethanol reinforcement (Di Chiara and

Imperato, 1988; Koob, 1992) and because 5-HT_3 receptors synapse on these dopamine neurons (Fadda et al., 1991; Wozniak et al., 1990, Yoshimoto et al., 1996), 5-HT_3 antagonists may modulate the release of dopamine and its consequent reinforcing effects after alcohol consumption (Dyr and Kostowski, 1995; Fadda et al., 1991; Hodge et al., 1993; Tomkins et al., 1995). Consistent with this hypothesis, Johnson et al. (1993a) found that ondansetron, given as a single 4-mg dose, reduced both the pleasurable effects of alcohol and the desire to drink. In contrast, Swift et al. (1996) found that a single 8-mg dose of ondansetron augmented certain stimulant, sedative, and discriminant effects of alcohol.

In this study, although ondansetron was generally well tolerated, EOAs were significantly more likely to report some adverse effects of the drug. The time course of the appearance of adverse effects differed by group, with significant reductions in both groups during the first 6 weeks, followed by an increase in the number of adverse events during the last 2 weeks of treatment, particularly among EOAs. These findings are consistent with the suggestion by Swift et al. (1996) that the reduction in alcohol consumption in humans and animals treated with ondansetron is mediated by increases in the adverse effects of alcohol (Swift et al., 1996). However, subjects were not asked to identify reasons for reducing their drinking. Consequently, no direct relationship can be drawn between adverse events and the reduction in drinking behavior. Future studies of ondansetron for alcohol dependence should include information to test this hypothesis directly.

The major limitation of the study was the lack of a placebo control. There were also group differences on demographic and clinical variables that existed before treatment. Although alcoholic subtypes are known to differ on a variety of measures (Babor et al., 1992; Cloninger, 1987), higher pretreatment drinking intensity and alcohol-related consequences among EOAs created a greater opportunity for EOAs to show reductions in these measures, irrespective of a medication effect. However, the analytical methods that were used took pretreatment levels of drinking and alcohol-related problems into account. Consequently, our conclusions are based on between-group differences in the slope of these measures over time.

The small sample size and short duration of treatment also limited the statistical power to detect some between-group effects. In summary, future studies with placebo controls, in which all treatment groups are balanced on key variables, are needed to directly replicate the findings of Johnson et al. (2000b) and to characterize the magnitude of ondansetron's treatment response among EOAs.

Results from this study support the feasibility of using an oral solution of ondansetron in alcoholism treatment. An oral solution makes it easier to deliver the low dosage of ondansetron that has been found to be optimal in the treatment of alcohol dependence (Johnson et al., 2000b). The use of an oral solution also circumvents the need for a double-dummy design in the conduct of placebo-controlled trials in which ondansetron is compared with one or more active medications. Findings from the use of the oral liquid are consistent with those reported by Johnson et al. (2000b) and suggest that additional studies of the effects of ondansetron among subjects differentiated by age of onset of alcohol dependence are warranted. Of particular interest would be a study contrasting the effects of ondansetron in EOAs with those of an SSRI, such as sertraline, in LOAs.

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