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Ondansetron Reduces Mood Disturbance Among Biologically Predisposed, Alcohol-Dependent Individuals

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Background: Early-onset alcoholics (EOA) differ from late-onset alcoholics (LOA) by developing problem drinking during youth, experiencing severe behavioral problems, having a familial disease history, and possessing a tendency toward subsyndromal mood disturbance, including symptoms of depression, anxiety, and hostility. Subsyndromal mood disturbance is, therefore, an important component of the early-onset syndrome and may be mediated by serotonin dysfunction. Therefore, the serotonin-3 antagonist ondansetron, which has been shown to be effective at improving drinking outcomes and promoting abstinence among EOA, presumably by ameliorating serotonin dysfunction, also may exert its beneficial effects by alleviating mood disturbance among EOA.

Methods: After one lead-in week of single-blind placebo administration, subjects underwent 11 weeks of double-blind outpatient treatment using a 2×4 factorial design that examined age of onset (EOA versus LOA) and medication dose (placebo, or ondansetron 1, 4, or 16 μg/kg twice daily) combined with weekly standardized group cognitive-behavioral therapy. The placebo lead-in week was used to adjust for study entrance effects but not for excluding subjects. Assessments of mood were performed by using the overall score and subscales of the Profile of Mood States both at screening and at weekly intervals during the study.

Results: Subsyndromal mood disturbance was shown to be an important component of early-onset alcoholism. Ondansetron (16 μg/kg twice daily) showed greater therapeutic efficacy at alleviating symptoms of overall mood disturbance, fatigue, vigor, confusion/bewilderment, and depression among EOA compared with LOA. EOA-associated improvements in mood disturbance seemed to be independent of drinking behavior.

Conclusions: Ondansetron has been shown to be an effective treatment for early-onset alcoholism. Ondansetron's ability to improve symptoms of depression, anxiety, and hostility among EOA may make an additional contribution to its therapeutic effect. Mechanistic studies are needed to delineate more clearly the relationship between serotonin dysfunction and pathophysiology among various subtypes of alcohol-dependent individuals.

Key Words: Alcoholism, Serotonin (5-HT), Ondansetron (5-HT_3 Antagonist), Mood, Anxiety, Hostility.

SUBTYPING ALCOHOL-DEPENDENT INDIVIDUALS into clinically meaningful groups provides a more accurate guide as to the course, character, and prognosis of the alcoholism disease (Babor et al., 1992a; Brown et al., 1994; Johnson et al., 2000a). Of these classification systems, age of onset of problem drinking (Buydens-Branchey et al., 1989) has emerged as an important factor for segregating subtypes of alcohol-dependent individuals. This classification approach offers the potential of targeting optimal pharmacological, psychotherapeutic, or combined treatments toward the appropriate subtype. Recently, a comparison of 11 different typologies demonstrated age of onset to be a critical parameter for segregating subtypes of alcohol-dependent individuals (Penick et al., 1999), and there is reasonable concordance between age of onset and the common hypothetically (Cloninger et al., 1981; Cloninger, 1987) and empirically (Babor et al., 1992a; Litt et al., 1992) derived typologies. Briefly, early-onset alcoholics (EOA) develop problem drinking during youth, experience severe behavioral problems, have a tendency toward subsyndromal mood disturbance (including symptoms of depression, anxiety, and hostility), and have a high familial or biological propensity toward alcoholism. In contrast, late-onset alcoholics (LOA) acquire drinking problems in adulthood, often as a consequence of psychosocial stressors, and have little familial or genetic predisposition to alcoholism (Johnson et al., 2000a). Mood disturbance may, therefore, be an important component of the early-onset syndrome in alcohol-dependent individuals.

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Serotonergic abnormality has been posited to underlie early-onset alcoholism (Buydens-Branchey et al., 1989; Johnson, 2000; Lahiri and Nurnberger, 1991; Linnoila, 1990, 1997; Linnoila and Virkkunen, 1992, 1994; Linnoila et al., 1993a,b). EOA also may have reduced serotonin (5-HT) turnover rates (Swann et al., 1999), also a feature of individuals with mood disturbance and impulse-control disorders (Csernansky and Sheline, 1993; Heinz et al., 2001), and therapeutic response to serotonergic medications may be associated with decreased 5-HT turnover (Hall et al., 1995). We have shown that the 5-HT_3 antagonist ondansetron improves drinking outcomes and promotes abstinence among EOA (Johnson et al., 2000b), presumably by blockade of postsynaptic 5-HT_3 receptors, a phenomenon that would be expected to decrease 5-HT turnover rate (Edwards et al., 1996). It would, therefore, be reasonable to hypothesize that ondansetron would ameliorate symptoms of depression, anxiety, and hostility, particularly among EOA. Here, in a randomized, double-blind, placebo-controlled trial, we tested this prediction by examining ondansetron's effects on mood among EOA and LOA.

MATERIALS AND METHODS

Subjects

Using the Structured Clinical Interview for DSM (First et al., 1994), we enrolled 321 male and female DSM-III-R (American Psychiatric Association, 1987)–diagnosed alcohol-dependent individuals. Enrollees were 25 to 65 years old; scored more than 5 on the Michigan Alcoholism Screening Test (Selzer, 1971), which assessed the severity of alcohol-related problems; reported, during the telephone screen, drinking three or more standard drinks per day; and had a negative urine toxicological screen for narcotics, amphetamines, and sedative hypnotics at enrollment. Exclusion criteria were a current psychiatric diagnosis other than alcohol or nicotine dependence, alcohol withdrawal symptoms that necessitated inpatient detoxification, clinically significant abnormalities (i.e., findings on physical examination, electrocardiographic recording, or hematological evaluation, or increased bilirubin levels), pregnancy, lactation, taking medications with a potential effect on alcohol consumption, mandated incarceration or employment loss for not receiving alcoholism treatment, and receipt of alcoholism treatment 30 days before enrollment. Additional demographic and addiction-related data that demonstrated psychopathologic differences between EOA and LOA were collected at screening by using the Addiction Severity Index (McLellan et al., 1985).

Ethics approval was provided by the Committee for the Protection of Human Subjects at The University of Texas Health Science Center at Houston. Subjects were recruited by newspaper or radio advertisement.

Experimental Design

The study was a randomized, controlled trial with a 2 (EOA versus LOA) × 4 [ondansetron 0, 1, 4, and 16 μg/kg twice daily (bid)] factorial design. Treatment groups were balanced on chronological age, age of problem drinking onset [EOA or LOA, <25 or ≥25 years, respectively, using item B 28 of the Comprehensive Drinker Profile (Miller and Marlatt, 1984)], and past-90-days drinking level. Abstinence was not a study criterion; however, subjects reported a desire to stop drinking and to participate in psychosocial treatment. All subjects received weekly standardized cognitive-behavioral therapy (US Department of Health and Human Services, 1995) for 12 weeks.

Experimental Measures

Self-reported drinking and mood were measured at baseline and at weekly intervals during the study by using the following measures.

1. The timeline follow-back method (Sobell and Sobell, 1992) was used to characterize drinking behavior. Drinks per day was calculated as the average amount of alcohol consumed across all study days.
2. The Profile of Mood States (POMS) is a standardized and reliable 65-item inventory on which adjectival variables on mood are rated on a five-point Likert scale. Seven factors can be derived from this scale: anger/hostility, fatigue, vigor, confusion/bewilderment, tension/anxiety, depression/dejection, and friendliness. Additionally, the POMS data were summarized as the total POMS score (McNair et al., 1971, 1992).

Safety and other experimental measures were collected at scheduled intervals based on the protocol.

Statistical Analyses

Data quality was supervised by a doctoral-level database coordinator and statistician. Individual subject plots were checked for unusual values and completeness. Efficacy values were validated as correct against the case records. Data were analyzed with SAS™ version 8.2 (SAS Institute Inc., 1999).

For baseline characteristics, POMS scores and other continuous variables were reported descriptively as their mean and SE. Percentages were used to describe categorical variables.

For inferential analyses, subjects' data were examined as randomized, by using an urn (Stout et al., 1994) procedure, to treatment after the screening visit (i.e., visit 0). Subjects did not receive their randomized double-blind study medication (i.e., ondansetron or placebo) until the end of the 1-week single-blind placebo period (i.e., at visit 2). The first recorded response to medication was, therefore, not measured until the end of the first week of double-blind treatment (i.e., visit 3). Response to the double-blind study medication treatment was, therefore, measured from visits 3 to 13, and all subjects randomized were included in the analyses (Meinert, 1986), irrespective of whether or not they completed the study. Previous-visit values of POMS measures (i.e., before visit 3) were used as covariates to control for study entrance and placebo pill-taking effects (Senn, 1994).

The changes in the overall POMS score and its respective subscales between the pre–double-blind and double-blind periods were summarized as their means and 95% confidence intervals. To analyze the effects of ondansetron dosages and age of onset on the mood changes, the mixed-effects model with autoregressive covariance structure was used. In this analysis, dosage grouping (ondansetron 0, 1, 4, or 16 μg/kg bid) and age of onset (EOA versus LOA) were the between-subject factors, and visits during the double-blind period served as the within-subject factor. We evaluated several covariance structures for modeling within-subject variability. We chose the autoregressive covariance structure because it provided the best-fitting model. Moreover, the autoregressive covariance structure is appealing for longitudinal data due to its underlying assumption that two consecutive visits were more correlated than those further apart. Baseline characteristics including gender, age at baseline, and drinks per day before medication administration were used to adjust the model. Additionally, for each POMS subscale or the total score, the model was adjusted for its corresponding baseline mood subscale score and total baseline score, respectively.

Ondansetron's treatment effects were examined as the mean difference among the three dosage groups (1, 4, or 16 μg/kg bid) and the placebo group. The Proc Mixed procedure in SAS was used to analyze the longitudinal POMS overall score and associated subscales by using a repeated-measures model. Inclusion of 0 in the 95% confidence intervals for the treatment effect indicates a nonsignificant treatment effect. Pearson's correlation coefficients were used to examine the relationship between the change in drinking and POMS scores between the pre–double-blind and double-blind periods.

Table 1. Demographic and Psychopathologic Characteristics of Early- and Late-Onset Alcoholic Patients at Intake[a]

Variable	Early onset (n = 161)	Late onset (n = 160)	p Value
Group assignments			
Placebo	30	42	
Ondansetron			
1 μg/kg bid	38	39	0.29
4 μg/kg bid	45	43	
16 μg/kg bid	48	36	
Demographic variables			
Age, years	37.16 (0.64)	44.03 (0.61)	<0.001
Sex, n (%)			
Men	124 (77.1)	102 (63.7)	0.01
Women	37 (22.9)	58 (36.3)	
Ethnicity, n (%)			
White	108 (67.1)	119 (74.3)	
Black	29 (18.1)	27 (16.9)	0.44
Hispanic	22 (13.7)	14 (8.8)	
Other	2 (1.0)	1 (0)	
Social class, n (%)[b]			
1–3	61 (38.2)	89 (55.6)	
4–6	82 (51.2)	58 (36.3)	0.007
7–9	17 (10.6)	13 (8.1)	
Weight, kg	79.21 (1.41)	79.08 (1.53)	0.93
Measures of alcohol drinking			
Years since first report of problems with alcohol use	17.12 (0.66)	9.76 (0.53)	≤0.001
Mean drinks per day at intake (past 90 days)	8.48 (0.49)	7.60 (0.43)	0.39
Mean drinks per day at single blind	4.67 (0.87)	4.65 (0.85)	0.64
Breath alcohol level	0.00 (0.00)	0.01 (0.00)	0.18
Carbohydrate-deficient transferrin level, units/liter	20.31 (1.45)	21.61 (1.15)	0.05
Michigan Alcoholism Screening Test	30.91 (0.93)	24.92 (0.86)	<0.001
Addiction Severity Index composite scores			
Medical	0.11 (0.02)	0.12 (0.02)	0.77
Employment	0.22 (0.02)	0.11 (0.02)	<0.001
Alcohol	0.57 (0.01)	0.51 (0.02)	0.02
Drug	0.03 (0.00)	0.01 (0.00)	0.001
Legal	0.06 (0.01)	0.02 (0.01)	0.005
Family/social	0.33 (0.01)	0.29 (0.01)	0.02
Psychiatric	0.22 (0.02)	0.14 (0.01)	<0.001
Clinical Institute Withdrawal Assessment (revised)	5.20 (0.44)	4.57 (0.39)	0.30
DSM-III-R diagnosis of antisocial personality disorder, n (%)	28 (17.4)	14 (8.75)	0.03
Safety measures: liver function tests, units/liter			
γ-Glutamyl transferase	101.16 (14.78)	123.78 (17.74)	0.28
Glutamate oxalate transaminase	43.84 (4.45)	50.51 (4.78)	0.28
Glutamate pyruvate transaminase	49.60 (5.09)	45.94 (3.87)	0.62
Profile of Mood States (POMS)[c]			
POMS overall	90.25 (3.65)	72.93 (2.96)	<0.001
Anger/hostility	10.65 (0.78)	7.63 (0.58)	0.002
Fatigue	9.10 (0.55)	6.42 (0.43)	<0.001
Vigor	13.54 (0.49)	15.04 (0.49)	0.03
Confusion/bewilderment	9.10 (0.46)	6.86 (0.37)	<0.001
Tension/anxiety	11.91 (0.54)	9.73 (0.47)	0.002
Depression/dejection	18.15 (1.15)	12.92 (0.95)	<0.001
Friendliness	15.11 (0.38)	15.61 (0.39)	0.37

[a] Adapted in part from Johnson et al. (2000b). Values are expressed as mean (SE) unless otherwise indicated.
[b] Defined by Hollingshead and Redlich (1958).
[c] McNair et al. (1971).

RESULTS

EOA and LOA were equally represented and had similar levels of self-reported and objective drinking within the cohort. EOA, compared with LOA, were younger; were of lower social class; were more severely addicted, with a longer history of alcoholism; had higher rates of antisocial personality disorder; and experienced a greater frequency of symptoms of depression, anxiety, and hostility (Table 1).

Between the pre–double-blind and double-blind periods, there were significant decreases in the overall POMS score, fatigue, tension/anxiety, and depression/dejection for EOA. In contrast, there was only one significant change—a reduction in fatigue—among LOA, but even this was a marginal effect given that there was no significant change in the overall POMS for this subgroup. Further, these significant effects on EOA-related mood disturbance were seen at the highest and middle dose levels of ondansetron (i.e., 16 and 4 μg/kg bid, respectively; Table 2). As an illustration, Fig. 1 shows the difference across the 12-week trial period between ondansetron (16 μg/kg bid) and placebo among EOA on target POMS variables. Notably, there was a significant decrease (all p values <0.05) on all POMS mea-

Table 2. Mean Difference on the POMS and Its Subscales Between the Pre–Double-Blind and Double-Blind Periods for the Ondansetron (1, 4, and 16 μg/kg) and Placebo Groups Among Early- and Late-Onset Alcoholics

		Overall			Early onset			Late onset		
POMS subscale[a]	Dose (μg/kg)	Mean difference	95% Confidence interval	*p* Value	Mean difference	95% Confidence interval	*p* Value	Mean difference	95% Confidence interval	*p* Value
POMS overall	1	−9.36	−16.72 to −2.01	0.01	−11.60	−22.81 to −0.40	0.04	−6.76	−16.88 to 3.36	0.19
	4	−3.71	−10.66 to 3.23	0.29	−11.16	−21.49 to −0.84	0.03	3.33	−6.23 to 12.88	0.49
	16	−11.86	−19.07 to −4.64	0.001	−17.18	−27.95 to −6.41	0.002	−7.11	−17.02 to 2.81	0.16
Anger/hostility	1	0.19	−1.31 to 1.69	0.80	0.75	−1.69 to 3.19	0.54	−0.53	−2.42 to 1.36	0.58
	4	0.27	−1.15 to 1.70	0.71	−0.55	−2.83 to 1.73	0.63	1.04	−0.74 to 2.81	0.25
	16	−1.19	−2.68 to 0.29	0.11	−2.02	−4.41 to 0.36	0.095	−0.13	−2.0 to 1.74	0.89
Fatigue	1	−1.31	−2.36 to −0.26	0.01	−1.36	−3.10 to 0.38	0.12	−1.09	−2.40 to −0.22	0.10
	4	−0.77	−1.76 to 0.22	0.13	−2.14	−3.74 to −0.53	0.01	0.69	−0.54 to 1.93	0.27
	16	−1.61	−2.63 to −0.58	0.002	−2.46	−4.13 to −0.78	0.004	−0.85	−2.12 to 0.43	0.19
Vigor	1	2.05	0.84 to 3.26	0.001	2.89	1.13 to 4.65	0.002	1.30	−0.39 to 3.0	0.13
	4	0.71	−0.43 to 1.86	0.22	1.38	−0.25 to 3.0	0.10	0.005	−1.59 to 1.60	0.995
	16	1.82	0.63 to 3.0	0.003	2.70	0.99 to 4.40	0.002	1.13	−0.52 to 2.78	0.10
Confusion/bewilderment	1	−0.80	−1.67 to 0.06	0.07	−1.10	−2.50 to 0.29	0.12	−0.37	−1.46 to 0.72	0.51
	4	−0.42	−1.24 to 0.39	0.31	−1.16	−2.46 to 0.14	0.08	0.29	−0.73 to 1.31	0.58
	16	−1.19	−2.04 to −0.34	0.006	−1.71	−3.07 to −0.36	0.01	−0.76	−1.82 to 0.30	0.16
Tension/anxiety	1	−1.07	−2.20 to −0.07	0.06	−1.11	−2.96 to 0.74	0.24	−0.74	−2.17 to 0.68	0.30
	4	−0.91	−1.98 to 0.15	0.09	−1.91	−3.62 to −0.21	0.03	0.16	−1.184 to 1.50	0.81
	16	−0.84	−1.94 to 0.27	0.14	−1.25	−3.03 to 0.53	0.17	−0.51	−1.90 to 0.88	0.47
Depression/dejection	1	−2.52	−4.74 to −0.29	0.03	−2.88	−6.20 to 0.44	0.09	−1.78	−4.91 to 1.36	0.26
	4	−0.61	−2.71 to 1.49	0.57	−2.49	−5.55 to 0.57	0.11	1.24	−1.72 to 4.21	0.41
	16	−3.48	−5.66 to −1.30	0.002	−5.33	−8.53 to −2.14	0.001	−1.91	−4.99 to 1.17	0.22
Friendliness	1	0.88	−0.02 to 1.79	0.06	1.27	−0.17 to 2.71	0.08	0.54	−0.66 to 1.73	0.38
	4	0.53	−0.33 to 1.39	0.23	0.87	−0.47 to 2.21	0.20	0.22	−0.90 to 1.34	0.69
	16	0.95	0.05 to 1.84	0.04	1.11	−0.29 to 2.51	0.12	0.79	−0.36 to 1.95	0.18

[a] POMS, Profile of Mood States (McNair et al., 1971).

sures for both EOA and LOA between the beginning and end of treatment (data not shown); that is, there was a trend for mood disturbance to improve over time for all the alcohol-dependent individuals in treatment.

Table 3 shows the correlation coefficients of the mean change in POMS scores between the pre–double-blind and double-blind periods and drinks per day for the double-blind period. Among LOA and EOA combined, this correlation was statistically significant for the overall POMS and all subscales except for vigor and friendliness. In the LOA group alone, overall POMS, fatigue, tension/anxiety, and depression/dejection were significantly associated with drinks per day. In contrast, among EOA, only a reduction in anger/hostility was correlated with decreases in drinks per day.

There was no significant effect of gender except for its effect on the POMS subscale of friendliness for LOA. Only 34% of alcoholic patients failed to attend the eighth or a later double-blind visit.

DISCUSSION

Age of onset discriminates between subtypes of alcohol-dependent individuals based on psychopathology and the course of the illness. Notably, EOA, compared with LOA, are more likely to have subsyndromal mood disturbance, including symptoms of depression, anxiety, and hostility. The exact nature of this relationship between mood disturbance and our cohort of alcohol-dependent individuals can be conceptualized according to at least three models.

First, over and above an age-of-onset classification, these alcohol-dependent individuals frequently had symptoms of mood disorder, even though this did not achieve diagnostic criteria for a comorbid axis I diagnosis. This model would include the possibility of there being a nested group of alcohol-dependent individuals with subsyndromal mood disturbance, somewhat more common among EOA, but also with some dispersion among LOA. Therefore, the differential response to ondansetron is related to sensitivity—that is, greater relative disturbance among EOA, compared with LOA, yielding a larger therapeutic response to ondansetron. In support of this concept, there were significant differences on at least one of the ondansetron treatment doses compared with placebo on the overall POMS and its subscales (except for anger/hostility) that were independent of age of onset, and the analysis by subtype did show that these distinctions were more robust for the EOA.

A more encompassing concept would be that early-onset alcoholism encapsulates a range of impulse-dyscontrol or antisocial-type disorders, one facet of which is mood disturbance (Johnson and Ait-Daoud, 2000). This premise is supported by the relatively higher frequency of mood disturbance among EOA compared with LOA, a phenomenon that also has been described by others using a lower cutoff age of onset (i.e., <20 or ≥20 years; Buydens-Branchey et al., 1989) and the conceptually similar type B alcoholism (Babor et al., 1992b). Indeed, Cloninger's (1987) typology recognizes the core of the conceptually similar type II alcoholics as being high novelty-seeking (i.e., impulsive, exploratory, excitable, disorderly, and distractible). An interesting phenomenological feature of these EOA or type B alcoholics is the co-occurrence of impulsive or antisocial-

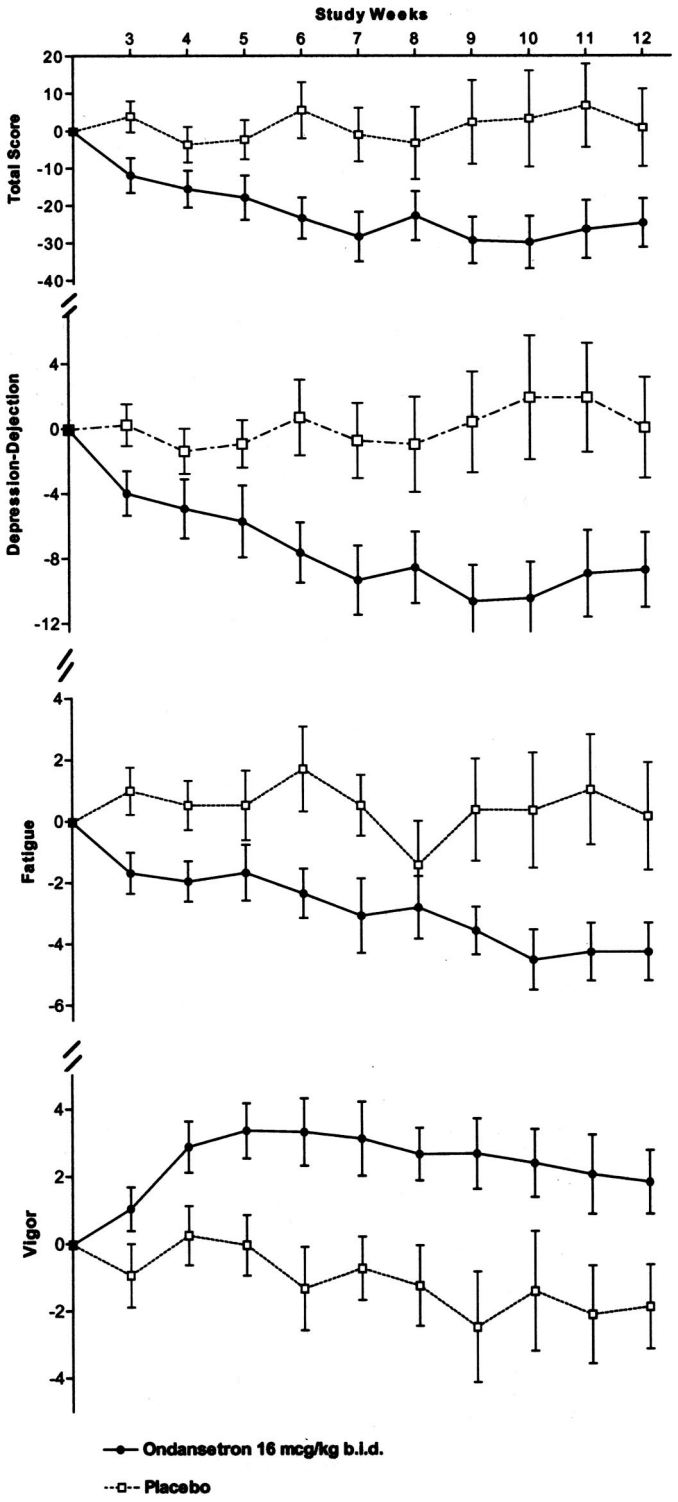

Fig. 1. Mean difference (95% confidence interval) between ondansetron (16 μg/kg bid) and placebo on target POMS variables among EOA.

type disorder and mood disturbance. We think that this observation is due to the fact that these alcohol-dependent individuals were studied close to middle age, and as they "matured out", their reflection on early losses may have made them prone to mood disturbance. Gender differences were not prominent. Although we need to be cautious about the implications of this finding because only one third of our cohort were women, these results would support the premise that phenomenological differences between EOA and LOA predominate over those of gender.

Table 3. Correlation Coefficients of Mean Change in POMS Scores Between the Pre–Double-Blind and Double-Blind Periods and Drinks Per Day for the Double-Blind Period Among Early- and Late-Onset Alcoholics[a]

POMS Subscale[b]	Overall	Early onset	Late onset
POMS overall	0.18 (0.005)	0.15 (0.10)	0.19 (0.03)
Anger/hostility	0.17 (0.006)	0.18 (0.05)	0.17 (0.06)
Fatigue	0.16 (0.01)	0.11 (0.20)	0.19 (0.03)
Vigor	−0.08 (0.21)	−0.05 (0.62)	−0.10 (0.27)
Confusion/bewilderment	0.15 (0.01)	0.15 (0.10)	0.15 (0.08)
Tension/anxiety	0.18 (0.004)	0.11 (0.23)	0.24 (0.007)
Depression/dejection	0.17 (0.008)	0.15 (0.08)	0.17 (0.05)
Friendliness	−0.05 (0.43)	0.006 (0.95)	−0.10 (0.28)

[a] Values are expressed as Pearson correlation coefficient (*p* value).
[b] POMS, Profile of Mood States (McNair et al., 1971).

We considered the possibility that the improvement in mood disorder was only secondary to changes in drinking. This is because even though the larger treatment effects of ondansetron on mood disturbance were seen with EOA rather than LOA, significant correlations between the overall POMS and its subscales were seen only for LOA. In other words, ondansetron-induced reductions in EOA-associated mood disturbance seemed to be independent of drinking level. There are, however, at least three caveats to this premise. First, the correlations reported were generally low (i.e., <0.2), even when statistical significance was achieved. Second, another potential source of imprecision in the data is that small differences in correlation could yield quite different p values (for example, POMS overall $r = 0.15$, $p = 0.10$ in EOA and $r = 0.19$, $p = 0.03$ in LOA). Third, due to the need to conserve statistical power, we did not formally explore in a regression analysis whether, and by how much, a change in drinking resulted in an alteration in POMS scores for each of the age-of-onset groups. Therefore, it remains to be established whether our impression that the significant correlations between the overall POMS and its subscales and drinks per day for EOA and LOA combined came mostly from the LOA group would be germane in a subsequent trial with a larger sample size.

We considered restricting our α level to 0.01 rather than 0.05 to provide additional control for type I error. We, however, decided that this was not strictly necessary because our analyses included testing multiple endpoints in the same group rather than testing for the same response in multiple groups. In any case, such a restriction (i.e., to an α level of 0.01) would not have markedly affected the results. Essentially, in all cases in which the α level for the effect of ondansetron (16 μg/kg bid) on the POMS score was <0.05, it also was ≤ 0.01. No other comparisons of ondansetron dose and POMS score would have achieved significance except for the 4 μg/kg bid dose to decrease fatigue among EOA.

Interestingly, ondansetron's effects on EOA-associated mood disturbance were predominantly seen at the highest

dose, 16 μg/kg bid. In contrast, even though the between-dose group contrasts did not achieve statistical significance, the middle ondansetron dose (4 μg/kg bid) showed the largest trend toward improving drinking outcomes and promoting abstinence (Johnson et al., 2000b). Therefore, it is possible that ondansetron's mechanistic effects on mood disturbance and early-onset drinking may be mediated differently or that there might be a third, more encompassing neurochemical process, as yet undetermined, that governs both phenomena. In any case, this study illustrates the importance of conducting dose-ranging paradigms in pharmacotherapy trials for alcoholism.

We emphasize that neither subtype of our cohort of alcohol-dependent individuals met DSM-III-R diagnostic criteria for any mood or anxiety-related disorder. That is, even among our EOA, the amount of psychopathology was relatively low compared with that which would be associated with the respective syndromic disorders. Hence, although our results are promising, it would be premature to extend our findings as proof that ondansetron is effective as a treatment for alcohol-dependent individuals with comorbid mood or anxiety disorder or among individuals with a primary axis I mood or anxiety disorder.

We conclude that among EOA, ondansetron seems to be effective at ameliorating subsyndromal mood disturbance, including symptoms of depression, anxiety, and hostility. Although we did not test this directly, we hypothesize that ondansetron's effects may be related to its ability in chronic administration to decrease 5-HT turnover. Nevertheless, further studies comparing comorbid alcohol-dependent individuals with different clusters of syndromic disorders and incorporating biological assessments are needed to more fully elucidate the mechanistic processes that underlie ondansetron's therapeutic effects.

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