Ondansetron for Reduction of Drinking Among Biologically Predisposed Alcoholic Patients

A Randomized Controlled Trial

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Context Early-onset alcoholism differs from late-onset alcoholism by its association with greater serotonergic abnormality and antisocial behaviors. Thus, individuals with early-onset alcoholism may be responsive to treatment with a selective serotonergic agent.

Objective To test the hypothesis that drinking outcomes associated with early vs late-onset alcoholism are differentially improved by the selective 5-HT_3 (serotonin) antagonist ondansetron.

Design Double-blind, randomized, placebo-controlled clinical trial.

Settings University of Texas Health Science Center in Houston (April 1995-June 1998) and University of Texas Health Science Center in San Antonio (July 1998-December 1999).

Participants A total of 321 patients with diagnosed alcoholism (mean age, 40.6 years; 70.5% male; 78.6% white) were enrolled, 271 of whom proceeded to randomization.

Interventions After 1 lead-in week of single-blind placebo, patients were randomly assigned to receive 11 weeks of treatment with ondansetron, 1 µg/kg (n=67), 4 µg/kg (n=77), or 16 µg/kg (n=71) twice per day; or identical placebo (n=56). All patients also participated in weekly standardized group cognitive behavioral therapy.

Main Outcome Measures Self-reported alcohol consumption (drinks per day, drinks per drinking day, percentage of days abstinent, and total days abstinent per study week); and plasma carbohydrate deficient transferrin (CDT) level, an objective and sensitive marker of transient alcohol consumption.

Results Patients with early-onset alcoholism who received ondansetron (1, 4, and 16 µg/kg twice per day) compared with those who were administered placebo, had fewer drinks per day (1.89, 1.56, and 1.87 vs 3.30; $P=.03$, $P=.01$, and $P=.02$, respectively) and drinks per drinking day (4.75, 4.28, and 5.18 vs 6.90; $P=.03$, $P=.004$, and $P=.03$, respectively). Ondansetron, 4 µg/kg twice per day, was superior to placebo in increasing percentage of days abstinent (70.10 vs 50.20; $P=.02$) and total days abstinent per study week (6.74 vs 5.92; $P=.03$). Among patients with early-onset alcoholism, there was a significant difference in the mean log CDT ratio between those who received ondansetron (1 and 4 µg/kg twice per day) compared with those who received the placebo (–0.17 and –0.19 vs 0.12; $P=.03$ and $P=.01$, respectively).

Conclusion Our results suggest that ondansetron (particularly the 4 µg/kg twice per day dosage) is an effective treatment for patients with early-onset alcoholism, presumably by ameliorating an underlying serotonergic abnormality.

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SELECTIVE 5-HT_3 (SEROTONIN) RECEPTORS mediate alcohol's important brain effects.[1] Molecular studies show that alcohol potentiates selective 5-HT_3 receptor-mediated ion currents, an effect blocked by selective 5-HT_3 receptor antagonists.[2,3] Mesocorticolimbic dopamine pathways mediate alcohol's rewarding effects and that of other abused substances.[4-8] Densely distributed 5-HT_3 receptors in mesocorticolimbic neuronal terminals regulate dopamine release.[9,10] Selective 5-HT_3 receptor blockade, by attenuating dopamine release, reduces alcohol consumption in several animal models and across species.[11-19]

We were the first, to our knowledge, to show that pretreatment with the selective 5-HT_3 receptor antagonist ondansetron attenuates low-dose alcohol–induced positive, subjective effects and the "urge to drink" in hu-

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mans.[20,21] Swift et al,[22] using higher alcohol and ondansetron dosages, found that ondansetron pretreatment decreased alcohol preference. However, a mixture of stimulant and sedative interactions between ondansetron and alcohol were also reported. In contrast, Doty et al[23] found that ondansetron did not alter alcohol-induced mood, presumably because using intravenous rather than oral ondansetron and a group rather than an individual experimental setting reduced the sensitivity of their mood assessments.

In a preliminary 6-week, double-blind study of 71 patients not severely dependent on alcohol, 0.5 mg/d but not 4 mg/d of ondansetron was almost superior to placebo ($P = .06$) at reducing alcohol consumption.[24] These results strengthened the rationale for testing ondansetron's efficacy in treating alcoholism within a larger-scale trial but raised also the possibility that ondansetron's dose-response curve was an inverted U-shape.

Psychopathological factors distinguish alcoholic subtypes based on course, prognosis,[25-27] and differential treatment response. Alcoholic patients with early onset compared with late onset develop problem drinking earlier, exhibit a broad range of antisocial behaviors, and have a higher predisposition toward alcoholism. High concordance between age of onset and other hypothetically-derived[28,29] and empirically-driven typologies[26,30] validated age of onset for a priori segregation of alcoholic subtypes in a recent trial.[31]

Solid evidence exists that an early compared with late alcoholism onset is associated with serotonergic dysfunction.[32-38] While this 5-HT dysfunction among patients with early-onset alcoholism has been hypothesized to be a deficient state,[39,40] newer evidence implicates the interaction between chronic drinking and mechanistic processes regulating serotonergic function.

Our double-blind, randomized, placebo-controlled clinical trial tested the hypothesis that patients with early-onset alcoholism compared with late-onset alcoholism (classified a priori), would experience better drinking outcomes in response to ondansetron treatment due to the amelioration of serotonergic dysfunction. We examined ondansetron's dose-dependent effects by testing a 16-fold dose range (ie, 1, 4, and 16 µg/kg twice per day) encompassing those used in a previous clinical trial.[24]

METHODS

Subjects

The 321 enrollees (70% male; 78.6% white) were diagnosed as having alcoholism by the *Diagnostic and Statistical Manual of Mental Disorders, Revised Third* Edition.[41] Enrollees were 25 to 65 years old; scored more than 5 on the Michigan Alcoholism Screening Test,[42] which assessed the severity of alcohol-related problems; reported drinking 3 or more standard drinks per day during the telephone screening; and had a negative urine toxicological screen for narcotics, amphetamines, or sedative hypnotics at enrollment. Abstinence was not a study entry criterion; however, participants reported a desire to stop drinking and to participate in psychosocial treatment. Exclusion criteria were a current psychiatric diagnosis other than alcohol or nicotine dependence; alcohol withdrawal symptoms necessitating inpatient detoxification; clinically significant abnormalities (ie, on physical examination, electrocardiographic recording, hematological evaluation, or elevated 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 prior to enrollment. Ethics approval was provided by the Committee for the Protection of Human Subjects, Health Science Center, University of Texas, Houston. Subjects were recruited by newspaper or radio advertisement.

General Procedures

All testing took place at the University of Texas Health Science Center in Houston between April 1995 and June 1998. Data was analyzed at the University of Texas Health Science Center in San Antonio between July 1998 and December 1999. At enrollment (visit 0), after providing written, informed consent, we assessed subjects on (1) physical health, which included a medical history and physical examination, vital signs (ie, blood pressure, pulse, and temperature), 12-lead electrocardiogram, and laboratory studies including a urine pregnancy test; (2) breath alcohol concentration (BAC); (3) urine drug and biochemical screens; (4) psychiatric diagnosis, which included a Structured Clinical Interview for *DSM-III-R*[43,44]; (5) age of onset, which was determined using item B 28 of the Comprehensive Drinking Profile[45]; (6) the Michigan Alcoholism Screening Test[42]; (7) addiction severity, which was assessed using the Addiction Severity Index[46]; (8) self-reported drinking based on a timeline follow-back (TLFB) over the past 90 days[47]; (9) objective quantification of alcohol consumption using the sensitive and specific marker, plasma carbohydrate deficient transferrin (CDT) level[48-51]; and (10) an assessment of alcohol withdrawal symptoms assessed by the revised Clinical Institute Withdrawal Assessment (CIWA-Ar) scale.[52] Eligible subjects were invited back to the clinic at visit 1, following a review of the hematological, biochemical, and urine tests, in which they received the single-blind placebo for 1 week and attended their first cognitive behavioral therapy (CBT) session.

At visit 2 (after 1 week of receiving single-blind placebo), we assessed subjects' vital signs, BAC, TLFB, and CIWA-Ar. Subjects were also assessed for adverse events, concomitant medication use, pill count (amount of study medication prescribed and amount returned), and psycho-social treatment attendance outside the study. Double-blind medication (ie, placebo or ondansetron 1, 4, or 16 µg/kg twice per day) was randomly dispensed across medication dosage and onset groups, and the subjects attended their second CBT session.

From visits 3 through 12, subject assessment included weekly vital signs, BAC, TLFB, CIWA-Ar, an adverse event profile, concomitant medications, pill count, percentage of urine riboflavin (an inert tracer for assessing medication compliance), and psycho-social treatment attendance outside the study. At visits 4, 8, and 12, subjects received a plasma CDT measurement; an electrocardiogram; a urine pregnancy test; hematological, biochemical, and urine drug screens. Subjects were expected to attend weekly CBT sessions throughout the study period. At visit 12 (study end), a physical examination and the hematological and biochemical checks were repeated to establish health status (FIGURE 1). Visits were interspersed by a period of 1 study week, which was a maximum of 11 days (from Monday of the previous week to Friday of the current week).

Supply, Dosages, Blinding, and Compliance for Medication

Ondansetron, obtained from Glaxo-Wellcome Inc as 8-mg tablets ($19.50/tablet), was compounded and dispensed using procedures approved by the Food and Drug Administration under investigational new drug No. 45 228. Crushed ondansetron tablets (1, 4, and 16 µg/kg twice per day) were packed into opaque size 1 gelatin capsules (Shinogi Qualicaps SA, Madrid, Spain) with cornstarch filler. Placebos were opaque gelatin capsules of the same size, shape, and color containing cornstarch. Body weight categories were used for the microgram per kilogram dosing procedure (mean [SD] ondansetron dosages taken vs those assigned were 0.99 [0.02] vs 1.00, 4.00 [0.05] vs 4.00, and 16.18 [0.38] vs 16.00 µg/kg twice per day, which is equivalent to 0.15, 0.63, and 2.56 mg/d, respectively based on mean body weight). Medication was packaged with the inert tracer (a 50-mg crushed riboflavin tablet),[53,54] and dispensed in bottles labeled with identification, study and visit numbers, and the date. The returned medication bottle at each weekly visit was used to calculate the pill count.

Ultraviolet fluorescence of the subjects' urine samples were compared against a background control sample that contained 7 µmol of riboflavin per milliliter using an AMINCO-Bowman spectrofluorimeter (Spectronic Unicam, Rochester, NY) with an excitation wavelength of 464 nm and an emission wavelength of 530 nm. The relative optical density of the riboflavin control sample was set at a high cut-off point (70%) and the samples were read as a percentage of optical density (a percentage of urine riboflavin).

Cognitive Behavioral Therapy

Cognitive behavioral therapy, an integration of cognitive behavioral and social learning theory, enables alcoholic patients to achieve and maintain abstinence by enhancing their ability to manage high-risk situations, which can trigger alcohol-seeking behavior.[55,56] All study patients received standardized CBT in groups of up to 8 individuals using the *Cognitive Behavioral Coping Skills Therapy*[57] manual, and selected exercises from *Treating Alcohol Dependence: A Coping Skills Therapy Guide*.[58]

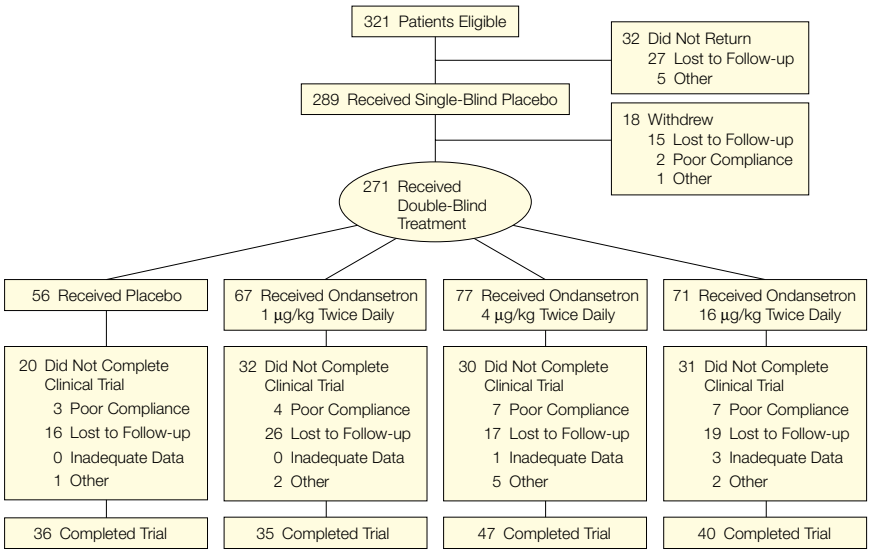
Statistical Analysis

Data quality was supervised by a 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 using SAS statistical software.[59]

Efficacy variables were self-reported alcohol consumption from visit 3 through 12 using the TLFB (drinks per day, drinks per drinking day, percentage of days abstinent, and total days abstinent), and plasma CDT level, which is an objective measure of drinking, at visits 4, 8, and 12. Treatment compliance measures were study attendance rate and medication compliance (both pill count and percentage of urine riboflavin). Physical health and safety measures were BAC at clinic attendance; CIWA-Ar; vital signs; hematological, biochemical, and urine drug screens; use of concomitant medications; attendance at psycho-social treatments outside the study; and adverse events profile.

Subjects' data were analyzed as randomized using an urn[60] procedure after the screening visit. Subjects did not

Figure 1. Trial Flow Diagram of Early-Onset and Late-Onset Alcoholic Patients



Patients diagnosed as having early-onset and late-onset alcoholism were similar in number, age, sex, and drinking level at enrollment. Trial completers were those patients who completed all 11 double-blind visits or 10 double-blind visits plus the final physical health evaluation.

receive their randomized, double-blind study medication (ie, ondansetron or placebo) until the end of the 1-week single-blind placebo period (at visit 2). The first recorded response to medication was, therefore, not measured until the end of the first week of double-blind treatment (visit 3). Response to the double-blind study medication treatment was, therefore, measured from visits 3 to 12 and all subjects randomized were included in the efficacy analyses,[61] irrespective of whether they completed the study. Previous visit values of outcome measures (before visit 3) were used as covariates to control for study entrance and placebo pill taking effects.[62]

Alcoholic patients with early vs late onset developed alcoholism at 25 years or younger and older than 25 years, respectively. Subjects were randomly assigned to 1 of the 4 dosage groups (placebo, or ondansetron 1, 4, or 16 µg/kg twice per day) after balancing based on age of onset, sex, and the average intake drinking level (drinks per day). The 2 × 4 factorial study design examined age of onset (patients with early-onset vs late-onset alcoholism) and medication dosage (placebo, or ondansetron 1, 4, and 16 µg/kg twice per day), and their interaction. Treatment response was measured over visits 3 to 12 (10 double-blind visits using the TLFB technique) after adjusting for differences in study entrance, study enrollment effect (visit 1), and placebo pill taking effect (visit 2).

Counts and/or percentages for categorical items were compared among groups with the χ^2 test for independence when measured at either 1 time or accumulated over multiple time points. Continuously distributed data were reported as mean (SE) for raw measures or as mean change (SE) from baseline (visit 2) for calculated outcome measures, and as 95% confidence intervals (CIs) for mean response from the primary efficacy analyses.

If a 2-way analysis of variance at visits 0, 1, or 2 was significant either for the age of onset or dosage main effects or their interaction, then the groups were unequal on that measure and the baseline values (study entry, visits 1 or 2) were included as a covariate in the efficacy analysis to adjust for these differences. Covariate values from other visits were excluded if they were not significantly related to outcome and did not reduce variability by controlling for individual study entrance and placebo pill taking effects. These covariates removed the study entrance and placebo pill taking effects from the double-blind efficacy response. Any covariate for inclusion in the final model was tested for its interaction with the age of onset, dosage groups, and their interaction. Additionally, covariates were plotted against the residuals to determine their random normal distribution. In all cases, these plots showed significant covariates to be linear and resulted in valid analyses.

As a data reduction technique, self-reported drinking response was calculated as the mean of visits 3 through 12. This average response analysis preserved sample size since all subjects with at least one outcome measure (ie, any of visits 3-12) were included in the efficacy analysis. Since these means have a variance inversely proportional to the number of visits attended,[63] the outcome analysis was weighted by the number of visits. The residuals of this 2-way analysis of covariance, weighted for missing data effects, were checked for normality by computing their skewness, kurtosis, and homogeneity of variance by histogram plots and against the predicted outcome. When needed, standard transformations (eg, square root for percentages or the log when residual variability increased with response) were used to satisfy the assumptions of the analytic procedure. The objective drinking marker, plasma CDT, was analyzed using a similar statistical strategy to the self-reported measures except that enrollment was used as the baseline (CDT was only obtained monthly) and response was calculated over the monthly visits (ie, 4, 8, and 12) as an average log ratio with enrollment values. Type I errors were minimized by conducting only a priori pairwise dosage comparisons within the patient groups with early-onset or late-onset alcoholism when there was a main effect of ondansetron or an interaction between age of onset and treatment dosage.

RESULTS

Study Sample

Patients with early-onset and late-onset alcoholism were equally represented, and had similar levels of self-reported and objective drinking within the cohort. Alcoholic patients with early compared with late onset were younger, of lower social class, more severely addicted with a longer history of alcoholism, and had higher rates of antisocial personality disorder (TABLE). There was no significant interaction between age of onset and treatment dosage for any of the intake variables except for drinks per day, which was addressed by the analysis of covariance. By visit 2 (start of the double-blind period), all 8 groups had similar drinking levels.

Efficacy Measures

Among patients with early-onset alcoholism, ondansetron (1, 4, and 16 µg/kg twice per day) compared with placebo, significantly reduced self-reported drinking. For patients with early-onset alcoholism, significant improvements between the start of the double-blind response period (visit 3) and study end were seen on (1) all drinking measures for those who received 4 µg/kg of ondansetron twice per day and (2) percentage of days abstinent and total days abstinent for those who received 16 µg/kg of ondansetron twice per day. In contrast, only the placebo and 16 µg/kg ondansetron group patients with late-onset alcoholism had significantly improved drinking outcomes during double-blind treatment (FIGURE 2).

There was a significant interaction between age of onset and treatment dosage on the self-reported drinking variables of drinks per day ($F_{3,245}=3.65$; $P=.01$); drinks per drinking day ($F_{3,174}=3.17$; $P=.03$); percentage of days abstinent ($F_{3,237}=2.9$; $P=.04$), and total days abstinent ($F_{3,237}=2.9$; $P=.04$). Patients with early-onset alcoholism who

received dosages of ondansetron of 1, 4, or 16 µg/kg twice per day reported significantly lower numbers of drinks per day or drinks per drinking day compared with those who received placebo. Also, patients with early-onset alcoholism who received ondansetron 4 µg/kg twice per day, compared with placebo, had more percentage of days abstinent and total days abstinent. Effect sizes were as follows for drinks per day, drinks per drinking day, percentage of days abstinent, and total days abstinent for (1) 1 µg/kg of ondansetron twice per day: 0.26, 0.25, 0.13, and 0.06; (2) 4 µg/kg of ondansetron twice per day: 0.37, 0.41, 0.26, and 0.24; and (3) 16 µg/kg of ondansetron twice per day: 0.22, 0.23, 0.17, and 0.18. Effect sizes of 0.2, 0.5, and 0.8 are small, medium, and large, respectively.[64]

On the objective drinking measure (plasma CDT), there was a main effect during the study on the mean log CDT ratio ($F_{3,177}$=3.15; P=.03). Among patients with early-onset alcoholism, the mean log CDT ratio was significantly reduced when ondansetron dosages 1 and 4 µg/kg twice per day were compared with placebo (FIGURE 3). For patients with early-onset alcoholism, effect size on mean log CDT ratio for the ondansetron 1, 4, and 16 µg/kg twice per day dosages were 0.55, 0.58, and 0.21, respectively. While there was a decrease in mean log CDT ratio for groups of patients with late-onset alcoholism, none of the ondansetron dosage groups were superior to placebo.

Our results yielded a significant effect on 5 response variables related to actual drinking measures. The probability of making a type I error on any 1 to all 5 ranges from .05 to less than .001. A factor analysis of cases for all 5 ranges indicates 2 dimensions; so for any 2 independent comparisons, the type I error rate is less than .0025. Even when all baseline measures related to outcome were used in the model,[62] rather than just the confounding[61] baseline measures, the results were similar. For example, the interaction between patients with early-onset and late-onset alcoholism receiving ondansetron was significant for drinks per day (P=.006) with the patients with early-onset alcoholism in the ondansetron 4 µg/kg twice per day dosage group being superior to placebo (P<.001).

Compliance Measures

Patients with early-onset and late-onset alcoholism did not differ significantly in mean (SE) percentage of pills taken of 92.43 (3.29) vs 92.39 (2.98) and urine

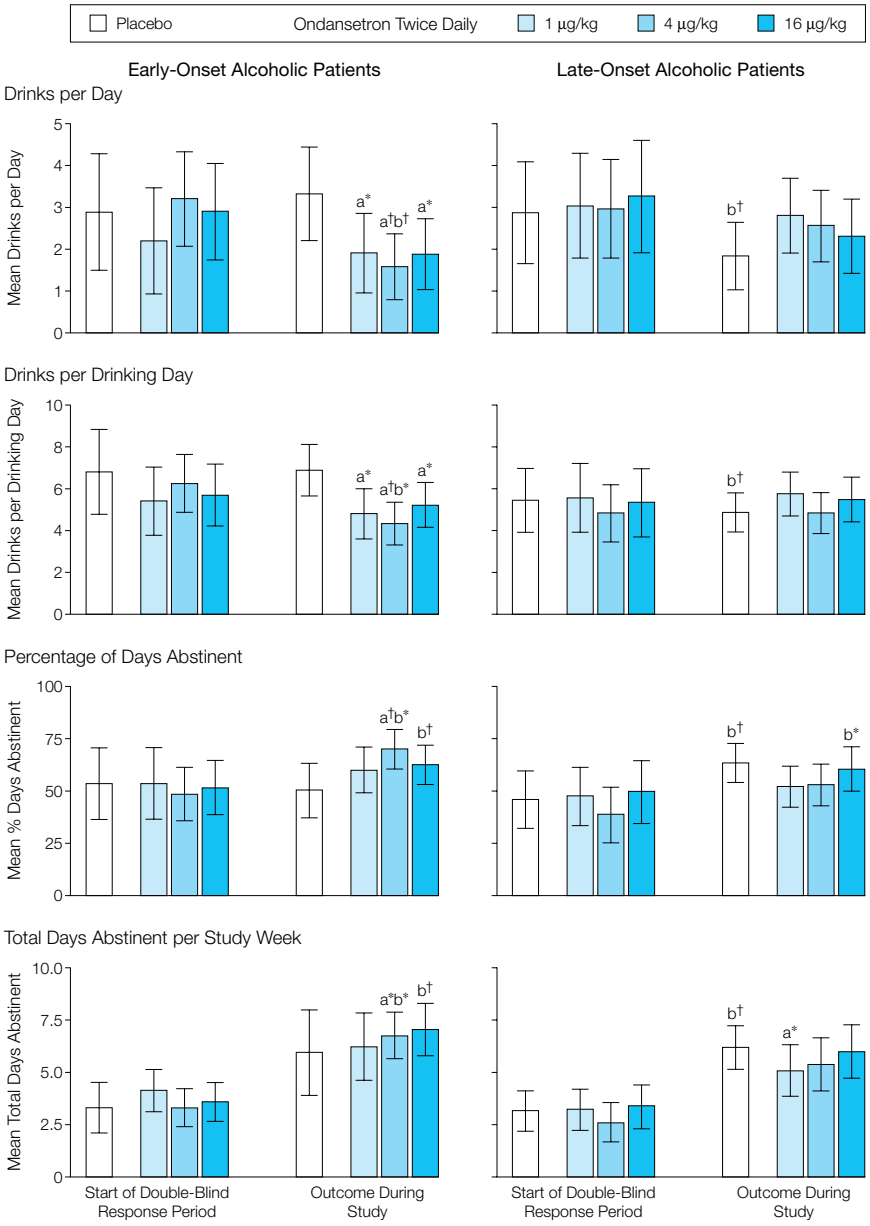
Table. Demographic and Psychopathological Characteristics of Early-Onset and Late-Onset Alcoholic Patients at Intake*

	Early Onset (n = 161)	Late Onset (n = 160)	*P* Value
Group Assignments			
Placebo	30	42	.29
Ondansetron twice dailly			
1 µg/kg	38	39	
4 µg/kg	45	43	
16 µg/kg	48	36	
Demographic Variables			
Age, y	37.16 (0.64)	44.03 (0.61)	<.001
Sex, No. (%)			
Men	124 (77.1)	102 (63.7)	.01
Women	37 (22.9)	58 (36.3)	
Ethnicity, No. (%)			
White	108 (67.1)	119 (74.3)	.44
Black	29 (18.1)	27 (16.9)	
Hispanic	22 (13.7)	14 (8.8)	
Other	2 (1.0)	1 (0)	
Social class, No. (%)†			
1-3	61 (38.2)	89 (55.6)	.007
4-6	82 (51.2)	58 (36.3)	
7-9	17 (10.6)	13 (8.1)	
Weight, kg	79.21 (1.41)	79.08 (1.53)	.93
Measures of Alcohol Drinking			
Years since first report of problems with alcohol use	17.12 (0.66)	9.76 (0.53)	≤.001
Mean drinks per day at intake (past 90 days)	8.48 (0.49)	7.60 (0.43)	.39
Mean drinks per day at single blind	4.67 (0.87)	4.65 (0.85)	.64
Breath alcohol level	0.00 (0.00)	0.01 (0.00)	.18
Carbohydrate deficient transferrin level, U/L	20.31 (1.45)	21.61 (1.15)	.05
Michigan Alcoholism Screening Test	30.91 (0.93)	24.92 (0.86)	<.001
Addiction Severity Index composite scores			
Medical	0.11 (0.02)	0.12 (0.02)	.77
Employment	0.22 (0.02)	0.11 (0.02)	<.001
Alcohol	0.57 (0.01)	0.51 (0.02)	.02
Drug	0.03 (0.00)	0.01 (0.00)	.001
Legal	0.06 (0.01)	0.02 (0.01)	.005
Family/social	0.33 (0.01)	0.29 (0.01)	.02
Psychiatric	0.22 (0.02)	0.14 (0.01)	<.001
Clinical Institute Withdrawal Assessment (revised)	5.20 (0.44)	4.57 (0.39)	.30
Antisocial Personality Disorder, No. (%)			
Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition diagnosis of antisocial personality disorder	28 (17.4)	14 (8.75)	.03
Safety Measures			
Liver function tests, U/L			
γ-Glutamyl transferase	101.16 (14.78)	123.78 (17.74)	.28
Glutamate oxalate transaminase	43.84 (4.45)	50.51 (4.78)	.28
Glutamate pyruvate transaminase	49.60 (5.09)	45.94 (3.87)	.62

*Values are expressed as mean (SE) unless otherwise indicated.
†Defined by Hollingshead and Redlich.[74]

riboflavin of 93.68 (0.01) vs 94.73 (0.01), respectively. Generally, patients with early-onset alcoholism attended fewer study sessions than patients with late-onset alcoholism (mean [SE], 7.30 [0.36] vs 8.24 [0.37], respectively; $F_{1,313}=4.10$; $P=.04$); however, differences between dosage groups were insignificant. Only 34% of alcoholic patients failed to attend the eighth or a later double-blind visit.

Figure 2. Mean (95% Confidence Interval) Drinking Outcomes During the Double-Blind Response Period of Early-Onset and Late-Onset Alcoholic Patients



Data are responses observed at the start of double-blind (visit 2) and the mean outcome observed during study (mean of visits 3-12). Analyses refer to pairwise comparisons between the ondansetron treatment groups and placebo. The a* and a† represent significant differences between an ondansetron dosage and placebo groups at the 5% and 1% levels, respectively. The b* and b† denote significant differences within a given treatment group from the start of the double-blind response period to the outcome during study at the 5% and 1% levels, respectively.

Physical Health and Safety Measures

No serious adverse events occurred. Adverse event rates were similar for the ondansetron and placebo groups, and required no supervised medical intervention. The most common adverse events by organ system for the ondansetron vs placebo dosages were central nervous system (headache), 3.4% vs 4.2%; gastrointestinal tract (constipation), 5.0% vs 1.4%; cardiovascular (tachycardia), 0.3% vs 0.0%; skin (rash/pruritis), 2.2% vs 2.8%; and others, 1.8% vs 1.0%. One fatality unrelated to the study medication occurred due to the subject falling down a flight of stairs at home.

Positive BACs were rare (mean, .01%) with no difference between patients with early-onset and late-onset alcoholism. Alcohol withdrawal symptoms were infrequent (mean [SE] for CIWA-Ar, 2.8 [0.25] and 2.5 [0.23]; patients with early-onset and late-onset alcoholism, respectively). Testing positive for 1 or more of 9 agents in the urine drug screen was similar for patients with early-onset (15.5%) and late-onset alcoholism (15.6%). Drug use frequencies for patients with early-onset vs late-onset alcoholism were 44% vs 29% for marijuana; 24% vs 19% for cocaine; 16% vs 26% for opiates; and 16% vs 26% for benzodiazepines. Rates of concomitant medication use and of psychosocial attendance outside the study were similar for patients with early-onset (13.6% and 4.9%) and late-onset alcoholism (14.4% and 4.3%).

COMMENT

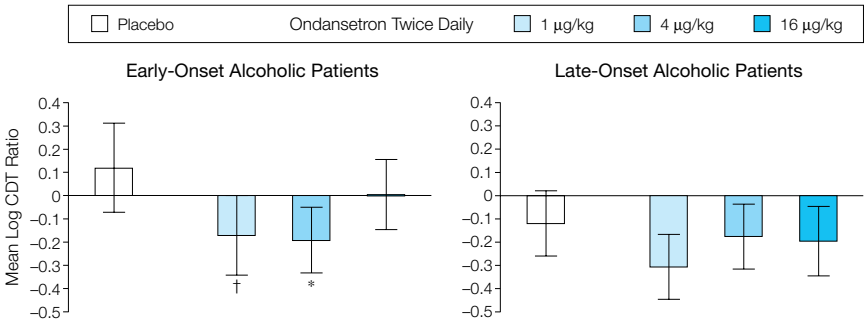
Ondansetron significantly reduced alcohol consumption and increased abstinence among patients with early-onset but not late-onset alcoholism. A dosage of ondansetron of 4 µg/kg twice per day was most efficacious; however, its superiority over the other ondansetron dosages was statistically insignificant. We did not detect an inverted U-shaped dose-response curve for ondansetron among patients with early-onset alcoholism; however,

increased efficacy at higher dosages appears unlikely. Limitations of a short treatment period and the inclusion of only white males in the Sellers et al[24] study precluded direct comparison with this study. Nevertheless, finding ondansetron efficacious among patients with early-onset alcoholism is not inconsistent with their observation[24] that excluding heavy drinkers (ie, >10 drinks per day) rendered ondansetron-related drinking reductions compared with placebo statistically significant as this procedure simply decreased variance in their smaller sample size study.

Abstinence at enrollment was not a study entry requirement but the treatment goal. Enrolling actively drinking alcoholic patients represented a more naturalistic point related to when help was sought. By not requiring an abstinence period at enrollment, the potential for postcessation rebound into drinking was reduced. Yet, abstinence rate for the 4 µg/kg of ondansetron twice per day group among patients with early-onset alcoholism was relatively high (about 70%). Exploratory analyses indicated that ondansetron's antidrinking effects did not differ between abstainers and active drinkers at the start of double-blind analysis (data not shown). Consistently, the visit 2 baseline covariate was not needed in our full analyses; thus, drinking status was not a determinant of ondansetron response. Ondansetron does not alter alcohol pharmacokinetics[65]; hence, its utility in actively drinking alcoholic patients was an additional therapeutic benefit.

Participants nearly halved their drinking between enrollment and the end of the lead-in, single-blind placebo period. Emphasis on drinking quantification probably evoked self-regulatory measures. The single-blind placebo, lead-in period enabled measurement of how the psychological effect of pill taking contributed to the overall treatment response. Promise or delivery of psychosocial treatment might also have improved drinking outcomes. Since all subjects received CBT, it was impossible to discern if, and by how much, psychotherapy type or intensity would interact with ondansetron treatment response, or whether psychotherapy alone is sufficient in treating patients with late-onset alcoholism due to their limited disease predisposition.

Figure 3. Mean (95% Confidence Interval) Log Plasma Carbohydrate Deficient Transferrin (CDT) Ratio for Early-Onset and Late-Onset Alcoholic Patients



Mean log CDT ratio was the mean log CDT at a given visit (ie, 4, 8, or 12) divided by the mean log CDT at enrollment. The dagger indicates $P<.01$ and the asterisk indicates $P<.05$.

We discounted the remote possibility that ondansetron's effectiveness among ondansetron-receiving patients with early-onset alcoholism was due to a less pronounced placebo effect in those who received placebo. The placebo lead-in period should have controlled for any differential placebo effects. Extensive exploratory analyses of all data collected in this trial revealed no significant baseline outcome predictor that would selectively impair drinking behavior among patients with early-onset alcoholism who received placebo compared with the ondansetron recipients. Patients with early-onset alcoholism in treatment groups were similar on baseline drinking measures and psychosocial characteristics. Hence, among patients with early-onset alcoholism, the significant drinking reduction and cessation in ondansetron compared with placebo recipients was due to the efficacy of the pharmacological treatment.

Another study strength was the use of a dose-ranging paradigm, still a rarity in medications in development for alcoholism.[66] Future studies can now focus on testing different treatment options using ondansetron's most efficacious dosage. Ondansetron was well tolerated and its adverse event profile was similar to that of placebo.

Pill-taking rates were high (>92%). Although the analyses of percentage urine riboflavin could have been confounded by dietary changes, including the intake of multivitamin supplements, its close agreement with the pill count data would argue that each measure provided validation of the other. Additionally, use of riboflavin dosages greater than 50 mg/d increases this measure's reliability since the dosage greatly exceeds that commonly found in over-the-counter multivitamin preparations.[54]

Patients with early-onset alcoholism had higher rates of antisocial personality disorder than patients with late-onset alcoholism. Also, baseline data from a cohort of the current sample, which are detailed elsewhere, showed that patients with early-onset compared with late-onset alcoholism have higher rates of childhood risk behaviors, hostility, impaired social functioning, and an increased number of male relatives with alcoholism.[25] Further, age of onset in the current sample was significantly correlated with a family history of alcoholism in a male parent or grandparent; that is, the earlier the subjects' age of onset the greater was the likelihood that they had either a male parent or grandparent who was an al-

coholic (data not shown). Hence, an early age of onset was associated with a range of variables that contribute to biological vulnerability toward alcoholism.

Mechanistically, it is intriguing that a selective 5-HT_3 receptor antagonist was efficacious for treating patients with early-onset alcoholism whereas a selective serotonin reuptake inhibitor had failed[67] because these classes of compounds have opposite effects on serotonergic function. Serotonergic function augmentation by a partial selective serotonin 1_A agonist was also an ineffective treatment for patients with early-onset alcoholism.[32] Patients with early-onset alcoholism do not have a simple selective 5-HT deficiency state. Instead, patients with early-onset alcoholism may be more likely to possess a high-functioning polymorphic variant of the serotonin transporter[68,69] that is more readily damaged by chronic alcohol consumption.[70] As these raphe transporters are somatodendritic rather than axonal, the net result is a reduced 5-HT firing rate due to increased self-inhibition.[71] We hypothesize that reduced 5-HT neurotransmission in patients with early-onset compared with late-onset alcoholism, differentially upregulates postsynaptic 5-HT_3 receptors, a blockade of which may account for ondansetron's differential treatment effectiveness.[66,72]

Efficacy of such small ondansetron dosages in treating patients with early-onset alcoholism is consistent with animal studies of its antirewarding effects on ethanol consumption,[11,13,17] and strengthen the proposal that 5-HT_3 receptors are an important site of alcohol's brain effects[1] and that chronic 5-HT_3 receptor blockade is not associated with neuroadaptation of mesocorticolimbic dopamine or 5-HT neurons.[73]

Scientific frustration had grown because promising animal studies[66] showing that medications which alter serotonergic function could attenuate the urge to drink or drinking per se were not confirmed by clinical trials. Earlier clinical trials with serotonergic agents looked for their effects on drinking among heterogeneous alcoholic groups. We show that alcoholic subtypes varying in selective 5-HT function respond differently to treatment with a specific serotonergic agent. Medication trials specifically targeting treatment of underlying biological abnormalities in particular alcoholic subtypes heralds a new vista in the alcoholism field.

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