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ORIGINAL INVESTIGATION

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Ondansetron reduces the craving of biologically predisposed alcoholics

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Abstract *Rationale:* Early onset alcoholics (EOA) differ from late onset alcoholics (LOA) by having greater serotonergic abnormality, familial history, and a range of antisocial behaviors. Previously, we showed that ondansetron, a selective 5-HT_3 antagonist, effectively treated EOA. Proximate motivational drives such as craving could have determined drinking behavior. We therefore investigated whether ondansetron treatment would reduce alcohol craving significantly among EOA. *Objectives:* We tested the hypothesis that the craving outcomes of EOA, compared with LOA, would be differentially improved by ondansetron. We also tested the prediction that craving would be significantly correlated with drinking behavior. *Methods:* We studied a cohort of 253 out of 321 enrolled alcohol dependent subjects. These 253 subjects were entered into a 1-week lead-in single-blind placebo period followed by 11 weeks of double-blind outpatient treatment. Study design was a 2 (EOA versus LOA)×4 medication dose (placebo, or ondansetron 1, 4, or 16 µg/kg b.i.d)×13 (visits) factorial analysis of variance. Craving was measured at each visit using seven visual analogue scales. Subjects received 12 weekly sessions of standardized group cognitive behavioral therapy. *Results:* Data reduction by factor analysis of the visual analog scale items yielded one dimension, overall craving. Ondansetron 4 µg/kg b.i.d. reduced overall craving significantly among EOA. In contrast, ondansetron (1 µg/kg b.i.d.) increased craving significantly in LOA. Decreased overall craving was positively correlated with reduced drinking and negatively associated with increased abstinence. *Conclusions:* Compared with placebo, ondansetron (4 µg/kg b.i.d.) was associated with significant reductions in overall craving in EOA but not LOA, presumably by ameliorating serotonergic abnormality.

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Introduction

Mesocorticolimbic dopamine (DA) pathways mediate the rewarding effects of alcohol and other abused substances (Wise and Bozarth 1987; Di Chiara and Imperato 1988; Koob 1992; Hemby et al. 1997; Bloom and Morales 1998). Densely distributed 5-HT_3 receptors in mesocorticolimbic DA-containing neuronal terminals regulate DA release (Kilpatrick et al. 1987, 1996). 5-HT_3 receptor blockade, by attenuating DA release, reduces alcohol consumption in several animal models and across species (Costall et al. 1987; Fadda et al. 1991; Hodge et al. 1993; Meert 1993; Tomkins et al. 1995; McBride and Li 1998; Barnes and Sharp 1999; Rodd-Henricks et al. 1999; cf. Beardsley et al. 1994).

Human laboratory studies show that the 5-HT_3 antagonist ondansetron reduces alcohol-induced positive subjective effects (Johnson and Cowen 1993) and alcohol preference (Swift et al. 1996), both characteristics which have been associated with reduced craving. Reduced craving may, therefore, be one mechanism by which ondansetron exerts its anti-rewarding effects.

Clinically, we have shown that ondansetron significantly reduces alcohol consumption and promotes abstinence among early onset alcoholics (EOA) but not late onset alcoholics (LOA) (Johnson et al. 2000b). These EOA, compared with LOA, had an earlier history of problem drinking, a broad range of antisocial behaviors, familial disease history among first degree relatives, and greater serotonergic abnormality (Johnson et al. 2000a). If ondansetron's demonstrated effects in the clinic and human laboratory are, at least partially, mediated through similar mechanisms, it would be reasonable to postulate that ondansetron also would reduce craving among EOA.

The present double-blind placebo controlled clinical trial tested the hypothesis that EOA who received ondan-

setron would experience greater craving reductions than those who had placebo. Additionally, we tested the prediction that these craving reductions would be positively correlated with decreased drinking but negatively associated with increased abstinence.

Materials and methods

Subjects

Materials and methods were identical to those described previously (Johnson et al. 2000b). Here, we describe an analysis of craving in 253 subjects who were part of that larger study of 321 subjects (Johnson et al. 2000b), all of whom had a DSM-III-R (American Psychiatric Association 1994) diagnosis of alcohol dependence.

Briefly, subjects were recruited by radio and newspaper advertisement. Subjects were segregated a priori as being either EOA or LOA (based upon an age of onset of problem drinking <25 years or ≥25 years, respectively) derived from item B 28 of the Comprehensive Drinking Profile (Miller and Marlatt 1984). Of the 253 subjects, 125 were EOA and 128 were LOA. We confirmed that subjects were in good physical health by conducting hematological and biochemical screens, a 12-lead electrocardiogram, and physical examinations. Females were not pregnant or lactating. Abstinence was not a study criterion; however, participants had to report a desire to stop drinking and willingness to participate in psychosocial treatment to qualify for enrollment. Ethics approval was provided by the Committee for the Protection of Human Subjects, University of Texas Houston Health Science Center.

General procedures

Enrolled subjects at baseline (visit 1) attended weekly for a further 12 weeks. The first week was a single blind placebo lead-in period (from visit 2 to visit 3) followed by 11 weeks (visits 4–13) of randomized, double-blind medication assignment to placebo or one of three ondansetron doses (1, 4, or 16 µg/kg b.i.d.). Each visit was interspersed by a period of 1 study week (defined as a maximum of 11 days occurring in successive weeks from Monday of the previous week to Friday of the current week). At each visit from 2 to 13, all subjects received standardized manual-driven cognitive behavioral therapy in groups of up to eight individuals using the eight core sessions of the *Cognitive-Behavioral Coping Skills Therapy* (US Department of Health and Human Services 1992), and selected exercises from the handbook *Treating Alcohol Dependence: A Coping Skills Therapy Guide* (Monti et al. 1989).

Self-reported drinking data for visits 2–13 was collected at each visit using the Time-Line Follow Back (TLFB) method (Sobell and Sobell 1992). Baseline data (visit 1) included assessment of self-reported drinking behavior during the past 90 days and all remaining visits accounted for drinking since the last visit. The three self-report measures of drinking were drinks per day (total standard drinks/total days), drinks per drinking day (total standard drinks/days of drinking), and percent days abstinent (% of total days on which no drinking occurred). Objective assessment of transient alcohol consumption was quantified using the sensitive and specific marker, serum carbohydrate deficient transferrin level (Stibler 1991; Huseby et al. 1997), at visits 1, 5, 9 and 13 using the BioRad kit.

Craving data at each visit was collected using seven target 100 mm visual analogue scales (VAS). Five of these VAS were anchored on the right by “extremely” and on the left with “not at all” with the following adjectival variables: “Right now”: a) I am thinking about how I can get alcohol; b) I am thinking about the next time I will use alcohol; c) I want to buy alcohol; d) I have the urge or desire to use alcohol, and e) if I was offered alcohol I could resist. The other two target VAS were: f) greatest craving over the last 24 h anchored on the left by “none” and on the right by “more than ever”, and g) change in craving from visit 1 anchored on the left by “much less craving” and on the right by “a lot more craving”.

Safety and compliance measures at baseline (visit 1) which included hematological and biochemical tests, urine toxicology, serum pregnancy screen, electrocardiographic examination, and a physical examination were repeated at scheduled intervals and at study end (visit 13). Adverse events, pill count, concomitant medication, breath alcohol concentration, and standardized assessment of alcohol withdrawal were reported at each visit. Procedures for obtaining the medication supply, dosing, packaging, and blinding have been detailed previously (Johnson et al. 2000b).

Statistical analysis

Data quality was supervised by a database coordinator and statistician. Individual subject plots were checked for unusual values and completeness. Statistical summaries also were used to identify missing and outlying values. Values were validated as correct against the case records. Although the larger study included 321 subjects (Johnson et al. 2000b), complete craving data using the currently-described craving scales were validated only for 253 subjects who completed at least 1 week of randomized double-blind medication (i.e. up to visit 4). Analyses were conducted using the Statistical Package for the Social Sciences (SPSS) version 10.0 (SPSS 1999). Missing data occurring between two bordering visits with collected values were estimated using the Expectation-Maximization (EM) method in SPSS-Missing Value Analysis (Version 7.5) (SPSS 1997). The E step of this procedure found the conditional expectation of the missing data, given the observed values. These expected values were then substituted for the missing data. Estimated data rates for EOA and LOA were only 3.9% and 4.1%, respectively. No extrapolation for missing observations was conducted after a subject had dropped out. The M step of SPSS-EM program used the available data to compute maximum likelihood estimates of the parameters as though the missing data had been filled in. This permitted a full-factorial analysis of visit effects with appropriate adjustment for the degrees of freedom due to the loss of subject observations.

Eligible subjects after the screening visit (visit 1) were randomized to a treatment condition using an URN procedure (Stout et al. 1994). The URN procedure balanced groups through stratification on age of onset, gender, and drinking level. Subjects did not receive their randomized double-blind study medication (i.e. one of three ondansetron doses or the placebo condition) until the end of the 1-week single-blind placebo period (i.e. visit 3). The first recorded response to medication was therefore not measured until the end of the first week of double-blind treatment (i.e. visit 4). Thus, response to the double-blind study medication treatment was measured from visits 4 to 13. All randomized subjects were included in the efficacy analyses (Meinert 1986), irrespective of whether or not they completed the study.

Data from the seven VAS craving items were described by their means±SE. As a data reduction technique, these seven VAS craving items were subjected to factor analysis. The derived craving factor(s) were treated as dependent variables in a factorial repeated measures analysis of covariance (ANCOVA) examining the main effects of visit (13 levels), dose (four levels), and age of onset (two levels), and their two and three-factor interactions. Due to the putative relationship between craving and drinking, the self-reported drinking assessments (drinks/day, drinks/drinking day, and percent days abstinent) were considered as candidate covariates. Any covariate for inclusion in the final model was tested for its interaction with treatment condition. The significant three-way interaction of age of onset×dose×visit was further examined by post-hoc *t*-test contrasts between onset and dose groups. These tests employed the data reduction technique of examining the mean post-treatment effect (mean of all visits 4–13) as a difference from the mean pre-treatment effect (mean of visits 1–3). Pearson’s correlation coefficients were used to describe the relationship between self-reported drinking and the derived craving factor(s). Counts and/or percentages for categorical items were compared among groups with the Chi-square test for independence when measured at either one time or accumulated over multiple time points. All statistical tests of significance were two-tailed.

Results

EOA compared with LOA had similar levels of drinking in the 90 days prior to enrollment (8.54±0.59 drinks/day versus 7.60±0.48 drinks/day; t=1.24, P>0.05). EOA compared with LOA were significantly younger (38.38+0.71 years versus 44.52+0.69 years; t=6.21, P<0.0001) and had longer histories of problem drinking (18.37±0.73 versus 9.95±0.57years; t=9.11, P<0.0001). They also had higher Michigan Alcoholism Screening Test scores (30.96±1.07 versus 24.35±1.01; t=4.51, P<0.0001), and a trend towards greater rates of antisocial personality disorder (19 or 15.2% versus 11 or 8.6%; P=0.08).

Factor analysis of the seven VAS craving items yielded one dimension (Eigenvalue <1). Due to the high intercorrelation between individual craving items, a single craving score (i.e. overall craving) was calculated as the mean score of the seven individual items to prevent type I errors associated with multiple univariate analyses. This overall craving score was used in all subsequent analyses. An analysis of variance (ANOVA) conducted on the baseline (visit 1) overall craving scores for the eight treatment groups (EOA versus LOA at each of the four dose levels) revealed only a main effect difference for age of onset where the EOA had greater overall craving than the LOA [33.4±1.5 mm versus 28.4±1.4 mm; F(1,241)=5.85, P=0.02, respectively]. Consequently, all craving analyses adjusted other visit observations for this baseline difference by calculating difference scores for each subject as the "post" score minus baseline (i.e. "pre") score.

In the ANCOVA analyses of the full design model (visit×dose×age of onset), all three self-report measures of pre-treatment alcohol drinking were significant when tested individually as covariate predictors of post-treatment effects. They also were highly inter-correlated with one another precluding their concurrent use. The percent days abstinent measure was selected as the covariate in the final analysis because it showed the strongest effect [F(1,139)=14.83, P<0.0001]. Also, percent days abstinent showed an interaction with visit [F(12,128)=2.42, P=0.04]. Thus, both of these effects were retained in the final ANCOVA model to control for baseline variance.

There was a significant main effect of visit [F(12,128)=14.4, P<0.0001] as observed by a general trend towards decreased overall craving across study visits. There were no significant dose [F(3,139)=1.05, P<0.05] or dose×visit [F(36,390)=1.34, P>0.05] effects. Although there was no main effect of age of onset [F(1,139)<1.0, P>0.05], the visit effects varied by age of onset [F(12,128)=2.32, P=0.006] and as a three-way interaction of visit×dose×age of onset [F(36,390)=1.41, P=0.05].

Figure 1 (below) shows the within group dose comparisons in overall craving for EOA and LOA. It can be seen that for the LOA, the placebo group had the greatest

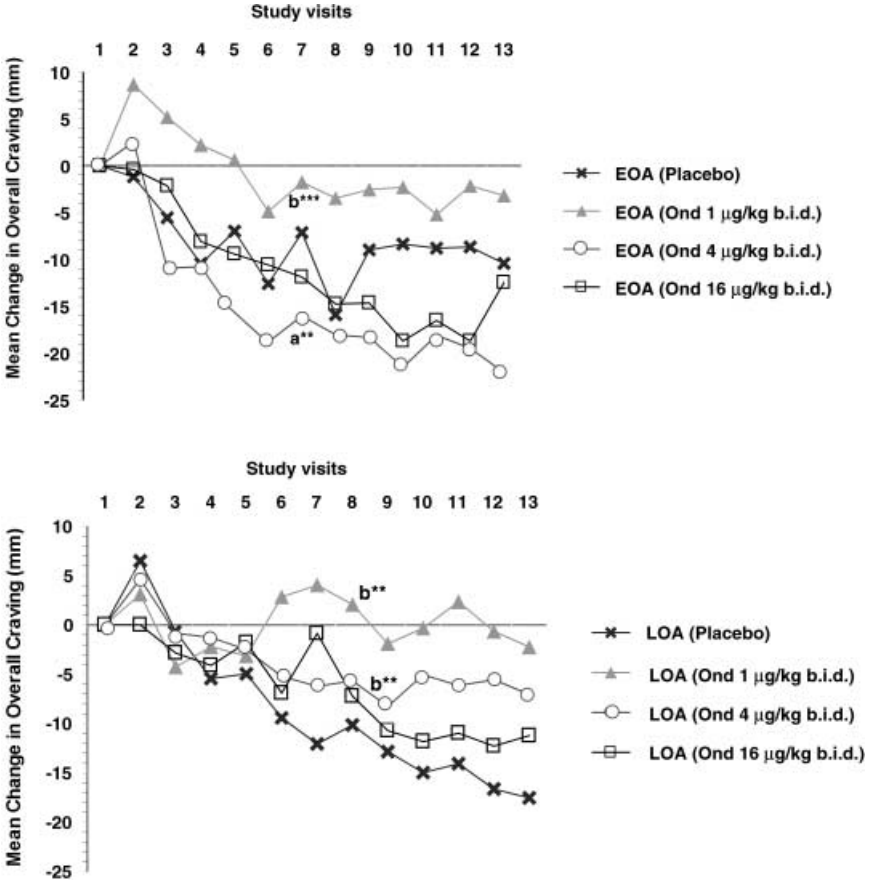

Fig. 1 Mean change in overall craving across study visits among early onset alcoholics (*EOA*) and late onset alcoholics (*LOA*) who received ondansetron (1, 4, or 16 µg/kg b.i.d.) or placebo. The symbol *a* denotes that the ondansetron dose significantly lowers overall craving relative to placebo. Symbol *b* indicates that the ondansetron dose significantly raises overall craving relative to placebo. *P≤0.05; **P<0.01; ***P<0.001; P>0.05 NS. *Ond* ondansetron

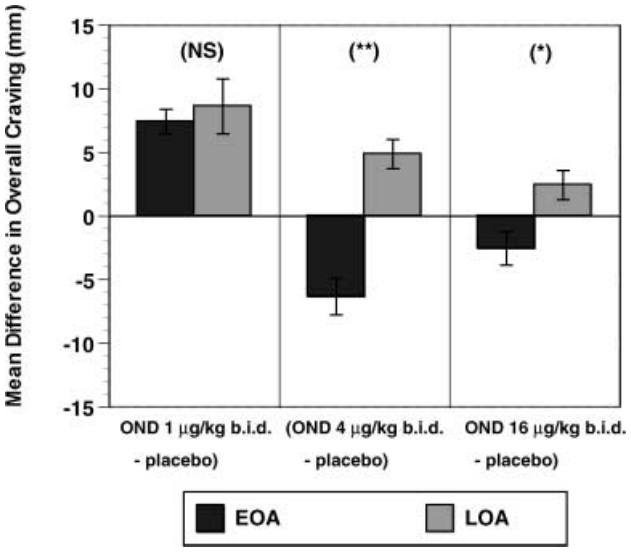

Fig. 2 Mean±SE difference on overall craving in ondansetron–placebo responses between early and late onset alcoholics. **P*≤0.05; ***P*<0.01; *P*>0.05 NS. *Ond* ondansetron

decreases in overall craving relative to the ondansetron 1 and 4 µg/kg b.i.d groups [mean=–8.61±2.15 mm, *t*(12)=–3.99, *P*=0.002; mean=–4.86±1.15 mm, *t*(12)= –4.21, *P*=0.001, respectively], and a trend towards significance for the ondansetron 16 µg/kg b.i.d group [mean=–2.42±1.14 mm, *t*(12)=–2.11, *P*=0.06]. Notably, for EOA, ondansetron 4 µg/kg b.i.d. decreased overall craving significantly relative to placebo [mean=6.33 ±1.43 mm, *t*(12)=4.40, *P*=0.001]. Also among EOA, while the reduction in overall craving between ondansetron 16 µg/kg b.i.d and placebo approached statistical significance [mean=2.55±1.31 mm, *t*(12)=1.94, *P*=0.08]; in contrast, ondansetron 1 µg/kg b.i.d increased overall craving relative to placebo [mean=–7.40±0.97 mm, *t*(12) =7.62, *P*<0.0001].

Figure 2 shows the net difference between the ondansetron and placebo (i.e. ondansetron–placebo) dose group comparisons in overall craving for EOA and LOA. Importantly, it can be seen that the overall craving decreases for the ondansetron 4 µg/kg b.i.d.–placebo (*P*<0.001), and the ondansetron 16 µg/kg b.i.d. (*P*<0.04)–placebo groups, were significantly lower for EOA than its corresponding LOA group. Indeed, the trends were orthogonal: towards reduced and increased overall craving among EOA and LOA, respectively. Contrasts across age of onset were not significant for the ondansetron 1 µg/kg b.i.d.–placebo groups indicating that this medication dose produced a similar effect in both age of onset groups.

For EOA and LOA, craving was positively correlated with: a) Drinks/Day (*r*=0.46 and *rp*=0.36 versus *r*=0.41 and *rp*=0.37, respectively; for both *P*<0.05), and b) Drinks/Drinking day (*r*=0.40 and *rp*=0.31 versus *r*=0.33 and *rp*=0.35, respectively; for both *P*<0.05) but negatively associated with c) Percent days abstinent (*r*=–0.48 and *rp*=–0.37 versus *r*=–0.46 and *rp*=–0.37, respectively; for both *P*<0.05) regardless of whether or not treatment condition was accounted for in the regression model.

Discussion

Ondansetron 4 µg/kg b.i.d. was effective at reducing overall craving among EOA. These results were consistent and consolidated our previous finding that ondansetron 4 µg/kg b.i.d. treatment decreased drinking and increased abstinence among EOA but not LOA (Johnson et al. 2000b).

Interestingly, there was a biphasic dose response curve with respect to ondansetron's treatment effectiveness among EOA. While the lower ondansetron dose (1 µg/kg b.i.d.) increased overall craving; in contrast, the middle ondansetron dose (4 µg/kg b.i.d.) resulted in significant overall craving reductions. Even the highest ondansetron dose (16 µg/kg b.i.d.) was associated with a marked but less pronounced directional trend towards decreased overall craving. Although this falls short of the inverted U-shaped dose-response curve reported in some animal studies (Goudie and Leathley 1990), and not seen in the previous drinking analysis study (Johnson et al. 2000b), it would be reasonable to predict that ondansetron doses higher than those used in the present study would be ineffective at decreasing overall craving among EOA.

For both EOA and LOA, decreased overall craving was positively correlated with reduced drinking and negatively associated with increased abstinence. Also, overall craving accounted for no more than 25% of the variance (i.e. R^2) in self-reported drinking. Thus, beyond the relationship between craving and ondansetron dose effects, other biological or psychosocial factors could be important determinants of the differential treatment response among alcoholic subtypes. One putative pharmacogenetic determinant could be the variation in serotonin transporter polymorphism frequency between EOA and LOA (Johnson 2000). Preliminary data from our laboratory showed that EOA compared with LOA had higher rates of serotonin uptake (Javors et al. 2000). If substantiated by our further studies, this would suggest that EOA have greater propensity to possess the long form of the serotonin transporter polymorphism, and that ondansetron treatment response in this subgroup may be associated with the blockade of upregulated post-synaptic 5-HT_3 receptors (Johnson 2000). Psychologically, while affective state, which appears greater for EOA than LOA may have increased craving response, these effects are complex and non-linear; however, formal investigation of this relationship is beyond the focus of this manuscript.

No universal agreement exists as to what constitutes craving (Rohsenow and Monti 1999). One proposed concept has been that craving either resulted from a psychological or physiological response to certain environmental triggers or cues with which substance use had become associated or was a direct consequence of substance-

taking. Such craving responses were capable of provoking or maintaining substance taking (Johnson et al. 1998; Westerberg 2000). Craving also could be conceptualized as a multi-dimensional representation of cognitive and emotional stimuli which reflected some aspect of a proximate motivational drive to consume abused substances (Tiffany 1999). While we attempted to capture some multi-dimensional aspects of craving using our construct-driven VAS, one limitation of the present study was that factor analysis accounted for all the scales as a single dimension. Post-dating initiation of the present study, we have shown the utility of a newer multi-dimensional alcohol craving assessment (Ait-Daoud et al. 2001), the Obsessive Compulsive Drinking Scale (Anton et al. 1996), which afforded greater exploration of the various craving components (see also Drobes and Thomas 1999 for further discussion of multi-dimensional rating scales). Likert scales or questionnaires, compared with VAS, also could be less subject to large inter-individual variability in clinical trials where extensive pre-study reliability training on the assessment is not practical. Nevertheless, central to the use of all craving scales has been their ability to ascertain proximate motivational drives that could explain variation in drinking behavior. Consequently, our finding of a predictable relationship between overall craving and drinking supported the construct of a direct or indirect association between these variables and provided validation for the use of our VAS items.

Coupled with the previous report (Johnson et al. 2000b), we concluded that for EOA, ondansetron (4 µg/kg b.i.d.) produced therapeutically beneficial effects on subjective (i.e. craving), behavioral (i.e. self-reported drinking), and objective laboratory measurements (i.e. serum carbohydrate deficient transferrin) of alcohol consumption.

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