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ORIGINAL INVESTIGATION

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Combining ondansetron and naltrexone reduces craving among biologically predisposed alcoholics: preliminary clinical evidence

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Abstract *Rationale:* Previously, we have reported that the combination of ondansetron (a 5-HT_3 antagonist) and naltrexone (a mu opioid antagonist) appears to act synergistically at improving the drinking outcomes of early onset alcoholics (EOA), a subtype of alcoholic characterized by developing problem-drinking earlier, antisocial behaviors, high familial loading, and biological disease predisposition. Presumably, this medication combination counteracts the interaction between activated central 5-HT_3 receptors and the endogenous opioid system during the mediation of alcohol-induced reward. We now hypothesize further that an important mechanism by which the combination diminishes *alcohol consumption* is through a reduction in craving. *Objective:* To determine whether the combination of naltrexone and ondansetron is superior to a placebo at reducing craving among EOA, and the relationship between craving and drinking behavior in both treatment groups. *Methods:* We conducted an 8-week double-blind placebo-controlled clinical trial in which 10 EOA were randomized to receive ondansetron (4 µg/kg b.i.d.) + naltrexone (25 mg b.i.d.) and 10 EOA had a placebo (total *n*=20) as an adjunct to weekly standardized group cognitive behavioral therapy. Craving was measured by using the obsessive compulsive drinking scale (OCDS). *Results:* Craving ratings were scored on four subscales which where derived empirically by principal component structure analysis of the OCDS. EOA who received the medication combination, compared with the placebo, had significantly lower scores on "*automaticity of drinking*" and "*alcohol consumption*". Reduction in *automaticity of drinking* was correlated with self-reported drinking for only the medication combination group. *Conclusions:* By reducing *automaticity of drinking*, the medication combination presumably decreased drinking salience and intensity. Larger scale studies testing these medications, both alone and together, among alcoholic subtypes are needed to establish and extend these promising findings.

Keywords Serotonin (5-HT) · Ondansetron · 5-HT_3 antagonist · Naltrexone · Opioid antagonist · Alcoholism · Subtype · Craving · Treatment · Obsessive compulsive drinking scale · Human

Introduction

There are at least two subtypes of alcoholic: early and late onset alcoholics (EOA and LOA, respectively). Biologically predisposed or EOA, compared with LOA, develop problem drinking earlier, are more antisocial, and have a greater family history of disease in first degree relatives (Babor et al. 1992; Johnson et al. 2000b).

The 5-HT_3 antagonist, ondansetron, (1) reduces alcohol-induced positive subjective effects and craving in healthy social drinkers (Johnson et al. 1993), and (2) diminishes drinking and increases abstinence among alcoholics with a biological disease predisposition (Johnson et al. 2000a).

Naltrexone (a mu opioid receptor antagonist) may be most efficacious in biologically predisposed alcoholics. For instance, the ability of naltrexone to diminish *alcohol consumption* is (1) negatively correlated with baseline β-endorphin level (Gianoulakis et al. 1996), and (2) greatest in individuals at high genetic or familial risk for alcoholism (King et al. 1997).

The combination of ondansetron with naltrexone appears to act synergistically at reducing *alcohol consumption* among biologically predisposed alcoholics (i.e., EOA; Johnson et al. 2000c). Effect sizes reported for the combination of ondansetron with naltrexone were much larger than have been shown for either medication alone. Preclinical evidence for such pharmacological synergism has also been demonstrated in animals where the combination of ondansetron and naltrexone is more effective

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than either medication alone at reducing ethanol intake (Le and Sellers 1994). Based upon the finding that (1) alcohol-induced increases in dopamine (DA) levels can be attenuated by both mu and delta opioid receptor antagonists, and (2) that ondansetron attenuates morphine-induced or TAN-67 (a selective delta opioid agonist)-induced alcohol place preference (Matsuzawa et al. 1999), we speculated that the mechanism for this synergism is associated with extensive modulation of the DA system via 5-HT_3 receptors and the endogenous opioid system (Johnson et al. 2000c).

Craving reduction may be one process by which the combination of medication counteracts the rewarding effects of alcohol. Whereas craving is an often-used term in human behavioral addiction research, its meaning has increasingly become a subject for debate. Some researchers have advocated abandoning the term altogether because of the lack of an operational definition because of its limited utility as a one-dimensional construct of addiction behavior or subjective experiences, and its apparent lack of correlation in some studies with substance-taking behavior (Baker et al. 1986; Foltin and Fischman 1990, 1994). In contrast, there is ample evidence that certain triggers or cues, either as a direct consequence of substance-taking or as an indirect association in the environment with which use has become associated, can provoke or maintain substance-taking. Thus, it is possible to understand craving along a multi-dimensional construct of cognitive and emotional stimuli that affect motivational aspects of substance-taking. Despite problems with interpretation, this concept of conditioning has parallels both in animal and human research. Specifically, in previously addicted animals and humans, it offers an explanation for the concept of reinstatement, especially after a period of abstinence.

Despite the lack of universal consensus regarding its definition, standardized multi-dimensional scales (Anton et al. 1996; Tiffany et al. 1993), rather than single item methods (Schuster et al. 1995), have become the norm in assessing craving because of their greater sensitivity and reliability. In the alcoholism field, the obsessive compulsive drinking scale (OCDS; Anton et al. 1996) is a well-validated, reliable, and sensitive multi-dimensional measure of alcohol craving.

In the present double-blind placebo-controlled clinical trial, we used the OCDS to test the hypothesis that EOA receiving a combination of ondansetron (4µm g/kg b.i.d.) and naltrexone (25 mg b.i.d.) experience a significantly larger reduction in craving compared with their counterparts receiving a placebo as an adjunct to standardized manual-driven cognitive behavioral therapy (CBT). We also have tested the additional hypothesis that craving and drinking reduction are correlated.

Materials and methods

Patients

Twenty DSM-IV (American Psychiatric Association 1994) diagnosed alcohol-dependent subjects participated: 10 were randomized to receive ondansetron + naltrexone, and the remainder (i.e., 10) received a placebo. Age of onset was determined by using item B 28 of the comprehensive drinking profile (Miller and Marlatt 1984). Subjects had an onset age of less than 25 years, drank more than three standard drinks/day, and tested negative for narcotics, amphetamines, or sedatives on a urine toxicological screen at intake. Exclusion criteria were a current psychiatric diagnosis other than alcohol or nicotine dependence, alcohol withdrawal necessitating inpatient detoxification, clinically significant abnormalities (i.e., on physical examination, electrocardiographic recording, or hematological evaluation, or elevated bilirubin levels), pregnancy, lactation, taking medication 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 granted by the Institutional Review Board at the University of Texas – Health Science Center at San Antonio. The treatment goal was sobriety, even though patients were enrolled while currently drinking.

General procedures

At visit 1, subjects received their randomized medication (either the combination of ondansetron and naltrexone or the placebo) and attended their first standardized CBT session. Standardized CBT was delivered weekly for the eight study weeks in groups of up to six individuals by using the eight core sessions of the Cognitive-Behavioral Coping Skills Therapy Manual (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). CBT was accompanied by weekly assessments of self-reported drinking (time-line follow back, TLFB; Sobell and Sobell 1992) and craving (OCDS).

On the OCDS, subjects responded to 14 items comprised of four empirically derived factors (Bohn et al. 1996). The first factor, "*drinking obsessions*", was composed of four items that addressed obsessive thoughts related to drinking. The second factor, "*alcohol consumption*", consisted of two items that evaluated the quantity and frequency of *alcohol consumption*. The third factor, "*automaticity of drinking*", contained five items that assessed the extent to which drinking was controlled or uncontrolled. The fourth factor, "*interference*", was comprised of three items that evaluated the extent to which drinking interfered with work and social functioning, and the degree to which being prevented from drinking was distressing.

Safety and compliance measurements collected included the Clinical institute withdrawal assessment – revised (Sullivan et al. 1989) for quantifying withdrawal symptoms, breath alcohol concentration, hematological, and biochemical checks, and pill count.

Procedures for obtaining the supply of medication, dosing, packaging, and blinding have been detailed previously (Johnson et al. 2000c).

Database validation was conducted by rechecking all entries on each subject's responses to the experimental measurements. Verified data were analyzed by using Statistical Analysis System version 6.12 (SAS II 1997).

Statistical analyses

Efficacy drinking data have been reported previously (Johnson et al. 2000c) and are only presented here as they pertain to their correlational relationship with OCDS-assesed craving. The analytic procedures below, which focus on the OCDS, were similar to those used for the evaluation of drinking outcome (Johnson et al. 2000c).

Subjects were assigned randomly to one of two groups (placebo or ondansetron + naltrexone) after stratification based on the average drinking level (drinks/day) at intake (i.e., visit 0). All subjects randomized to double-blind study medication were included in the analyses. Repeated measures analysis of covariance (ANCOVA) was used to examine the main effects of treatment with baseline measurements as potential covariates (see below) and summary measurements of the outcome from visits 1–8. Continuously distributed data were reported as their means ± standard error (SE).

OCDS scoring was analyzed by using the empirically derived four principal component structure of Bohn and co-workers (1996) described above. For each of the OCDS factors, the value at visit 0 was considered as a possible baseline covariate. If an analysis of variance (ANOVA) for visit 0 was significant or the baseline measurement was significantly related to the outcome measurement for the comparison between treatment conditions, then the groups were unequal on that measurement or the baseline reduced variance. In either case, the baseline value was included as a covariate in the efficacy analysis to adjust for these differences. The covariate(s) removed the effects of baseline difference and increased the precision for ascertaining the double-blind effectiveness response. Any covariate for inclusion in the final model was tested for its interaction with treatment condition. 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, responses to the OCDS factors were calculated as the mean of visits 1–8. This average response analysis preserved sample size, since all subjects with at least one outcome measurement (i.e., any of the visits 1–8) were included in the efficacy analysis. Since these means have a variance inversely proportional to the number of visits attended (Graybill 1970), the outcome analysis was weighted by the number of visits. The residuals of this repeated measurement of ANCOVA, weighted for missing data effects, were checked for normality by computing their skewness and kurtosis, and for homogeneity of variance by plotting them in a histogram and against the predicted outcome.

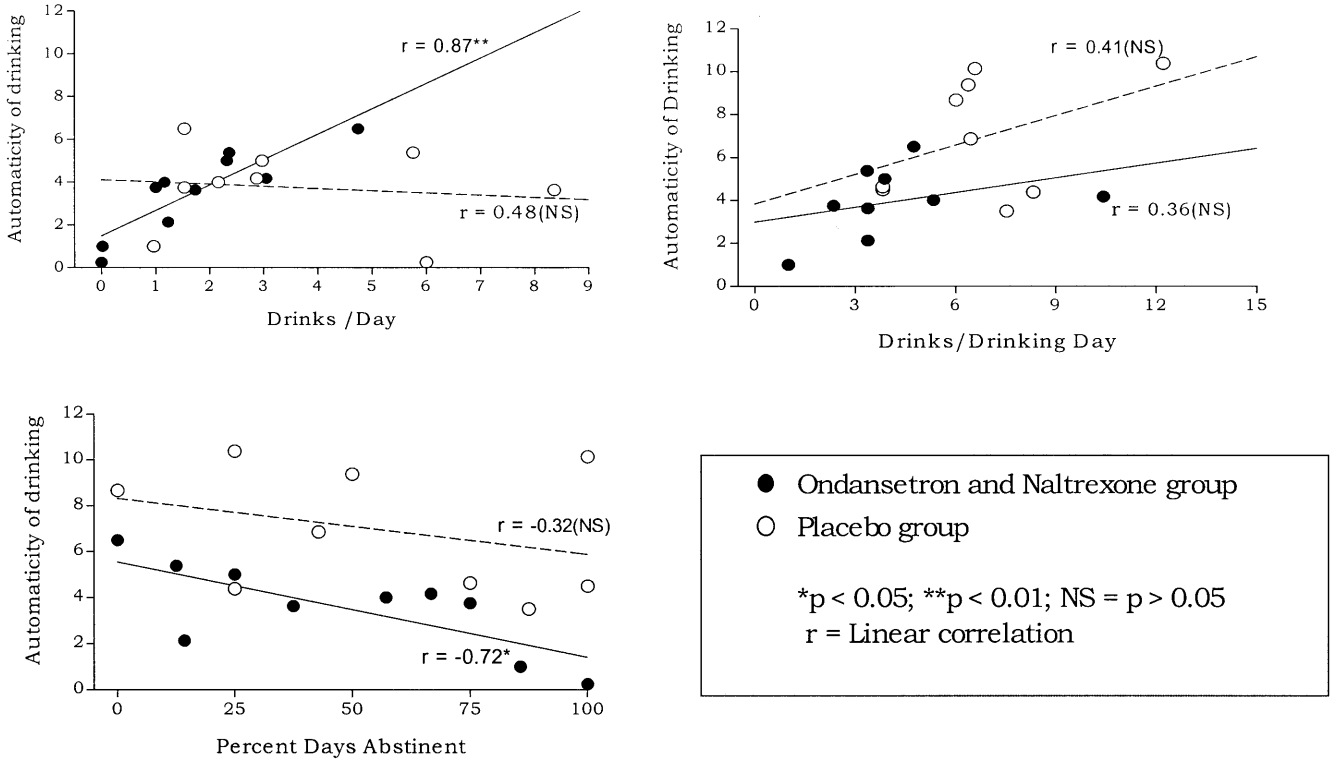
For each statistically significant factor on the OCDS that predicted efficacy for the medication combination, we tested for correlations of this factor with drinking outcome.

Results

The treatment groups were similar, and the cohort had the following demographic characteristics: (1) age (mean age =38.0±1.78 years), (2) gender (totals: females =5; males =15), (3) ethnicity (totals: Caucasian =12, Hispanics =8), (4) past 90 days drinking level (mean =7.44±0.79 drinks/day), and (5) on the Michigan alcoholism screening test (mean =32.94±2.14).

On the OCDS, the combination of ondansetron + naltrexone was superior to the placebo at: reducing the *automaticity of drinking* (adjusted mean =3.81±0.72 vs 6.40±0.73, $F_{1, 16}$=5.89, P=0.03; effect size =0.45), and *alcohol consumption* (adjusted mean =3.13±0.36 vs 4.96±0.38, $F_{1, 16}$=11.83, *P*=0.003; effect size =0.59). There was no significant difference between the medication combination and placebo with regard to *interference* due to drinking (adjusted mean =3.34±0.57 vs 2.56±0.56, $F_{1, 16}$=0.77, *P*=0.17; effect size =0.17), and *drinking obsessions* (adjusted mean =8.16±0.79 vs 6.66±0.80, $F_{1, 16}$=0.29, *P*=0.59; effect size =0.10). From Fig. 1, it can be seen that reduced *automaticity of drinking* was only significantly correlated with decreased self-reported drinking in those who received the medication combination. We did not perform correlational analyses between *alcohol consumption* and self-reported drinking with the TLFB, since these measurements were obviously co-linear.

Fig. 1 Relationship between *automaticity of drinking* on the OCDS and self-reported drinking using the time-line follow-back technique



Discussion

The combination of ondansetron and naltrexone significantly reduced the *automaticity of drinking* and *alcohol consumption* on the OCDS. The reduction on the *alcohol consumption* scale of the OCDS is consistent with drinking decreases previously reported with the TLFB technique (Johnson et al. 2000c). The OCDS could, therefore, be used as a guide to drinking outcome and craving in generic treatment settings where there is insufficient opportunity to collect more comprehensive drinking data (e.g., TLFB).

Mechanistically, it is interesting that the medication combination did not reduce all aspects of alcohol craving. Saliency of the effect manifested as decreased *automaticity of drinking*. This may be of importance, because the effect of both medications is to reduce the urge to drink (Johnson et al. 1993; Monti et al. 1999), and naltrexone is associated with decreased conditioned responses to drinking (Palfai et al. 1999). No TLFB recorded drinking behaviour pattern was uniquely associated with decreased *automaticity of drinking*.

Two limitations based upon the sample size of the present study merit consideration. First, the small sample size may have reduced the power of detecting potentially important but less striking differences in other OCDS craving components between the two treatment groups. Second, the independent effect on craving produced by naltrexone and ondansetron was not assessed. Future testing of the anti-craving effects of ondansetron and naltrexone, both alone and combined, among alcoholic subtypes is, therefore, needed. This would improve our "proof-of-concept" understanding of the way in which mechanistic processes associated with biological disease predisposition interact with the pharmacological changes produced by the medications.

The combination of ondansetron and naltrexone was well tolerated with no difference in side-effect profile between the active treatment and placebo conditions (data not shown). Only one subject had a breath alcohol concentration of greater than 0.08% at a study visit. No subject experienced significant withdrawal symptoms, and medication compliance was about 96% (Johnson et al. 2000c).

We conclude that the combination of ondansetron and naltrexone reduced *automaticity of drinking* and *alcohol consumption*, both of which contributed to its efficacy as a treatment for early onset alcoholism.

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