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Clinical Efficacy of the 5-HT_3 Antagonist Ondansetron in Alcohol Abuse and Dependence

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Medications that act on the serotonergic system have been found to be of benefit in the treatment of alcohol-dependent individuals. In a randomized, placebo-controlled study, the efficacy of 6 weeks of ondansetron, a 5-HT_3 antagonist (0.25 mg bid or 2.0 mg bid), in the treatment of 71 nonseverely alcohol-dependent males was tested. The results showed reduction of drinking differences were steadily increasing toward the end of the treatment period approached significance at week 7 in the 0.25 mg group ($p = 0.06$). Twice as many patients in this group showed >2 standard deviations decrease in drinking compared with the other groups. When patients drinking >10 drinks/drinking day at baseline ($n = 11$) were excluded from the analysis, significant group differences were found at both treatment and follow-up, with the lower ondansetron dose producing the greatest reduction from baseline (i.e., 2.8 standard drinks; −35% compared with baseline and −21% compared with placebo; $p <$ 0.02–0.001). Within this group, there was an almost 4-fold greater number of patients showing a clinically meaningful decrease in drinking. Lower baseline drinking and higher level of education were significant and strong predictors of drinking reduction during treatment. Ondansetron was very well tolerated; hence, further long-term studies with 5-HT_3 antagonists alone or in combination with other treatment components may offer promise for treatment of alcoholism.

Key Words: Serotonin Antagonists, Alcohol Abuse, Ondansetron.

EFFECTIVE PHARMACOLOGICAL treatments of alcohol abuse and dependence are needed.[1-3] Studies in laboratory animals have shown that treatments that increase the synaptic availability of serotonin (5-HT), such as reuptake inhibitors (e.g., fluoxetine) and releasers (e.g., dexfenfluramine), can reduce alcohol consumption.[3] On the basis of such preclinical data, the uptake inhibitors have also been clinically tested. A number of short-term clinical trials (2–4 weeks duration) have demonstrated the effectiveness of fluoxetine, zimelidine, citalopram, and viqualine in individuals with mild to moderate alcohol dependence who consume an average of 50 standard drinks (SDs)/week in the pretreatment period.[1,4-6] Their subsequently proven efficacy in clinical trials suggests some predictive validity for preclinical models of ethanol self-administration.[3] However, because the average reduction in alcohol consumption achieved by these medications is rather modest, ranging from 9 to 17%, the search continues for other medications that alone, or in combination with nonpharmacological treatment approaches, will yield a larger effect.[3] In addition, although the uptake inhibitors in the previously cited studies were accepted by patients and tolerable, their use was associated in ~20% of patients with mild gastrointestinal side effects, reports of sexual dysfunction, and altered sleep.

Perhaps paradoxical to the evidence that enhancement of central serotonergic tone may diminish certain rewarding stimuli, 5-HT_3 receptor antagonists (e.g., MDL72222, ICS205-930, ondansetron) appear to also decrease drug effects associated with drug abuse. Several studies demonstrate an interaction between 5-HT_3 antagonists and some of ethanol's effects using electrophysiological,[7] biochemical,[8,9] and behavioral techniques.[10] Ethanol can induce a release of dopamine within the nucleus accumbens[11-14] that has been proposed to play a role in the reinforcing properties of ethanol,[15] and this release can be decreased by 5-HT_3 antagonists using both in vitro and in vivo preparations.[8,9,13] Ondansetron and other 5-HT_3 antagonists also reduce the behavioral and neurochemical consequences of stimulation of the mesolimbic dopaminergic system. The hyperactivity induced by infusion of dopamine into the nucleus, accumbens in rats and marmosets was inhibited by ondansetron at doses of 1–100 μg/kg ip.[16] In the rat, Hagan et al.[17] showed that ondansetron markedly reduced the hyperactivity and increased dopamine metabolism in the nucleus accumbens induced by injections of diMeC7 into the ventral tegmental area. These various actions within the mesolimbic and dopaminergic system may provide the neuroanatomic explanation for the effects of these compounds on drug reinforced behaviour. Moreover, Grant and Barrett[10] have recently presented data that suggest that the interactions between ethanol and 5-HT_3 receptors described at the electrophysiological and biochemical levels may be behaviorally relevant, because they have shown that 5-HT_3 antagonists can block the discriminative stimulus properties of ethanol. Pretreatment with ondansetron significantly attenuated several of the subjective pleasurable

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effects of alcohol, and also decreased the subjective desire to drink in 16 healthy male volunteers.[18]

If 5-HT_3 antagonists can modify the pharmacological, including reinforcing, properties of ethanol they might be expected to decrease ethanol self-administration. The majority of studies reported confirm this expectation[18–24] (D. M. Tomkins, personal communication), but not all,[25] in spite of the numerous species investigated and differences in the procedure and/or experimental design used. Other laboratories have reported that the administration of 5-HT_3 antagonists for up to 6 days produces a robust and stable reduction in ethanol intake with little evidence for tolerance.[20,22] This is consistent with biochemical evidence that chronic blockade of central 5-HT_3 receptors does not result in adaptive changes in the activity of mesolimbic dopaminergic neurons.[26] For these reasons, a clinical trial to determine the efficacy of ondansetron, a 5-HT_3 antagonist, in patients with DSM-III-R alcohol dependence was conducted.

METHODS

Patients and Design

A randomized, double-blind, placebo-controlled, parallel design study was conducted using 71 male, socially stable, patients who met criteria for DSM-III-R for alcohol dependence and were seeking treatment. They were 24–62 years of age, reported alcohol-related consequences, and expressed a desire to decrease their alcohol use. Patients were self-referred, referred from other treatment programs, or recruited by advertisement. The study was approved by an Addiction Research Foundation and University of Toronto Ethics Committee. Patients who met the eligibility criteria gave informed consent, had completed the 2-week baseline period, and were randomly assigned to 1 of 3 treatment conditions: ondansetron, 0.25 mg ("low dose," $n = 23$); ondansetron, 2.0 mg ("high dose," $n = 25$); or placebo ($n = 23$). Patients were instructed to take their medication twice daily, at 8:00 AM and 6:00 PM. Riboflavin (20 mg), as a measure of compliance, was included in the capsules.

Table 1 summarizes selected characteristics of the patients for all groups combined. No between-group differences were found for any demographic, drinking, or drinking-related variable.

Procedure

Potential patients were first screened by telephone to assess their suitability for the study and then scheduled for an assessment to determine their eligibility. Patients were excluded if they had: a medical or psychiatric problem requiring investigation or treatment; a social stability index <7[27]; an Alcohol Dependence Scale score >21[28]; used prescription or nonprescription psychoactive medications on at least 10 days in the past 3 months; were currently using illegal medications; had a positive medication screen for illicit or unreported medications on two occasions; met DSM-III-R[29] criteria for severe alcohol dependence in the past year; had a Montgomery/Asberg Depression rating scale >15[30]; had a Spielberger State-Trait Anxiety Inventory score >55[31]; had biochemical, hematological, or urinalysis abnormalities requiring investigation; had participated in a treatment program for alcohol or medication dependence in the past year; had self-reported symptoms of major alcohol withdrawal; had attended a formal self-help treatment group in the past month; or had donated blood within the previous 3 months.

Table 1. Patient Characteristics

Variable	Value
Age (yr) (mean ± SD)	43.55 ± 9.7
Education (yr) (mean ± SD)	15.32 ± 3.6
Alcohol-related arrests (mean ± SD)	0.62 ± 1.3
Alcohol-related hospitalizations (mean ± SD)	0.32 ± 1.9
Ethnic background (% white)	99
Marital status (% married)	55
Employment status (% employed)	90
Problem self-description (% major or very major problem)	62
SDs/drinking day at baseline (mean ± SD)	8.0 ± 3.1

Approximately 1 week after the assessment, eligible patients began a 2-week baseline period during which alcohol consumption was self-monitored. At the start of the baseline period, the following were completed: Timeline Follow-Back Interview for the previous 90 days[32]; Situational Confidence Questionnaire[33]; a Tobacco and Caffeine Consumption Form; Multiple Adjective Check List (MACL)[34]; Goal Setting[35]; Inventory of Drinking Situations (IDS)[33]; and Adverse Events Enquiry.

At the conclusion of the 2nd week of baseline, patients were instructed in the completion of a Daily Log Book to be completed throughout the 6 weeks of medication treatment. Patients recorded amount and time of all alcohol consumption. Twice daily, at 8:00 AM and 6:00 PM, patients also rated, on 11-point scales, their urge to drink alcohol, stress level, affective state, and perceived efficacy of alcohol to alter affective states.

The efficacy of ondansetron was evaluated as part of a treatment program that incorporated the following nonpharmacological components. First, all patients received the comprehensive assessment outlined. Second, at the beginning of the treatment period, each patient was asked to specify the drinking goal (abstinence or reduced drinking) to be achieved during the treatment program. Finally, all patients were instructed in "Guided Self-Change," a structured, problem-solving treatment emphasizing the self-recognition and use of coping skills to resolve their drinking problems[33] and incorporating a relapse prevention component.[36] As part of the Guided Self-Change treatment, patients received two short booklets (readings I and II) and completed a homework assignment. Reading I and the corresponding homework assignment were given at the beginning of the medication treatment period. The homework asked patients to analyze functionally their three most serious problem-drinking situations. Reading II was given at the end of the 1st week of the medication treatment, and the completed homework was reviewed. At subsequent treatment visits, patients were given the opportunity to discuss their progress in reaching their drinking goal with trained and experienced research assistants. The amount of time spent on these discussions was <30 min/week.

Patients were followed-up at 1 week postmedication, at which time a blinded tape recorded 1-hr semistructured interview was conducted. The interview covered how patients felt about the treatment program, their alcohol use, and any observations of medication side effects or action.

Compliance to the study protocol was determined by weekly capsule counts, extent of completion of monitoring booklets, appointments kept, determination of riboflavin concentrations in urine, and correlation of urine ethanol and self-reports of alcohol consumption.

At each patient visit, clinical emergent/adverse medication events were documented, along with any patient reports of potential adverse medication effects. These events were carefully recorded with respect to timing of onset and severity. Causality was assessed by a blinded physician. No clinically important medication-related side effects were found.

Statistical Analysis

The major statistical analyses consisted of a one-way analysis of variance comparing alcohol consumption in SDs (equal to 13 g ethanol/drinking day during the 2-week baseline period with four medication periods: medication period I (treatment weeks 1–6); medication period II (treatment weeks 1–3); medication period III (treatment weeks 4–6); and medication period IV (the posttreatment visit at week 7). Drinking data were calculated for each week for each patient over the 9-week

duration of the study (2 baseline weeks, 6 treatment weeks, and 1 follow-up week). The average for each medication period was subtracted from baseline average, yielding difference scores that were subsequently averaged over all patients. Two additional analyses of variance were conducted.

Lighter Drinkers Only. It was hypothesized that the therapeutic response to ondansetron might be attenuated in heavy drinking patients that would mask effects that were obtained for less heavy drinkers. Also, an analysis of the frequency distributions for each group showed that heavier drinking patients were somewhat (but not significantly) unevenly distributed among the three groups despite random assignment. Thus, data were reanalyzed following the removal of individuals who reported consuming >10 SDs/drinking day (n = 11) during baseline.

Heavier Drinkers Only. Although all patients self-reported their drinking to be problematic, there were several (n = 10) whose alcohol consumption was quite low (i.e., <4 SDs/drinking day during at least 1 of the 2 weeks comprising baseline). This drinking pattern might preclude large drinking reductions and thus restrict the sensitivity of the assessment of the effect of the intervention, especially because many patients (93%; 66/71) were working toward a reduced level of consumption rather than abstinence. We therefore analyzed the data, excluding the very light drinkers (SD < 4).

Effect of Beliefs About Which Drug Was Administered. At the end-of-treatment interview, all patients were asked whether they believed they had received active or placebo medication. Only 27 (38%) said they believed they had received ondansetron, and 44 (62%) said they believed they had received placebo. There was no interaction between actual drug condition and belief. Although this outcome was encouraging in terms of the low identifiability of the drug and lack of significant side effects, it did pose a potential problem from the perspective of attribution and dissonance theory, because the therapeutic response might be expected to be affected by beliefs that a drug had been administered. A more complete analysis of the perception data is reported elsewhere.[37]

The standard statistical analysis described herein while providing a measure of how reliable group differences are, are unrelated to the clinical meaningfulness of the changes in drinking. Clinical importance is usually determined by judgments as to the degree to which changes produced by treatment return individuals toward the level of functioning shown by healthy nonaffected populations. Jacobson[38] and colleagues[39] have proposed the Reliable Change (RC) score as an indicator of clinical importance, and is calculated as the difference between pre- and posttest scores divided by the standard error of measurement of the instrument used to measure the dependent variable. Jacobson[38] suggests that changes exceeding 1.96 (or 2 standard deviations beyond the mean of the dysfunctional group) are usually clinically meaningful changes. Thus, in addition to the traditional statistical analyses based on the difference between pre- and posttest, RC scores for the three populations were also calculated.

Other Analyses

Regression analyses were performed with difference scores for medication periods I and IV as the dependent variable. The predictor variables consisted of those variables that were significantly correlated with the difference scores. These included group assignment (0.25 mg ondansetron, 2.0 mg ondansetron, and placebo), drug perception (drug and placebo), years of education, perceived effectiveness of the drug (ranging from none to strong), baseline drinking, and drinking goal (in SDs/drinking day).

RESULTS

A total of 509 individuals were screened by telephone. Of these, 231 were potentially eligible, 159 came for assessment, 63 were unsuitable, and 96 entered into the baseline period. Seventy-one patients completed the 6-week medication period and also attended the 1-week follow-up visit (Table 1). Fifteen patients who reached randomization did not complete the entire 6-week treatment period. A χ^2 test of drop-outs by group revealed no significant differences ($p > 0.05$). Drop-outs were placebo = 6; low dose = 5; and high dose = 4. The reasons were: adverse event = 1; (low dose); refused to comply = 5 (low dose = 3, high dose = 2); unable to comply = 2 (placebo); defaulted = 3 (one each group); and medical reason unrelated to study = 4 (placebo = 3, high dose = 1).

Compliance

Among those who completed the program, all measures indicated high compliance with the study protocol, with >95% of all visits kept, urines returned, capsules consumed, and urine riboflavins positive. No individual patient who completed the study was noncompliant on any measure by >10%. Significant correlations of urine ethanol levels with self-reports were found as previously found in similar studies,[37] with the exception of seven patients. In these patients, when a correction for the actual time of drinking in relation to the actual time of the urine sample was calculated, the urine ethanol levels and self-report were appropriately correlated.

Effects on Alcohol Consumption

All Patients. Figure 1 shows the mean difference scores for the medication periods by group. A one-way analysis of variance found no significant differences between baseline drinking and medication periods I–III. However, the mean difference score between baseline and follow-up (medication period IV) approached statistical significance ($F_{2,68} = 2.88$, $p = 0.063$).

Lighter Drinkers Only. When the analyses of variance were repeated excluding the heavier drinkers, significant differences were found for several medication periods (medication period I: $F_{2,57} = 4.17$, $p = 0.02$; medication period III: $F_{2,57} = 4.17$, $p = 0.02$; medication period IV: $F_{2,57} = 5.82$, $p = 0.005$; see Fig. 2). In each analysis, the

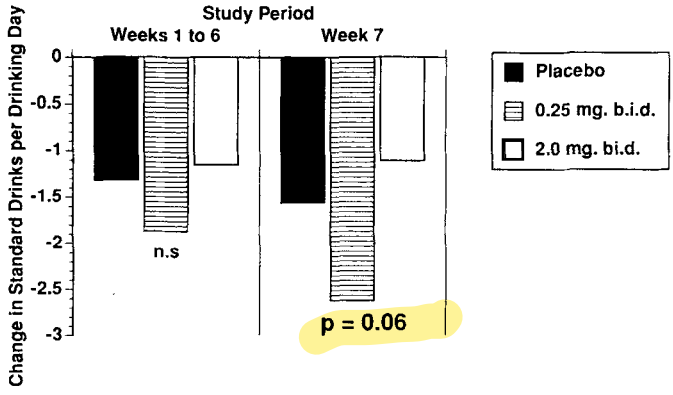

Fig. 1. Change in alcohol consumption between baseline, treatment, and follow-up (n.s = not significant; for follow-up period, $F_{2,68} = 2.88$, $p = 0.06$) for subjects (n = 71) by condition (SD). Placebo, 6.15 SDs; 2.0 mg ondanstron, 6.51 SDs; and 0.25 mg ondansetron, 6.97 SDs.

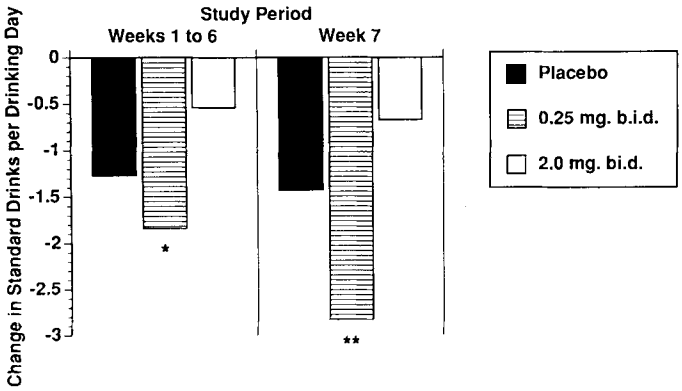

Fig. 2. Change in alcohol consumption between baseline and both treatment (*) ($F_{2,57} = 4.17$, $p = 0.02$) and follow-up (**) ($F_{2,57} = 5.82$, $p = 0.005$), with heavy drinkers excluded ($n = 60$). Placebo, 6.15 SDs; 2.0 mg ondanstron, 6.51 SDs; and 0.25 mg ondansetron, 6.97 SDs.

lower dose group attained a significantly greater reduction than the higher dose group [M(SD) = −1.83 (1.84) SDs vs. M(SD) = −0.54 (1.14) SDs, $t_{57} = 2.87$, $p = 0.006$ (medication period I); M(SD = −2.35 (2.01) SDs vs. M(SD = −0.82 (1.40) SDs, $t_{57} = 2.87$, $p = 0.006$ (medication period III); M(SD) = −2.83 (2.00) SDs vs. M(SD = −0.67 (1.99) SDs, $t_{57} = 3.38$, $p = 0.001$ (medication period IV)]. The placebo group always placed in between the two medication groups. The lower dose group was also significantly different than the placebo group for medication period IV, with the 0.25 mg ondansetron group reducing their drinking 2.83 (2.00) SDs compared with 1.43 (1.92) SDs by the placebo group ($t_{57} = 2.23$, $p = 0.029$).

Heavier Drinkers Only. The exclusion of the lighter drinks did not yield statistically significant differences for any medication period.

RC Scores

Table 2 shows the proportion of patients with RC scores >1.96 (i.e., a change of at least 2 standard deviations) for the baseline week, the six treatment weeks, and the one posttreatment visit (week 7). By week 6, there were twice as many patients receiving the 0.25 mg dose (compared with the two other groups), showing improvements of at least 2 standard deviations. Similar results are observed in the subsample including only heavy drinkers.

The effects of the lower dose of ondansetron are even more dramatic in the subsample including only lighter drinkers. Within this group, the ratio of patients showing a change of at least 2 standard deviations is between 3 and 4 times that found in the other two groups.

Regression Analyses

Table 3 displays the unstandardized regression coefficients and intercept, the standardized regression coefficients, the squared semipartial (sr) correlations (a measure of the unique proportion of variance attributable to an independent variable), R, and R^2 for the regression analyses. Only two independent variables contributed significantly and uniquely to the prediction of the decrease in alcohol consumption during treatment (medication period I) for the entire sample: baseline drinking ($sr^2 = 0.095$) and education ($sr^2 = 0.095$). Together, these two variables uniquely account for 19% of the variation in the difference scores during treatment. Bivariate correlations (cf. Table 3) showed that patients who drank less at baseline and had more years of education achieved larger decrements in alcohol consumption. In total, all six independent variables accounted for 35% of the variance in the dependent variable.

At the follow-up, education ($sr^2 = 0.05$) was the only significant predictor of drinking reduction and accounted for 5% of the unique variation in the difference scores. All six predictors combined accounted for 18% of the variance in the dependent variable. Bivariate correlations (cf. Table 3) showed that patients who had more years of education achieved larger decrements in alcohol consumption.

Other Dependent Variables

No group effects on mood, as measured by the Speilberger State or MACL total score were observed for any period of the study. The IDS response patterns were classified into three categories (negative affect profile; positive affect profile; total score); however, no differences in

Table 2. Percentage of Group Showing a Change in Drinking at Least 2 Standard Deviations from Baseline Mean

	Week								
	0*	1	2	3	4	5	6	7†	*n*
All subjects									71
Placebo	4.3	4.3	0	4.3	17.4	17.4	21.7	17.4	23
2.0 mg	0	8.0	12.0	16.0	16.0	20.0	16.0	16.0	25
0.25 mg	0	17.4	26.1	30.4	34.8	34.8	39.1	34.8	23
Lighter drinkers									60
Placebo	4.5	4.5	0	4.5	13.6	13.6	18.2	13.6	22
2.0 mg	0	5.0	10.0	10.0	10.0	15.0	10.0	15.0	20
0.25 mg	0	11.1	22.2	27.8	33.3	33.3	44.4	38.9	18
Heavier drinker									61
Placebo	5.3	5.3	0	5.3	21.1	21.1	26.3	21.1	19
2.0 mg	0	5.0	10.0	20.0	20.0	25.0	20.0	20.0	20
0.25 mg	0	18.2	27.3	31.8	36.4	36.4	40.9	36.4	22

* Baseline week.
† One-week posttreatment.

Table 3. Regression of Selected Predictor Variables on the Change in Drinking between Baseline and Treatment

Predictor variables	Change in drinking (*r*)	*B*	*β*	sr^2 unique
All subjects ($n = 71$)				
Perception (drug or placebo)	0.23*	0.57		
Education (yr)	0.30*	0.16	0.31	0.095*
Perceived efficacy of drug (1 = low; 5 = high)	0.29*	0.26		
Drinking goal (SDs/drinking day)	−0.25*	−0.09		
Baseline drinking (SDs/drinking day)	−0.42*	−0.26	−0.39	0.095*
Group (0.25 and 2.0 mg ondansetron, placebo)	−0.12	0.06		
Intercept		−3.84		
Excluding heavy drinkers ($n = 61$)				
Perception (drug or placebo)	0.16	0.59		
Education (yr)	0.23†	0.16	0.23	0.05†
Perceived efficacy of drug (1 = low; 5 = high)	0.16	0.11		
Drinking goal (SDs/drinking day)	−0.22†	−0.10		
Baseline drinking (SDs/drinking day)	−0.30†	−0.17		
Group (0.25 and 2.0 mg ondansetron, placebo)	−0.19†	−0.27		
Intercept		−3.41		

*$p < 0.05$ ($R = 0.59$; $R^2 = 0.35$).
† Baseline week.

patterns among the three treatment groups was observed. When these two variables were used as covariates in the analysis of the drinking data, no effect was observed.

There were no significant within-subject effects of ondansetron or placebo on weight at any point in the treatment. However, the lower dose group was consistently and significantly lower in weight than the higher dose ondansetron group throughout the entire study.

DISCUSSION

On the basis of the preclinical studies with 5-HT_3 antagonists, several hypotheses can be proposed to explain why these medications might decrease alcohol consumption in humans.[3] First, these medications may decrease ethanol self-administration by modifying the reinforcing properties of alcohol.[3,21,40] Second, these medications decrease place conditioning, particularly to opiates and hence may modify the importance of the conditioned stimuli that can precipitate drinking.[41] Third, because anxiety disorders coexist with alcoholism in many patients, treatment of a concurrent anxiety problem might produce a secondary reduction in alcohol consumption.[3] Fourth, through enhancement of cognitive function, they may facilitate the learning of new behaviors that are important to the achievement or maintenance of nonhazardous drinking. We have no evidence from this study that any of the latter three mechanisms were important. Furthermore, our clinical data raise several other possibilities and suggest that the preclinical data do not adequately explain the mechanism of medication effects in these patients.

The pattern of response observed in this study is particularly interesting. Previous studies with 5-HT_3 uptake inhibitors have shown a therapeutic response occurs within a few days.[1,4–6] In our study, the decrease in drinks on drinking days peaked 1 week following the medication period for the low dose group, the last point at which monitored drinking data was gathered. This pattern of slow onset is also seen in preclinical findings. In male ethanol-preferring Wistar rats, the effects of ondansetron (0.1 mg/kg ip) in suppressing free choice ethanol consumption in a continuous access model are maximal 9 hr after medication.[21] Similarly, Fadda et al.[20] observed a maximum suppression of alcohol consumption by MDL72222 in Sardinian ethanol-preferring rats after 3 days of treatment. The effects of zacopride are also delayed in onset.[22] These preclinical data suggest that some of the pharmacological effects of 5-HT_3 antagonists are rather subtle alterations in the reinforcing value and properties of the reinforcer. In simple terms, it takes some time for the animals' behavior to change, because the change in the introceptive cues are changed slightly. Unpublished, but reported, results of a double-blind, randomized trial of ondansetron, 1.0 and 4.0 mg, and placebo, 3 times daily in over 400 patients with "anxiety" showed increasing anxiolytic efficacy in the active medication groups over a period of 4 weeks.[42] This anxiolytic effect continued to increase for 2 weeks after the medication period. A recent study (H. Kranzler, personal communication) found a similar pattern of an increasing medication treatment response following the formal medication administration period of fluoxetine in treatment of alcohol dependence as we observed.

In contrast, recent studies in our laboratory have found that, in a limited access model of ethanol, self-administration by rats or mice ondansetron (0.01 mg/kg) had an immediate effect (D. M. Tomkins, unpublished observations). Apart from paradigm difference, this suggests that one factor that may determine the rate of detection of an effect and the size of the effect of the 5-HT_3 antagonists is the level of motivation exhibited by the animals to consume the fluid, because it has been demonstrated that dopamine release in the nucleus accumbens resulting from both the anticipation of and subsequent intake of ethanol is greater in rat lines bred for high ethanol preference than other low ethanol-preferring lines.[43,44] Some analogy may be drawn from other behavioral models, such as dopamine-induced hyperactivity, in which rats must be exhibiting a high behavioral output before 5-HT_3 antagonists exhibit any efficacy.[16] One means to examine if the suggestion holds some validity is to use behavioral manipulations to increase the incentive to consume ethanol. One such manipulation may be to train the rats to consume ethanol using a limited access schedule, because it has been shown that rats trained to expect ethanol have enhanced dopamine release during the waiting period,[43] and that under similar training conditions, rats consuming ethanol exhibit more active behaviors than those consuming water alone.[45] In this regard, the limited access paradigm is associated with more intense drinking directed behaviors than a continuous access paradigm. We would

therefore propose that the slow onset of effect of the medication seen herein reflects in behavioral terms a pattern of extinction due to a small change in the incentive properties of alcohol in the patients and the differential response patterns depending on drinking level reflect some as yet poor understood differences in the tone of some important neurochemical regulators of alcohol consumption. The pattern of a slow disappearance of a behavior caused by extinction is common in preclinical behavioral studies. From a therapeutic perspective, such a pattern may be more likely to provide a better opportunity for the effective integration of pharmacological and nonpharmacological treatment elements. Although there may be a strong clinical prejudice for medications that suddenly change behavior, such medications may not be associated with the best long-term outcomes.

Unfortunately, the present study's relatively short treatment duration makes it impossible to determine the maximum effect attainable by the combination of ondansetron with the other treatment components. The reduction in average drinking of 18% over the 6-week treatment period (i.e., 15% for the 2.0 mg dose; 21% for the 0.25 mg dose) is similar to that observed with 5-HT_3 uptake inhibitors. However, this previous work did not show evidence of an increasing effect over 4–6 weeks of treatment and did not show as many large responders to treatment.[1,4–6] When the effect of treatment was analyzed using a measure of clinical importance, meaningful improvement (of at least 2 standard deviations) was much more frequent among the low dose group. The number of individuals who demonstrated meaningful change in drinking in effect of the 2.0 mg dose group appeared to peak midway through the treatment and then plateau thereafter. There appeared to be little difference between the higher dose group and the placebo group. The observation that the treatment effect was greatest in the low dose group is unusual in a human drug trial, but is similar to dose-effect patterns seen preclinically in the behavioral pharmacology of ondansetron, where an inverted U-shaped dose-response curve has been observed for anxiolytic and blockade of place conditioning effects.[41] Such nonlinearity is not observed with all 5-HT_3 antagonists, suggesting that the receptor selectivity and specificity of these agents is not identical. Interspecies differences in 5-HT_3 receptor structure may exist, and this ligand gated ion channel receptor complex may have variable subunits.[3] One implication of such a pattern of response is that future studies must include a sufficiently wide range of medication doses and anticipate differences among chemically different 5-HT_3 antagonists.

The observation that the medication effect was greatest when the heaviest drinkers were excluded from the analysis suggests the heavier drinkers were less susceptible to medication effect or were particularly susceptible to various uncontrolled nonpharmacological factors that contribute to regulation of drinking level. We had expected that removal of 11 patients from the analysis would decrease the power of the study to an extent that any main effects would disappear. Because the opposite occurred, this indicates that the higher drinkers were responsible for added variation to the data. The regression analyses showed treatment per se when viewed in the context of other predictors to be a minor factor in accounting for changes in drinking. Lowered baseline drinking and higher education were the most powerful predictors of drinking outcome in the patient voluntarily entering treatment and taking a medication of potential utility in helping them. This raises the issue of the context in which a treatment such as the one described in this study is maximally effective. The hypothesis tested in most clinical trials asks: Is the drug efficacious? Our study indicates that a more appropriate question would be: Under what conditions, with which patient population, at what dose, is the drug efficacious?

In the present study, there were only a few clinical emergent events, and none could be definitely attributed to the medication (e.g., several patients receiving ondansetron reported mild constipation). The 5-HT_3 antagonists, in general, are very well tolerated and seem very safe; thus, future studies can use much broader patient inclusion criteria. Future studies should consider the following: a longer parallel design study that incorporates a wider dose range, stratification by alcohol consumption level, and belief and expectancy with respect to medication. Preclinical experience with various chemical classes of 5-HT_3 antagonists in ethanol self-administration is currently limited and should there be expanded to compare ondansetron with other 5-HT_3 antagonists, and determine if our clinical results with ondansetron also occur with all 5-HT_3 antagonists. Studies of the mechanism of the ondansetron effect in humans are also important. The clinical utility of 5-HT_3 antagonists in treatment of other substance use disorders could also be examined, because their preclinical pharmacology indicates they can also modify the pharmacological properties of opiates.[41,46]

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