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ORIGINAL INVESTIGATION

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Olanzapine reduces urge to drink after drinking cues and a priming dose of alcohol

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Abstract *Rationale:* Haloperidol, a D_2 antagonist, has been shown to moderate the effects of alcohol consumption on craving. *Objective:* The present study was designed to determine whether a single 5-mg dose of olanzapine (a D_2/5-HT_2 antagonist) would influence responses to alcohol cues or an alcohol challenge. It was hypothesized that olanzapine would attenuate cue-elicited urge to drink, attenuate the effects of alcohol consumption on urge to drink, and reduce the rewarding effects of alcohol. *Methods:* To test these hypotheses, 26 heavy social drinkers were randomized to receive either 5 mg olanzapine or placebo approximately 8 h before each of two experimental sessions. Participants consumed a moderate dose of alcohol in one experimental session and a non-alcohol control beverage in another session. *Results:* Results indicated that mere exposure to alcohol cues and consumption of alcohol increased urge to drink and that olanzapine attenuated these effects. Results also indicated that alcohol increased subjective stimulation and high while olanzapine did not moderate these effects. *Conclusions:* These results suggest that olanzapine did not influence the rewarding effects of alcohol but did attenuate the effects of alcohol cues and an alcohol challenge on urge to drink.

Portions of these data were previously presented at the 1998 meeting of the Research Society on Alcohol in Hilton Head, NC

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Introduction

Research on pharmacotherapies designed to promote and maintain abstinence from drinking alcohol has received considerable attention in the past decade (see, for example, Litten et al. 1996). Recently, investigators have used a cue exposure approach to test whether promising medications may alleviate cue-elicited appetitive responses (Robbins et al. 1992; Hersh et al. 1995; Berger et al. 1996). With respect to alcohol cues, a recent double-blind, placebo-controlled study demonstrated that patients receiving daily doses of 50 mg naltrexone were significantly less likely to demonstrate a cue-elicited urge to drink, as compared to patients treated with placebo (Monti et al. 1999). Another recent study showed that a single 50-mg dose of naltrexone reduced the probability of having a cue-elicited urge to drink as well as the intensity of that reaction (Rohsenow et al. 2001). Naltrexone has also been shown to reduce urge to drink alcohol among heavy social drinkers in a bar setting (Davidson et al. 1999).

The pharmacological mechanisms that explain the clinical effects of naltrexone have not been well characterized. Reviews of the literature suggest that the stimulatory and reinforcing effects of alcohol are mediated by the activation of mesolimbic dopamine neurons and that anticipatory craving for alcohol may also be related to this system (see, for example, Samson and Harris 1992; Littleton and Little 1994). Several reports have suggested that naltrexone may moderate this activation via opioid receptors that exist along these mesolimbic dopamine neurons (see, for example, Benjamin et al. 1993; Swift et al. 1994). A role for dopamine in the effects of alcohol consumption on craving has been further supported by a study in which a D_2 antagonist (haloperidol) was reported to block increases in craving after a priming dose of alcohol (Modell et al. 1993). Finally, clinical trials in Eu-

rope have suggested that a D_2 antagonist (tiapride) effectively increases abstinence among alcoholics, although the clinical significance of these findings are tempered by the risk for extrapyramidal side effects (Shaw et al. 1987, 1994; Litten et al. 1996).

If traditional dopamine antagonists, such as haloperidol, block cue-elicited urge to drink or the ability of one drink to prime craving for another, newer atypical dopamine antagonists might also be expected to share this ability without many of the adverse effects, such as extrapyramidal side effects, that are associated with traditional antagonists. Recent clinical trials with olanzapine have demonstrated that olanzapine is safe and effective for the treatment of psychosis with an extrapyramidal side effect profile that is significantly less than haloperidol and indistinguishable from placebo treatment (Beasley et al. 1996; Tollefson et al. 1998; Stahl and Clarizio 1999). Olanzapine may have an additional advantage because it is also a potent 5-HT_2 antagonist. Preclinical studies have suggested that 5-HT_2 antagonists may reduce alcohol consumption (see, for example, Meert et al. 1991; Myers et al. 1992, 1993), although a recent multi-site clinical trial did not demonstrate any significant clinical effects for the 5-HT_2 antagonist ritanserin (Johnson et al. 1996).

The objective of the present research was to determine whether pretreatment with 5 mg olanzapine would attenuate alcohol cue-elicited appetitive responses, attenuate the ability of one alcohol drink to prime craving for a subsequent drink, and attenuate the stimulatory effects of alcohol in a sample of heavy social drinkers. Based on the preclinical literature suggesting that alcohol cue-elicited urge may be associated with dopamine activation, it was hypothesized that pretreatment with olanzapine would attenuate cue-elicited responses as compared to a placebo control. Based on the preclinical literature suggesting that alcohol priming may be associated with dopamine activation, it was hypothesized that pretreatment with olanzapine would attenuate the ability of one drink to prime craving for another drink. It was also hypothesized that olanzapine would moderate subjective stimulation after alcohol consumption based on reports suggesting that the stimulatory effects of alcohol are related to dopamine activation.

Materials and methods

Participant characteristics

The investigation was approved by the Brown University IRB and the Roger William's Medical Center IRB, and participants gave their written informed consent before participating. Participants were recruited from the greater Providence, Rhode Island community. Participants were included in the study if they reported drinking at least twice per week and at least three drinks per occasion (two for women), did not report ever having received treatment for alcohol problems, did not have any history of cardiac illness, did not report any hearing loss, were not taking medications contraindicated for concurrent use with olanzapine, were over 21 years of age, did not have a breath alcohol level (BAL) greater than 0 prior to the beginning of either of the experimental sessions, and, if female, were not positive on a pregnancy test or nursing. All participants received a physical examination by a physician prior to the study, and only those with a normal physical examination were included. Participants received $100 for completing the study.

Twenty-six participants were recruited from the communities surrounding Providence, Rhode Island, and were randomly assigned to receive olanzapine (5 mg) or a matching placebo. There were 13 participants (four women) who were assigned to the olanzapine group and 13 participants (seven women) who were assigned to the placebo group. *T*-tests indicated that the groups were not different prior to the administration of the medication on any demographic or alcohol-related characteristics (*P* values >0.10). The mean age and standard deviation of the placebo and olanzapine groups were 23.3 (4.0) and 23.3 (3.1), while the number of alcohol drinks in the last 30 days averaged 111 (98) and 90.7 (84.3), respectively. The mean number of drinking days averaged 17.1 (4.9) and 15.2 (4.3), while the mean number of drinks per drinking occasion was 6.2 (5.1) and 5.4 (4.3). The mean of the alcohol dependence scale (ADS; Skinner and Allen 1982) total score for the placebo and olanzapine groups was 8.9 (4.4) and 7.8 (5.7), while the alcohol use disorders identification test (AUDIT; Saunders et al. 1993) was 12.8 (6.4) and 11.6 (8.3), respectively.

Procedure

Participants came to the laboratory in the morning for each of two experimental sessions that were 1 week apart. Participants were randomly assigned to receive either a placebo or a 5-mg dose of olanzapine 8 h prior to each of the experimental sessions. Participants were told that they would receive either olanzapine or an inactive medication (placebo). Participants were instructed to take the medication prior to going to bed in order to diminish the impact of any drowsiness experienced as a result of the olanzapine. Participants called the experimental office immediately after taking the medication to confirm when it was taken. In order to confirm that participants took the medication, the placebo (vitamin C) and the olanzapine were packed into an opaque capsule with 50 mg riboflavin. A urine sample was collected on the morning of the experimental session. The urine sample was tested for riboflavin content by examining it under an ultraviolet light, which makes the riboflavin detectable (Del Boca et al. 1996). The samples indicated that all of the subjects in the current study were compliant. At the end of each experimental session, participants were asked whether they believed that they had received olanzapine or placebo medication. Participants guessed correctly on 75% of the sessions.

Table 1 represents a timeline for all of the experimental procedures and measures. At the beginning of each session, participants were seated at a desk and instructed to relax in order to allow them to habituate to the laboratory before completing baseline measures of urge, stimulation, and sedation (see description of measures below). Participants were subsequently exposed to both the control cues and the alcohol cues in each session. The order of the cues was the same during each experimental session (Monti et al. 1987). In the control cue condition, a commercially labeled bottle of water and a glass was placed in front of the participants. The participants were instructed to pour the glass half full with water and were instructed to lift the glass and smell the water. The exposure continued for 3 min. After the exposure period, the cues were removed and the participants were instructed to complete another battery of assessments. Participants were then exposed to alcohol cues. In the alcohol cue condition, each individual's favorite alcohol beverage in its commercially labeled container was placed in front of them with a glass. The participants were then instructed to pour the beverage into the glass, lift the glass to their face, and smell the beverage.

Participants consumed alcohol after the cue exposure period during one session and a placebo beverage during the other session. The order of presentation was counterbalanced across sessions. Participants were randomly assigned to an order. Fourteen

Table 1 Sample timeline for experimental procedures and measures for each session. *AUQ* Alcohol urge questionnaire, *BAES* biphasic alcohol effects scale, *PANAS* positive affect/negative affect scale

Time	Task	Measures completed
10:00 a.m.	Relaxation/habituation	AUQ, BAES
10:10 a.m.	Exposure to water cues	Urge, AUQ, attention, PANAS
10:20 a.m.	Exposure to alcohol cues	Urge, AUQ, attention, PANAS
10:30 a.m.	Drink 1	AUQ, BAES, drink ratings
10:45 a.m.	Drink 2	AUQ, BAES, drink ratings
11:00 a.m.	Drink 3	AUQ, BAES, drink ratings
11:20 a.m.	Post-drink	BAES

subjects received alcohol on the first session and non-alcohol on the second session. Twelve subjects received non-alcohol on the first session and alcohol on the second session. The dose of alcohol was adjusted by gender, height, and weight to achieve a desired peak BAL (Watson 1989). During the alcohol session, participants consumed three beverages that consisted of beer with a high alcohol content (i.e., ca 9%). Each alcoholic drink contained the equivalent of 0.15 g/kg doses of alcohol (0.11 g/kg for females). During the non-alcohol session, participants consumed three placebo beverages (i.e., non-alcohol beer with food coloring to make its appearance equivalent to the dark brown color of the beer with alcohol). During both sessions, participants were instructed to consume each beverage at an even pace over 2 min. After the 2-min consumption period, subjects relaxed for 3 min before beginning a battery of measures. At 15 min after beginning the first drink, participants were instructed to consume the second drink and followed the same procedures. The third and final drink was consumed at 15 min after the second drink. A final self-report assessment was conducted at 20 min after the third drink. These drinking procedures avoid methodological problems associated with the use of ethanol/juice mixtures (i.e., ecological validity, poor taste, and nausea/vomiting) and have been used in previous investigations of the effects of naltrexone on responses to alcohol (King et al. 1997). In addition, these procedures provide a closer approximation to drinking in the environment (for example, one drink every 15 min) as opposed to traditional procedures that involve the administration of a single bolus dose of alcohol.

Measures

Individual differences measures

Prior to the first experimental session, participants completed a battery of individual difference measures that included demographic questions as well as measures of drinking behavior. The AUDIT and ADS were used as measures of problem drinking behavior, while a 30-day TLFB procedure (TLFB; Sobell and Sobell 1980) was used to measure the quantity and frequency of drinking in the 30 days prior to the experiment.

Positive affect/negative affect scale (PANAS)

The PANAS is a 20-item measure with subscales for positive affect and negative affect. The PANAS is a reliable and valid measure of both positive and negative affect (Watson et al. 1988). The PANAS was completed after each cue exposure.

Urge to drink alcohol

After each cue exposure, urge to drink alcohol was rated on an 11-point Likert scale that was anchored by “No urge at all to drink alcohol” at 0 and “Very strong urge to drink alcohol” at 10. This measure is valid and reliable across repeated administrations of cue exposure (see, for example, Monti et al. 1993, 1999).

Alcohol attention scale

Attention to the beverage was measured using three ratings which have been found to form a reliable scale (Monti et al. 1993). For this measure, participants rate the amount of attention they paid to the sight and smell of the beverage and to thoughts about drinking the beverage using 11-point anchored Likert scales (from 0 to 10) after being exposed to the control cue and after being exposed to the alcohol cue. The mean of the three ratings is used as the scale score.

Alcohol urge questionnaire (AUQ)

The AUQ was also used to assess urge to drink at baseline and after each beverage was consumed. The AUQ consists of eight items related to urge drink that are rated on a seven-point Likert scale with the extremes anchored by “Strongly Disagree” and “Strongly Agree.” The AUQ has demonstrated internal consistency and reliability (Bohn et al. 1995).

Biphasic alcohol effects scale (BAES)

The BAES was used to collect information on self-reported stimulation and sedation at baseline and after each beverage was consumed. The BAES has a subscale for stimulation and a subscale for sedation. This measure has previously demonstrated reliability and validity in investigations of the stimulatory and sedative effects of alcohol (Martin et al. 1993; Earleywine and Erblich 1995) and for assessing medication effects (Swift et al. 1994).

Drink ratings

Participants were asked to make ratings after each drink regarding how much alcohol was in the beverage (“How much alcohol was in the beer?”), how high they were feeling [“How high (as in drug high) do you feel?”], how much they liked the beverage (“How much did you like the beer?”), and how much they wanted another beverage (“Do you want more beer?”) after consuming each beverage. Each rating was made on a ten-point Likert scale.

Design and analysis

The hypotheses with respect to cue-elicited responses were tested in a 2 (Medication: olanzapine or placebo) × 2 (Cue: water cue exposure or alcohol cue exposure) × 2 (Session: session 1 vs session 2) mixed between- and within-subjects factorial design. Medication was a between-subjects factor while Cue and Session were within-subjects factors. The data were analyzed with repeated measures analyses of variance (ANOVA).

The hypotheses regarding the effects of alcohol and olanzapine on urge and the hedonic ratings of the drinks were tested in a double-blind, placebo-controlled, 2 (Medication: 5 mg olanzapine vs placebo) × 2 (Alcohol: drink containing alcohol vs drink that does not) × 3 (Trial: drink 1 vs drink 2 vs drink 3) mixed between- and within-subjects factorial design. Alcohol and Trial were within-

subjects factors. Data were analyzed with repeated measures ANOVAs. In order to test the hypotheses regarding subjective stimulation and sedation, a fourth assessment (post-drinking) was added to the analyses. For variables assessed at baseline (i.e., AUQ, BAES stimulation, and BAES sedation), change scores (i.e., change from baseline) were used in the analyses.

Results

Baseline analyses

The analysis of baseline urge to drink using the AUQ score did not show any significant effects for olanzapine, the alcohol factor, or an interaction ($P>0.10$). The analysis of baseline stimulation indicated a significant main effect for olanzapine, $F(1,24)=8.48$, $P<0.01$, suggesting that olanzapine decreased baseline stimulation relative to the placebo medication. Furthermore, the analysis of baseline sedation revealed a significant main effect for olanzapine, $F(1,24)=6.37$, $P<0.05$, suggesting that olanzapine also increased baseline sedation. The mean and standard deviations for baseline sedation, collapsed across experimental sessions, was 2.53 (2.02) for the olanzapine group and 4.63 (2.59) for the placebo group.

Cue exposure

The analysis of the rating of urge to drink alcohol during exposure revealed a significant main effect for Cue, $F(1,24)=61.20$, $P<0.01$, and a significant Medication by Cue interaction, $F(1, 24)=14.11$, $P<0.01$, indicating that olanzapine moderated the effect of alcohol cue exposure on urge to drink consistently across sessions (see Fig. 1A). Simple effects tests indicated that participants who received olanzapine still demonstrated a significant cue-elicited increase in urge to drink alcohol ($P<0.05$), although this increase was attenuated by olanzapine. The main effect for Medication was not significant ($P>0.05$), although there was a significant main effect for Session, $F(1,24)=5.63$, $P<0.05$, suggesting that urge reactivity generally decreased from the first exposure session to the second exposure session.

With respect to the score for the AUQ, an ANOVA revealed a similar main effect for Cue, $F(1,24)=26.08$, $P<0.01$, as well as a significant Medication by Cue inter-

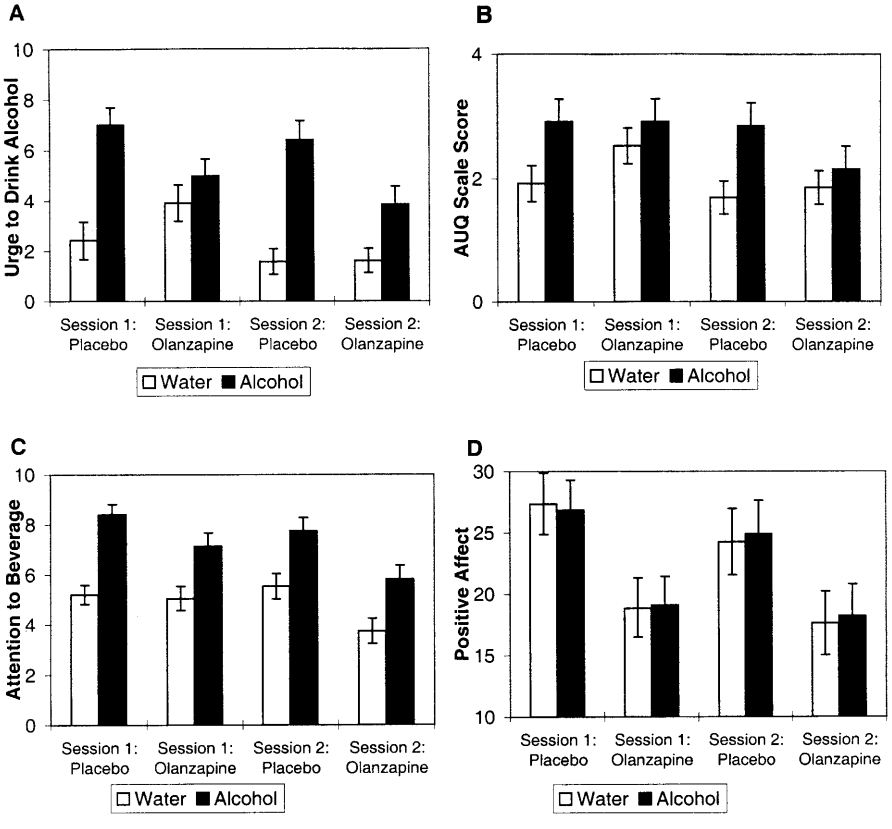

Fig. 1 **A** Mean urge to drink and standard errors after exposure to control cues and alcohol cues for session 1 and session 2. Tests indicated that exposure to alcohol cues increased urge to drink in all conditions, although this effect was attenuated by olanzapine ($P<0.05$). **B** Mean alcohol urge questionnaire (AUQ) scores and standard errors after exposure to control cues and alcohol cues for session 1 and session 2. Tests indicated that alcohol cue exposure significantly increased the AUQ score although this effect was reduced by olanzapine ($P<0.05$). **C** Mean attention to beverage after exposure to control cues and alcohol cues for session 1 and session 2. Tests indicated that attention to beverage was greater after alcohol cues ($P<0.05$), greater in the placebo condition ($P<0.05$), and greater in session 1 as opposed to session 2 ($P<0.05$). **D** Mean positive affect and standard errors after exposure to control cues and alcohol cues for session 1 and session 2. Tests revealed that olanzapine significantly reduced positive affect across cue presentations and sessions ($P<0.05$)

action, $F(1,24)=6.88$, $P<0.05$, suggesting that olanzapine moderated the effects of alcohol cue exposure on the AUQ scores consistently across sessions (see Fig. 1B). Simple effects tests indicated that participants who received olanzapine still demonstrated a significant cue-elicited reaction on the AUQ across sessions ($P<0.05$), although this reaction was diminished relative to the placebo condition. There was also a main effect for Session, $F(1,24)=6.60$, $P<0.05$, suggesting that reactivity was diminished during the second session. The main effect for medication was not significant ($P>0.05$). The mean correlation between urge to drink and the AUQ score after alcohol cue exposure was $r=0.80$ across sessions, $P<0.01$, indicating that the two measures were highly consistent with one another.

The analysis of attention to beverage after alcohol cue exposure revealed a significant effect for Cue, $F(1,24)=104.28$, $P<0.01$, a significant main effect for Session, $F(1,24)=8.19$, $P<0.01$, a significant main effect for Medication, $F(1,24)=5.16$, $P<0.05$, and a significant Medication by Session interaction, $F(1,24)=4.91$, $P<0.05$ (see Fig. 1C). Simple effects tests suggested that attention to the beverages decreased across sessions for the olanzapine group ($P<0.05$), but did not diminish across sessions in the placebo group ($P>0.05$). The main effects indicated that attention to beverage was greater to alcohol than to water, greater in the placebo condition than the olanzapine condition, and greater in the first session than the second session.

The analysis of positive affect using the PANAS indicated a significant main effect for Medication, $F(1,24)=4.83$, $P<0.05$, but no significant effects for Session, Cue, or any significant interactions ($P>0.10$), indicating that olanzapine reduced positive affect after exposure to both water and alcohol consistently across sessions (see Fig. 1D). An analysis of the negative affect scale of the PANAS did not reveal any significant differences ($P>0.10$).

Alcohol levels

An analysis of BALs in the alcohol condition revealed a significant effect for Trial, $F(3,72)=220.40$, $P<0.01$, indicating that BALs increased across trials as expected. There was not a significant main effect for Medication or an interaction ($P>0.10$). These data suggest that olanzapine did not influence the metabolism of the alcohol.

Effects of a priming dose of alcohol on urge

The analysis of the AUQ change scores (i.e., change from baseline AUQ) revealed a significant Medication by Alcohol by Trial interaction, $F(2,48)=6.53$, $P<0.01$, indicating that olanzapine attenuated the effect of alcohol on urge to drink across trials (see Fig. 2A). A simple effects analysis of data within the non-alcohol condition did not reveal any significant effects ($P>0.10$), indicating that olanzapine did not have any effect on urge to drink in the non-alcohol condition. However, an analysis of the data within the alcohol condition revealed a significant Medication by Trial interaction, $F(2,48)=4.68$, $P<0.05$, suggesting that olanzapine reduced urge to drink in the alcohol condition. Following the interaction, further simple effects tests indicated that AUQ scores increased significantly in the placebo condition ($P<0.05$) but did not increase in the olanzapine condition ($P>0.10$).

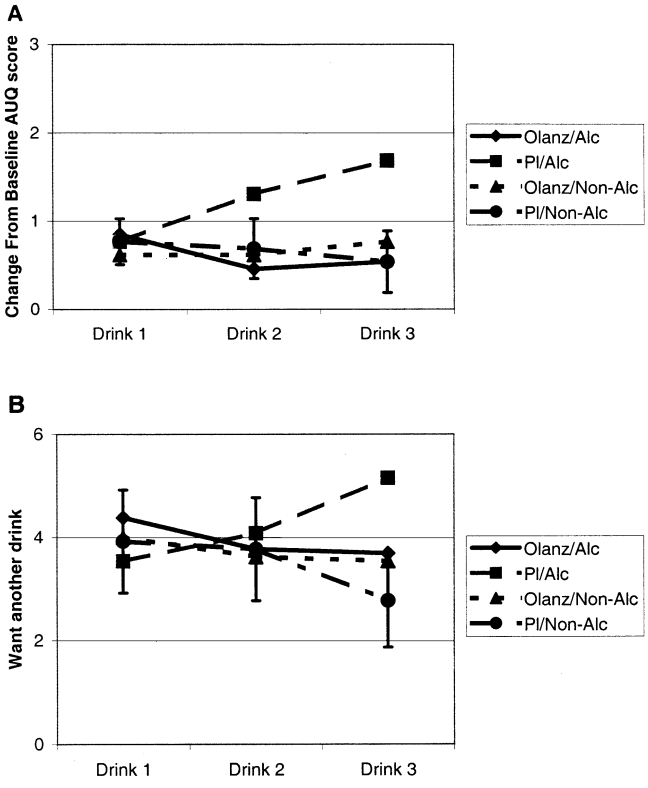

Fig. 2 **A** Mean AUQ change scores and standard errors after consumption of an alcoholic or non-alcoholic beverage. Tests indicated that AUQ scores increased significantly across drinks when subjects were pretreated with placebo medication and consumed alcohol ($P<0.05$), but did not increase when subjects received olanzapine and alcohol or non-alcohol beverages. **B** Mean wanting another drink scores and standard errors after consumption of an alcoholic or non-alcoholic beverage. Tests suggested that wanting increased when subjects were pretreated with placebo medication and consumed alcohol ($P=0.07$), but did not increase when subjects received olanzapine and alcohol or non-alcohol beverages

Analyses of the subjective "want" for another drink revealed a significant Alcohol by Trial interaction, $F(2,48)=4.21$, $P<0.05$, as well as a significant Medication by Alcohol by Trial interaction, $F(2,48)=5.43$, $P<0.05$, suggesting that olanzapine attenuated the effects of alcohol on the subjective want for another drink across trials (see Fig. 2B). A simple effects analysis of data within the non-alcohol condition did not reveal any significant effects ($P>0.10$), while an analysis of the data within the alcohol condition revealed a significant Medication by Trial interaction, $F(2,48)=4.79$, $P<0.05$, suggesting that olanzapine did not influence subjective want in the non-alcohol condition but did reduce subjective

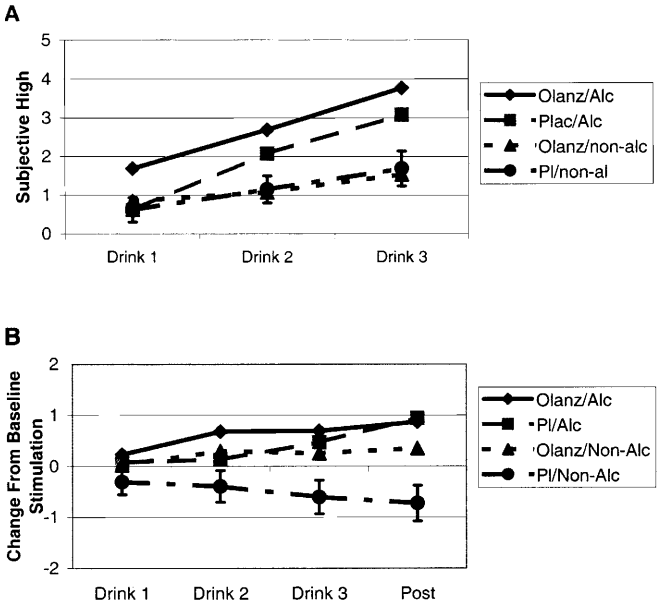

Fig. 3 **A** Mean scores and standard errors for subjective high after consumption of an alcoholic or non-alcoholic beverage. Tests indicated that subjective high increased significantly across drinks when subjects consumed alcohol regardless of whether they received olanzapine or placebo medication ($P<0.05$). **B** Mean change scores for and standard errors for subjective stimulation after consumption of an alcoholic or non-alcoholic beverage. Tests revealed that that the consumption of alcohol increased stimulation regardless of whether subjects received olanzapine or the placebo medication ($P<0.05$)

want across trials in the alcohol condition. Following the interaction, further simple effects tests indicated a trend for wanting another drink to increase significantly in the placebo condition ($P=0.07$) but no trend in the olanzapine condition ($P>0.10$).

Effects on subjective intoxication

The analyses of subjective high after consumption revealed a significant main effect for Alcohol, $F(1,24)=19.13$, $P<0.01$, a significant effect for Trial, $F(2,48)=20.68$, $P<0.01$, and a significant Alcohol by Trial interaction, $F(2,48)=6.76$, $P<0.01$. Simple effects tests revealed that subjective high increased across trials in the alcohol condition ($P<0.05$) but did not increase across trials in the non-alcohol condition (see Fig. 3A). There was no main effect for Medication or any significant interaction with Medication ($P>0.10$). An analysis of the ratings of how much the participants liked the beverage did not reveal any significant main effects for Medication, Alcohol, Trial, or a significant interaction ($P>0.10$). The analysis of ratings of how much alcohol was present in the beverage revealed a main effect for Alcohol, $F(1,24)=47.85$, $P<0.01$, indicating that subjects consistently rated the alcoholic beverage as containing more alcohol than the non-alcoholic control beverage. However, it is important to note that subjects believed there was a moderate amount of alcohol in the non-alcoholic control beverages. There were no significant effects for Medication or a significant interaction. To determine whether the perception of the amount of alcohol in the beverages was associated with the other dependent measures, correlations were calculated between the alcohol ratings and other dependent measures (for example, urge to drink). There were no significant correlations, suggesting that expectancies about the alcoholic content of the beverages did not significantly influence the other measures.

The analyses of change from baseline on the stimulation scale of the BAES revealed a significant main effect for Alcohol, $F(1,24)=5.44$, $P<0.05$, but no effect for Medication, Trial, or any interaction ($P>0.10$), suggesting that alcohol increased subjective stimulation as compared to the control beverage, while olanzapine did not moderate this effect (see Fig. 3B). The analysis of subjective sedation after consumption did not reveal any significant effects ($P>0.10$), suggesting that the dose of alcohol did not produce significant sedation. However, it should be noted that the assessments of sedation were conducted during the ascending arm of the blood alcohol curve when the effects of alcohol on sedation are minimal. Thus, the current study does not provide an adequate test of whether olanzapine influences the sedative effects of alcohol.

Analysis of order effects

Finally, the ANOVAs described above were repeated with the order of alcohol administration (alcohol in the first session vs non-alcohol in the first session) in order to test for a significant interaction between the order of alcohol administration and the effects of the medication. The analyses did not reveal any significant effects involving treatment order ($P>0.05$).

Discussion

The primary findings of the present study were that olanzapine attenuated the effects of alcohol cues on two separate measures of urge to drink across two separate experimental sessions and that olanzapine prevented increases in urge to drink after alcohol consumption. Olanzapine did not appear to have an effect on urge to drink in general, but rather only attenuated urge to drink when participants were exposed to alcohol cues or consumed alcohol. The findings also suggested that olanzapine generally reduced attention and positive affect across exposure to the control and alcohol cues but did not have any effect on negative affect. With respect to the effects on urge to drink, the findings of this study are generally consistent with the theoretical premise that this appetitive behavior is partially mediated by mesolimbic dopamine activation.

The fact that the effects of olanzapine were specific to cue-elicited urge supports the value of using cue expo-

sure when assessing medication effects on urges. Urges to drink in the absence of cues are often low, even in clinical populations, and these "floor effects" may mask the effects of medications (Monti et al. 1999, 2000). Eliciting urges to drink creates a more powerful test of medication effects. Cue exposure also provides a more realistic scenario as drinking is more likely to occur in a high-risk situation such as in the presence of alcoholic beverages.

The finding that olanzapine attenuated the effects of alcohol consumption on urge to drink is consistent with a report demonstrating that a dopamine antagonist, haloperidol, blocked the ability of alcohol consumption to prime craving for more alcohol in a sample of alcohol-dependent patients (Modell et al. 1993). The current study extends this previous finding by demonstrating that an atypical antipsychotic (olanzapine) has a similar effect to that of haloperidol. In terms of clinical potential, olanzapine and other atypical antipsychotics have a distinct advantage over traditional antipsychotics, such as haloperidol and tiapride, because they do not have the same propensity to induce extrapyramidal side effects. Thus, patient comfort and safety is demonstrably greater with these new medications. One of the implications of this study is that olanzapine may have some promise for clinical use with alcohol dependence and should be evaluated further. One of the hypothetical therapeutic actions of naltrexone is its ability to prevent one drink from leading to a full relapse (O'Malley et al. 1996). The results of the current study suggest that olanzapine may be similar to naltrexone in this respect, although further testing in a clinical population is needed.

The hypotheses concerning subjective stimulation and the rewarding effects of alcohol were not supported by the current study. The results suggested that olanzapine attenuated subjective stimulation at baseline and that alcohol increased stimulation consistently across trials as compared to the control beverage. However, the analyses failed to show the hypothesized interaction effect between olanzapine and alcohol on subjective stimulation. Although alcohol increased the subjective feeling of being high across drinks, the results also indicated that olanzapine did not influence the effects of alcohol on subjective high. In sum, these results suggest that the rewarding and stimulatory effects of alcohol may not be related to the action of alcohol on dopamine or 5-HT_2 receptors. It is possible that other neurotransmitter systems (for example, opioid, GABA, glutamate) may be more involved in the rewarding effects of alcohol (Volpicelli et al. 1995).

The findings that olanzapine reduces the ability of alcohol cues to elicit urges to drink, reduces attention to an alcoholic beverage, and reduces the ability of one drink to prime the urge for another are promising. The results suggest that individuals may be less likely to drink in the presence of alcohol cues or less likely to relapse after a slip when taking olanzapine. It would be of great interest to replicate these findings with alcoholics who are trying to stay sober. If olanzapine demonstrated similar effects in a sample of alcoholics, the results would demonstrate the potential benefit of using a dopamine antagonist such as olanzapine in this population. The finding that olanzapine increased sedation might be a potential disadvantage, although the sedating effects of olanzapine may lessen with repeated administration.

Because olanzapine has moderate to high affinity for a number of other receptors (for example, 5-HT_2, H_1, $M_{1–4}$), this investigation does not provide direct evidence that the effects of olanzapine are mediated by a specific dopamine receptor or by dopamine receptors in general. As noted previously, several preclinical studies have suggested that 5-HT_2 antagonists may reduce drinking behavior (see, for example, Meert et al. 1991; Myers et al. 1992, 1993), and it is possible that the action of olanzapine on this receptor or another receptor underlies the effects of olanzapine noted in this study, although a large clinical trial in humans suggested no effect for a 5-HT_2 antagonist (Johnson et al. 1996). Another potential explanation for the effects of olanzapine in the present study is that olanzapine may have increased sedation through its action on histaminergic and muscarinic receptors. However, the urge to drink and wanting another drink were not influenced by olanzapine after the consumption of the non-alcohol beverage, suggesting that olanzapine exerted an influence only in combination with alcohol rather than exerting influence through a non-specific side effect such as sedation. In addition, there were no significant differences in urge to drink in the control cue condition, suggesting that sedation due to olanzapine did not have a general effect on urge to drink.

Although the association between specific neurotransmitter receptors and cue-elicited craving for alcohol cannot be established because of the heterogeneous nature of olanzapine, this limitation is one that is not limited to olanzapine or this specific study. None of the dopamine antagonists (for example, haloperidol, pimozide, etc.) that are approved for use with humans have effects that are specific to just dopamine receptors. Future research should compare several different active medications within the same investigation in order to examine the relative contributions of different mechanisms. Another limitation of the present study is the non-clinical sample, which reduces the generalizability of the findings. In addition, only a single dose of olanzapine was used. In order to establish the clinical potential of olanzapine and other atypical antipsychotic medications, future trials should investigate the effects of multiple doses over multiple days in a clinical population.

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