Published in final edited form as:

Psychopharmacology (Berl). 2015 April ; 232(7): 1261–1268. doi:10.1007/s00213-014-3757-1.

Dose Specific Effects of Olanzapine in the Treatment of Alcohol Dependence

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Abstract

Rationale—It is well-established that the rewarding effects of alcohol are modulated by the mesolimbic dopaminergic system. Olanzapine, a D2 dopamine antagonist, has been shown to reduce alcohol craving and consumption.

Objective—To clarify whether olanzapine has clinical utility in the treatment of alcohol dependence, a 12-week, double-blind, randomized clinical trial was conducted.

Methods—One-hundred twenty-nine treatment-seeking alcohol dependent adults were randomly assigned to 12-weeks of olanzapine (5mg vs. 2.5mg) or placebo. Outcomes examined were average drinks per drinking day (DDD), proportion of drinking days to total days in treatment (PDD), alcohol craving, and impaired control over alcohol use. Mixed models were used to examine medication effects during the course of treatment on specified outcomes.

Results—All of the analyses indicated a main effect for time, such that there were reductions in alcohol use and craving and an increase in control over alcohol use across treatment conditions. Dose-response analyses indicated that, in comparison to placebo, participants in the 5mg group experienced reduced craving for alcohol and participants in the 2.5mg group decreased in PDD and increased in their control over alcohol use. Better control over alcohol use remained significant 6 months post-treatment for the 2.5mg group. Subjective experiences of the medication suggest that 2.5mg and 5mg were equally well-tolerated.

Conclusions—Results provide some support for the notion that dosage is an important consideration in relation to effectiveness; however, the cost-benefit balance does not support the clinical utility of olanzapine in treating alcohol dependence.

Keywords

Alcohol dependence; olanzapine; addiction; pharmacotherapy; treatment; dose response; atypical antipsychotic

There is increasing evidence supporting the conceptualization that neuroadaptations in the circuits underlying the incentive salience of alcohol and executive control over the use of alcohol are critical in terms of the etiology of alcohol dependence and relapse after treatment (Hutchison, 2010; Karoly, et al., 2013; Koob, 2013). This conceptualization has spurred research investigating pharmacotherapies that target these systems. For example, previous studies provide rationale for the use of atypical antipsychotics and have examined the effects of quetiapine (Litten, et al., 2012; Martinotti, et al., 2008; Ray, et al., 2010), aripiprazole (Anton, et al., 2008; Brunetti, et al., 2012; Voronin, et al., 2008), and olanzapine (Guardia, et al., 2004; Hutchison, et al., 2006), among others. While a few studies have suggested some potential for atypical antipsychotics (Martinotti, et al., 2008; Ray, et al., 2010; Voronin, et al., 2008), large clinical trials (Anton, et al., 2008; Guardia, et al., 2004; Litten, et al., 2012) and a recent meta-analysis (Kishi et al., 2013) find little evidence of therapeutic effectiveness for alcohol dependence.

Olanzapine, a D₂/5-HT₂ antagonist, is one of several atypical antipsychotics to be evaluated in the past decade for use in treating alcohol dependence. The side effect profile for olanzapine includes dry mouth, drowsiness, nausea, and increased appetite in addition to risk for serious adverse effects (e.g., metabolic syndrome, diabetes, tardive dyskinesia). Determining what dosage will produce a therapeutic effect, without the negative side effects that often result from these medications, is a critical factor in evaluating efficacy.

Previous studies may have included doses that were greater than necessary and may have resulted in side effects that undermined the therapeutic effect of the medication. For example, one prior investigation of olanzapine efficacy used a target dose of 15 mg and found no difference as compared to placebo in reducing alcohol use (Guardia, et al., 2004). Whereas studies with lower doses have indicated positive effects. For example, a laboratory based study suggested that 5 mg of olanzapine reduced cue elicited craving, especially among individuals with a specific genetic risk factor (Hutchison, et al., 2003). In addition, a randomized, placebo controlled trial suggested that 2.5 to 5 mg of olanzapine reduced craving and alcohol consumption, especially among individuals with a specific genetic risk factor (Hutchison, et al., 2006). A similar pattern has been observed in research evaluating aripiprazole, another atypical antipsychotic. A low dose of aripiprazole (5–15mg) was shown to reduce relapse (Janiri, et al., 2007), decrease alcohol consumption (Voronin, et al., 2008), and decrease the euphoric effects of alcohol in a laboratory bar setting (Kranzler, et al., 2008); whereas, in a randomized-controlled trial involving a treatment seeking population, a higher dose of aripiprazole (15–30 mg) failed to show significant differences in alcohol use (Anton, et al., 2008).

Variability in the doses of olanzapine that have been studied in previous trials may be a key factor in the mixed findings regarding efficacy. The present study was designed to examine two different doses of olanzapine (2.5 mg vs. 5 mg) on alcohol consumption, craving, and control over alcohol consumption in the context of a 12 week randomized, placebo controlled trial. The aim of this study was to evaluate the dose response relationship of olanzapine in the treatment of alcohol dependence. Results showing that both 2.5 mg and 5 mg are superior to placebo would support a treatment model consistent with a standard dose response relationship for medications targeting frontal-striatal circuits. Alternatively, results

showing that a lower dose is superior to a higher dose and placebo would support a treatment model in which higher doses undermine the positive effects of medications that target these circuits.

Methods

Clinical Trial Design

A double-blind, placebo-controlled 3 (**Medication:** Olanzapine 5 mg, Olanzapine 2.5 mg, placebo control) $\times$ 4 (**Time:** Baseline, 4, 8, 12 weeks) mixed factorial design, where medication is a between-subjects factor and time is a within-subjects factor, was used to test the treatment outcome hypotheses. Subjects were randomly assigned to receive olanzapine (5 mg), olanzapine (2.5 mg), or a placebo control for a period of 12 weeks. All subjects also received seven sessions of medication management and motivational enhancement therapy (detailed below). Assessments were obtained at 4, 8, and 12 weeks (the end of treatment), 24 weeks, and 36 weeks. There were a total of eleven visits to complete the screening, treatment, and follow-up phases of the RCT.

Participant Selection

Participants were recruited via radio, newspaper, and flyers to participate in a medication study that was advertised to assist in quitting drinking. Interested persons received information about the study and responded to initial screening questions via phone. Treatment-seeking adults between the ages of 21–55 who reported 4 consecutive weeks of heavy alcohol use (at least 21 drinks per week for men and 14 for women) in the past 90 days and were within 21 days of last alcohol use were brought in for an 8 hour screening session that involved: self-report measures, structured clinical interview (SCID; alcohol, drug, mood, and psychosis modules), blood draw, history and physical, electrocardiogram, urine drug screen, and urine pregnancy test. The study physician conducted a history and physical and reviewed lab results for each participant to determine eligibility. Participants were excluded if they screened positive for any of the following: history of injury to the brain or brain related medical problems (as determined by self-report or MRI results), metabolic syndrome, elevated liver function test (3 times greater than normal), abnormal ECG (as determined by a cardiologist), illicit drug use (excluding marijuana), use of psychiatric medication contraindicated for use with olanzapine, pregnancy, uncontrolled diabetes, uncontrolled hypertension, psychotic disorder, bipolar disorder, or current major depression with suicidal ideation, or any other clinically significant abnormalities (determined by study physician).

Procedures

During the baseline session, participants completed self-report measures, met with a therapist for the therapy and medication management component of the trial (described below), and received enough medication to last one week.

Medication Administration—Participants were instructed to take the medication before going to bed in order to diminish the impact of any drowsiness experienced as a result of the olanzapine. Participants' experiences of side effects from the medication were assessed

using a 40-item measure of physical and psychological symptoms designed specifically for this study based on side effects reported in FDA safety investigations. Side effects were assessed at each assessment and participants were instructed to report adverse effects to project staff or the study physician immediately. For each symptom endorsed, participants were asked to provide timeframe, frequency, severity, and whether they attributed the symptom to the medication or something else. To confirm that participants took the medication, the medications were packed in an opaque capsule with 50mg of riboflavin. A urine sample was collected at each appointment and tested for riboflavin content by examining it under an ultraviolet light, a procedure that makes the riboflavin detectable (Del Boca et al., 1996). None of the samples tested negative for riboflavin.

Individual therapy—Participants were asked to attend 7 sessions of individual therapy over the course of the 12-week medication trial. The content of therapy sessions consisted of medication management, motivational enhancement, and relapse prevention and was designed in accordance with the Combined Behavioral Intervention Treatment Manual (COMBINE, 2004). At the baseline session, participants were provided with personalized feedback regarding their alcohol use and engaged in open-ended discussion with their therapist regarding their motivation to quit drinking alcohol and personal goals related to drinking. Throughout the course of treatment, the participant and therapist worked collaboratively to develop and enact a change plan aimed at quitting drinking and to problem solve around drinking-related or medication adherence challenges. To be consistent with the spirit of motivational interviewing and to optimize retention, participants who were not successful in abstaining from alcohol in the first two to four weeks of treatment were encouraged to incorporate sober days in order to facilitate the positive effects of the medication on craving, to use behavioral strategies for coping with craving and triggers, and to reduce their alcohol consumption as much as possible. Two female post-doctoral clinicians and four clinical psychology graduate student clinicians conducted therapy sessions.

Outcome Measures

The primary efficacy outcome variables were the proportion of days during treatment that participants drank alcohol (drinking days/total days; PDD) and the average number of drinks per drinking occasion (DDD) during study weeks 4 through 12. The time-line follow-back procedure (TLFB; Sobell & Sobell, 1992) was used to assess quantity and frequency of drinking in the 60 days prior to screening as well as the time elapsed between each assessment. Secondary outcome measures included subjective craving for alcohol, assessed using the alcohol urge questionnaire (AUQ), an eight-item Likert scale with high reliability (Bohn, et al., 1995), severity of alcohol dependence, assessed using the Alcohol Dependence Scale (ADS; Skinner, 1984), and failed control, assessed with the Impaired-control Scale (ICS; Heather, et al., 1998; Heather, et al., 1993; Marsh, et al., 2002). The ICS consists of 25 items in three subscales: attempted control (AC), failed control (FC), and predicted control (PC) and has established validity and reliability in alcohol dependent samples. Our analyses focus on the failed control subscale because this construct has been shown to correlate with alcohol consumption and treatment outcome (Heather, et al., 1998).

Results

Participant Characteristics

Three hundred thirty-nine individuals were consented and completed the initial screening session. One hundred twenty-nine individuals passed the initial screening and were randomized to a medication condition and scheduled for a baseline session. One hundred twenty-nine alcohol dependent, treatment-seeking volunteers (32% female) were randomly assigned to a medication condition and completed a baseline session. Forty participants were recruited from and completed the study in Colorado (2006–2007) and eighty-nine participants were recruited from and completed the study in New Mexico (2007–2011)¹.

The mean age of participants was 40 years old ($SD = 8.8$). The vast majority of participants identified their race as Caucasian (65%), 6% as Multi-Racial, 4% as Native American, and less than 1% identified as African-American and Asian. A majority of participants reported that they were employed (52%), 25% were students or employed part-time, and 23% were unemployed. Approximately half of participants reported a yearly income of less than \$30,000 and 15% greater than \$60,000. Nearly all participants had graduated from high school (95%) and almost half of them had completed at least some college. As shown in Table 1, there were no differences between medication groups on demographic characteristics or pre-treatment alcohol use or outcome variables ($ps > .05$). There were no differences in pre-treatment alcohol use characteristics (ADS, PDD, DDD) between sites.

Treatment Retention

Seventy-seven percent of participants ($n = 99$) were retained through four weeks of treatment and fifty-two percent of participants ($n = 65$) were retained through the full 12-week treatment period (see Figure 1). Medication groups did not differ with respect to the total number of study visits attended (placebo = 5.8; 2.5mg = 5.6; 5mg = 5.35; $F(2, 128) = .28, p > .05$). There were no differences between treatment groups with respect to retention through twelve weeks of treatment, $\chi^2 = 2.01, p = .366$.

Side Effects & Adverse Events

Four adverse events involved randomized participants and were reported to human subjects protection (2 participants in the 2.5mg group and 2 in the 5mg group); only one of the adverse events was likely attributed to the study medication (i.e., onset of diabetes in one participant taking 5mg olanzapine for 8 weeks). Eleven participants discontinued the medication prior to the end of the 12 week treatment period due to side effects or an adverse event: three in the placebo condition, four in the 2.5mg condition, and four in the 5mg condition. Side effects that led to discontinuation of the medication in the medication conditions were: vomiting, anxiety, nausea, weight gain, depressed mood, gastro-intestinal irritation, non-specified “feeling bad”, and one participant developed diabetes. Side effects that led to discontinuation of the placebo were: urinary retention, fatigue, irritability, depressed mood, and dizziness.

¹The primary investigator, Kent Hutchison, PhD, moved his lab from CU-Boulder to MRN-Albuquerque in 2007. The grant funding this study was also moved.

In order to assess the tolerability of the study medication, two variables were computed based on side effects endorsed by participants at each study visit: a) total number of symptoms attributed to the study medication and b) cumulative severity of endorsed symptoms (i.e., for each symptoms endorsed, we summed the severity rating provided for that symptom). Medication group differences for the number of side effects endorsed were observed only at week 1 and week 4. After taking the study medication for one week, participants in the 2.5mg group endorsed greater symptom severity as compared to participants in the 5mg ($t(115)=2.20, p<.05$) and the placebo group ($t(115)= -2.57, p<.05$) and also endorsed a greater number of symptoms than participants in the placebo group ($t(115)= -3.1, p<.05$). At week 4, participants in the placebo group endorsed fewer symptoms as compared to 2.5mg ($t(97)= -2.8, p<.05$) and 5mg ($t(97)= -2.5, p<.05$); the same pattern held for symptom severity. There was no difference in side effects between participants in the 2.5mg group and those in the 5mg group at week 4.

Drinking Outcomes

Our primary drinking outcomes were proportion of drinking days (drinking days/total days) and average number of drinks per drinking occasion. To analyze the effects of olanzapine a series of random coefficient regression (RCR) models were utilized (Cohen, et al., 2002). These models were estimated in SAS version 9.1 using the PROC MIXED procedure (Singer, 2002). RCR within the PROC MIXED procedure allows for the specification of repeated observations across time within individuals, as well as allowing for full information maximum likelihood estimation of missing data (Schafer & Graham, 2002). In these models, the fixed main effects of medication group, time, and their interaction were estimated, and study site was included as a covariate in all analyses. These models tested whether the change in the outcome variables of PDD, AUQ, ICSFC was associated with medication condition.

Dose-response analysis—The first set of models treated dose as a linear contrast, such that medication condition was coded as placebo=0, 2.5mg=1, and 5mg=2. For DDD, PDD and ICSFC, the main effect of time was significant ($p<.001$ in all cases) but there was no significant time $\times$ medication group interaction. For AUQ, however, both the main effect of time (Est.= -3.45, S.E.=1.42, $p<.05$) and the time $\times$ medication group interaction (Est.= -3.66, S.E.=1.17, $p<.01$) were significant. To examine longer term dose response relationships, we re-estimated the models including a third time point, the 36 week follow-up. Including this timepoint there were still no significant dose response effects for DDD, PDD, or ICSFC, however the time $\times$ medication group interaction was still significant for AUQ (Est.= -1.94, S.E.=.69, $p<.01$). As can be seen in Figure 2a, participants in the placebo condition experienced little change in their AUQ scores, those in the 2.5mg condition experienced a moderate decrease in AUQ, and those in the 5mg group experienced the greatest decrease in AUQ at 12 weeks. By 36 weeks, both of the medication conditions continued to show lower craving for alcohol in contrast to the placebo group.

Contrasting 2.5mg dose with 5mg dose and placebo—The next set of models tested two contrasts that pitted the 2.5mg condition against the 5mg condition (Contrast A) and a second contrast that pitted the 2.5mg condition against the placebo (Contrast B). For

ICSFC, both time $\times$ medication contrasts were significant. This indicates that the pattern of change was significantly different in the 2.5mg condition versus the 5mg condition (Est.= 3.69, S.E.=1.45, $p=.01$) and the pattern of change was significantly different in the 2.5mg condition versus the placebo condition (Est.= -3.49, S.E.=1.30, $p<.01$; see Figure 2b). For PDD, the pattern of the results was identical, but in this case the change in PDD was significantly different in the 2.5mg condition versus the placebo condition (Est.= -.13, S.E.=.05, $p=.01$; see Figure 2c) but was not significantly different in the 2.5mg condition versus the 5mg condition (Est.= .095, S.E.= .057, $p=.10$). Finally, for AUQ, there was a significant difference between the 2.5mg and placebo condition (Est.= -3.08, S.E.=1.39, $p<.05$) but there was no significant difference between the 2.5mg condition and the 5mg condition (Est.= -.96, S.E.=1.30, $p=.46$).

Again, we re-estimated the models including a third time-point, the 36 week follow-up, using the same two contrast codes described above. Including this timepoint, for ICSFC there was no significant difference between the 2.5mg and the 5mg condition (Est.= 1.48, S.E.=1.05, $p=.16$), but there was still a significant difference between the 2.5mg condition and the placebo condition (Est.= -2.22, S.E.=1.00, $p<.05$). The pattern was essentially the same for PDD. The difference between the 2.5mg condition and the placebo condition was significant (Est.= -.069, S.E.=.033, $p<.05$) and difference between the 2.5mg and the 5mg condition was not significant (Est.= .057, S.E.=.034, $p=.10$). Neither of the contrasts was significant for the AUQ when including the 36-week timepoint.

Discussion

The aim of this study was to evaluate the dose response relationship of olanzapine in the treatment of alcohol dependence. Results indicate that the effectiveness of olanzapine on craving for alcohol is dose-dependent, such that reductions in urge for alcohol during the course of 12 weeks of treatment were greatest for the 5mg group, intermediate for the 2.5mg group, and least for the placebo group. This result suggests that olanzapine attenuates craving in a dose-dependent fashion, with higher doses producing lower momentary craving for alcohol. Participants in the 2.5mg group showed greater improvements in control over alcohol use and lower PDD as compared to the placebo group over the course of 12 weeks; the 5mg group did not differ from placebo. There was no effect of medication on the quantity of alcohol consumed during drinking days; all medication groups showed a significant main effect for time such that DDD decreased across groups. At 6 months post-treatment, the 2.5mg group had fewer drinking days and a stronger sense of control over their drinking than participants in the placebo group. Differences between 2.5mg and 5mg for both PDD and ICSFC did not reach significance, but the direction of the means suggests that the 2.5mg group showed better response to treatment than the 5mg group. In summary, our findings provide some evidence that a lower dose of olanzapine is superior to a higher dose and placebo for reducing craving and increasing subjective control over alcohol use; however, the absence of significant differences in alcohol consumption by medication condition detracts support for the clinical utility of olanzapine in treating alcohol dependence.

Given the risks associated with olanzapine, and more generally with other drugs that target the same systems, it is essential to identify the safest and most well tolerated dosage. To answer this question, we examined group differences for: a) the rate at which participants discontinued from the study, b) the number of adverse events reported to the human subjects board, and c) the number and intensity of side effects that were endorsed by participants and attributed to the medication. There was no difference in attrition between groups and there were an equal number of adverse events in each group of participants taking olanzapine. With regard to participants' subjective experiences on the study medication, it appears that dosages of 2.5mg and 5mg of olanzapine were equally well tolerated.

The cost-benefit balance of atypical antipsychotics varies across treatment populations. In psychiatric populations, such as bipolar disorder and schizophrenia, olanzapine can be extremely effective in controlling mania and psychotic symptoms. In that context, the benefits of treatment significantly outweigh the discomfort of drowsiness/sedation, dry mouth, and increased appetite and the risks for more serious side effects are justified. In treating alcohol dependence, the benefits of atypical antipsychotics have not balanced out the risks for more serious side effects (Kishi et al., 2013). Indeed, our findings, added to the small body of research investigating olanzapine for treatment of alcohol dependence, suggest that, even at a low-dose, the cost-benefit balance does not favor the use of olanzapine.

Several limitations warrant consideration. First, there are limitations in using riboflavin as an indicator of adherence because riboflavin is rapidly eliminated (~91% excreted in urine within 24 hours of administration orally; Zemleni et al., 1996); thus, patients could have missed doses of the study medication between sessions and this would not be detected by the riboflavin screening. Second, the AUQ assessed craving for alcohol "right now." This approach provides only a brief snapshot of craving. A stronger method for assessing craving would have been the use of ecological-momentary assessment over time and during a variety of contexts. On the other hand, our approach allowed for a "clean" assessment of craving and did reveal the dose-dependent effect we anticipated. Attrition is another limitation in the present study; although the data analytic method we employed is the recommended approach for the unbiased estimation of treatment effects in the presence of missing data. While statistical methods that account for missing data are a necessary and useful tool, better follow-up methods would reduce the overall need for these tools. Retention will likely increase with better treatments, and the relatively high dropout rate in the current study may be directly related to the challenges of olanzapine – side effects and a medication that is not very effective for reducing drinking.

On the whole, our findings do not support the clinical utility of olanzapine and add to a small body of research showing that atypical antipsychotics are not a viable option for clinical use in the treatment of alcohol dependence (Kishi et al., 2013). To advance pharmacological interventions for alcohol dependence, greater attention should be directed towards identifying brain circuits and mechanisms underpinning alcohol dependence and the pathways by which medications that target dopamine signaling may interact with and affect these systems. It may then be possible to use baseline neuroimaging assessments of these circuits as predictors of successful response to treatment, which could improve treatment/

patient matching. For example, neuroimaging studies have already identified neural measures of cue reactivity (a proxy for craving) that predict relapse after treatment (e.g., Myrick, et al., 2008), but there is a lack of studies using baseline neuroimaging indicators to determine who will respond to a given treatment. Careful assessment of circuits that are targeted by new medications (e.g. those that target dopamine signaling) using biological markers may help to elucidate the optimal dose and medication prior to clinical trials.

Acknowledgments

Funding Source: 5R01AA014886

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Fig 1. CONSORT participant flow diagram

*Reasons participants were ineligible: medical contraindications (n=133), drinking criteria not met (n=22), did not complete screening (n=19), positive urine drug screen (n=18), psychiatric contraindications (n=9), daily marijuana user (n=4).

Figure 2a.

Figure 2b.

Figure 2c.

Fig 2.

Fig 2a – 2c. Effects of medication condition on alcohol craving (AUQ), failed control (ICSFC), and proportion of drinking days (PDD).

Table 1

Pre-treatment demographic and psychosocial characteristics

	Placebo (<i>n</i> = 45)	Olanzapine 2.5mg (<i>n</i> = 44)	Olanzapine 5mg (<i>n</i> = 40)	Test Statistic
Age	40.2 (9.3)	38.5 (8.9)	41.6 (7.9)	$F(1, 128) = 1.29$, n.s.
Gender (% male)	24.8	21.7	21.7	$\chi^2 = .72$, n.s.
Race (% Caucasian)	22.5	19.4	18.6	$\chi^2 = .55$, n.s.
Drinking days (during previous 60)	43.7 (14.7)	43.1 (15.0)	42.3 (14.5)	$F(1, 128) = .09$, n.s.
Drinks per drinking occasion	9.2 (5.4)	8.7 (5.3)	8.9 (5.1)	$F(1, 127) = .09$, n.s.
Alcohol dependence score	17.1 (8.0)	18.0 (6.8)	16.2 (7.3)	$F(1, 127) = .67$, n.s.
Alcohol craving (AUQ)	18.6 (10.1)	19.7 (9.9)	19.8 (10.0)	$F(1, 128) = .21$, n.s.
Failed control (ICSFC)	24 (9.0)	25.2 (5.6)	23.4 (7.8)	$F(1, 127) = .57$, n.s.

^aStandard deviations appear in parentheses adjacent to means for continuous variables.