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Addictive Behaviors 30 (2005) 1630–1637

ADDICTIVE BEHAVIORS

Reductions in and relations between "craving" and drinking in a prospective, open-label trial of ondansetron in adolescents with alcohol dependence

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Abstract

Recently, we reported that ondansetron (a 5-HT_3 antagonist) as an adjunct to cognitive behavioral therapy (CBT) produced significant within-group decreases (improvement) in drinking in adolescents with alcohol dependence. We previously have hypothesized that the mechanism of ondansetron treatment response in adolescents with alcohol dependence should be similar to early onset adult alcoholics, wherein blockade of serotonin-3 receptors may decrease dopamine release and subsequent alcohol consumption and craving. We now suggest that one mechanism by which ondansetron diminishes drinking in adolescents with alcohol dependence is through a reduction in "craving" as

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[1] Disclosure: The lead author currently receives no research funding from pharmaceutical companies.

doi:10.1016/j.addbeh.2005.07.004

measured by the Adolescent Obsessive–Compulsive Drinking Scale (A-OCDS). We conducted an 8-week, prospective, open-label study of ondansetron (4 μg/kg b.i.d.) in 12 adolescents (age 14–20 years) who had alcohol dependence. Results showed that "irresistibility" and total scores as measured by the A-OCDS were correlated significantly with drinking indices (drinks/day, percent days abstinent) at the end of treatment, and that "irresistibility" and total A-OCDS scores decreased significantly by the end of treatment. These preliminary results suggest that the A-OCDS can be useful as an outcome measure in clinical studies of adolescents with alcohol dependence.

Keywords: Adolescence; Alcohol dependence; Ondansetron; Open-label trial; Craving; Obsessive–compulsive drinking

1. Introduction

Recent prospective findings have shown that untreated alcohol problems in adolescence often lead to alcohol and other drug dependencies by young adulthood (Fleming, Kellam, & Brown, 1982; Tubman, Vicary, von Eye, & Lerner, 1990). Unfortunately, most current treatments for adolescent alcohol dependence have been limited to psychosocial therapies (Deas & Thomas, 2001). Although many alcohol-dependent adolescents do not benefit from psychosocial treatments alone (Brown & D'Amico, 2003), few open-label or placebo-controlled medication studies have been conducted in this population (Dawes & Johnson, 2004). Although well-designed studies are near completion, no adequately powered, double-blind, placebo-controlled medication studies for adolescents with alcohol use disorders have been published. Controlled clinical trials of medications as adjunctive treatments to psychosocial interventions are clearly warranted (Dawes & Johnson, 2004). The lack of treatment studies using medications as adjuncts to psychosocial treatments is unfortunate, since studies in adults suggest this combined approach holds the promise of greater efficacy compared to psychosocial treatment alone (Johnson, 2004a,b; Johnson & Ait-Daoud, 2000).

Ondansetron, a serotonin-3 antagonist, is of particular interest in early onset alcohol dependence (EOA; i.e., alcohol dependence that onsets before age 25 years). Ondansetron has been shown to be efficacious in the treatment of EOA adults (Johnson et al., 2000; Johnson & Ait-Daoud, 2000; Kranzler, Pierucci-Lagha, Feinn, & Hernandez-Avila, 2003). In a recent prospective, open-label study, Dawes, Johnson, Ait-Daoud, Ma, and Cornelius (2005) showed that ondansetron along with cognitive behavioral therapy (CBT) produced significant within-group decreases (improvement) in drinks/drinking day and drinks/day and increases in percent days abstinence in adolescents with alcohol dependence.

Adolescents with alcohol dependence may share some of the phenomenology seen with their adult counterparts, including alcohol cue reactivity and intrusive thoughts and urges to drinking (Thomas, Drobes, & Deas, 2005). Intrusive thoughts and urges to drink, often described as components of "craving"(Anton, Moak, & Latham, 1995; Modell, Glasser, Mountz, Schmaltz, & Cyr, 1992) have been hypothesized to be associated with maintenance of drinking, alcohol withdrawal, and relapse (Ludwig & Wikler, 1974; Rankin, Hodgson, &

Stockwell, 1979). Reduction in the urge to drink may be one process by which ondansetron diminishes the rewarding effects of alcohol in dependent adolescents.

To quantify the craving phenomena, standardized multidimensional measures are used commonly in adult alcoholics. In the adult alcoholism literature, the Obsessive–Compulsive Drinking Scale (OCDS) (Anton et al., 1995) is one such measure that is validated, reliable, and sensitive to measuring change following treatment. An adolescent version of the OCDS, the Adolescent Obsessive–Compulsive Drinking Scale (A-OCDS), has been developed recently (Deas, Roberts, Randall, & Anton, 2001). The A-OCDS yields a total score and two subscales, "irresistibility" and "interference." The A-OCDS has been shown to be specific and sensitive to identify problematic drinking in adolescents and young adults who were college students (Deas, Roberts, Randall, & Anton, 2002) or were admitted to a dual-diagnosis inpatient unit (Deas, Thomas, Randall, & Anton, 2002). In both of these studies, threshold scores were used to indicate the presence of problem drinking, though none of the participants had been diagnosed with an alcohol use disorder. The utility of the A-OCDS as a quantitative measure of the severity of craving in adolescent alcoholics is the topic of an article in this issue of Addictive Behaviors (Thomas & Deas, 2005). The A-OCDS has yet to be used to examine changes in drinking and craving in adolescents over the course of treatment for alcohol use disorders, which is the focus of the present study.

The hypothesis of the present study is that the A-OCDS and drinking reduction are correlated significantly and the A-OCDS total and subscale scores decrease significantly, in a prospective, open-label treatment study using ondansetron with cognitive behavioral therapy in treating adolescents with alcohol dependence.

2. Methods

2.1. Participants

This study was conducted at the South Texas Addiction Research and Technology (START) Center in San Antonio, Texas. Participants were treatment-seeking adolescents with alcohol dependence who were recruited primarily by health practitioners working in the community. Before study entry the potential risks and benefits of participation were explained to participants, and, when applicable, to their parents. Participants who were 18 to 20 years old gave their written informed consent. For 14 to 17 year olds, parents gave informed consent and their child his or her assent. The study was approved by the University of Texas Health Science Center Institutional Review Board.

Enrolled participants were seeking treatment for DSM-IV alcohol dependence (7 males and 5 females) and were between the ages of 14 and 20 years. Details on drinking history have been reported previously (Dawes et al., 2005). Participants were required to be in good physical health as determined by a complete physical examination, EKG, and laboratory screening tests. All enrolled participants agreed to participate in behavioral and pharmacological treatment for alcohol problems.

We excluded participants if they had a current substance use disorder other than alcohol, marijuana, or nicotine or other psychiatric disorder of sufficient severity to preclude participation in the study. We also excluded individuals currently treated with medication for attention deficit hyperactivity disorder.

2.2. Design

The design was an 8-week, prospective, open-label study.

2.3. General procedures

At baseline, trained therapists who were post-doctoral candidates from clinical psychology programs administered the Children's Interview for Psychiatric Syndromes (ChIPS) (Rooney, Fristad, Weller, & Weller, 1999), Adolescent Diagnostic Interview (ADI) (Winters & Henley, 1993; Winters, Stichfield, Fulkerson, & Henley, 1993), and the Timeline Follow-Back (TLFB) (Sobell & Sobell, 1992) to assess quantity and frequency of drinking in the past 90 days. The TLFB was also administered weekly during treatment.

The Adolescent Obsessive–Compulsive Drinking Scale (A-OCDS) is a 14-item self-administered instrument that putatively detects two factors, "irresistibility" and "interference", that have been shown to be sensitive and specific to problematic drinking in college students (Deas, Roberts et al., 2002). The irresistibility subscale is thought to reflect the adolescent's self-reported loss of the control over alcohol use. The interference subscale is thought to reflect the adolescent's intrusive thoughts about alcohol use. Because the irresistibility scale includes two items that describes drinking behavior ("How many drinks of alcohol do you drink each day?" and "How many days each week do you drink alcohol?"), we followed the recommendation of Deas, Roberts et al. (2002) and created a corrected irresistibility measure without these two items. The A-OCDS has been confirmed as a scale for identifying certain dimensions of "craving" and problematic drinking in adolescents and young adults (Deas, Roberts et al., 2002). The A-OCDS was obtained as baseline screening and weekly during treatment.

Details of the treatment have been described in Dawes et al. (2005) and involved 4 μg/kg p.o. b.i.d. of ondansetron and use of weekly cognitive behavioral therapy (CBT) with motivational enhancement. Therapy was conducted by post-doctoral therapists who were trained to conduct CBT adapted for the needs of adolescents. All ratings for the study, including baseline assessments and subsequent outcome ratings, were conducted by trained research assistants.

2.4. Outcome variables

Primary drinking outcomes were derived from the TLFB. Drinking severity was quantified as drinks/day (DD) and drinks/drinking day (DDD); drinking frequency was quantified as percentage of days abstinent (PDA) each week in treatment.

The primary A-OCDS variables included "interference," and corrected "irresistibility"; total scores were calculated from the sum of items from "interference" and corrected "irresistibility."

2.5. Statistical analyses

Drinking outcome data have been reported previously (Dawes et al., 2005) and are presented here only as they pertain to the correlations with the A-OCDS each week in treatment. Continuous drinking outcomes such as drinks/day, drinks/drinking day, and percentage of days abstinent, and the A-OCDS factors (total score, corrected irresistibility, and interference) were reported as their mean (standard deviation). Statistical analyses were performed using paired *t*-tests for continuous measures and Pearson correlation coefficients. All tests were two-tailed. Intention-to-treat analyses were employed for outcome measures. We used the paired *t*-tests for the intent-to-treat analyses to test whether there were significant declines in the A-OCDS factors at the end of treatment for all 12 subjects.

3. Results

3.1. Sample characteristics

The mean age was 18.0 years (range 14–20 years). Eight of 12 adolescent participants had a disruptive behavior disorder, and 3 participants had a mood disorder. All participants had DSM-IV-TR alcohol dependence, and 10 of 12 subjects also met DSM-IV-R criteria for cannabis dependence.

3.2. A-OCDS and drinking outcomes

For the analyses of A-OCDS factors and drinking outcomes, we used the corrected irresistibility scale with the drinking items 7 and 8 removed. At baseline assessment, 2 items from the baseline corrected irresistibility score were found to be missing in 2 of 12 participants. Therefore, we imputed the missing values with the average values from the items within the same subscale.

Table 1
A-OCDS scores before and after treatment

A-OCDS measure	Before treatment		After treatment	
	Mean	SD	Mean	SD
Corrected irresistibility[a]	7.87	3.72	4.25	4.83
Interference[b]	5.83	3.71	3.08	4.36
Total[c]	13.70	6.57	7.33	8.91

[a] $t=2.46$, $df=11$, $p=0.03$.
[b] $t=1.89$, $df=11$, $p=0.08$.
[c] $t=2.29$, $df=11$, $p=0.04$.

Table 2
Pearson correlation coefficients (p =) for A-OCDS scores and drinking indices at the end of treatment

A-OCDS measure	Drinking indices		
	DD	DDD	PDA
Interference	0.49 (0.11)	0.29 (0.36)	−0.57 (0.05)
Corrected irresistibility	0.72 (0.008)	0.46 (0.13)	−0.77 (0.003)
Total	0.63 (0.03)	0.39 (0.21)	−0.70 (0.01)

For drinking indices, DD is the drinks/day, DDD is the drinks per drinking day, and PDA is the percent days abstinent. For A-OCDS measures, Corrected irresistibility has drinking items 7 and 8 removed, and Total is the corrected total score after removing the drinking items.

To test the hypotheses that the A-OCDS scores decreased significantly from baseline to study end, we used paired t-tests. Table 1 shows the means (standard deviations) for A-OCDS scores before and after treatment. Analyses revealed significant within-group decreases in corrected irresistibility ($t=2.46$, $df=11$, $p=0.03$) and total score ($t=2.29$, $df=11$ $p=0.04$). During the course of the study, interference also decreased, although not significantly ($t=1.89$, $df=11$, $p=0.08$).

For endpoint analyses, we compared correlations for A-OCDS and drinking indices. Table 2 presents the Pearson Correlation Coefficients for the A-OCDS measures and the drinking indices. Both the A-OCDS total score and the corrected irresistibility subscale score were significantly correlated with DD and PDA (p values <0.05). The interference subscale was correlated only with PDA. None of the A-OCDS scores were correlated with DDD.

4. Discussion

To our knowledge, this is the first prospective, open-label treatment study to report on the use of the Adolescent Obsessive–Compulsive Drinking Scale (A-OCDS) as a clinical outcome measure in adolescent alcohol-dependent outpatients. The results showed that irresistibility and total A-OCDS scores decreased significantly during treatment. The results also revealed that these measures were significantly positively correlated with drinks/day and significantly negatively correlated with percent days abstinent at the end of treatment. Our findings, along with the findings of Thomas and Deas (2005), suggest that the A-OCDS total score provides information about severity of alcohol craving in adolescents. Our findings also suggest that the A-OCDS may be an important measure of clinical outcome in treatment-seeking adolescents with alcohol dependence. These results support the hypothesis that ondansetron diminishes drinking in adolescents with alcohol dependence through a reduction in "craving" as measured by the A-OCDS. Taken together, these results provide additional evidence to our recently published drinking data (Dawes et al., 2005) that ondansetron is worthy of further consideration in double-blind, randomized, controlled clinical trials for the treatment of adolescent alcoholism.

Caution is warranted when interpreting the results from this study. Our sample size was small ($n=12$) and the p values modestly significant. Furthermore, the effects of CBT may

have accounted for some of the changes in the A-OCDS, as well as the drinking improvement.

Despite these limitations, the significant improvement in A-OCDS measures, along with the previously reported significant improvement in self-reported drinking (Dawes et al., 2005) suggest that ondansetron with CBT may be an important combined treatment for adolescent alcohol dependence. Future controlled studies should formally test the hypothesis that ondansetron as an adjunct to CBT is superior to placebo and CBT in a double-blind, randomized controlled trial, and test whether the A-OCDS is an important measure of clinical outcome of craving severity in treatment-seeking adolescents with alcohol dependence. Specifically, future clinical studies should determine the value of the A-OCDS total score and subscale assessing craving severity, and whether the irresistibility subscale actually reflects loss of control over alcohol use and whether the interference subscale accurately reflects intrusive thoughts about alcohol use.

Acknowledgements

This work was supported in part by a donation from a private foundation that wishes to remain anonymous, and by grants to Dr. Johnson from the National Institute on Alcohol Abuse and Alcoholism (R01 AA010522 and R01 AA012964-03).

References

Anton, R., Moak, D., & Latham, P. (1995). The obsessive–compulsive drinking scale: A self-rated instrument of the thoughts about alcohol and drinking behavior. *Alcoholism, Clinical and Experimental Research*, *19*, 92–99.

Brown, S. A., & D'Amico, E. J. (2003). Outcomes of alcohol treatment for adolescents. *Recent Developments in Alcoholism*, *16*, 289–312.

Dawes, M., & Johnson, B. A. (2004). Pharmacotherapeutic trials in adolescent alcoholism: Opportunities and challenges. *Alcohol and Alcoholism*, *39*(3), 166–177.

Dawes, M. A., Johnson, B. A., Ait-Daoud, N., Ma, J. Z., & Cornelius, J. R. (2005). A prospective, open-label trial of ondansetron in adolescents with alcohol dependence. *Addictive Behaviors*, *30*(6), 1077–1085.

Deas, D., Roberts, J., Randall, C., & Anton, R. (2001). Adolescent obsessive–compulsive drinking scale: An assessment tool for problem drinking. *Journal of the National Medical Association*, *93*, 92–103.

Deas, D., Roberts, J. S., Randall, C. L., & Anton, R. F. (2002). Confirmatory analysis of the Adolescent Obsessive Compulsive Drinking Scale (A-OCDS): A measure of "craving" and problem drinking in adolescents/young adults. *Journal of the National Medical Association*, *94*(10), 879–887.

Deas, D., & Thomas, S. E. (2001). An overview of controlled studies of adolescent substance abuse treatment. *American Journal of Addiction*, *10*, 178–189.

Deas, D., Thomas, S., Randall, C. L., & Anton, R. (2002). The utility of the Adolescent Obsessive–Compulsive Drinking Scale (A-OCDS) in an inpatient adolescent substance abusing sample. *Alcoholism: Clinical and Experimental Research*, *26*(5 Supplement), 24A.

Fleming, J. P., Kellam, S. G., & Brown, C. H. (1982). Early predictors of age at first use of alcohol, marijuana, and cigarettes. *Drug and Alcohol Dependence*, *9*(4), 285–303.

Johnson, B. A. (2004a). An overview of the development of medications including novel anticonvulsants for the treatment of alcohol dependence. *Expert Opinion on Pharmacotherapy*, *5*(9), 1943–1955.

Johnson, B. A. (2004b). The role of the serotonergic system in the neurobiology of alcoholism: Implications for treatment. *CNS Drugs*, *18*(15), 1105–1118.

Johnson, B. A., & Ait-Daoud, N. (2000). Neuropharmacological treatments for alcoholism: Scientific basis and clinical findings. *Psychopharmacology*, *149*, 327–344.

Johnson, B. A., Roache, J. D., Javors, M. A., DiClemente, C. C., Cloninger, C. R., Prihoda, T. J., et al. (2000). Ondansetron for the reduction of drinking among biologically predisposed alcohol patients: A randomized controlled trial. *Journal of the American Medical Association*, *284*(8), 963–971.

Kranzler, H. R., Pierucci-Lagha, A., Feinn, R., & Hernandez-Avila, C. (2003). Effects of ondansetron in early- versus late-onset alcoholics: A prospective, open-label study. *Alcoholism, Clinical and Experimental Research*, *20*(9), 1534–1541.

Ludwig, A., & Wikler, A. (1974). "Craving" and relapse to drink. *QJ Studies Alcohol*, *35*, 108–130.

Modell, J., Glaser, F., Mountz, J., Schmaltz, S., & Cyr, L. (1992). Obsessive and compulsive characteristics of alcohol abuse and dependence: Quantification by a newly developed questionnaire. *Alcoholism, Clinical and Experimental Research*, *16*, 266–271.

Rankin, H., Hodgson, R., & Stockwell, T. (1979). The concept of craving and its measurement. *Behaviour Research and Therapy*, *17*, 389–396.

Rooney, M. T., Fristad, M. A., Weller, E. B., & Weller, R. A. (1999). *Administration manual of the ChIPS*. Washington, D.C.: American Psychiatry Press.

Sobell, L. C., & Sobell, M. B. (1992). Timeline follow-back: A technique for assessing self-reported alcohol consumption. In R. Z. Littten, & J. P. Allen (Eds.), *Measuring alcohol consumption: Psychosocial and biochemical methods* (pp. 41–72). Totwa, N.J.: Humana Press Inc.

Thomas, S.E., & Deas, D. (2005). The A-OCDS predicts craving and alcohol cue reactivity in adolescent alcoholics. *Addictive Behaviors*, *30*, 1638–1648.

Thomas, S. E., Drobes, D. J., & Deas, D. (2005). Alcohol cue reactivity in alcohol-dependent adolescents. *Journal of Studies on Alcohol*, *66*(3), 354–360.

Tubman, J. G., Vicary von Eye, A., & Lerner, J. V. (1990). Longitudinal substance use and adult adjustment. *Journal of Substance Abuse*, *2*(3), 317–334.

Winters, K. C., & Henley, G. A. (1993). *Adolescent diagnostic interview schedule and manual*. Los Angeles: Western Psychological Services.

Winters, K. C., Stinchfield, R. D., Fulkerson, J., & Henley, G. A. (1993). Measuring alcohol and cannabis use disorders in an adolescent clinical sample. *Psychology of Addictive Disorders*, *7*, 185–196.