Addiction Biology

HUMAN EXPERIMENTAL STUDY

doi:10.1111/adb.12050

Effects of naltrexone on adolescent alcohol cue reactivity and sensitivity: an initial randomized trial

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ABSTRACT

Adolescent alcohol use is associated with myriad adverse consequences and contributes to the leading causes of mortality among youth. Despite the magnitude of this public health problem, evidenced-based treatment initiatives for alcohol use disorders in youth remain inadequate. Identifying promising pharmacological approaches may improve treatment options. Naltrexone is an opiate receptor antagonist that is efficacious for reducing drinking in adults by attenuating craving and the rewarding effects of alcohol. Implications of these findings for adolescents are unclear; however, given that randomized trials of naltrexone with youth are non-existent. We conducted a randomized, double-blinded, placebo-controlled cross-over study, comparing naltrexone (50 mg/daily) and placebo in 22 adolescent problem drinkers aged 15–19 years (M = 18.36, standard deviation = 0.95; 12 women). The primary outcome measures were alcohol use, subjective responses to alcohol consumption, and alcohol–cue-elicited craving assessed in the natural environment using ecological momentary assessment methods, and craving and physiological reactivity assessed using standard alcohol cue reactivity procedures. Results showed that naltrexone reduced the likelihood of drinking and heavy drinking (P's ≤ 0.03), blunted craving in the laboratory and in the natural environment (P's ≤ 0.04), and altered subjective responses to alcohol consumption (P's ≤ 0.01). Naltrexone was generally well tolerated by participants. This study provides the first experimentally controlled evidence that naltrexone reduces drinking and craving, and alters subjective responses to alcohol in a sample of adolescent problem drinkers, and suggests larger clinical trials with long-term follow-ups are warranted.

Keywords Adolescents, alcohol sensitivity, craving, cue reactivity, naltrexone.

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INTRODUCTION

Adolescence is a key period in the development of alcohol use disorders, with nearly 15% of youth meeting diagnostic criteria for alcohol abuse or dependence by 18 years of age (Merikangas & McClair 2012; Swendsen *et al.* 2012). Yet, less than one-third of treated youth experience sustained benefit from existing psychosocial interventions (Chung & Maisto 2006). Inadequate treatment for this age group is an important public health concern given that alcohol misuse during adolescence predicts future alcohol dependence in adulthood (Buu *et al.* 2011). Although pharmacotherapy research has expanded treatment options for adults with drinking problems, medication development for adolescents has not progressed. Randomized controlled pharmacotherapy trials for alcohol problems in the youth are few, and published reports bear substantial limitations that preclude inferences about the efficacy of the medication studied. This gap in knowledge impedes treatment practices, as the safety and efficacy of medications for adolescents cannot be inferred from adult data (Bridge *et al.* 2007).

Naltrexone is an opiate receptor antagonist that is efficacious for treating alcohol dependence in adults. In most clinical trials, naltrexone lowered the risk of relapse and reduced the frequency of drinking and heavy drinking days, with a modest effect size ($g = 0.20$; see Maisel *et al.* 2013). Considering its promise, researchers have attempted to elucidate the behavioral mechanisms by which naltrexone exerts beneficial effects. Retrospective patient reports in the initial clinical trials suggested that

naltrexone reduced day-to-day craving and subjective high following alcohol consumption (O'Malley *et al.* 1992; Anton *et al.* 1999). These observations spurred researchers to more carefully investigate naltrexone's effects in controlled laboratory settings. Studies found naltrexone blunted craving in response to alcohol and alcohol cues (Davidson *et al.* 1999; O'Malley *et al.* 2002; Anton *et al.* 2004; Drobes *et al.* 2004) and dampened the reinforcing effects of alcohol (McCaul *et al.* 2000; Na & Lee 2002; O'Malley *et al.* 2002; Drobes *et al.* 2004; Ray & Hutchison 2007; Setiawan *et al.* 2011). Studies also tested whether naltrexone intensifies alcohol-induced sedation, but generally found little effect (de Wit, Svenson & York 1999; Drobes *et al.* 2004; Ray *et al.* 2008). On the whole, these data suggest that naltrexone reduces drinking primarily by dampening craving and alcohol's reinforcing effects.

Despite beneficial effects of naltrexone on adult drinking, implications of these findings for adolescents are unclear. Youth exhibit clinical characteristics that differ from adults, and adolescence is associated with substantial neuronal remodeling in brain regions that govern alcohol sensitivity (for a review, see Spear 2011). Inasmuch as naltrexone affects drinking by altering the subjective responses to alcohol, adolescents' unique patterns of alcohol sensitivity may influence how naltrexone affects youth. Published reports of its effects on adolescent drinking, however, are limited to case studies and open-label trials (Deas *et al.* 2005). Although most reports claim naltrexone reduces drinking and craving, causal inferences cannot be drawn from these studies.

In this randomized, double-blinded, placebo-controlled cross-over study, we examined the effects of naltrexone on adolescents' drinking, reactivity to alcohol cues and subjective responses to alcohol consumption in real time in their natural environments using ecological momentary assessment (EMA) methods. We also tested the effects of naltrexone on adolescents' reactivity to alcohol cues in a controlled laboratory setting. Empirical study of adolescents' responses to alcohol has relied almost exclusively on animal models because of restrictions on administering alcohol to underage drinkers. A primary goal of this study was to surmount this challenge by using an EMA approach to test naltrexone's effects on teenagers' momentary subjective responses to alcohol in their natural environments. Momentary assessments are particularly important when the phenomena of interest are subject to rapid change, such as craving and acute responses to alcohol. Other advantages of EMA include the large number of repeated observations (i.e. boosting statistical power), the ability to track compliance and eliminate the possibility of 'faking' compliance by recording the time and date of each entry, the low incidence of missing data because questions cannot be skipped, and the ecological validity of findings.

Informed by adult research, we tested four hypotheses. First, we tested the hypothesis that naltrexone, as compared with placebo, reduces alcohol use in adolescent problem drinkers. Second, we tested the hypothesis that naltrexone dampens the subjective reinforcing effects of alcohol consumption (i.e. stimulation). Third, we tested the hypothesis that naltrexone blunts alcohol cue-elicited craving in the natural environment. Lastly, we tested the hypothesis that naltrexone dampens alcohol cue-induced craving and physiological reactivity in a laboratory setting. Given that this is the first controlled pharmacotherapy study on adolescent drinking, we also explored the effects of naltrexone on ratings of sedation and alcohol high during drinking episodes.

MATERIALS AND METHODS

Participant selection

Adolescents were recruited from the community to participate in a study of how a medication affects teenagers' reactions to alcohol. Inclusion criteria were 15–19 years old, consumed alcohol ≥2 times weekly in the past 30 days, able to read simple English, and postpubescent. Exclusion criteria were history of alcohol treatment or treatment seeking, opiate use in the past 30 days, current or lifetime opiate use disorder based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR; American Psychiatric Association 2000), positive urine toxicology screen for narcotics, amphetamines, sedative hypnotics or opiates; alcohol withdrawal (>10 on the Clinical Institute Withdrawal Assessment for Alcohol; Sullivan *et al.* 1989), suicidal or psychotic, and medical conditions or medications that contraindicated taking naltrexone (medications stabilized for ≥4 weeks were permissible, medications known to affect drinking were exclusionary). Women were ineligible if they were pregnant, nursing or unwilling to use birth control.

Procedures

Study design

This double-blind cross-over trial compared naltrexone (up to 50 mg daily) and placebo. Participants were randomized to each condition for 8 to 10 days [M = 9.93, standard deviation (SD) = 0.34] in counterbalanced order with a 4- to 11-day washout period (M = 4.52, SD = 1.72) to allow for clearance of naltrexone (Gonzalez & Brogden 1988). At the end of each condition, participants underwent a laboratory-based alcohol cue reactivity assessment (CRA); variability in the duration of each

arm permitted flexibility in scheduling CRA sessions. Conditions typically began on Thursdays, included two weekends, and avoided events that might impact drinking (e.g. holiday breaks). We contacted participants daily to assess side effects. Procedures were identical across conditions, except for the medication administered. No instructions were given to reduce or otherwise alter drinking habits. The Brown University Institutional Review Board approved this study.

Schedule of assessments

Volunteers completed a telephone screening ($N = 461$). Potentially eligible youths underwent additional in-person screening. The study was fully described to participants and, if <18 years, their parents. Consent was obtained from 18- and 19-year-olds and from the parents of minors; minors provided assent. Adolescents completed baseline assessments and learned our EMA protocol, which was designed for this study and implemented on handheld devices (Samsung Electronics, Ridgefield Park, NJ, USA). EMA response options included: visual analog bars (converted to discrete point scales); multiple checkboxes when more than one option was appropriate; and categorical checkboxes when only one response was warranted. Other features made it user-friendly, such as an alarm clock feature to avoid assessments while sleeping.

Participants learned to discern standard alcoholic drink volumes using a graphic manual that depicted standard drinks by beverage type. To simplify the instructional set, participants were instructed to initiate begin- and end- drink reports on their handheld device directly before and after each standard drink, respectively. However, the EMA battery was delivered only before the first drink and after the first three drinks of a drinking episode. We selected three drinks based on evidence that the minimum blood alcohol concentration (BAC) at which reinforcing effects are reported is 0.04 g/dl (Davidson, Camara & Swift 1997). Participants also responded to device-initiated auditory prompts (random assessments), which occurred once randomly within 3 hours blocks and did not overlap with drinking, to assess craving outside drinking episodes. The program recorded if participants failed to respond within 2 minutes. Youths could 'suspend' random assessments for up to 7 hours when necessary (e.g. school, driving). Finally, each morning participants recorded the number and type of standard drinks consumed the previous day.

Alcohol cue reactivity

CRA sessions mirrored published protocols (Miranda *et al*. 2010). All participants tested negative for breath alcohol using an Alco-Sensor IV breathalyzer (Intoximeters Inc., Saint Louis, MO, USA) before the session. Cigarette users smoked their last cigarette 1 hour prior to cue exposure. Experimental manipulations occurred in a sound-attenuated room equipped with a one-way mirror. Participants were fitted with a Scholar II 507EP blood pressure cuff (Criticare Systems Inc., Waukesha, WI, USA) and underwent a 3 minutes period to habituate to the inflation cycle (approximately every 40 seconds) and setting. Participants were then presented with a glass of water accompanied by its commercially labeled bottle. Audio recordings instructed participants to sniff the glass when high tones signaled and stop sniffing when low tones signaled; thirteen 5 seconds olfactory exposures occurred in variable intervals during each trial. Following the water trial, participants underwent a 3-minute relaxation period followed by two alcohol cue exposure trials that were identical to the water trial except the glass contained their most commonly consumed alcoholic beverage and was accompanied by its commercially labeled bottle. At the end of each trial, participants rated their craving (see *Measures*). Trials were presented in the same order for all participants because of known carryover effects (Monti *et al*. 1987).

Medication administration and compliance

Naltrexone was compounded into 25-mg capsules. Placebo capsules contained inert filler and were identical to naltrexone capsules except for content. Participants were prescribed one capsule the first 2 days of each condition and two capsules daily thereafter. Compliance was assessed using the medication event monitoring system (MEMS; Aardex Group Ltd., Geneva, Switzerland), an electronic bottle cap that records the date/time the bottle was opened. At CRA appointments youths ingested the medication at our laboratory 1 hour prior to procedures.

Measures

Alcohol use

Baseline drinking was assessed using the 90-day timeline follow-back interview (TLFB; Sobell & Sobell 1992). Drinking during the trial was assessed using the EMA program and TLFB. EMA data were our primary outcome measure, with missing data culled from the TLFB (Carney *et al*. 1998).

Momentary subjective responses

Two items from the stimulation (energized, excited) and sedation (sedated, sluggish) subscales of the Biphasic Alcohol Effects Scale (BAES; Martin *et al*. 1993) were administered to reduce burden. Items were selected based on an unpublished principal components analysis of data from college-age heavy drinkers. Youths rated items on

visual analog scales from 0 (not at all) to 10 (extremely); items were combined into a mean score for each dimension. Urge to drink (i.e. craving) and high were measured using single items rated from 0 (no urge and not at all, respectively) to 10 (strongest ever and extremely, respectively). This craving assessment is widely used in alcohol administration and EMA studies (Tidey *et al.* 2008). The measure of high originated from the Subjective High Assessment Scale (SHAS; Schuckit 1984) and was selected because it strongly correlates with the total SHAS score across BAC levels (Ray *et al.* 2009). Participants also rated their craving during random assessments using the same scale.

Estimated BAC

Subjective effects of alcohol are dose-dependent (Anton *et al.* 2004; Drobes *et al.* 2004; Ray & Hutchison 2007); therefore, we estimated BAC (eBAC) levels at each drink report using a standard algorithm (see Piasecki *et al.* in press; Ray *et al.* 2010).

Person-level variables

Demographic and clinical information was collected at baseline. Psychiatric diagnoses, including alcohol use disorders, were derived using the Kiddie Schedule for Affective Disorders for School-Age Children (KSADS; Kaufman *et al.* 1997). Diagnostic decisions were based on adolescents' reports, made by case consensus, and used for descriptive purposes. To further describe the sample, adolescents also completed the Rutgers Alcohol Problem Index (RAPI; White & Labouvie 1989), a continuous measure of alcohol-related problems, and the Kaufman Brief Intelligence Test (Kaufman & Kaufman 1990).

Event-level variables

In the natural environment, participants recorded whether alcohol was directly visible (e.g. bottle, glass, etc.) at random assessments. Other event-level data were collected to include as covariates in models examining cue-elicited craving in the natural environment. EMA software date and time stamped each entry. We classified entries based on whether they occurred on a weekend (6:00 PM on Friday through 6:00 PM on Sunday). Additionally, time of day was represented by four exclusive 6 hours blocks, with 6:00 PM to midnight serving as the reference category. Participants recorded their location from a list of options (home, friend's house, other's house, school, work, public place, vehicle, other location); home served as the reference category. Participants also reported others present by selecting all applicable options (mother, father, brother, sister, child, other relative, boy/girlfriend, friend, teacher, other, no one). Each entry was coded for the presence (1) or absence (0) of peers. Finally, entries were categorized as occurring on drinking (1) or non-drinking (0) days.

Laboratory measures

Urge to drink was measured during CRA procedures using the same item delivered during EMA. The Alcohol Urge Questionnaire (AUQ; Bohn, Krahn & Staehler 1995), an 8-item measure of craving, was also administered in the laboratory. Craving was assessed immediately after each cue exposure. Measures of physiological arousal during cue exposures included mean arterial pressure (MAP) and heart rate measured in beats per minute.

Statistical methods

Analyses were performed using the Statistical Package for the Social Sciences, version 19.0 (IBM, Armonk, NY). Comparisons between participants and youths screened, but not enrolled were evaluated using independent sample *t*-tests and chi-squared analyses. We tested for differences in paired proportions of side effects between conditions using the McNemar statistic, with side effect categories coded as present (1) or not present (0). To garner the full benefit of the extensive collection of repeated observations from each participant, we used generalized estimating equation (GEE) models to analyze our primary outcomes (Zeger, Liang & Albert 1988). GEE models are essentially regression equations that allow for inclusion of participants with some missing data and varying numbers of observations while controlling for autocorrelation. Several covariance structures were compared using the quasi-likelihood under the independence model criterion to select the optimum working correlation matrix (Pan 2001). An autoregressive structure provided the best fit for all data except subjective responses to alcohol; an unstructured matrix provided the best fit for subjective response data. Models assumed a normal link function when the dependent measure was continuous and a logit link function when the outcome of interest was binary. Additionally, in all models, condition was coded with an orthogonal contrast (–0.5 for placebo versus 0.5 for naltrexone) and treatment order was included as a between-subjects covariate to control for possible order effects.

We first examined the effect of condition on drinking outcomes. The primary units of analysis were repeated daily assessments of drinking variables. This variable followed a count distribution (i.e. number of standard drinks) with overdispersion because of positive skewness. We therefore used a binomial distribution (non-drinking day = 0, drinking day = 1) to analyze this outcome. We also used GEE analyses to predict heavy drinking days

using a binomial distribution (non-heavy or non-drinking day = 0, heavy drinking day = 1); heavy drinking days were defined as ≥5 standard drinks for males and ≥4 standard drinks for females.

Our next set of analyses examined the effects of condition on adolescents' subjective responses to alcohol consumption. Adult studies indicate subjective responses to alcohol are heavily influenced by the biphasic nature of intoxication. We evaluated whether drink reports were recorded during the ascending or descending limb of the blood alcohol curve by computing successive differences in eBAC across reports within each drinking episode. Results identified a small number of reports recorded during the descending limb ($n = 3$, 1.4%). To facilitate interpretation of our data, we restricted analyses to data collected in the ascending limb. Separate models tested the main and interactive effects of condition and eBAC on each dependent variable. Only subjective high required transformation (logarithmic) to correct for positive skewness. To disentangle within-person drink-to-drink variation in eBAC and subjective intoxication from the effects of between-person variability in typical eBAC and subjective intoxication, we entered both momentary eBAC after each of the first three drinks each day *and* each participant's average eBAC level across the trial into all models (Palta 2003). The momentary variable reflects the within-person effect, whereas the average variable reflects the between-person effect of typical intoxication. All variables were standardized to ease interpretation of results; the model coefficients represent differences in standard deviation units associated with the predictors (effect size *d*).

We also tested whether naltrexone dampened craving in the natural environment outside of drinking episodes after accounting for event- and person-level covariates. Data were culled from random assessments. Assessments recorded during or after drinking episodes each day ($n = 59$, 3.8%) were excluded from analyses to curtail confounding effects with alcohol intoxication. The single-item measure of craving was square-root-transformed because of positive skewness and standardized.

Laboratory CRA data were also analyzed using GEE. Separate models tested the main and interactive effects of condition and cue type (water versus alcohol) on craving and physiological outcomes (i.e. heart rate, MAP). Craving measures were square-root-transformed because of positive skewness, and craving and physiological measures were standardized.

RESULTS

Sample characteristics

Twenty-eight adolescents entered the study and were randomized. Participants did not differ from youths screened, but not enrolled on demographic (age, sex, race and ethnicity; Ps > 0.10) or baseline drinking characteristics (percent drinking and heavy drinking days; Ps > 0.08). Figure 1 illustrates the flow of participants through the study. Six participants did not complete either arm of the study and were excluded from analyses (see Fig. 1). One participant completed all measurements during the naltrexone arm, but did not complete the placebo arm because of time constraints. This participant was included in the analyses. Table 1 depicts the characteristics of the final sample. The final sample ($N = 22$) was 15–19 years of age and more than two-thirds met criteria for an AUD; 27.3% met criteria for abuse ($M_{\text{age of onset}} = 16.93$, SD = 2.17) and 50.0% met criteria for dependence ($M_{\text{age of onset}} = 17.20$, SD = 1.81).

Medication compliance and tolerability

Participants completed a similar number of days in each condition, $t(20) = 1.37$, $P = 0.19$ (naltrexone: M = 9.86, SD = 0.48; placebo: M = 10.00, SD = 0.00). Participants were highly compliant with the medication regimen, with an average compliance rate of 95.0% in the placebo arm (range = 80–100%) and 97.2% in the naltrexone arm (range = 80–100%), and condition was not associated with daily compliance [odds ratio (OR) = 1.85, $P = 0.33$, 95% confidence interval (CI) (0.53, 6.44)]. We also tested whether participants were less likely to take medication on drinking days compared with non-drinking days and found no association [OR = 2.24, $P = 0.24$, 95% CI (0.59, 8.50)]. Regarding side effects, two participants withdrew during the naltrexone arm because of gastrointestinal symptoms (i.e. nausea, loss of appetite, vomiting). We tested for differences in paired proportions of side effects between conditions among those who completed both arms of the study using the McNemar statistic. Completers were marginally more likely to report nausea while taking naltrexone ($P = 0.06$). Otherwise, there were no differences between conditions in terms of the paired proportions of side effects reported (Ps > 0.13). Table 2 summarizes side effects reported by 10% or more of the sample.

Findings in the natural environment

EMA compliance

Participants completed 1551 random assessments during the trial, of which 1493 (96%) occurred prior to the onset of drinking each day. We evaluated participants' compliance with random assessments by calculating the percentage of assessments completed by each participant in each study arm and averaged rates across participants. Participants completed 86.1% (SD = 7.1) of random assessments in the placebo arm and 86.9%

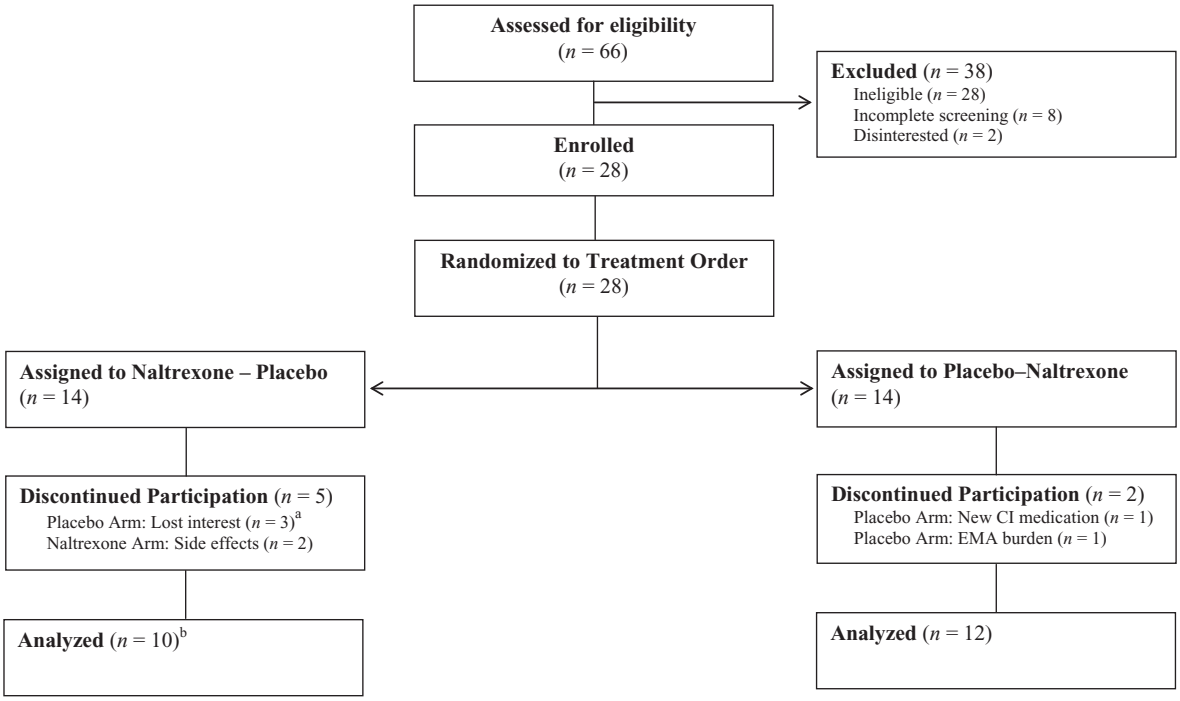

Figure 1 Participant flow through the double-blind cross-over study; [a]Two participants did not complete all measures in the naltrexone arm, proceeded to the placebo arm, and then discontinued participation. [b]Analyses included one participant who completed all measurements in the naltrexone arm but discontinued during the placebo arm; CI = contraindicated

Table 1 Summary of participant characteristics at baseline by sex.

Characteristic	*Males (n = 10)* *N (%) or M ± SD*	*Females (n = 12)* *N (%) or M ± SD*	*Full sample* *N (%) or M ± SD*
Age	18.00 ± 1.25	18.67 ± 0.49	18.36 ± 0.95
Race			
White	7 (70.0)	9 (75.0)	16 (72.7)
African-American	0 (0.0)	1 (8.3)	1 (4.5)
American Indian	1 (10.0)	0 (0.0)	1 (4.5)
Asian/Pacific Islander	2 (20.0)	2 (16.7)	4 (18.1)
Ethnicity (Hispanic)[a]	3 (30.0)	0 (0.0)	3 (13.6)
Full scale IQ score	100.70 ± 16.55	106.92 ± 17.98	104.09 ± 16.74
Disruptive behavior disorder[b]	3 (30.0)	1 (8.3)	4 (18.2)
Mood disorder[b]	1 (10.0)	0 (0.0)	1 (4.5)
Anxiety disorder[b]	0 (0.0)	1 (8.3)	1 (4.5)
Cigarette smoker[b]	5 (50.0)	1 (8.3)	6 (27.3)
Cannabis use disorder[b]	5 (50.0)	2 (16.7)	7 (31.8)
Alcohol abuse[b]	3 (30.0)	3 (25.0)	6 (27.3)
Alcohol dependent[b]	4 (40.0)	7 (58.3)	11 (50.0)
AUD symptom count[b]	3.4 ± 2.88	4.33 ± 2.27	3.91 ± 2.54
RAPI	6.00 ± 5.42	9.75 ± 8.80	8.05 ± 7.54
Drinking days[c]	26.44 ± 11.06	28.70 ± 8.14	27.68 ± 9.40
Drinks per drinking day[c]	4.82 ± 1.76	3.74 ± 1.35	4.23 ± 1.61
Heavy drinking days[c]	12.56 ± 8.73	15.37 ± 8.70	14.09 ± 8.62

Note. [a]Ethnicity and race were not mutually exclusive; [b]Diagnoses were identified in accordance with the *Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition, Text Revision)* using the Kiddie Schedule for Affective Disorders for School-Age Children; [c]Derived from the 90-day Timeline Follow-Back interview conducted at baseline; AUD = Alcohol Use Disorder; RAPI = Rutgers Alcohol Problem Index.

Table 2 Summary of adverse events reported by ≥10% of participants in either arm of the study.

	Naltrexone		*Placebo*		*McNemar's test*
Adverse event	*n*	*%*	*n*	*%*	*P*
Neurocognitive					
Difficulty sleeping	4	19.0	1	4.8	0.38
Drowsiness	4	19.0	4	19.0	1.00
Excessive tiredness	4	19.0	0	0.0	0.13
Fatigue or lack of energy	8	38.1	8	38.1	1.00
Headache	5	23.8	4	19.0	1.00
Gastrointestinal					
Abdominal pain	1	4.8	3	14.3	0.50
Decreased appetite	3	14.3	0	0.0	0.25
Nausea	7	33.3	2	9.5	0.06
Otolaryngolic					
Nasal symptoms	1	4.8	5	23.8	0.22
Sore throat	2	9.5	4	19.0	0.63
Sneezing	3	14.3	3	14.3	1.00
Cough/dry mouth	2	9.5	7	33.3	0.13

Note. McNemar's test was used to test paired proportions of side effects between medication conditions. Consequently, analyses included participants who completed both arms of the study ($n = 21$). This approach excluded two participants who withdrew during the naltrexone arm due to gastrointestinal symptoms and one participant who completed the naltrexone arm only. This participant endorsed the following adverse events: fatigue or lack of energy, difficulty sleeping, and drowsiness.

(SD = 9.38) in the naltrexone arm, with no significant difference between conditions [$t(20) = -0.43$, $P = 0.68$].

Drinking outcomes

EMA and TLFB drinking data were highly correlated in both conditions in terms of percent drinking ($rs = 0.85$, 0.90) and heavy drinking ($rs = 0.72$, 0.78) days ($Ps < 0.001$), supporting our decision to use EMA data in analyses. On average, participants consumed alcohol on 3.1 days (SD = 2.0; 30.7%) in the placebo arm and on 2.4 days (SD = 1.4; 24.6%) in the naltrexone arm. With respect to heavy drinking days, participants drank heavily on an average of 1.6 days (SD = 1.8; 15.3%) while assigned to placebo compared with 1.1 days (SD = 1.0; 9.3%) while assigned to naltrexone. Naltrexone reduced the likelihood of drinking on a study day [OR = 0.69, 95% CI (0.50, 0.97), $P = 0.03$, effect size $d = 0.17$]. Participants were also less likely to drink heavily while taking naltrexone compared with placebo [OR = 0.54, 95% CI (0.35, 0.81), $P = 0.003$, effect size $d = 0.20$]. The frequency distribution of individual responses shows that 48% of participants had fewer drinking days in the naltrexone arm compared with placebo, and 48% had fewer heavy drinking days (see Fig. 2).

Subjective responses to alcohol

Participants recorded data for 213 alcoholic drinks during the study, with fewer drinks recorded in the naltrexone arm ($n = 87$) compared with placebo ($n = 126$). As shown in Table 3 and Fig. 3, condition produced a main effect on alcohol-induced stimulation, sedation and high. Specifically, participants reported lower stimulation and greater sedation while in the naltrexone arm compared with placebo. Naltrexone also potentiated subjective high; however, the Condition × Average eBAC interaction in this model was marginally significant ($P = 0.06$), suggesting that individuals with higher average eBAC levels experienced greater high while drinking in the naltrexone arm compared with placebo. Additionally, the Condition × Momentary eBAC interaction was a significant predictor of craving, such that naltrexone blunted alcohol-induced urge to drink more strongly at higher eBAC levels.

Urge to drink (random assessments)

Youths reported that alcohol was directly visible in 218 (14.6%) of the 1492 random assessments completed. When alcohol was present, participants were typically at home or a friend's house (73.4%). We modeled the main and interactive effects of alcohol cues and condition on urge to drink in the natural environment while controlling for event- and person-level covariates. As summarized in Table 4, some event-level covariates were associated with heightened levels of craving (i.e. presence of peers, drinking day, friend's house), while others were associated with lower levels of craving (i.e. time of day). As hypothesized, there was a Condition × Alcohol Cue interaction ($P = 0.02$), such that the presence of alcohol

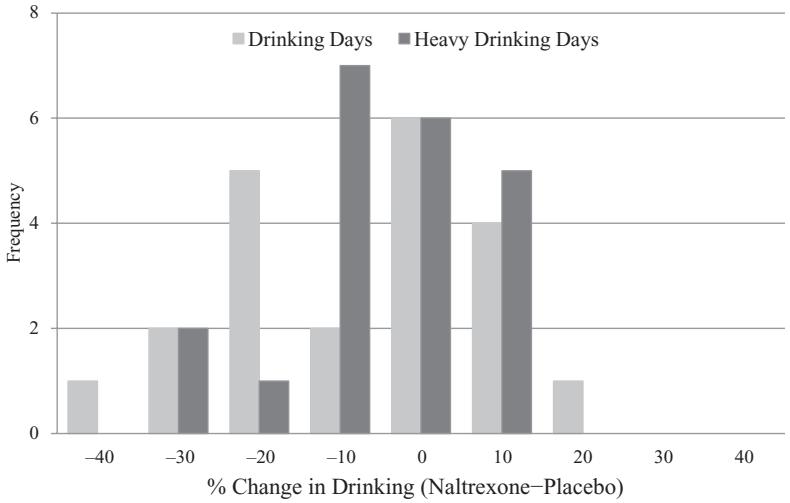

Figure 2 Frequency of percent change in drinking days and heavy drinking days from the naltrexone to the placebo arm (i.e. naltrexone—placebo) of the study among participants who completed both arms of the study ($n = 21$)

Table 3 Summary of GEE models predicting momentary subjective responses from medication condition fitting between- and within-individual effects for eBAC.

			95% CI		
Model and predictor variables	*β*	*SE*	*LL*	*UL*	*P*
Craving					
Average eBAC	–0.06	0.13	–0.32	0.19	0.628
Momentary eBAC	0.05	0.05	–0.05	0.15	0.353
Medication condition	–0.11	0.07	–0.24	0.03	0.109
Medication condition × average eBAC	0.24	0.14	–0.03	0.51	.083
Medication condition × momentary eBAC	–0.43	0.17	–0.76	–0.11	0.010
Stimulation					
Average eBAC	–0.28	0.14	–0.55	–0.02	0.035
Momentary eBAC	0.16	0.03	0.10	0.22	<0.001
Medication condition	0.35	0.08	0.20	0.50	<0.001
Medication condition × average eBAC	–0.13	0.11	–0.33	0.08	0.239
Medication condition × momentary eBAC	–0.16	0.10	–0.36	0.04	0.112
Sedation					
Average eBAC	0.09	0.14	–0.17	0.36	0.490
Momentary eBAC	0.00	0.04	–0.08	0.08	0.960
Medication condition	0.66	0.07	0.53	0.79	<0.001
Medication condition × average eBAC	–0.08	0.18	–0.43	0.27	0.651
Medication condition × momentary eBAC	0.13	0.12	–0.11	0.36	0.285
High					
Average eBAC	–0.39	0.13	–0.63	–0.14	0.002
Momentary eBAC	0.23	0.04	0.16	0.30	<0.001
Medication condition	0.39	0.05	0.29	0.50	<0.001
Medication condition × average eBAC	0.28	0.15	–0.01	0.57	0.057
Medication condition × momentary eBAC	0.03	0.08	–0.12	0.18	0.714

Note. Subjective responses are continuous and standardized variables. In all models, medication condition was coded with an orthogonal contrast (–0.5 for placebo versus 0.5 for naltrexone) and treatment order was included as a between-subjects covariate to control for possible order effects. The reported coefficients represent the standardized effects (effect size *d*). Average eBAC = average eBAC across all momentary drink reports during the monitoring period and reflects the between-person effect; CI = confidence interval; eBAC = estimated blood alcohol concentration; GEE = generalized estimating equations; *LL* = lower limit; Momentary eBAC = person-centered eBAC and reflects the within-person effect; *UL* = upper limit.

cues potentiated craving in the placebo condition, but significantly less so in the naltrexone condition (see Fig. 4), indicating that adolescents experience increased craving when exposed to alcohol cues in the natural environment and that naltrexone blunts this effect.

Laboratory findings

Urge to drink

As illustrated in Fig. 4, analysis of the single-item measure of craving showed a main effect of cue type in

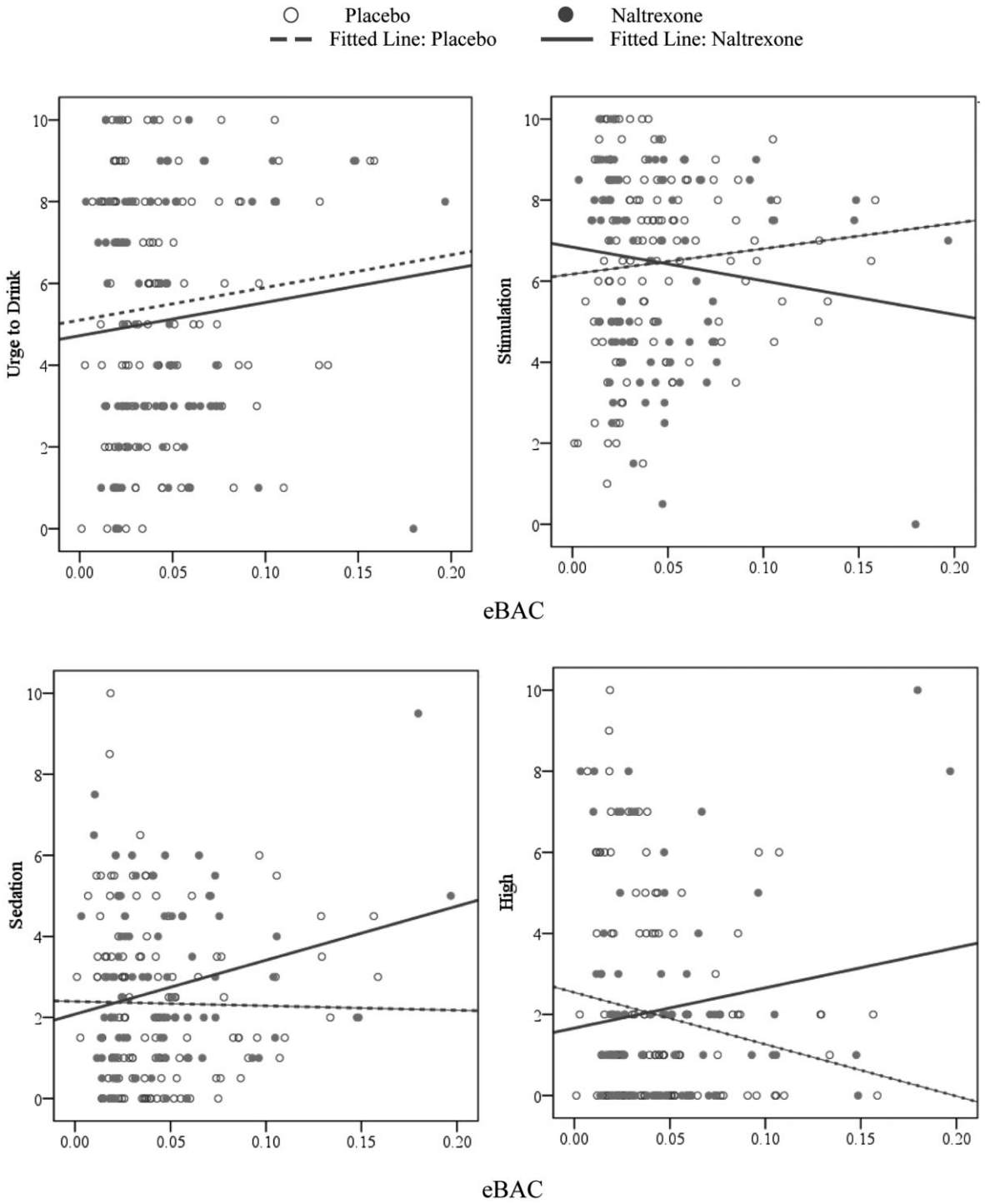

Figure 3 Predicted raw values for subjective alcohol response from momentary estimated blood alcohol concentrations (eBAC) as a function of medication condition. Best fitting lines for the naltrexone and placebo arms are illustrated in each panel

the CRA [β = 0.55, 95% CI (0.26, 0.84), $P < 0.001$], such that alcohol cues increased urge to drink relative to water cues. Neither the main effect of condition [β = –0.25, 95% CI (–0.58, 0.08), $P = 0.14$] nor the Cue Type × Condition interaction [β = 0.01, 95% CI (–0.29, 0.32), $P = 0.93$] was significant. Analysis of the AUQ indicated a similar main effect of cue type, β = 0.46, 95% CI [0.16, 0.76], $P = 0.003$, as well as a significant main effect of condition, β = –0.29, 95% CI [–0.56, –0.02], $P = 0.04$; participants reported less craving on the AUQ while taking naltrexone compared with placebo (see Fig. 5). The Cue Type × Condition interaction

Table 4 Summary of GEE models predicting momentary craving in the natural environment from alcohol cues, medication condition, and occasion- and person-level covariates.

	Craving			
		95% CI		
Predictor	*β*	*LL*	*UL*	*P*
Alcohol cues	0.13	0.00	0.25	0.048
Medication condition	–0.09	–0.26	0.08	0.302
Alcohol cues × medication condition	–0.42	–0.77	–0.08	0.016
Treatment order	0.38	–0.17	0.93	0.172
Occasion-level covariates				
Time of day				
12:00 AM–5:59 AM	–0.14	–0.27	–0.01	0.042
6:00 AM–11:59 AM	–0.36	–0.58	–0.14	0.001
12:00 PM–5:59 PM	–0.21	–0.28	–0.13	<0.001
6:00 PM–11:59 AM (reference)	–	–	–	–
Drinking day	0.22	0.07	0.37	0.004
Weekend	0.07	–0.02	0.16	0.136
Peers present	0.09	0.00	0.17	0.046
Location				
Friend's house	0.26	0.02	0.49	0.033
Other's house	0.03	–0.10	0.16	0.686
School	–0.09	–0.18	0.00	0.052
Work	0.29	–0.30	0.88	0.339
Public location	0.02	–0.07	0.11	0.620
Vehicle	0.06	–0.07	0.18	0.389
Other location	–0.03	–0.14	0.09	0.673
Home (reference)	–	–	–	–
Person-level covariates				
Age (centered predictor)	–0.09	–0.37	0.20	0.548
Female	–0.14	–0.85	0.57	0.697

Note. The coefficients reported for alcohol cues and medication condition represent standardized effects (effect size *d*). CI = confidence interval; GEE = generalized estimating equations; *LL* = lower limit; *UL* = upperlimit.

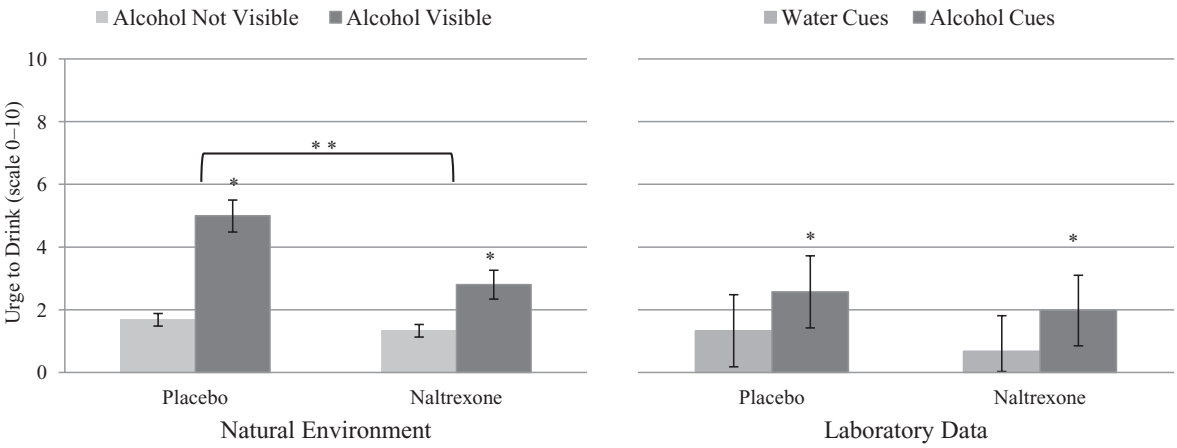

Figure 4 Marginal means for raw scores depicting momentary rating of craving during alcohol cue reactivity by medication condition across the laboratory and natural environments. Error bars represent 95% confidence intervals for the estimated means. Single asterisks denote significant main effect of cue type (P's ≤ 0.05). Double asterisks denote a significant Cue Type × Medication Condition interaction (P = 0.02), such that cues elicited greater craving in the placebo arm than the naltrexone arm

was not significant [β = –0.07, 95% CI (–0.26, 0.12), P = 0.46], suggesting that naltrexone attenuated tonic levels of craving measured by the AUQ across cue exposures.

Physiological reactivity

Cue type produced a main effect on MAP, β = 0.29, 95% CI [0.10, 0.47], P = 0.002, such that participants had

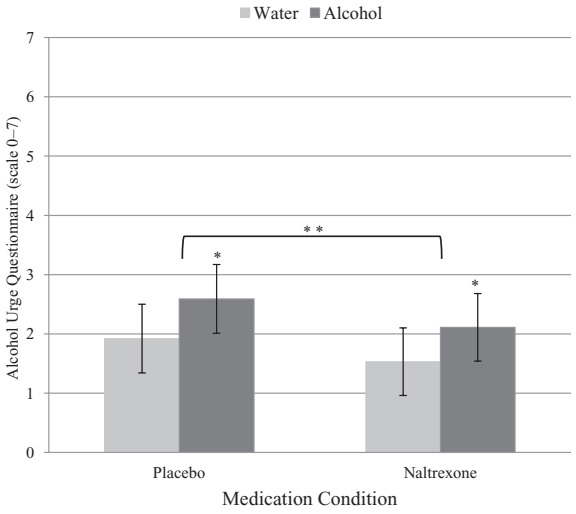

Figure 5 Marginal means for raw scores depicting the main effects of Beverage Cue Type and Medication Condition on craving in the laboratory, as measured using the Alcohol Urge Questionnaire. Error bars represent 95% confidence intervals for the estimated means. Single asterisks denote significant main effect of cue type ($P = 0.003$). Double asterisks denote significant main effect of medication condition ($P = 0.04$)

greater MAP while exposed to alcohol cues (M = 82.89, SD = 7.58) compared with water cues (M = 80.66, SD = 8.13). Neither the main effect of condition [β = –0.22, 95% CI (–0.60, 0.16), $P = 0.25$] nor the Cue Type × Condition interaction [β = 0.06, 95% CI (–0.32, 0.45), $P = 0.75$, was significant. In terms of heart rate, the effects cue type [β = 0.04, 95% CI (–0.09, 0.18), $P = 0.52$], condition [β = –0.22, 95% CI (–0.48, 0.04), $P = 0.09$] and the Cue Type × Condition interaction [β = –0.13, 95% CI (–0.42, 0.16), $P = 0.38$], were non-significant.

DISCUSSION

Adolescent problem drinkers were randomized to placebo and naltrexone using a cross-over design. Naltrexone reduced the likelihood of drinking and heavy drinking. Additionally, naltrexone blunted craving across methods and contexts. EMA data from drinking episodes revealed that alcohol potentiated craving in a dose-dependent fashion, such that adolescents reported greater craving as their eBAC levels increased. Importantly, naltrexone blunted this effect. Results also showed that naltrexone blunted alcohol-induced stimulation and increased sedation. Naltrexone also potentiated high while drinking, especially among participants with greater average eBAC levels. EMA data from random assessments demonstrated that alcohol cues elicited craving outside drinking episodes and that naltrexone also dampened this response. Finally, laboratory data showed that alcohol cues elicited craving and physiological reactivity compared with water cues, and that naltrexone attenuated subjective craving assessed by the AUQ across both cue types. It is noteworthy, however, that alcohol cues elicited greater craving in the natural environment than in the laboratory. This relatively weak effect of alcohol cues on craving in the laboratory may have compromised our ability to detect alcohol-specific medication effects in a controlled environment.

Our finding that naltrexone reduced drinking is noteworthy given the brief medication period, the exclusion of treatment-seeking youths, and the fact that we did not include a behavioral intervention in order to isolate the pharmacological effects of naltrexone. Moreover, the magnitude of the estimated effects on drinking outcomes observed in this study, albeit modest, mirrors those found with adults (Maisel *et al.* 2013). Our finding that naltrexone blunted craving is also significant. Although craving remains a cornerstone of research on alcoholism in adults, relatively few studies have examined this construct in adolescents. Our findings are consistent with initial research showing that craving is common among adolescent drinkers (Martin *et al.* 1995). In addition, this study offers further evidence that alcohol cues reliably elicit craving among adolescents under controlled conditions (Curtin *et al.* 2005; Thomas, Drobes & Deas 2005) and, perhaps more notably, extends previous work by demonstrating findings from the laboratory generalize to the natural environment. Effect size estimates indicated the effects of naltrexone on craving were in the medium range, which is similar to those observed with adults (Maisel *et al.* 2013). Clinical data further underscore the potential relevance of these findings by showing that adolescents experience difficulty utilizing skills learned in treatment when faced with alcohol cues and that post-treatment relapses among teenagers are frequently associated with exposure to alcohol cues (Meyers, Brown & Mott 1993; Brown *et al.* 2000). Thus, our finding that naltrexone blunts craving across contexts may hold significant clinical utility. Moreover, recent data highlight the role of naltrexone in attenuating craving associated with goal directed (as opposed to habitual) drinking (Ray, Chin & Miotto 2010). As such, naltrexone may be particularly effective for adolescents.

This study extends pharmacotherapy research on alcoholism in several meaningful ways. At the fundamental level, we demonstrated the utility of pairing laboratory paradigms with EMA methods to more fully capture the effects of medications on purported behavioral mechanisms of pharmacotherapy action. Our findings indicate that laboratory CRA methods, which are designed to simulate clinically relevant phenomena under experimentally controlled conditions, may not adequately capture what happens in the real world. These

novel findings highlight the utility of EMA methods for understanding addiction processes and testing treatment effects. This study also presents the first randomized controlled evidence that an opioid antagonist attenuates drinking and craving in adolescents, along with novel data on subjective responses to alcohol. Although the neuropharmacological mechanisms of naltrexone's effects on drinking are not fully delineated, most animal studies suggest that competitive binding of opioid antagonists to opioid receptors attenuate the rewarding effects of alcohol by decreasing dopamine release in the mesolimbic pathway following alcohol ingestion (for review, see Ray *et al*. 2010). Laboratory studies with adults generally support this notion by demonstrating that naltrexone and other opioid antagonists (e.g. nalmefene) blunt alcohol-induced stimulation (Anton *et al*. 2004). There is substantial remodeling of dopaminergic and other neurotransmitter systems during adolescence, however, including major changes in mesolimbic brain regions. Our findings showed that alcohol potentiates stimulation among adolescents and that naltrexone attenuates this effect. This suggests that alcohol exerts rewarding effects through similar mechanisms during adolescence as in adulthood.

Several limitations qualify our findings. First and foremost, drinking outcomes are inherently limited by the short duration of treatment. Although results support the promise of naltrexone for reducing adolescent drinking, this hypothesis must be tested in larger randomized clinical trials with long-term follow-up assessments. Second, we selected a sample of non–treatment-seeking teenagers, which may not represent the types of youth who engage in alcohol treatment. The majority of participants in this sample met diagnostic criteria for an alcohol use disorder, however, thereby increasing the applicability of our findings to clinical practice. Third, there were inherent limitations of our EMA approach to capturing drinking episodes, including the lack of a placebo control for alcohol consumption and the restriction of analyses to the ascending limb of the blood alcohol curve. It is possible that naltrexone also affected the descending limb in this sample (Ray *et al*. 2008). Finally, our sample size is small; an important goal for future research is to replicate these findings in a larger sample and to examine individual difference factors associated with patient responsiveness, such as sex or familial alcoholism.

On balance, this study provides the first experimental evidence that naltrexone reduces alcohol use and craving, and alters subjective responses to alcohol, in adolescent problem drinkers. This study supports our experimental paradigm, which combined human laboratory and EMA methods, as an innovative approach for testing medication effects. A major clinical implication of our findings is that naltrexone shows promise for treating alcohol misuse in this challenging population during an instrumental period in the development of alcohol use disorders.

Acknowledgements

The National Institute of Alcohol Abuse and Alcoholism at the National Institutes of Health supported this work (AA017273, AA019681). The authors thank Bethany Rallis, Justin Souliere, Jacqueline Lee, and Jason Frezza for their assistance with this project. Lara Ray is now at Department of Psychology, University of California, Los Angeles. Elizabeth K. Reynolds is now at Department of Psychiatry and Behavioral Sciences, Johns Hopkins School of Medicine.

Disclosure/Conflict of Interest

CG is a consultant with ERT, which provides electronic diary solutions for use in clinical trials. LR is consulting with GlaxoSmithKline. RS is a consultant for D&A Pharma, CT San Remo and Transcept Pharmaceuticals. Otherwise, the authors have no conflicts to disclose.

Authors Contribution

RM was responsible for the study concept. RM, LR, AB, PM, AJ, RS, JT and CG were responsible for the study design. RM, AB, ER, AJ, TC and JR were responsible for the acquisition of study data. TC and RS conducted medical exams on study applicants and provided medical coverage for this study. RM and AJ provided clinical coverage during alcohol cue reactivity assessments. RM, AB, ER and CG were responsible for data analysis, and all authors contributed to interpretation of findings. RM drafted the manuscript and all authors critically reviewed content and approved the final version for publication.

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