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Reduction of Alcohol Drinking in Young Adults by Naltrexone: A Double-Blind, Placebo-Controlled, Randomized Clinical Trial of Efficacy and Safety

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Abstract

Objective—Naltrexone, an opioid antagonist, may facilitate reduction in drinking among young adults. We compared the efficacy and safety of naltrexone administered daily plus targeted dosing with placebo to reduce drinking in heavy drinking young adults.

Methods—Randomized, double-blind, placebo-controlled study, outpatient research center, March 2008-January 2012. Participants were ages 18-25, reporting 4 heavy drinking days in the prior 4 weeks. Interventions included naltrexone 25 mg daily plus 25 mg targeted (at most daily) in anticipation of drinking (n = 61) or daily/targeted placebo (n = 67). All received a personalized feedback session and brief counseling every other week. Primary outcomes were percent days heavy drinking (PHDD) and percent days abstinent (PDA) over the 8-week treatment period. Secondary outcomes included drinks/drinking day and percent days with estimated blood alcohol levels 0.08 g/dL.

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Disclosure: Dr. O'Malley has been a consultant to Alkermes. Dr. O'Malley has had contracts as an investigator on clinical trials supported by Lilly, may receive a contract from Arkeo and received study medication from Pfizer. She has received honoraria from the Hazelden Foundation. Drs. O'Malley and Kranzler have received honoraria from the American College of Neuropsychopharmacology/American Society of Clinical Psychopharmacology's Alcohol Clinical Trials Initiative, which has received support from Abbott, Alkermes, Ethypharma, Lilly, Lundbeck, and Pfizer. Dr. Kranzler has been a consultant to Alkermes, Lilly, Lundbeck, Pfizer, and Roche. Dr. Kranzler has filed a US provisional patent entitled, "Diagnostic test predicting treatment response to topiramate for the reduction of heavy drinking and treatment of alcohol use disorder."

Results—Of 140 randomized, 128 began treatment, comprising the evaluable sample. During treatment, PHDD (Naltrexone M=21.60, SD=16.05; Placebo M=22.90, SD=13.20) ($p=0.58$) and PDA (Naltrexone M=56.60, SD=22.52; Placebo M=62.50, SD=15.75) ($p=0.39$) did not differ by group. Naltrexone significantly reduced drinks per drinking day (Naltrexone M=4.90, SD=2.28; Placebo M=5.90, SD=2.51) ($p=0.009$) and percentage of drinking days with estimated BAC ≥ 0.08 g/dL (Naltrexone M=35.36, SD=28.40; Placebo M=45.74, SD=26.80) ($p=0.042$). There were no serious adverse events. Sleepiness was more common with naltrexone.

Conclusions—Naltrexone did not reduce frequency of drinking or heavy drinking days, but reduced secondary measures of drinking intensity. While effects were modest, the risk-benefit ratio favors offering naltrexone to help young adult heavy drinkers reduce their drinking.

Registration [clinicaltrials.gov NCT00568958](https://clinicaltrials.gov/ct2/show/study/NCT00568958)

INTRODUCTION

Frequent, heavy drinking, commonplace in young adults¹, is associated with serious negative consequences (e.g., fatal traffic crashes²) and high rates of alcohol dependence³. Although many young adults will reduce heavy drinking by their mid-to-late twenties, a considerable minority will continue to drink heavily and encounter clinically significant problems⁴.

Individual interventions for young adults are primarily based on skills building and motivational-interviewing approaches^{5,6} (including Brief Alcohol Screening and Intervention for College Students [BASICS])⁷, but have relatively small effects, particularly on drinking intensity. These interventions are also less effective for the heaviest drinkers⁸, who are at greatest risk of failing to “mature out” of heavy drinking⁴. It would be desirable to have a “low burden”, safe, flexible drinking reduction intervention for this population.

Naltrexone, an opioid antagonist medication approved by the U.S. Food and Drug Administration for the treatment of alcohol dependence, has demonstrated efficacy and safety in the general adult population⁹ and may be suited for use in young adults. Young adults are generally not motivated to abstain but may consider reduced drinking^{7,10} and prefer taking medication as needed¹⁰. Accordingly, naltrexone reduces the frequency of heavy drinking¹¹ and can be used on a “targeted” or “as needed” basis¹²⁻¹⁵. Because naltrexone reduces the speed of drinking, naltrexone should also result in lower blood alcohol levels^{16,17}, a goal of many risk reduction strategies⁵. Preliminary evidence supporting naltrexone in this population includes two small open-label studies^{18,19} and a small cross-over study of non-treatment seeking adolescents²⁰.

We report the results of a randomized, double-blind, placebo-controlled, 8-week clinical trial of daily (25 mg) plus targeted (25 mg) naltrexone to augment brief motivational counseling in frequent heavy drinking young adults. This is the first adequately-powered, randomized clinical trial to test the efficacy of pharmacotherapy to reduce drinking among young adults. The intent of targeted dosing in anticipation of drinking (e.g., parties) was to heighten awareness of drinking situations and to reach the FDA-approved 50 mg/day dose on drinking days. Low, daily dosing provided coverage in case participants omitted the

targeted dose. We hypothesized that naltrexone (i.e., combined daily and targeted), would result in a greater reduction in frequency of heavy and any drinking than daily + targeted placebo. We also examined alternative drinking intensity measures: drinks per drinking day and percent of drinking days when estimated blood alcohol levels reached 0.08 g/dL. Although the National Institute on Alcohol Abuse and Alcoholism (NIAAA) Council defined binge drinking as drinking to blood alcohol concentration (BAC) ≥ 0.08 g/dL²¹, this outcome has not been examined in naltrexone clinical trials.

METHODS

Design Overview

This was a double-blind, 2-group, parallel, placebo-controlled study of naltrexone. One hundred forty outpatients were randomly assigned to either naltrexone (25 mg targeted + 25 mg daily) or placebo naltrexone (placebo targeted + placebo daily) for 8 weeks (Figure 1). Enrollment occurred March 2008-January 2012. Institutional review boards at Yale University and Arizona State University approved the study and NIAAA issued a Certificate of Confidentiality.

Setting and Participants

Recruitment occurred primarily through Facebook advertisements and fliers. Following initial screening by phone or online surveys, individuals were invited for intake conducted by a research assistant at an outpatient research clinic where written informed consent was obtained. The intake included diagnostic evaluations for substance use and other psychiatric disorders, physical examination, laboratory analysis and urine pregnancy test for women. Other assessments were obtained through in-person interview and self-reports administered on a secure website.

Eligible participants were: 1) 18-25 years old, 2) reported ≥ 4 heavy drinking days (i.e., ≥ 4 drinks/women, ≥ 5 drinks/men) in the prior 4 weeks; 3) able to read English and without significant cognitive impairment. Women of child-bearing potential were practicing reliable birth control with negative urine pregnancy test results and not breast feeding.

Exclusion criteria were: 1) current, clinically-significant physical disease/abnormality according to history, physical examination, or laboratory evaluation; 2) serious psychiatric illness by history or examination; 3) past 12-month diagnosis of DSM-IV drug dependence other than nicotine, or lifetime opioid dependence history; 4) current, clinically-severe alcohol dependence (i.e., history of seizures, delirium, or hallucinations during withdrawal; Clinical Institute Withdrawal Assessment scale²² score ≥ 8 ; drinking to avoid withdrawal; prior withdrawal treatment); 5) past month use of opioids or concomitant therapy with psychotropic drugs, except a stable dose of a selective serotonin reuptake inhibitor for ≥ 2 months or non-benzodiazepine medications for performance anxiety; 6) naltrexone hypersensitivity; 7) failure to complete $\geq 50\%$ of baseline daily questionnaires.

Randomization and Interventions

Eligible participants were randomly assigned to medication condition by a pharmacist using a list generated by the statistician (others were blind to assignment). Blocked stratified randomization (block size = 4) by sex and parental alcoholism was used to balance treatment groups.

Medication Conditions—Naltrexone or matching placebo was provided for 8 weeks. For Week 1, participants were instructed to take only a single dose of medication on a targeted basis at least 2 hours prior to drinking situations. The daily dose was not added until Week 2 to maximize tolerability. The maximum daily dose was 50 mg (25 mg daily + 25 mg targeted), which was dispensed every other week in separate bottles for daily and targeted dosing. Naltrexone (50 mg) and matching placebo were purchased from Mallinckrodt Pharmaceuticals (St. Louis, Missouri), divided into 25 mg doses and encapsulated by a pharmacist.

Counseling Components—Counseling used the BASICS framework^{7,15,23}, with naltrexone added to reduce heavy drinking. The manual²⁴ integrated aspects from existing BASICS and medication management manuals^{7,15,23}. The first appointment (approximately 1.5 hours), included an individualized feedback session with a masters- or doctoral-level therapist followed by a meeting with the nurse practitioner. Based on intake assessments, personalized feedback covered drinking patterns including estimated average and recent peak BACs, perceived norms and alcohol-related consequences. The therapist also discussed drinking-reduction strategies (e.g., spacing drinks, drink-refusal skills) and provided a personalized BAC chart.

The nurse obtained a baseline assessment of adverse events using the SAFTEE²⁵; dispensed study medication; reviewed how naltrexone could support drinking-reduction strategies; and discussed drinking goals and medication adherence. At subsequent 15-20-minute every other week sessions, the nurse monitored safety, provided support, reviewed alcohol consumption, drinking goals, medication use and drinking-reduction strategies. Participants were advised to avoid acetaminophen and non-steroidal anti-inflammatory drugs due to possible interaction with alcohol.

Outcomes and Follow-up

Following intake through end of treatment, participants completed web-based daily diaries (DatStat™) including medication taking, number of standard alcohol drinks and approximate times of first and final drinks for the prior day. Self-reported drinking was also obtained using the Timeline Follow-Back Interview²⁶ (TLFB) at baseline and at each visit over the 8 weeks. The Brief Young Adult Alcohol Consequences Questionnaire²⁷, a 24-item dichotomous response (yes/no) measure was administered at baseline and weeks 4 and 8. The recall period was 3 months at baseline and 4 weeks at weeks 4 and 8. Adverse events were monitored at each appointment using the SAFTEE²⁵. Liver enzyme concentrations were measured at baseline and monthly thereafter. Participants received up to \$415 for appointments and assessments.

Outcomes—The protocol specified two primary efficacy analyses for comparisons between naltrexone and placebo: percent days abstinent (PDA) and percent heavy drinking days (PHDD) during the 8-week treatment. A standard drink was equivalent to 0.6 fluid ounces of absolute alcohol (e.g., 12-oz beer, 5-oz wine, 1.5-oz, 80-proof liquor). Daily diary data were the primary source for outcome variables (days with data in both groups >75%) with TLFB data inserted to replace missing data (bringing days with data in both groups to >90%). Because of data completeness and comparable missing data rates between groups, we based analyses on available data.

Pre-specified secondary drinking intensity measures included number of drinks per drinking day (DDD) and percentage of drinking days with estimated BAC ≥ 0.08 g/dL. BAC was estimated using daily diary data based on number of drinks, duration of drinking, and total body water (calculated from gender, age, height and weight)²⁸. We also examined average estimated BAC per drinking day. Medication adherence was monitored with 1) capsule counts and 2) daily diary reports. We calculated total capsule count because participants frequently disregarded labels that differentiated daily from targeted medication bottles. Count was based on 49 daily doses and up to 56 targeted doses, with adherence equal to number of capsules taken divided by 105. Adherence based on daily diaries was as follows: Daily adherence = doses taken/number of possible doses; Targeted adherence = drinking days when a dose was taken/drinking days reported.

Statistical Analyses

Differences in baseline characteristics and adverse events by treatment group were analyzed with ANOVA for continuous variables and χ^2 or Fisher's Exact tests for categorical variables. Outcome analyses of drinking measures and alcohol-related consequences were conducted by fitting general linear models (GLM) for summary measures averaged over 8 weeks for each outcome specified *a priori*. Group was the main predictor in the models. Gender and family history of alcoholism were included as covariates. Baseline percent days abstinent was included as a covariate in the analysis of this outcome due to a group difference that approached significance ($p = .06$, Table 1). *P* values are two-tailed. Effect sizes are reported as least square means differences (LSMDiff) between the treatment groups. Analyses were performed using SAS version 9.2 (SAS Institute, Inc., Cary, NC).

Initially, 66 subjects per group were targeted for enrollment to detect a medium effect size ($f=0.26$), assuming 80% power, $\alpha=0.05$, and 10% dropout. Due to a higher than anticipated rate of randomized participants who did not attend the first appointment ("non-starters"; see details below), we increased total enrollment to 140 participants to preserve power to detect the same effect. We included in the analyses participants who attended the first appointment and received study medication.

RESULTS

Study Population

140 patients were randomized (Consort Diagram, Figure 1). Of these, 128 attended the first session and were evaluable. Relative to the 12 non-starters, this sample had lower percent

heavy drinking days (PHDD ($P = 0.004$; $M=33.84$, $SD=15.17$ versus $M=47.22$, $SD=13.47$) and DDD ($P = 0.011$; $M=6.75$, $SD=2.69$ versus $M=8.90$, $SD=3.60$). Baseline characteristics of the evaluable sample were comparable between groups except for PDA ($P = .06$) which was higher for the placebo group (Table 1).

Treatment Effects on Drinking Outcomes

The effect of treatment group (Table 2) was not significant for the primary outcomes: PHDD ($p=0.58$) and PDA ($p=0.39$). Mean PDA was 56.6 ($SD=22.52$) for naltrexone and 62.5 ($SD=15.75$) for placebo (LSMDiff = -2.55, 95% CI: (-8.46, 3.36)) and mean PHDD was 21.6 ($SD=16.05$) for naltrexone and 22.9 ($SD=13.20$) for placebo (LSMDiff = -1.44, 95% CI: (-6.60, 3.71)). Because prior studies of the efficacy of naltrexone relied on TLFB data rather than on daily diaries combined with TLFB data, we also conducted exploratory analyses using TLFB data only, which revealed a significant group difference for PHDD ($p=0.04$) favoring naltrexone ($M=15.9\%$, $SD=11.84$) over placebo ($M=20.3\%$, $SD=1.73$) (LSMDiff = -4.45, 95% CI: (-8.78, -0.13)). The difference on PDA using this approach was not significant.

Naltrexone was associated with a lower intensity of drinking, as reflected in the secondary outcomes (Table 2). Naltrexone reduced drinks per drinking occasion ($p=0.009$) (LSMDiff = -1.07, 95% CI: (-1.87, -0.28)) and lowered the percent of drinking days with estimated BAC 0.08 g/dL ($p = 0.042$) (LSMDiff = -9.85, 95% CI: (-19.33, -0.37)). Paralleling the DDD findings, estimated BAC/drinking day was significantly lower in the naltrexone group than the placebo group ($p = 0.03$; LSMDiff = -0.017, 95% CI: (-0.033, -0.0015)). To further explore the clinical significance of the results, we compared the groups on the proportion with an average estimated BAC/drinking day 0.08 g/dL. Only 35% (21/60) of the naltrexone group met this threshold compared to 61.5% (40/65) of the placebo group ($p=0.003$; OR=0.322, 95% CI: (0.152, 0.683)).

Treatment Effects on Alcohol-Related Consequences

At baseline, the groups had comparable alcohol consequences scores (Table 1, $M = 12.1$, $SD = 4.90$). Although the total score for the treatment period was numerically lower in the naltrexone (mean=4.7, $SD=3.59$) than the placebo group ($M=5.6$, $SD=3.90$), the difference was not significant (LSMDiff: -0.92, 95% CI: (-2.32, 0.47), $p=0.19$). Supplemental eTable 1 presents individual consequences by group.

Adherence

There was no difference between groups on counseling sessions attended ($p=0.41$) or medication adherence, including capsule counts ($p=0.80$), daily dosing ($p=0.97$) and targeted dosing ($p=0.15$) (Table 3).

Adverse Events

Table 4 presents adverse events. Sleepiness ($p=0.01$) and headache ($p=0.06$) occurred more frequently in patients treated with naltrexone. Incidence of liver enzyme concentrations exceeding entrance criteria in the naltrexone ($n=6$, 10%) and placebo conditions ($n=9$, 13%)

were equivalent ($p = 0.57$). No participant reported suicidal ideation, intent or behavior²⁹. There were no serious adverse events during treatment.

DISCUSSION

This is the first adequately-powered, randomized clinical trial to test the efficacy of pharmacotherapy to reduce drinking among young adults. The results demonstrate that naltrexone, in conjunction with BASICS and brief follow-up, can help some young adults reduce their drinking. Although results for our primary outcomes were not significant, naltrexone was significantly better than placebo on measures of drinking intensity (i.e., drinks per drinking day; drinking to an estimated BAC > 0.08 g/dL). These findings have important public health implications, as most injuries and deaths in young adults occur under intoxication².

We specified primary outcomes based on studies in general adult alcohol dependent samples, and proposed to derive them from daily diaries with missing data supplemented by TLFB data. Using these integrated data, we did not find significant differences on the primary outcomes. However, exploratory analyses conducted using only TLFB data, the method used in most prior studies, found that the naltrexone group reported significantly fewer heavy drinking days than placebo and the difference (LSMDiff = -4.45, 95% CI: (-8.78,-0.13)) was similar to that observed in the Cochrane meta-analysis of opioid antagonists (MD - 3.25 (95% CI -5.51 to -0.99))⁹. This discrepancy may be due to higher reported quantities on daily diaries versus retrospective reports. Baseline differences in PDA may have made it difficult to demonstrate an effect on PHDD. The naltrexone group had significantly better outcomes on measures of drinking intensity. Compared to the placebo group, the naltrexone group reported approximately one fewer drink per drinking day, lower estimated BAC/drinking day and 23% fewer days on which drinking was estimated to reach the legal limit of intoxication, 0.08 g/dL, a clinically meaningful index of binge drinking²¹. Although this reduction translates into a reduction of about one day of drinking to the legal limit over 8 weeks, by augmenting the effects of counseling, naltrexone can play a useful role in helping young adults reduce heavy drinking.

Pending development of devices that can monitor actual BAC unobtrusively in real time³⁰, we used estimated BAC as an alternative measure of drinking intensity that has been evaluated in studies of brief motivational interventions and moderate drinking protocols^{31,32}. Based on daily reports, we estimated BAC based on drink number, drinking duration and total body water²⁸. This formula represents a more precise estimate of heavy drinking than standard drinks with a single adjustment for gender (e.g., 5+/4+ for men/women) or the requirement that this level of drinking occur in 2 hours. Clearly, there is substantial individual variability in both alcohol metabolism^{33,34} and other factors that limit the precision of estimated BAC. However, it seems unlikely that these complicating factors would be associated with treatment condition. Consequently, BAC estimates are a valuable metric to gauge the likely “real world” effects of treatment.

During treatment, both groups experienced large reductions in alcohol-related consequences. While the reduction was somewhat larger in the naltrexone group, this difference was not

significant statistically. Of interest, however, individual consequences associated with very high BACs, such as black-outs and passing-out, occurred less frequently in the naltrexone group. Importantly, all participants received counseling that emphasized avoiding consequences through indirect strategies (e.g., using a designated driver) that have been shown to reduce adverse consequences⁸.

Although previous studies have tested either targeted or daily doses in general adult populations^{12-14,35}, we evaluated a novel dosing strategy including daily naltrexone (easier to remember) and targeted low-dose naltrexone prior to drinking. Whereas young adults express a preference for taking medication as needed¹⁰, adherence to daily dosing was higher than targeted dosing. Lower adherence to targeted dosing (as defined by taking a dose on a drinking day) may occur because targeted dosing requires anticipation of drinking occasions. We did not, however, directly test the efficacy of daily versus targeted dosing which could be the focus of future research. We also did not compare naltrexone and medication counseling to BASICS alone, which is typically provided in 1-2 sessions. Instead, following the BASICS session, placebo participants received study medication, met every other week with a nurse practitioner, and completed daily diaries. Thus, the effect of adding naltrexone and medication counseling to the typical standard of care for young adults could be greater than that shown here relative to placebo. Regarding limitations, the number of randomized participants who failed to start treatment was higher than expected and this group drank more heavily than those who began treatment. Because this study recruited participants through advertisements and paid them for appointments and assessments, acceptability and adherence to treatment by young adults identified and treated in college counseling centers and other clinical settings remain to be determined. Nonetheless, recruitment of a sample with variable motivation to change drinking is relevant to the broader population of young adults seen in these settings. Whereas the inclusion of college students and non-students is a strength of the study, the overall sample was primarily Caucasian and the treatment period was relatively brief.

SUMMARY

Current behavioral interventions for heavy drinking in young adults show modest efficacy and are least effective for the heaviest drinkers. This study provides evidence that naltrexone can help young adults reduce the intensity of their drinking, with reductions in drinking amounts that are associated with the most severe consequences. The safety profile of naltrexone was also good. Thus, the risk-benefit ratio favors offering naltrexone as a therapeutic option to young adults who drink heavily. Given that the effects were modest, the development of new pharmacotherapies remains a priority.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Clinical Points

1. Young adults engage in frequent heavy drinking that is associated with adverse consequences.
2. Naltrexone, an FDA-approved treatment for alcohol dependence, can be used to help young adults modestly reduce the number of drinks they consume.

Flow Diagram

Figure 1.
Consolidated Standards of Reporting Trials diagram for patient allocation. D/C indicates discontinued

Table 1

Baseline Characteristics of the Evaluable Sample (128 participants who started treatment)

Characteristics	Overall (<i>n</i> = 128)	Naltrexone (<i>n</i> = 61)	Placebo (<i>n</i> = 67)
Demographics			
Age, mean (SD)	21.5 (2.15)	21.6 (2.1)	21.3 (2.1)
Gender, No. male (%)	88 (69%)	43 (71%)	45 (67%)
White ^a , No. (%)	99 (77%)	49 (80%)	50 (75%)
Weight, mean (SD) lbs.	173.4 (41.29)	174.7 (40.71)	172.1 (42.07)
Highest level of education			
HS or less, No. (%)	18 (14%)	7 (12%)	11 (16%)
Some college, No. (%)	72 (56%)	33 (54%)	39 (58%)
College/Post-Bacc, No. (%)	38 (30%)	21 (34%)	17 (25%)
Student status, enrolled, No. (%)	91 (71%)	43 (71%)	48 (72%)
Smoke at least weekly, No. (%)	38 (30%)	18 (30%)	20 (30%)
Alcohol Use Diagnosis			
No Diagnosis, No. (%)	27 (21%)	16 (26%)	11 (16%)
Alcohol Abuse, No. (%)	25 (20%)	11 (18%)	14 (21%)
Alcohol Dependence, No. (%)	76 (59%)	34 (56%)	42 (63%)
Alcohol Drinking ^b			
% days abstinent, mean (SD)	46.5 (18.60)	43.3 (21.77)	49.5 (14.69)
% days heavy drinking ^c , mean (SD)	33.8 (15.17)	34.3 (16.76)	33.4 (13.68)
Drinks per drinking day, mean (SD)	6.7 (2.69)	6.7 (2.90)	6.8 (2.51)
Brief Young Adult Alcohol Consequences Scale ^d , mean (SD)	12.5(4.96)	12.5 (4.79)	12.5(5.13%)
Readiness to change drinking ^e , mean (SD)	5.20 (2.16)	5.25 (1.97)	5.15 (2.34)
Marijuana Use, No. %			
At least 1 day per week	42 (33%)	20 (35%)	22 (34%)
Liver function tests, mean (SD)			
Bilirubin, Total, mg/dL, mean (SD)	0.63 (0.23)	0.61 (0.24)	0.65 (0.23)
AST, U/L, mean (SD)	20.68 (6.51)	20.72 (6.84)	20.64 (6.25)
ALT, U/L, mean (SD)	19.23 (8.99)	18.84 (8.85)	19.60 (9.17)
GGT, U/L, mean (SD)	22.8 (13.84)	23.9 (17.52)	21.8 (9.35)

Abbreviations. ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ -glutamyltransferase.^aOther Ethnicities: African-American (10), Native American (1), Asian (4), Multiple (6) Other/Refused/Unknown (8)^bMeasured with the Time-Line Follow-back Interview²⁶ for the prior 30 days.^cHeavy drinking = 5 or more standard drinks for men and 4 or more standard drinks for women. A standard drink contains 0.6g of absolute alcohol (e.g., 12 oz of beer, 5 oz of wine, or 1.5 oz of 80-proof liquor).^dThe scale range for the Brief Young Adult Alcohol Consequences Scale is 0-24.^eThe scale range for the Readiness scale is 1-10.

Table 2

Alcohol Consumption Outcomes by Medication Condition

Variable	Condition					<i>p</i> ^a
	Naltrexone (<i>n</i> = 61)		Placebo (<i>n</i> = 67)			
	Intake	Treatment	Intake	Treatment		
% days abstinent, mean (SD)	43.3 (21.77)	56.6 (22.52)	49.5 (14.69)	62.5 (15.75)	0.39	
% heavy days ^b , mean (SD)	34.3 (16.76)	21.6 (16.05)	33.4 (13.68)	22.9 (13.20)	0.58	
Drinks/drinking day, mean (SD)	6.7 (2.90)	4.9 (2.28)	6.8 (2.51)	5.9 (2.51)	0.009	
% drinking days with estimated BAL 0.08 g/dL ^c , mean (SD)	----- ^c	35.4 (28.40)	----- ^c	45.7 (26.80)	0.04	
Estimated BAL ^c /drinking day, mean g%(SD)	----- ^c	0.077 (0.047)	----- ^c	0.095 (0.043)	0.03	

^a *P*-value is for the comparison of naltrexone and placebo during treatment. The analysis of percent days abstinent co-varied for baseline percent days abstinent which differed at baseline (*p* = .06). Baseline values were not included in the remaining analyses.

^b Heavy drinking = 5 or more standard drinks for men and 4 or more standard drinks for women. A standard drink contains 0.6gms of absolute alcohol (e.g., 12 oz beer, 5 oz wine, or 1.5 of 80-proof liquor)

^c Estimated BALs were derived using data from the daily diaries and were based on the number of drinks consumed, the duration of drinking, and total body water (based on gender, age, height and weight) using Curtin's formula²⁸. These were not available at baseline because diaries were completed for a limited and inconsistent period prior to randomization.

Table 3

Treatment Adherence for Evaluable Sample

Variable	Naltrexone (n = 61)	Placebo (n = 67)	P
Counseling sessions ^a (M, SD)	4.77 (1.26)	4.65 (1.03)	.41
Capsule count ^b (M, SD)	64.6 (22.86)	65.5 (19.30)	.80
Daily dosing ^c (M, SD)	69.1 (29.84)	68.8 (29.40)	.97
Targeted dosing ^d (M,SD)	57.1 (25.5)	50.7 (24.6)	.15

^a Mean number of sessions attended out of 5 possible sessions.

^b Capsule counts were computed based on capsules taken from the targeted and daily bottles combined/total possible days of treatment.

^c Computed from daily diaries as the number of daily doses taken/number of possible daily diaries (missing = nonadherent)

^d Computed from daily diaries as the number of targeted doses taken on drinking days/number of drinking days. (missing targeted doses on drinking days were coded as nonadherent). Two cases (one naltrexone and one placebo) did not report any drinking days in the daily diaries and so were not included in the analysis of targeted adherence.

Table 4

Adverse Events Reported by 5% or More of the Sample

Frequency, No. (%)				
Adverse Event	Naltrexone (n = 61)	Placebo (n = 67)	Total (n = 128)	P
Dermatological				
Rash	9 (14.8)	6 (9.0)	15 (11.7)	0.31
Itching	8 (13.1)	5 (7.5)	13 (10.2)	0.29
Sweating	4 (6.6)	2 (3.0)	6 (4.7)	0.42
Gastrointestinal				
Nausea	22 (36.1)	16 (23.9)	38 (29.7)	0.13
Vomiting	14 (23.0)	11 (16.4)	25 (19.5)	0.35
Diarrhea	4 (6.6)	7 (10.5)	11 (8.6)	0.43
Abdominal	4 (6.6)	6 (9.0)	10 (7.8)	0.75
General Disorders				
Fatigue	11 (18.0)	6 (9.0)	17 (13.3)	0.13
Decreased Appetite	7 (11.5)	9 (13.4)	16 (12.5)	0.74
Increased Appetite	5 (8.2)	7 (10.5)	12 (9.4)	0.66
Neurological				
Headache	31 (50.8)	23 (34.3)	54 (42.2)	0.06
Insomnia	12 (19.7)	14 (20.9)	26 (20.3)	0.86
Dizziness	8 (13.1)	7 (10.5)	15 (11.7)	0.64
Sleepiness	10 (16.4)	2 (3.0)	12 (9.4)	0.01
Psychiatric				
Anxiety	18 (29.5)	14 (20.9)	32 (25.0)	0.26
Depression	4 (6.6)	7 (10.5)	11 (8.6)	0.43
Reproductive/Sexual				
Irregular Menses	4/18 (22.2)	4/22(18,1)	8/40 (20.0)	1.00
Change in Libido	2 (3.3)	6 (9.0)	8 (6.3)	0.28