See commentary by Hester

Notice of correction 9/6/2018: In Figure 1, the numbers of participants who discontinued intervention have been corrected.

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 young adults who engage in heavy drinking.

Method: A randomized, double-blind, placebo-controlled study was conducted in an outpatient research center in March 2008–January 2012. Participants were aged 18–25 years and reported ≥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 participants received a personalized feedback session and brief counseling every other week. Primary outcomes were percent heavy drinking days and percent days abstinent over the 8-week treatment period. Secondary outcomes included number of drinks per drinking day and percentage of days with estimated blood alcohol concentration (BAC) levels ≥ 0.08 g/dL.

Results: Of 140 randomized patients, 128 began treatment, comprising the evaluable sample. During treatment, percent heavy drinking days (naltrexone: mean = 21.60, SD = 16.05; placebo: mean = 22.90, SD = 13.20) ($P = .58$) and percent days abstinent (naltrexone: mean = 56.60, SD = 22.52; placebo: mean = 62.50, SD = 15.75) ($P = .39$) did not differ by group. Naltrexone significantly reduced the number of drinks per drinking day (naltrexone: mean = 4.90, SD = 2.28; placebo: mean = 5.90, SD = 2.51) ($P = .009$) and percentage of drinking days with estimated BAC ≥ 0.08 g/dL (naltrexone: mean = 35.4, SD = 28.40; placebo: mean = 45.7, SD = 26.80) ($P = .042$). 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 the amount of alcohol they drink.

Trial Registration: ClinicalTrials.gov identifier: NCT00568958

J Clin Psychiatry 2015;76(2):e207–e213

Submitted: *December 13, 2013; accepted June 16, 2014 (doi:10.4088/JCP.13m08934).*
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Frequent heavy drinking, commonplace in young adults,[1] is associated with serious negative consequences (eg, fatal traffic crashes[2]) and high rates of alcohol dependence.[3] 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 problems.[4]

Individual interventions for young adults are primarily based on skills building and motivational-interviewing approaches[5,6] (including the 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 drinkers,[8] who are at greatest risk of failing to "mature out" of heavy drinking.[4] 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 US Food and Drug Administration (FDA) for the treatment of alcohol dependence, has demonstrated efficacy and safety in the general adult population[9] and may be suited for use in young adults. Young adults are generally not motivated to abstain from drinking, but they may consider reduced drinking[7,10] and prefer taking medication as needed.[10] Accordingly, naltrexone reduces the frequency of heavy drinking[11] and can be used on a targeted or as needed basis.[12–15] Because naltrexone reduces the speed of drinking, naltrexone should also result in lower blood alcohol levels,[16,17] a goal of many risk-reduction strategies.[5] Preliminary evidence supporting naltrexone in this population includes 2 small open-label studies[18,19] and a small cross-over study[20] of non–treatment-seeking adolescents.

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 young adults who engage in frequent heavy drinking. 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 (eg, parties) was to heighten awareness of drinking situations and to reach the FDA-approved 50-mg/d dose on drinking days. Low, daily dosing provided coverage in case participants omitted the targeted dose. We hypothesized that naltrexone (ie, combined daily and targeted) would result in a greater reduction in frequency of heavy and any drinking than daily plus targeted placebo. We also examined alternative drinking intensity measures: number of drinks per drinking day and percent of drinking days when estimated blood alcohol concentration (BAC) levels reached 0.08 g/dL. Although

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Clinical Points

- Young adults engage in frequent heavy drinking that is associated with adverse consequences.
- Naltrexone, a US Food and Drug Administration–approved treatment for alcohol dependence, can be used to help young adults modestly reduce the number of drinks they consume.

the National Institute on Alcohol Abuse and Alcoholism (NIAAA) Council defined binge drinking as drinking to BAC ≥ 0.08 g/dL,[21] this outcome has not been examined in naltrexone clinical trials.

METHOD

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 in March 2008–January 2012. Institutional review boards at Yale University and Arizona State University approved the study and NIAAA issued a certificate of confidentiality. The study was registered on ClinicalTrials.gov (identifier: NCT00568958).

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 (1) were 18–25 years old, (2) reported ≥ 4 heavy drinking days (ie, ≥ 4 drinks for women, ≥ 5 drinks for men) in the prior 4 weeks, and (3) were able to read English and free of 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) presence of current, clinically significant physical disease/abnormality according to history, physical examination, or laboratory evaluation; (2) presence of serious psychiatric illness by history or examination; (3) diagnosis of *DSM-IV* drug dependence other than nicotine in the past 12 months or lifetime opioid dependence history; (4) presence of current, clinically severe alcohol dependence (ie, history of seizures, delirium, or hallucinations during withdrawal; Clinical Institute Withdrawal Assessment scale[22] score ≥ 8; drinking to avoid withdrawal; prior withdrawal treatment); (5) use of opioids or concomitant therapy with psychotropic drugs in the past month, except a stable dose of a selective serotonin reuptake inhibitor for ≥ 2 months or medications other than benzodiazepines for performance anxiety; (6) hypersensitivity to naltrexone; and (7) failure to complete ≥ 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 manual[24] 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 master's- or doctoral-level therapist followed by a meeting with the nurse practitioner. On the basis of 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 (eg, spacing drinks, drink-refusal skills) and provided a personalized BAC chart.

The nurse obtained a baseline assessment of adverse events using the Systematic Assessment for Treatment of Emergent Events (SAFTEE),[25] dispensed study medication, reviewed how naltrexone could support drinking-reduction strategies, and discussed drinking goals and medication adherence. At subsequent 15- to 20-minute sessions every other week, the nurse monitored safety, provided support, and reviewed alcohol consumption, drinking goals, medication use, and drinking-reduction strategies. Participants were advised to avoid acetaminophen and nonsteroidal 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 Interview[26] (TLFB) at baseline and at each visit over the 8 weeks. The Brief Young Adult Alcohol Consequences Questionnaire,[27] a 24-item dichotomous response (yes/no) measure, was administered at baseline and

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at 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 SAFTEE.[25] Liver enzyme concentrations were measured at baseline and monthly thereafter. Participants received up to $415 for appointments and assessments.

Outcomes. The protocol specified 2 primary efficacy analyses for comparisons between naltrexone and placebo: percent days abstinent and percent heavy drinking days during the 8-week treatment. A standard drink was equivalent to 0.6 fluid ounces of absolute alcohol (eg, 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.

Prespecified secondary drinking intensity measures included number of drinks per drinking day and percentage of drinking days with estimated BAC ≥0.08 g/dL. Blood alcohol concentration 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 estimated mean 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 analysis of variance for continuous variables and χ^2 or Fisher exact tests for categorical variables. Outcome analyses of drinking measures and alcohol-related consequences were conducted by fitting general linear models 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 2-tailed. Effect sizes are reported as least squares mean differences between the treatment groups. Analyses were performed using SAS version 9.2 (SAS Institute, Inc; Cary, North Carolina).

Initially, 66 subjects per group were targeted for enrollment to detect a medium effect size ($F = 0.26$), assuming 80% power, $\alpha = .05$, and 10% dropout. Due to a higher than anticipated rate of randomized participants who did not attend the first appointment ("nonstarters"), 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

One hundred forty patients were randomized (Consort diagram, Figure 1). Of these, 128 attended the first session and were evaluable. Relative to the 12 nonstarters, this sample had lower values of percent heavy drinking days ($P = .004$; mean = 33.84, SD = 15.17, versus mean = 47.22, SD = 13.47) and number of drinks per drinking day ($P = .011$; mean = 6.75, SD = 2.69, versus mean = 8.90, SD = 3.60). Baseline characteristics of the evaluable sample were comparable between groups except for percent days abstinent ($P = .06$), 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: percent heavy drinking days ($P = .58$) and percent days abstinent ($P = .39$). Mean percent days abstinent was 56.6 (SD = 22.52) for naltrexone and 62.5 (SD = 15.75) for placebo (least squares mean difference = −2.55; 95% CI, −8.46 to 3.36) and mean percent heavy drinking days was 21.6 (SD = 16.05) for naltrexone and 22.9 (SD = 13.20) for placebo (least squares mean difference = −1.44; 95% CI, −6.60 to 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 percent heavy drinking days ($P = .04$) favoring naltrexone (mean = 15.9%, SD = 11.84) over placebo (mean = 20.3%, SD = 1.73) (least squares mean difference = −4.45; 95% CI, −8.78 to −0.13). The difference on percent days abstinent 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 the number of drinks per drinking occasion ($P = .009$) (least squares mean difference = −1.07; 95% CI, −1.87 to −0.28) and lowered the percent of drinking days with estimated BAC ≥0.08 g/dL ($P = .042$) (least squares mean difference = −9.85; 95% CI, −19.33 to −0.37). In a result that parallels the findings for number of drinks per drinking day, estimated BAC per drinking day was significantly lower in the naltrexone group than in the placebo group ($P = .03$; least squares mean difference = −0.017; 95% CI, −0.033 to −0.0015). To further explore the clinical significance of the results, we compared the groups on the proportion with an average estimated BAC per 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 ($P = .003$; OR = 0.322; 95% CI, 0.152 to 0.683).

Treatment Effects on Alcohol-Related Consequences

At baseline, the groups had comparable alcohol consequences scores (Table 1; mean = 12.1, SD = 4.90). Although the total score for the treatment period was

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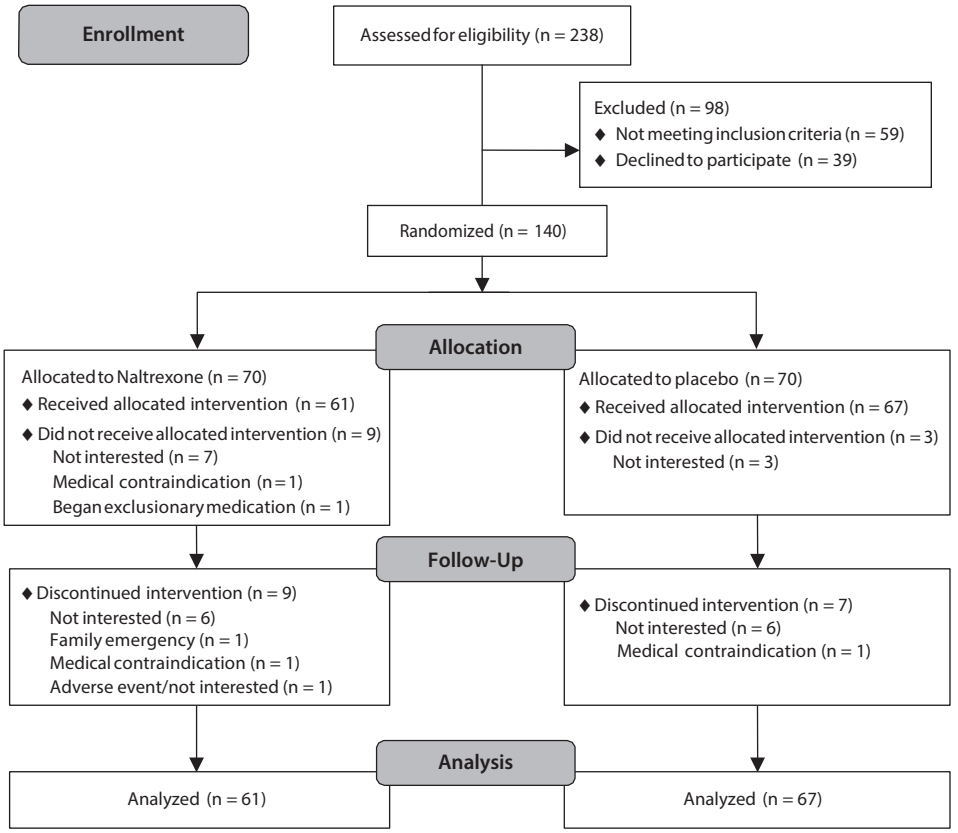
Figure 1. Consolidated Standards of Reporting Trials Diagram for Patient Allocation



numerically lower in the naltrexone (mean = 4.7, SD = 3.59) than the placebo group (mean = 5.6, SD = 3.90), the difference was not significant (least squares mean difference = –0.92; 95% CI, –2.32 to 0.47; $P = .19$). Supplementary eTable 1 presents individual consequences by group.

Adherence

There was no difference between groups on number of counseling sessions attended ($P = .41$) or medication adherence, including capsule counts ($P = .80$), daily dosing ($P = .97$), and targeted dosing ($P = .15$) (Table 3).

Adverse Events

Table 4 presents adverse events. Sleepiness ($P = .01$) and headache ($P = .06$) 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 ($P = .57$). No participant reported suicidal ideation, intent, or behavior.[29] 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 (ie, number of 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 intoxication.[2]

We specified primary outcomes based on studies in general samples of alcohol-dependent adults 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 (least squares mean difference = –4.45; 95% CI, –8.78 to –0.13) was similar to that observed in the Cochrane meta-analysis of opioid antagonists (mean difference = –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 percent days abstinent may have made it difficult to demonstrate an effect on percent heavy drinking days. The naltrexone group had significantly better outcomes on measures of drinking intensity. Compared to the placebo group, the naltrexone group reported approximately 1 less drink per drinking day, lower estimated BAC per drinking day, and 23% fewer days in which drinking was

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Table 1. Baseline Characteristics of the Evaluable Sample (128 participants who started treatment)

Characteristic	Overall (n = 128)	Naltrexone (n = 61)	Placebo (n = 67)
Demographic			
Age, mean (SD)	21.5 (2.15)	21.6 (2.1)	21.3 (2.1)
Male gender, n (%)	88 (69)	43 (71)	45 (67)
White, n (%)[a]	99 (77)	49 (80)	50 (75)
Weight, mean (SD), lb	173.4 (41.29)	174.7 (40.71)	172.1 (42.07)
Highest level of education, n (%)			
High school or less	18 (14)	7 (12)	11 (16)
Some college	72 (56)	33 (54)	39 (58)
College/postbaccalaureate degree	38 (30)	21 (34)	17 (25)
Enrolled student status, n (%)	91 (71)	43 (71)	48 (72)
Smoke at least weekly, n (%)	38 (30)	18 (30)	20 (30)
Alcohol use diagnosis, (%)			
No diagnosis	27 (21)	16 (26)	11 (16)
Alcohol abuse	25 (20)	11 (18)	14 (21)
Alcohol dependence	76 (59)	34 (56)	42 (63)
Alcohol drinking[b]			
Percent days abstinent, mean (SD)	46.5 (18.60)	43.3 (21.77)	49.5 (14.69)
Percent heavy drinking days, mean (SD)[c]	33.8 (15.17)	34.3 (16.76)	33.4 (13.68)
No. of drinks per drinking day, mean (SD)	6.7 (2.69)	6.7 (2.90)	6.8 (2.51)
Brief Young Adult Alcohol Consequences Scale, mean (SD)[d]	12.5 (4.96)	12.5 (4.79)	12.5 (5.13)
Readiness to change drinking, mean (SD)[e]	5.20 (2.16)	5.25 (1.97)	5.15 (2.34)
Marijuana use at least 1 d/wk, n (%)	42 (33)	20 (35)	22 (34)
Liver function tests, mean (SD)			
Total bilirubin, mg/dL	0.63 (0.23)	0.61 (0.24)	0.65 (0.23)
AST, U/L	20.68 (6.51)	20.72 (6.84)	20.64 (6.25)
ALT, U/L	19.23 (8.99)	18.84 (8.85)	19.60 (9.17)
GGT, U/L	22.8 (13.84)	23.9 (17.52)	21.8 (9.35)

[a]Other ethnicities: African-American (n = 10), Native American (n = 1), Asian (n = 4), multiple (n = 6), and other/refused/unknown (n = 8).
[b]Measured with the Time-Line Follow-Back Interview[26] for the prior 30 days.
[c]Heavy drinking = 5 or more standard drinks for men and 4 or more standard drinks for women. A standard drink contains 0.6 g of absolute alcohol (eg, 12 oz of beer, 5 oz of wine, or 1.5 oz of 80-proof liquor).
[d]The scale range for the Brief Young Adult Alcohol Consequences Scale is 0–24.
[e]The scale range for the Readiness Scale is 1–10.
Abbreviations: ALT = alanine aminotransferase, AST = aspartate aminotransferase, GGT = γ-glutamyltransferase.

Table 2. Alcohol Consumption Outcomes by Medication Condition

Variable	Naltrexone (n = 61)		Placebo (n = 67)		P[a]
	Intake	Treatment	Intake	Treatment	
Percent days abstinent, mean (SD)	43.3 (21.77)	56.6 (22.52)	49.5 (14.69)	62.5 (15.75)	.39
Percent heavy drinking days, mean (SD)[b]	34.3 (16.76)	21.6 (16.05)	33.4 (13.68)	22.9 (13.20)	.58
No. of drinks per drinking day, mean (SD)	6.7 (2.90)	4.9 (2.28)	6.8 (2.51)	5.9 (2.51)	.009
Percentage of drinking days with estimated BAC ≥ 0.08 g/dL, mean (SD)[c]	…	35.4 (28.40)	…	45.7 (26.80)	.04
Estimated BAC per drinking day, mean (SD), g/dL[c]	…	0.077 (0.047)	…	0.095 (0.043)	.03

[a]P value is for the comparison of naltrexone and placebo during treatment. The analysis of percent days abstinent covaried 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 0.6 gms of absolute alcohol (eg, 12 oz beer, 5 oz wine, or 1.5 oz of 80-proof liquor).
[c]Estimated BAC values 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 formula.[28]
Abbreviation: BAC = blood alcohol concentration.
Symbol: … = Not available at baseline because diaries were completed for a limited and inconsistent period prior to randomization.

estimated to reach the legal limit of intoxication, 0.08 g/dL, a clinically meaningful index of binge drinking.[21] Although this reduction translates into a reduction of about 1 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 time,[30] 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] On the basis of daily reports, we estimated BAC based on number of drinks, drinking duration, and total body water.[28] This formula represents a more precise estimate of heavy drinking than standard drinks with a single adjustment for gender (eg, ≥ 5 for men, ≥ 4 for 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

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Table 3. Treatment Adherence for Evaluable Sample

Variable	Naltrexone (n = 61)	Placebo (n = 67)	*P*
Counseling sessions, mean (SD)[a]	4.77 (1.26)	4.65 (1.03)	.41
Capsule count, mean (SD)[b]	64.6 (22.86)	65.5 (19.30)	.80
Daily dosing, mean (SD)[c]	69.1 (29.84)	68.8 (29.40)	.97
Targeted dosing, mean (SD)[d]	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 (1 naltrexone and 1 placebo) did not report any drinking days in the daily diaries so were not included in the analysis of targeted adherence.

Table 4. Adverse Events Reported by 5% or More of the Sample

Adverse Event, n (%)	Naltrexone (n = 61)	Placebo (n = 67)	Total (n = 128)	*P*
Dermatologic				
Rash	9 (14.8)	6 (9.0)	15 (11.7)	.31
Itching	8 (13.1)	5 (7.5)	13 (10.2)	.29
Sweating	4 (6.6)	2 (3.0)	6 (4.7)	.42
Gastrointestinal				
Nausea	22 (36.1)	16 (23.9)	38 (29.7)	.13
Vomiting	14 (23.0)	11 (16.4)	25 (19.5)	.35
Diarrhea	4 (6.6)	7 (10.5)	11 (8.6)	.43
Abdominal	4 (6.6)	6 (9.0)	10 (7.8)	.75
General disorders				
Fatigue	11 (18.0)	6 (9.0)	17 (13.3)	.13
Decreased appetite	7 (11.5)	9 (13.4)	16 (12.5)	.74
Increased appetite	5 (8.2)	7 (10.5)	12 (9.4)	.66
Neurologic				
Headache	31 (50.8)	23 (34.3)	54 (42.2)	.06
Insomnia	12 (19.7)	14 (20.9)	26 (20.3)	.86
Dizziness	8 (13.1)	7 (10.5)	15 (11.7)	.64
Sleepiness	10 (16.4)	2 (3.0)	12 (9.4)	.01
Psychiatric				
Anxiety	18 (29.5)	14 (20.9)	32 (25.0)	.26
Depression	4 (6.6)	7 (10.5)	11 (8.6)	.43
Reproductive/sexual				
Irregular menses[a]	4 (22.2)	4 (18.1)	8 (20.0)	1.00
Change in libido	2 (3.3)	6 (9.0)	8 (6.3)	.28

[a]Naltrexone, n = 18; placebo, n = 22; total, n = 40.

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 blackouts and passing out, occurred less frequently in the naltrexone group. Importantly, all participants received counseling that emphasized avoiding consequences through indirect strategies (eg, using a designated driver) that have been shown to reduce adverse consequences.[8]

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 needed,[10] 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 nonstudents is a strength of the study, the overall sample was primarily white, 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.

Drug names: naltrexone (Vivitrol, ReVia, and others).

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Author contributions: Dr O'Malley and Ms Wu had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Potential conflicts of interest: **Dr O'Malley** has been a consultant to Alkermes; has had contracts as an investigator on clinical trials supported by Lilly; may receive a contract from Arkeo; has received study medication from Pfizer; and 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 and Lundbeck and 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." **Dr Toll** has received a grant from Pfizer for medication for a smoking cessation study. **Drs Corbin**, **Leeman**, **DeMartini**, **Fucito**, **Ikomi**, **Sher**, **Gueorguieva**, and **Mss Romano** and **Wu** have no financial or other conflicts of interest.

Funding/support: The project described was supported by the State of Connecticut, Department of Mental Health and Addictions Services (DMHAS) and grant numbers R01 AA016621 and K05 AA014715 to Dr O'Malley, K24 AA013736 to Dr Kranzler, K05 AA01742 to Dr Sher, K01 AA019694 to Dr Leeman, and K23 AA020000 to Dr Fucito from the National Institute on Alcohol Abuse and Alcoholism (NIAAA), Bethesda, Maryland.

Role of the sponsor: The sponsors had no role in the design or conduct of the study; collection, management, analysis, or interpretation of the data; or preparation, review, or approval of the manuscript.

Disclaimer: The content is solely the responsibility of the authors and does not necessarily represent the official views of DMHAS, NIAAA, or the National Institutes of Health (NIH).

Previous presentation: Portions of the findings were presented at the annual meeting of the Research Society on Alcoholism; June 23–27, 2012; San Francisco, California.

Acknowledgments: The authors acknowledge Alan Marlatt, PhD (deceased) (contributions to the design of the study and intervention), University of Washington; and Ann Agro, MPH (administrative and recruitment); Elaine Lavelle, MS (data management); and Vanessa Costa-Massimo, MLIS; Susan Neveu, and Corey Roos, BA (data collection); Yale School of Medicine, New Haven, Connecticut. The assistance provided by the acknowledged individuals was supported by NIH funding.

Supplementary material: See accompanying pages.

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Supplementary material follows this article.

THE JOURNAL OF
CLINICAL PSYCHIATRY
THE OFFICIAL JOURNAL OF THE AMERICAN SOCIETY OF CLINICAL PSYCHOPHARMACOLOGY

Supplementary Material

Article Title: Naltrexone Reduces Alcohol Drinking in Young Adults: A Double-Blind, Randomized Clinical Trial of Efficacy and Safety

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DOI Number: 10.4088/JCP.13m08934

List of Supplementary Material for the article

1. eTable 1 Consequences Endorsed at Either Week 4 or Week 8 by Condition

Disclaimer

This Supplementary Material has been provided by the author(s) as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

Supplementary eTable 1. Consequences Endorsed at Either Week 4 or Week 8 by Condition

Item	Naltrexone Endorsed (n, %)	Placebo Endorsed (n, %)
Had a hangover	36 (68%)	49 (79%)
Said or done embarrassing things	32 (60%)	47 (76%)
Less energy/felt tired because of drinking	20 (38%)	36 (58%)
Ended up drinking on nights when I had planned not to	25 (47%)	27(44%)
Felt very sick or thrown up after drinking	22 (42%)	29 (47%)
Taken foolish risks	21 (40%)	28 (45%)
Difficult to limit how much I drink	14 (26%)	27 (44%)
Felt badly about myself	16 (30%)	27 (44%)
Passed out from drinking	12 (23%)	24 (39%)
Done impulsive things I've regretted	16 (30%)	22 (36%)
Not able to remember large stretches of time while drinking	9 (17%)	22 (36%)
Schoolwork quality has suffered	10 (19%)	19 (31%)
Needed larger amounts of alcohol to feel effects	18 (34%)	16 (26%)
Spent too much time drinking	17 (32%)	19 (31%)
Overweight because of drinking	15 (28%)	14 (23%)
Driven when knew I had too much to drink	12 (23%)	17 (27%)
Become rude, obnoxious or insulting after drinking	11 (21%)	18 (29%)
Not gone to work or missed classes	7 (13%)	13 (21%)
Neglected obligations to work, family, or school	3 (6%)	10 (16%)
Drinking has gotten me into sexual situations I have regretted	7 (13%)	8 (13%)

Drinking has created problems between myself and partner	7 (13%)	7 (11%)
Woken up in an unexpected place after heavy drinking	5 (9%)	8 (13%)
Physical appearance has been harmed by my drinking	5 (9%)	6 (10%)
Felt like I needed a drink after getting up	1 (2%)	1 (2%)

Note: At Week 4 and Week 8, participants indicated on the Brief Young Adult Alcohol Consequences Questionnaire (YAACQ) whether they had experienced any consequences in the past month. The scale yields a single total score. Individual items are presented for descriptive purposes. Naltrexone n = 53; placebo n = 62.