Original Investigation

Naltrexone vs Placebo for the Treatment of Alcohol Dependence
A Randomized Clinical Trial

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IMPORTANCE Alcohol use disorder is one of the leading causes of disability worldwide. While effective pharmacological treatments exist, they are efficacious only in certain individuals, contributing to their limited use. Secondary analysis of clinical trial data suggests that a functional polymorphism (rs1799971, Asn40Asp) of the μ-opioid receptor gene (*OPRM1*) is associated with the risk of relapse to heavy drinking following treatment with the opioid antagonist naltrexone.

OBJECTIVE To prospectively examine whether rs1799971 is predictive of naltrexone treatment response.

DESIGN, SETTING, AND PARTICIPANTS We conducted a 12-week, double-blind, randomized clinical trial of naltrexone vs placebo in individuals with alcohol dependence (intent-to-treat analysis). Participants were randomly assigned to study treatment based on the presence of 1 or 2 copies of the Asp40 allele compared with those homozygous for the Asn40 allele (2 × 2 cell design). Recruitment occurred between January 2009 and September 2013. All participants were seen in an outpatient clinical setting. A convenience sample of participants (n = 221) was recruited from 5 sites. All participants met *DSM-IV* criteria for alcohol dependence, with no concurrent psychotic or manic symptoms, no use of concurrent psychotropic medications, and no current dependence on illicit substances.

INTERVENTIONS The study drug was naltrexone (50 mg) given once daily or corresponding placebo.

MAIN OUTCOMES AND MEASURES The primary study outcome measure was relapse to heavy drinking measured using the timeline follow-back method.

RESULTS There was no evidence of a genotype × treatment interaction on the primary outcome of heavy drinking ($P = .32$). In the Asn40 group, the observed effect of naltrexone was similar to that in previous trials (odds ratio, 0.69; 95% CI, 0.41-1.18; $P = .17$), with a very small naltrexone effect in the Asp40 group (odds ratio, 1.10; 95% CI, 0.52-2.31; $P = .80$), contrary to the pattern expected a priori. A significant reduction in heavy drinking occurred across all groups ($P = .001$). Other drinking outcomes, and all secondary outcomes, demonstrated similar time effects, with no genotype × treatment interaction.

CONCLUSIONS AND RELEVANCE The results of this study do not support the hypothesis that the Asp40 allele moderates the response to naltrexone treatment. It is premature to use the Asn40Asp polymorphism as a biomarker to predict the response to naltrexone treatment of alcohol dependence.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT00831272

JAMA Psychiatry. 2015;72(5):430-437. doi:10.1001/jamapsychiatry.2014.3053
Published online March 11, 2015.

Supplemental content at jamapsychiatry.com

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Alcohol dependence is one of the leading causes of disability worldwide.[1] Over the last 2 decades, there have been dozens of randomized placebo-controlled trials of naltrexone for the treatment of alcohol dependence.[2] Despite the better group response to naltrexone in clinical trials, significant variability exists in the response among individuals treated with naltrexone. Based on both preclinical research and promising clinical trial data, it has been hypothesized that the functional, nonsynonymous single-nucleotide polymorphism (SNP) of the μ-opioid receptor gene ($A_{+118}G$, Asn40Asp, rs1799971) is a biomarker that predicts naltrexone treatment response.[3,4]

Retrospective analysis of clinical trial data showed that individuals with alcohol dependence and 1 or 2 copies of the Asp40 allele were significantly more likely not to relapse to heavy drinking with naltrexone treatment (73.9%) than individuals homozygous for the Asn40 allele (49.0%).[5] In individuals receiving placebo, there was no association between genotype and treatment response. This finding was replicated in a retrospective review of data from the Combined Pharmacotherapies and Behavioral Interventions (COMBINE) Study.[6] In that study, 87% of individuals assigned to medical management with naltrexone who had 1 or 2 copies of the Asp40 allele had a good treatment outcome compared with a 49% response among Asn40 allele homozygotes treated with naltrexone. However, other clinical studies[7-11] have failed to demonstrate this pharmacogenetic effect. Human laboratory settings also suggest clinical relevance of the Asp40 allele among individuals exposed to alcohol, including higher rates of stimulation,[12] which is blocked by naltrexone,[13] and greater cue-induced craving.[14-16]

While much of the literature supports the hypothesis that the Asp40 allele is a functional variant with clinical manifestations, there are important limitations to the existing treatment data that cast doubt on the use of this allele as a biomarker to predict naltrexone treatment response. In particular, the clinical studies to date have relied on secondary analysis of randomized clinical trials in which genotype was not available for all participants. Furthermore, while not a rare polymorphism, the Asp40 allele frequency in individuals of European ancestry is approximately 15%,[17] limiting the number of individuals with the allele in most studies. Moreover, given the substantial diversity in allele frequencies among African American, Asian, and European populations, sampling strategies and randomization in prior studies would not have been designed to address this diversification.[17]

The aim of this study was to examine prospectively the interaction between the Asp40 allele and the response to treatment of alcohol dependence with naltrexone. We hypothesized that individuals exposed to naltrexone who carry at least 1 copy of the Asp40 allele would have the greatest response to treatment, while the other 3 treatment groups (Asp40/placebo, Asn40/naltrexone, and Asn40/placebo) would have an equal but poorer response to treatment. The primary outcome was defined as the presence of heavy drinking during each week of the trial.

Methods

Trial Design and Participants

The study was a 12-week, double-blind, randomized clinical trial of naltrexone vs placebo with stratification by genotype. Eligible participants had to be at least 18 years of age, meet *DSM-IV* criteria for alcohol dependence as assessed by a structured diagnostic interview,[18] report a minimum mean of more than 21 standard drinks per week and 2 days per week of heavy drinking, and be of European or Asian descent. Before randomization, participants had to achieve at least 24 hours of self-reported abstinence. Individuals were not included if they had a current *DSM-IV* diagnosis of any psychoactive substance dependence other than alcohol or nicotine or provided a urine sample positive for the presence of cocaine or opioids. Individuals could not be taking psychotropic medications or have a current diagnosis of psychosis, mania, or posttraumatic stress disorder or be currently enrolled in an addiction treatment program. Other exclusion criteria included serious medical illness (eg, active hepatitis), elevations of alanine aminotransferase (upper limit, 45 U/L for men and 33 U/L for women) and aspartate aminotransferase greater than 5 times the upper limit of normal or elevation of bilirubin (upper limit, 1.2 mg/mL) of 1.3 times the upper limit of normal, and women who were pregnant, nursing, or not using a reliable method of contraception (to convert alanine aminotransferase level to microkatals per liter, multiply by 0.0167; to convert bilirubin level to micromoles per liter, multiply by 17.014).

Recruitment

A convenience sample of participants was recruited through advertisements in local media, referrals from physicians, or self-referrals. Recruitment occurred between January 2009 and September 2013. Participants were recruited from 5 sites, including Philadelphia, Pennsylvania (n = 151); Media, Pennsylvania (n = 20); the Philadelphia Veterans Affairs Medical Center (n = 26); the Veterans Affairs Pittsburgh Healthcare System (n = 16); and the Geisinger Medical Center (Danville, Pennsylvania) (n = 8). The study was reviewed and approved by the institutional review board at each of 5 sites. All participants provided written informed consent. The protocol manuscript is provided in Supplement 1.

Because the allele frequency for the Asp40 allele approximates 0.15 in European ancestry individuals, we oversampled participants with the risk allele. Genotyping was conducted at the time of informed consent and was reviewed by a nonblinded staff member who informed the study team of an individual's eligibility but did not report the genotype results. The nonblinded staff member used a random procedure to select every other consenting participant who was homozygous for the Asn40 allele.

Interventions

Treatment With Naltrexone

Participants randomized to naltrexone received a dosage of 50 mg/d as recommended by the US Food and Drug Admin-

istration. All medication was distributed in blister packs that included 8 days of medication.

Medical Management

Medical management (MM) is a manualized psychosocial intervention that was designed for the multisite COMBINE Study.[19] The goal of MM is to provide a basic, minimal form of clinical intervention supporting the use of effective pharmacotherapy and reduction in alcohol consumption. Sessions last approximately 30 minutes. The maximum number of sessions was 11. Session content included education about naltrexone, counseling on steps to reduce alcohol consumption, and monitoring of safety (adverse events), treatment adherence (pill counts and visit attendance), and drinking status.

Before participation, each therapist was certified in the delivery of MM. Fidelity to treatment was monitored by reviewing a random set of session tapes, with no significant therapeutic drift detected. There were 14 MM therapists who participated in the trial.

Outcome Measures

Standard research assessments measured the amount of drinking, severity of alcohol problems, and level of psychosocial functioning. Trained technicians who were blinded to randomization assignment and not directly involved in the treatment of participants administered the assessments. The primary outcome measure was obtained using the timeline follow-back method to assess alcohol consumption.[20-22] The timeline follow-back method is a semistructured interview that uses a calendar format to record the quantity and frequency of drinking per day during a stated period. Drinking reports were recorded for the 60 days preceding enrollment and throughout the intervention period. The quantity of alcohol was recorded in standard alcohol drinks containing 14 g of alcohol (eg, a 12-oz beer, a 5-oz glass of wine, or a 1½-oz shot of spirits). Heavy drinking was defined as 5 or more drinks in a single day for men or 4 or more drinks in a single day for women.[23,24] Secondary measures of outcome included subjective quality of life as measured by the Medical Outcomes Study 12-Item Short-Form Health Survey[25] and alcohol craving as measured by the Penn Alcohol Craving Scale.[26] Prestudy severity of problems related to drinking was measured by the Short Index of Problems.[27]

Medication adherence was measured using well-marked blister cards, pill counts, and participant interviews,[28] while clinic visit attendance was tracked by the therapist. Potential adverse events were recorded by the therapist at each visit.

For genotyping, all genetic testing was done at the University of Pennsylvania. Genomic DNA was extracted from blood samples by standard methods.[29] The $A_{+118}G$ SNP was genotyped using a TaqMan sample-to-SNP assay (C_8950074_1; Applied Biosystems). Sequencing-confirmed homozygous G DNA was used as a positive control, and sequencing-confirmed homozygous A DNA was used as a negative control. Genetic testing results were obtained before randomization and were used to confer eligibility and to stratify the randomization.

Sample Size

Based on the randomized sample of 221 and the observed dropout rates and within-participant correlation of 0.57, the study had 80% power to detect an interaction odds ratio of 3.72. Originally, the goal of the study was to randomize 150 participants with the Asp40 allele. With the same observed dropout and correlation, this would have yielded 80% power to detect an interaction odds ratio of 2.9.

Randomization

Participants were randomly allocated to the 2 treatment groups separately within each site and stratified by genotype (2 × 2 cell design). Blocked randomizations were used with a block size of 10 and PROC PLAN (SAS, version 9.3; SAS Institute Inc), created before the start of the study.

Statistical Analysis

Baseline characteristics of the 4 genotypes by medication group were compared using χ^2 test for categorical variables and Wilcoxon rank sum test for continuous variables. Repeated weekly measures of drinking outcomes were compared using generalized estimating equation (GEE) models.[30] In all GEE models, the explanatory variables of primary interest comprised binary indicators for intervention group, genotype, and their interaction; a linear trend for time; and terms for interactions involving time and the group and genotype factors. In addition, all models included a factor for site and the pretreatment version of the response as a covariate. The significance of the interaction terms was evaluated based on *P* values from score tests in the GEE models. A compound symmetry structure was used for the working correlation matrix, and empirical (robust) standard errors were used. The presence or absence of heavy drinking in a week was modeled using a GEE logistic regression model. The number of days of heavy drinking in a week was modeled as a binomial outcome (range, 0 to the number of days reported on for that week) using GEE binomial regression models, with the number of heavy days out of available days in each week as the event or trial response. The presence or absence of any drinking and the number of drinking days were analyzed in the same way. Secondary outcomes were also compared using GEE models.

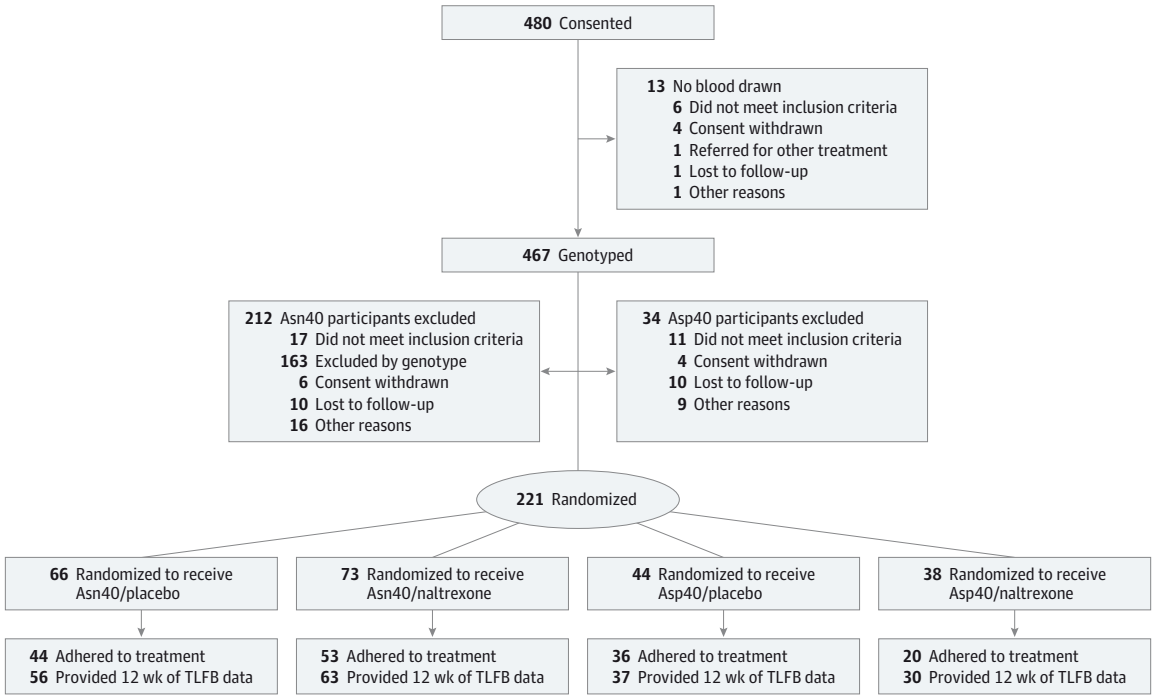
Inverse probability-weighted GEE models and pattern-mixture models comparing completers and noncompleters were used to assess the sensitivity of the primary timeline follow-back method models to missing data.[31,32] A set of nonintent-to-treat models was used to assess the effects of nonadherence on the analyses.[33]

Results

Randomization and Baseline Characteristics

There were 480 individuals who consented to participate in the study, of whom 221 were randomized (**Figure 1**). Most participants who were not randomized were excluded through the oversampling procedure. No differences were observed in sex, age, prestudy rates of heavy drinking, or prestudy percentage days of drinking between individuals who were random-

Figure 1. Consolidated Standards of Reporting Trials Diagram



Adherence is defined as taking at least 80% of medication. TLFB indicates timeline follow-back.

ized and Asn40 homozygotes who were not randomly selected to participate ($P > .06$). Recruitment was ended before reaching the specified sample size. Recruitment proceeded slower than anticipated, and the allele frequency among the participants was lower than anticipated. The observed allele frequency in those who consented was 12.7% (ie, 24.8% of screened individuals had at least 1 copy of the Asp40 allele).

For the randomized sample, the mean (SD) age of the participants was 48.5 (12.6) years, with most being male (85.9%) and of white race (98.2%). Clinical characteristics before treatment indicate that participants drank on a mean (SD) of 82.0% (20.7%) of days preceding enrollment and drank heavily on a mean (SD) of 69.6% (27.8%) of days. With regard to alcohol-related problems, the mean (SD) Short Index of Problems score was 17.7 (10.4). Overall, there were only minor differences in the baseline variables across the 4 study groups (**Table**) (additional prestudy characteristics are provided in the eResults in Supplement 2).

Drinking Outcome Measures

For the primary outcome of heavy drinking, a significant time-dependent decrease in heavy drinking during the trial was observed for all groups (GEE score test $\chi^2_1 = 12.18$, $P = .001$), with no significant group × time interactions. Percentage days of heavy drinking at baseline was a significant predictor (GEE score test $\chi^2_1 = 7.38$, $P = .007$), with higher rates of heavy drinking at baseline associated with higher probability of heavy drinking during the trial. The site variable was not significant (GEE score test $\chi^2_1 = 0.40$, $P = .53$). The genotype × treatment interaction was not significant (GEE score test $\chi^2_1 = 0.98$, $P = .32$) (**Figure 2**).

The model containing the genotype × treatment interaction provides separate estimates of the medication odds ratio for heavy drinking for the Asn40 and Asp40 strata. In the Asn40 stratum, the odds of heavy drinking in the naltrexone group was estimated to be 0.69 (95% CI, 0.41-1.18) times the corresponding odds in the placebo group ($P = .17$). In the Asp40 stratum, the odds of heavy drinking in the naltrexone group was estimated to be 1.10 (95% CI, 0.52-2.31) times the corresponding odds in the placebo group ($P = .80$).

Analyses of the numbers of heavy drinking days per week, the presence or absence of any drinking, and the numbers of drinking days per week showed similar results, with genotype × treatment interaction score statistics of 1.86 ($P = .17$), 1.60 ($P = .21$), and 0.31 ($P = .58$), respectively (eFigure 1 and eFigure 2 in Supplement 2). The survival analysis to the time of first heavy drinking was also not significant (eFigure 3 in Supplement 2). Weighted GEE models, pattern-mixture models, and analysis of secondary outcomes showed similar results (eFigure 4 and eFigure 5 in Supplement 2).

Treatment Adherence

The group proportions of participants adhering for at least 80% of all 12 weeks of treatment days were 66.7% (Asn40/placebo), 72.6% (Asn40/naltrexone), 79.6% (Asp40/placebo), and 50.0% (Asp40/naltrexone), with a significant geno-

Table. Baseline Demographics[a]

Variable	Asp40/Naltrexone (n = 38)	Asp40/Placebo (n = 44)	Test Statistic	Asn40/Naltrexone (n = 73)	Asn40/Placebo (n = 66)	Test Statistic
Age, mean (SD), y	45.8 (13.4)	46.9 (11.8)	Zw = −0.35	51.2 (13.0)	48.2 (11.9)	Zw = −1.73
Male sex, %	89.5	86.4	χ^2 = 0.18	86.3	83.3	χ^2 = 0.24
White race, %	97.3	95.5	χ^2 = 0.19	100	98.5	χ^2 = 1.11
Hispanic ethnicity, %	7.9	4.5	χ^2 = 0.40	0	4.5	χ^2 = 3.39
Days of heavy drinking, mean (SD), %	68.0 (29.8)	72.5 (27.8)	Zw = −0.61	67.5 (26.8)	70.9 (28.0)	Zw = 0.86
Days of drinking, mean (SD), %	78.9 (23.1)	82.7 (20.9)	Zw = −0.69	82.8 (20.2)	82.5 (19.8)	Zw = −0.10
Drinks per drinking day, mean (SD)	10.3 (8.0)	10.2 (6.1)	Zw = −0.09	8.4 (3.9)	9.1 (4.9)	Zw = 0.53
Days from last drinking day to randomization, mean (SD)	11.6 (18.0)	7.1 (7.4)	Zw = −0.05	7.6 (10.7)	6.3 (8.0)	Zw = 0.78
Days from last heavy drinking day to randomization, mean (SD)	13.8 (19.2)	8.6 (7.8)	Zw = 0.42	8.6 (10.2)	7.2 (8.1)	Zw = −0.41
γ-Glutamyltransferase level, mean (SD), U/L	88.9 (112.6)	80.8 (128.7)	Zw = 0.94	106.9 (208.6)	114.3 (308.3)	Zw = −0.33
Required inpatient detoxification before randomization, %	3	0	NA	0	0	NA
History of addiction treatment, %	81	77	χ^2 = 0.18	84	78	χ^2 = 0.58
Short Index of Problems score, mean (SD)	18.8 (11.5)	17.6 (9.8)	Zw = 0.41	17.7 (10.2)	17.1 (10.5)	Zw = −0.39
Penn Alcohol Craving Scale score, mean (SD)	3.1 (1.4)	2.9 (1.3)	Zw = 0.77	3.0 (1.2)	3.0 (1.2)	Zw = 0.03
Medical Outcomes Study 12-Item Short-Form Health Survey score, mean (SD)						
Physical component	53.9 (7.7)	50.6 (9.0)	Zw = 1.45	52.2 (9.5)	53.9 (7.0)	Zw = 0.99
Mental component	41.4 (11.1)	44 (8.9)	Zw = −1.08	42.5 (11.4)	41.7 (11.8)	Zw = −0.34

Abbreviations: NA, not applicable; Zw, standardized Wilcoxon rank sum test statistic.

SI conversion factor: To convert γ-glutamyltransferase level to microkatals per liter, multiply by 0.0167.

[a] The test statistics refer to within-genotype comparison using Wilcoxon rank sum test. None of these statistics are significant at $P < .05$. Further tests for genotype × treatment interaction for the baseline variables in the table showed a significant interaction for only the physical component of the Medical Outcomes Study 12-Item Short-Form Health Survey score ($P = .03$).

type × treatment interaction (GEE score test $\chi^2_1 = 7.28$, $P = .007$). Adherence rates in the Asp40/naltrexone group were significantly lower than those in the Asn40/naltrexone group ($P = .02$). Analysis of participants only adherent and analysis up to the time of dropout were also nonsignificant ($P = .23$ and $P = .12$, respectively), and estimates of naltrexone effects in the genotype groups were similar to those for the intent-to-treat analyses above (eResults in Supplement 2). The survival analysis to the time of discontinuation was not significantly different between groups (eFigure 6 in Supplement 2). Exploratory analyses demonstrated that the first occurrence of heavy drinking occurred before any evidence of nonadherence to treatment because 131 participants out of 155 with heavy drinking outcomes had perfect adherence before their heavy drinking. Participants attended a mean (SD) of 8.5 (2.9) MM sessions, with no significant differences in the number attended per group (GEE score test $\chi^2_3 = 1.93$, $P = .59$).

Adverse Effects

Five participants experienced a serious adverse event, all leading to early termination of treatment. Three participants (1 Asn40/placebo, 1 Asn40/naltrexone, and 1 Asp40/placebo) relapsed sufficiently to require inpatient detoxification. A fourth participant (Asn40/placebo) was hospitalized for a suicide attempt, and the fifth participant (Asp40/placebo) was hospitalized for diabetes mellitus. Adverse events rated as severe were infrequent and were unrelated to group assignment, and only 2 led to discontinuation. The frequencies of severe adverse events were 3 participants with gastrointestinal complaints, 3 participants with worsening pain, 2 participants with

nausea, 2 participants with change in libido,1 participant with headache, and 1 participant with disruption of sleep. Additional findings on the occurrence of adverse events are included in the eResults in Supplement 2.

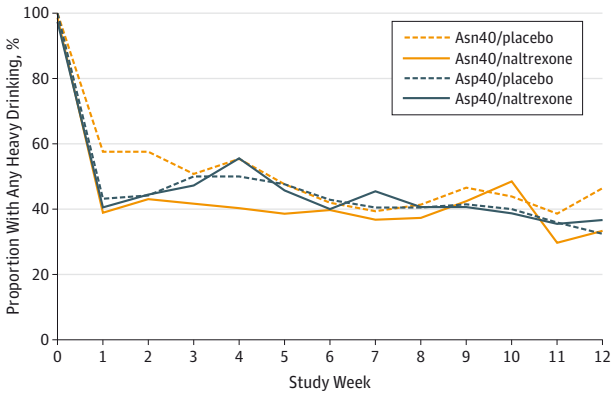
Discussion

The results from this prospective randomized trial failed to demonstrate a moderating effect of the Asn40Asp SNP in *OPRM1* (OMIM 600018) on naltrexone treatment response among individuals with alcohol dependence. We oversampled participants with the purported risk allele and stratified the randomization based on genotype. While there was not an overall significant effect of naltrexone in the entire sample, the reduction in heavy drinking in the Asn40/naltrexone group is comparable to the reductions in heavy drinking seen in most studies of naltrexone (odds ratio, 0.69).[34] In the Asp40 allele group, the effect of naltrexone was very small and opposite to the predicted direction. Therefore, while the study did not achieve the intended sample size due to early termination of the trial, it is highly unlikely that a larger sample would have resulted in the demonstration of the expected moderating effect of the Asp40 allele.

There were significantly more individuals in the Asp40/naltrexone group who did not adhere to a full course of treatment. Analysis of completers and those adherent and examination of the temporal relationship between nonadherence and heavy drinking were all consistent with the main analysis and do not suggest that the differential adherence affects the interpretation of the results. The finding that heavy drinking occurs before nonadherence is consistent with findings from the COMBINE Study.[35] While serious adverse events were uncommon, the Asp40/naltrexone group reported a higher frequency of adverse events, which may have contributed to higher rates of discontinuation, although that association was not apparent. Therefore, it is unclear what led to a higher dropout rate and what the implications are for this observation. While not significant, the results of the COMBINE Study[6] also showed the lowest adherence in the Asp40/naltrexone group.

These results of this prospective trial appear to differ from previous human laboratory research and retrospective analysis of clinical trials.[5,6,12-16] However, almost all of the human laboratory studies were conducted in social drinkers without alcohol dependence and were of relatively small size, which are prone to greater error rates in interpreting effect size.[36] As for the promising clinical trial data, all prior studies have been retrospective reanalyses of data, with one large study[6] and smaller studies[6,7] demonstrating a moderating effect of the SNP on naltrexone response but with other studies[10,11] showing no moderating effect of the Asp40 allele. Some of the inconsistencies could be related to differences in design such as not genotyping all participants and variation in methods for analyzing noncompliance. The COMBINE Study[6] only found a pharmacogenetic interaction with heavy drinking in weeks 12 through 16 and not earlier; therefore, the duration of treatment may affect the results. Unfortunately, this pattern of having very promising observational data not replicated in prospective clinical trials is not atypical for the pharmacogenetic field. To date, promising or even well-conceptualized pharmacogenetic findings have rarely influenced clinical practice. For example, despite clear evidence for differences in metabolism, genetic testing does not improve the clinical use of warfarin sodium.[37-39]

Figure 2. The Proportion of Participants With Any Heavy Drinking Within a Given Treatment Week Separated by Genotype and Treatment Group



There were no significant differences in outcomes among the 4 groups when adjusting for site and baseline rates of heavy drinking.

The present trial was specifically designed to study the possible moderating effects of the Asp40 allele and was not powered to test potential moderators of this effect. As such, there were major differences from previous efficacy studies[6,7,11] of naltrexone. The oversampling of the Asp40 allele substantially decreased the number of Asn40 homozygous participants. The exclusion of African Americans, while scientifically justified by the low Asn40 allele frequency, is also significantly different from other trials. Finally, many trials have used 100 mg/d of naltrexone, while this study used 50 mg/d as approved by the Food and Drug Administration. It is possible that 100 mg/d could be more effective through κ- or Δ-antagonism. In contrast, the design of the trial was reviewed by the Food and Drug Administration before the start of the study and was considered to be methodologically sound. Moreover, there was a high degree of fidelity to the protocol, with a small degree of missing data and no evidence of incorrect genotyping or errors in randomization (eAppendix in Supplement 2).

Conclusions

Despite the results of this trial, pharmacogenetics continues to hold promise as a way to improve the targeting of medications to improve treatment response. Linking genetics to such complex disease states as alcohol use disorders is not simple. Indeed, recent literature suggests that complex genetic interactions may have important roles in understanding treatment outcomes.[40,41] These prospective results are important in having the field pause and evaluate the methods of pharmacogenetic trials and application of genetics to predict treatment response in patients with alcohol use disorder.

ARTICLE INFORMATION

Submitted for Publication: May 8, 2014; final revision received December 1, 2014; accepted December 2, 2014.

Published Online: March 11, 2015. doi:10.1001/jamapsychiatry.2014.3053.

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Author Contributions: Drs Oslin and Lynch had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Oslin, Lynch, Berrettini, O'Brien.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Oslin, Lynch.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Lynch.
Obtained funding: Oslin.

Conflict of Interest Disclosures: Dr O'Brien reported providing consultation to Alkermes PLC. No other disclosures were reported.

Funding/Support: This study was supported in part by grant AA017164 from the National Institute on Alcohol Abuse and Alcoholism and by the Veterans Integrated Service Network 4 Mental Illness Research, Education, and Clinical Center.

Role of the Funder/Sponsor: The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Additional Contributions: Henry Kranzler, MD (Perelman School of Medicine at the University of Pennsylvania) contributed to preparation of the manuscript and interpretation of the results of the trial. No compensation was provided.

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