ORIGINAL ARTICLE

Effects of Naltrexone on Alcohol Sensitivity and Genetic Moderators of Medication Response

A Double-blind Placebo-Controlled Study

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Context: Clinical trials have suggested a modest effect of naltrexone as a pharmacotherapy for alcoholism, and a recent study has suggested that the effects may be moderated by variations in the μ-opioid receptor gene (*OPRM1*). However, the mechanism by which naltrexone may be differentially effective as a function of the *OPRM1* genotype is unclear.

Objectives: (1) To replicate and expand on the association between the A118G single nucleotide polymorphism (SNP) of the *OPRM1* gene and alcohol sensitivity, (2) to examine the effects of naltrexone on alcohol sensitivity, and (3) to test the A118G SNP of the *OPRM1* gene as a moderator of the effects of naltrexone on alcohol sensitivity.

Design: A within-subject, double-blind, placebo-controlled laboratory trial of naltrexone.

Setting: Participants were recruited from the community.

Participants: Non–treatment-seeking heavy drinkers were enrolled in the study. Prospective genotyping was conducted to oversample for the genetic variant of interest.

Intervention: After taking naltrexone (50 mg) or placebo, participants completed an intravenous alcohol challenge session in which they were assessed at baseline and at each of the 3 target breath alcohol concentrations: 0.02, 0.04, and 0.06 mg/L.

Main Outcome Measures: The Biphasic Alcohol Effects Scale, the Alcohol Urge Questionnaire, the Profile of Mood States, and the Alcohol Rating Scale were administered.

Results: Individuals with at least 1 copy of the *G* allele reported lower alcohol craving and higher alcohol-induced "high" across rising breath alcohol concentrations. Naltrexone was found to blunt alcohol's effects on stimulation, positive mood, craving, and enjoyment. The effects of naltrexone on blunting alcohol-induced high were stronger among individuals with the *G* allele.

Conclusion: This study advances the knowledge of mechanisms of action of naltrexone and genetic moderators of response to this pharmacotherapy.

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THE OPIOIDERGIC SYSTEM HAS been associated with the pathogenesis of substance use disorders, including alcoholism.[1-3] Opioid receptors are putatively involved in the rewarding properties of several substances, such as opiates, cocaine, and alcohol. Specifically, alcohol is thought to produce some of its reinforcing effects through the release of endogenous opioids in certain brain areas and through interactions with the dopaminergic system, particularly in the midbrain. Naltrexone is a pure opioid receptor antagonist that has been shown to have highest affinity for μ-opioid receptors and is thought to act selectively for those types of receptors.[4] Naltrexone is 1 of 3 pharmacotherapies currently approved for the treatment of alcoholism in the United States.

Results of clinical trials have supported the efficacy, albeit moderate, of naltrexone as a pharmacotherapy for alcohol dependence. Studies have found that naltrexone reduces the occurrence of heavy drinking days,[5-7] increases time to first relapse,[8-10] yields lower relapse rates,[11-13] and reduces the number of drinking days,[13,14] the number of drinks per drinking episode,[9,14-16] and the latency to the first and second drinks in social drinkers.[17] More recently, a large multisite controlled trial[18] found that naltrexone is an effective treatment for alcohol dependence when administered in combination with a medically oriented behavioral intervention. A few studies,[19-21] however, have not found support for the efficacy of naltrexone.

To better understand the biobehavioral mechanisms of action of naltrex-

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one, recent laboratory-based studies[22-28] have examined the effects of naltrexone on subjective responses to alcohol. Results of such studies revealed that naltrexone dampens feelings of alcohol-induced stimulation[23,27]; decreases ratings of liking of the alcohol[25]; causes an increase in self-reported fatigue, tension, and confusion[24]; reduces alcohol consumption; and slows the progression of drinking in a delayed-access laboratory paradigm.[22] Moreover, a study by King and colleagues[24] found that individuals with a family history of alcohol dependence showed greater naltrexone-induced attenuation of the stimulatory effects of alcohol. In short, laboratory-based studies have improved our understanding of the biobehavioral mechanisms of action of naltrexone. As suggested by Anton et al,[22] future research should focus on moderators of the response to naltrexone, including genetic variants that may predispose individuals to respond more positively to this pharmacotherapy.

Efforts to identify genetic variants that may moderate the effects of naltrexone have focused on the gene coding for μ-opioid receptors (ie, the *OPRM1* gene), which are the primary target of naltrexone.[29,30] One of the most widely studied polymorphisms of the *OPRM1* gene is the A118G single nucleotide polymorphism (SNP) located in the +118 position in exon 1, which codes for the Asn40Asp substitution (rs1799971). Molecular studies[31] of this polymorphism initially suggest that the A-to-G substitution affects receptor activity for endogenous ligand β-endorphin, leading to a gain in function such that the Asp40 variant was thought to bind β-endorphin 3 times stronger than the Asn40 allele. However, a more recent study[32] of the functional significance of this SNP suggests that the Asp allele has deleterious effects on messenger RNA and protein yield, leading to a loss of function rather than a gain.

The A118G SNP of the *OPRM1* gene has been associated with differential response to opioid antagonists in clinical[29] and laboratory[33,34] trials of naloxone. The relationship is such that individuals with the *G* allele demonstrate enhanced hypothalamic-pituitary-adrenal axis dynamics in response to an opiate blockade,[34] enhanced cortisol response and reduced agonist effect after treatment with naloxone,[33] and lower relapse rates in a clinical trial of naltrexone for alcoholism.[29] Thus, recent studies suggest that this SNP is functional on a cellular level and on a behavioral level, making it a theoretically and empirically strong candidate gene as a moderator of the effects of naltrexone.

Several studies[35-46] have tested the relationship between the A118G SNP of the *OPRM1* gene and substance use disorders, particularly alcoholism and opioid dependence. The results, however, are inconsistent, and whereas some investigations[39,42,44,45] have found support for the association between the A118G SNP and alcohol or opioid dependence, several studies[35-38,40,41,43,46] have not found an association. In our previous work,[47] we used an endophenotypic approach[48,49] to test the effect of the A118G SNP of the *OPRM1* gene. Instead of measuring alcohol dependence per se, that study tested the association between this SNP and measures of sensitivity to the effects of alcohol. Results revealed that individuals with at least 1 copy of the *G* allele showed greater response to the effects of alcohol as measured by subjective intoxication, sedation and stimulation, and changes in mood states than participants who were homozygous for the *A* allele. In short, this previous study[47] demonstrated an association between the A118G SNP and alcohol sensitivity, which in turn is a useful endophenotype for understanding the mechanisms of action of pharmacotherapies for alcoholism.

The present study was designed to integrate and expand on previous research[22-28] suggesting that naltrexone may alter subjective responses to the effects of alcohol and our previous work[47] on the association between the A118G SNP of the μ-opioid receptor gene (*OPRM1*) and alcohol sensitivity. Specifically, this double-blind placebo-controlled laboratory study tested the putative biobehavioral mechanisms of action of naltrexone by examining its effects on alcohol sensitivity and craving. The objectives of this study were 3-fold. The first objective was to replicate and expand on previous findings[47] of an association between the A118G SNP of the *OPRM1* gene and sensitivity to the effects of alcohol using an independent sample. The second objective was to test the effects of naltrexone on alcohol sensitivity and alcohol craving, thereby examining the biobehavioral mechanisms of action of naltrexone. The third objective was to determine whether the A118G SNP of the μ-opioid receptor gene (*OPRM1*) moderates the effects of naltrexone on subjective responses to alcohol.

On the basis of previous research,[47] we expected an association between the candidate gene and measures of alcohol sensitivity. In addition, we hypothesized that naltrexone would reduce the subjective responses to alcohol and alcohol craving compared with placebo.[23,28] Last, we expected that individuals with at least 1 copy of the *G* variant of the *OPRM1* gene would display greater medication-induced reductions in alcohol sensitivity and craving compared with individuals who were homozygous for the *A* allele. In short, this study was designed to improve our understanding of the genetic basis of alcohol sensitivity, the mechanisms of action of naltrexone, and their interaction. The ultimate goal of this line of research is to identify individuals who may be more responsive to certain pharmacotherapies on the basis of genetic variability, thereby promoting more targeted and effective interventions.

METHODS

PARTICIPANTS

This study was approved by the University of Colorado Human Research Committee, and all the participants provided written informed consent after receiving a full explanation of the study. Forty (12 women) non–treatment-seeking heavy drinkers completed this trial, and their mean ± SD age was 22 ± 2.18 years (range, 21-32 years). Inclusion criteria were as follows: (1) a score of 8 or higher on the Alcohol Use Disorders Identification Test (AUDIT),[50] indicating a heavy drinking pattern; (2) self-reported drinking frequency of 3 or more drinks (≥ 2 for women) at least twice per week; and (3) no history of adverse reactions to needle puncture. All the female participants had negative pregnancy test results before alcohol administration, and all the participants were required to have a breath alcohol concentration (BrAC) of 0 mg/L before each session.

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SCREENING AND EXPERIMENTAL PROCEDURES

Initial assessment of the eligibility criteria was conducted through a telephone interview. Eligible participants were invited to the laboratory for an additional screening session. On arrival at the laboratory, participants read and signed an informed consent form, provided a saliva sample for DNA analyses, completed a series of individual differences measures, and responded to an assessment of family history of alcohol problems. Based on the results of DNA analyses, participants were invited to the ethanol infusion sessions. The objective of prospective genotyping was to identify individuals who had at least 1 copy of the *G* allele of the A118G SNP of the *OPRM1* gene to oversample for the genotype of interest. Before participating in the alcohol challenge (ie, ethanol infusion session) participants underwent a physical examination at the General Clinical Research Center (GCRC). The purpose of the medical visit was to ensure that participants were in good physical health and were medically eligible to take the study medication and to participate in the ethanol infusion procedure. A total of 124 participants (39 women) were screened in the laboratory; 53 completed the physical examination, 7 of whom were ineligible for the study due to a medical reason and 6 of whom decided not to participate in the trial, leaving 40 participants (12 women) who completed the trial. Of the 124 participants screened, 95 (76.6%) were homozygous for the *A* allele, 28 (22.6%) had 1 copy of the *G* allele, and 1 (0.8%) was homozygous for the *G* allele. The allele frequencies observed in the screening sample conformed to Hardy-Weinberg equilibrium expectations (χ^2_2=0.47; $P>.05$) and agreed with the previously reported rate for this polymorphism in white patient samples, which is approximately 15%.[46] Given that we oversampled for the candidate gene of interest, 15 (3 women) of the 40 participants who completed the trial had at least 1 copy of the *G* variant (*AG*, n=14; *GG*, n=1), and the remaining 25 were homozygous for the *A* allele.

Each participant completed 2 experimental sessions: 1 after taking naltrexone (50 mg) for 3 days and 1 after taking a matched placebo for 3 days. Active medication and placebo were delivered in a counterbalanced and double-blind manner. During the experimental sessions, participants were seated in a recliner chair and the catheter was placed in the nondominant arm. After completing the baseline assessment, participants received intravenous doses of alcohol, as described in the following subsection. Participants then completed identical assessment measures at each of the following points in the ascending curve of BrACs: 0.02, 0.04, and 0.06 mg/L. After the infusion procedure was finished, participants were debriefed, given a meal, and asked to stay in the laboratory until their BrAC was less than 0.02 mg/L.

ALCOHOL ADMINISTRATION

A variety of studies[51-53] have highlighted the importance of effectively controlling blood alcohol levels to reduce experimental variability in alcohol challenge studies. This is particularly important when testing participants' sensitivity to the effects of alcohol. Therefore, the alcohol administration paradigm used in this study consisted of delivering doses of ethanol intravenously rather than orally. Consistent with the procedures developed in our previous work,[47] the ethanol infusion sessions took place at the GCRC and were performed by registered nurses under the direct supervision of a physician.

The infusion was performed using an intravenous 5% ethanol solution. An infusion nomogram was developed taking into account the participant's sex and weight. The formulas for determining target infusion rates were 0.166 mL/min × weight in kilograms, for men and 0.126 mL/min × weight in kilograms for women. Participants started the intravenous administration at their target rate, and BrAC was monitored every 3 to 5 minutes. Target BrACs were 0.02, 0.04, and 0.06 mg/L. On reaching each target level of intoxication, participants' infusion rates were reduced to half their target rate to maintain stable BrAC levels during the testing procedure. As with our previous work, the ethanol infusion yielded highly controlled BrACs such that the mean BrACs were 0.021, 0.041, and 0.060 mg/L in the placebo and naltrexone conditions. Details on the infusion procedures have been provided in previous articles.[47,54]

MEDICATION PROCEDURES

Medication was a double-blind within-subjects variable administered using a crossover design such that each participant completed 1 infusion session after taking naltrexone (50 mg) for 3 days and 1 session after taking a matched placebo for 3 days. Participants were required to take the first medication (naltrexone, 50 mg, or placebo) once a day for 2 days before the first experimental session and on the morning of their appointment. After the first session, participants were given the second medication, which they took for 3 days before, including the morning of, the second ethanol infusion session. Participants were instructed to report any adverse effects to the study physician or nurse at the GCRC. There were no dropouts as a result of medication adverse effects. Medication compliance was assessed by packing the medication and placebo into capsules with 50 mg of riboflavin. Urine samples were collected before each ethanol infusion session and were analyzed for riboflavin content under a UV light, a procedure that makes the riboflavin detectable.[55] None of the samples tested negative for riboflavin content.

DNA ANALYSES

Samples of DNA were collected following published procedures.[56,57] Participants swabbed their cheeks with 3 cotton swabs, followed by a rinse of the mouth with 10 mL of sucrose solution (4% in tap water). Genomic DNA was isolated from buccal cells using a modification of published procedures.[58,59] An ABI PRISM 7500 instrument was used to conduct 5′-nuclease (TaqMan) assays of the OPRM1 SNP using commercially available assays (all from Applied Biosystems, Foster City, California). This method relies on allele-specific hybridization of oligonucleotide probes.[60]

MEASURES

During the laboratory screening session, participants completed a battery of individual difference measures that included demographics, drinking behavior, and family history of alcohol problems. During the ethanol infusion, measures of subjective responses to alcohol and alcohol craving were administered at baseline and at each target BrAC (ie, 0.02, 0.04, and 0.06 mg/L). Previous studies[61] have indicated that the infusion protocol is comparable with an oral administration protocol, with identical target levels of BrAC, in terms of its ability to elicit craving and subjective intoxication. In addition, participants indicated which medication (naltrexone vs placebo) they believed they received before each infusion session. The 6 measures used in this study are described in the following subsections.

Adverse Effect Checklist

The short form of the Systematic Assessment for Treatment Emergent Events (SAFTEE) was administered before each etha-

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Table. Pretest Differences Between the Genotype Groups[a]

Variable	*AA* Allele (n = 25)	*AG/GG* Allele (n = 15)	Test for Difference	*P* Value
Female sex, %	36	20	$\chi^2_1 = 1.14$	.29
White race, %[b]	84	87	$\chi^2_1 = 1.48$	.48
Family history of alcohol problems, %	32	33	$\chi^2_1 < 1.00$	.93
Age, y	22.3 (2.65)	21.9 (1.06)	$t_{38} < 1.00$	.49
Alcohol problems in the past year (RAPI) (possible range, 0-92)	14.6 (8.45)	20.4 (13.3)	$t_{38} = -1.53$	.14
AUDIT score (possible range, 0-40)	12.04 (4.04)	13.07 (4.63)	$t_{38} < 1.00$	.47
Frequency of drinking episodes in the past year (6 = twice a week)	6.08 (1.47)	6.27 (1.22)	$t_{38} < 1.00$	.68
No. of drinks per drinking occasion in the past year	5.18 (2.44)	4.63 (2.36)	$t_{38} < 1.00$	.49
Frequency of drinking episodes in the past 30 d (6 = twice a week)	6.04 (1.74)	6.13 (2.10)	$t_{38} < 1.00$	.88
No. of drinks per drinking occasion in the past 30 d	4.86 (2.71)	4.63 (2.86)	$t_{38} < 1.00$	.80

Abbreviations: AUDIT, Alcohol Use Disorders Identification Test; RAPI, Rutgers Alcohol Problem Index.
[a] Data are given as mean (SD) except where noted otherwise.
[b] Participants were asked to self-classify their ethnic background/race and were presented the following options: white, black, Asian, Latino, Native American, or other. This information was collected to rule out the effects of population stratification, a potential confound in genetic studies.

nol infusion session. The SAFTEE consists of 24 common drug adverse effects and has been recommended for use in clinical trials.[62,63]

Alcohol Urge Questionnaire

The Alcohol Urge Questionnaire (AUQ) is composed of 8 items related to urge to drink alcohol; each item is rated on a 7-point Likert scale anchored by "Strongly Disagree" and "Strongly Agree." The AUQ has demonstrated high internal consistency in alcohol studies.[64,65] The mean scores for all the AUQ items (range, 0-6) were used in this study.

Subjective High Assessment Scale

The Subjective High Assessment Scale (SHAS) was used to assess subjective feelings of alcohol intoxication. This measure has been adapted by Schuckit[66] and has since been widely used in alcohol challenge studies.

Biphasic Alcohol Effects Scale

The Biphasic Alcohol Effects Scale (BAES) assesses feelings of alcohol-induced stimulation and sedation, with each subscale consisting of 7 items answered using a scale from 0 to 10. The BAES has been shown to be reliable and valid in investigations of sensitivity to the effects of alcohol.[67,68]

Profile of Mood States

The short version of the Profile of Mood States (POMS) consists of 40 items used in this study to assess mood changes after alcohol consumption.[69] The mean scores for the following subscales of the POMS, each consisting of 10 items and ranging from 0 to 4, were used: vigor, tension, positive mood, and negative mood.

Alcohol Rating Scale

The Alcohol Rating Scale (ARS) measures participants' responses to the hedonic properties of alcohol, such as "liking," "satisfaction," and alcohol-induced feelings of "high." Scores ranged from 0 to 10. The ARS was adapted to this study by consistently replacing references to "the beverage" with "the infusion of alcohol."

STATISTICAL ANALYSIS

A series of mixed-design repeated-measures analyses of variance (ANOVAs) were conducted to test the study hypotheses. Specifically, ANOVAs were used to examine the effects of medication, which was a 2-level within-subjects factor (ie, naltrexone vs placebo); the effects of genotype, which was a 2-level between-subjects factor (ie, *AA* vs *AG/GG* genotype); the effects of BrAC, which was a 3-level within-subjects factor (ie, BrAC=0.02, 0.04. and 0.06 mg/L); and their interactions. The dependent variables were measures of subjective responses to alcohol (ie, POMS, SHAS, BAES, and ARS) and alcohol craving (AUQ). Post hoc tests were conducted using simple effects tests comparing the groups that differed significantly in the ANOVAs at each target BrAC.

RESULTS

OVERVIEW

A series of pretest comparisons were conducted to determine whether the genotype groups differed on drinking and demographic variables (**Table**). Analyses of the baseline data suggested that the groups did not differ on these variables, including ethnic background. Therefore, it is highly unlikely that population stratification, sex, or other variables measured at baseline confounded the statistical analyses. In addition, there was no effect of medication or genotype on the baseline measures of alcohol sensitivity and craving, which are the primary dependent measures in this study. Thus, the analyses presented herein focus on the comparison of alcohol intoxication at the 3 levels of BrAC (ie, 0.02, 0.04, and 0.06 mg/L). Although medication was administered using a crossover design, we tested for order effects. There were no effects of medication order regarding all dependent variables ($P > .05$), except for alcohol-induced positive mood (POMS), which was rated highest in individuals receiving placebo in their last ethanol infusion session ($F_{1,38} = 7.55$; $P = .009$).

GENOTYPE EFFECTS

The first study objective was to test and expand on the association between the A118G SNP of the *OPRM1* gene

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and alcohol sensitivity. To test this hypothesis, a series of 2×3 mixed-design analyses of covariance were conducted in which *OPRM1* genotype (*AA* vs *AG/GG*) was a 2-level between-subjects factor, BrAC was a 3-level within-subjects factor (0.02, 0.04, 0.06 mg/L), and baseline scores were used as covariates. In these analyses, we were interested in the main effect of genotype and genotype × BrAC interactions. Given that we expect the effects of the medication to be moderated by genotype, we restricted this first set of analyses to the data on the placebo condition.

Consistent with our previous findings,[47] there was a significant genotype × BrAC interaction regarding subjective intoxication (SHAS) such that individuals with the *G* allele differed significantly in subjective feelings of intoxication across rising levels of BrAC ($F_{2,74}$=3.39; P=.04) compared with individuals who were homozygous for the *A* allele (**Figure 1**A). There was also a genotype × BrAC interaction on alcohol-induced high ($F_{2,76}$=4.30; P=.17) (Figure 1B). Results also revealed a main effect of genotype on alcohol craving (AUQ) such that individuals with at least 1 copy of the *G* allele reported lower levels of craving for alcohol during ethanol infusion ($F_{1,37}$=4.21; P=.047) (Figure 1C). There was no effect of genotype or genotype × BrAC interaction on measures of alcohol-induced stimulation, sedation, or mood changes (P>.05).

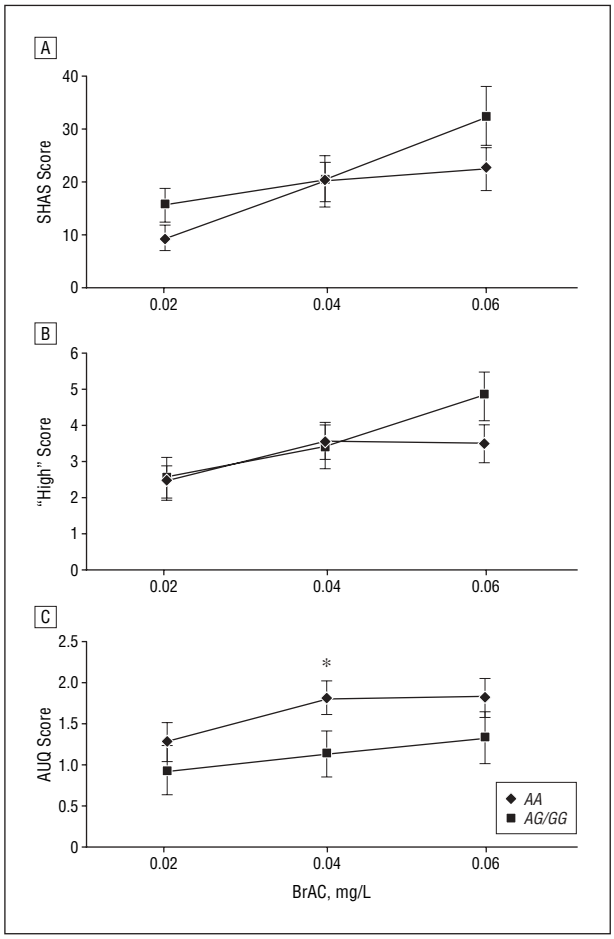

Figure 1. Mean scores on the Subjective High Assessment Scale (SHAS) (possible range, 0-130) (A), for alcohol-induced "high" (range, 0-10) (B), and on the Alcohol Urge Questionnaire (AUQ) (alcohol craving) (range, 0-6) (C) for the *AA* and *AG/GG* groups. The analyses indicated significant genotype × breath alcohol concentration (BrAC) interactions on SHAS scores and alcohol-induced high such that carriers of the *G* allele differed in subjective feelings of intoxication and alcohol-induced high across rising levels of BrAC (P<.05). In addition, there was a significant main effect of genotype on alcohol craving (P<.05) such that carriers of the *G* allele reported lower overall craving during alcohol exposure. Error bars represent SE. *Statistically significant group differences.

MEDICATION EFFECTS

To examine the effects of medication and medication × genotype interactions on the dependent measures of interest, a series of 2×2×3 mixed-design ANOVAs were conducted in which *OPRM1* genotype was a 2-level between-subjects factor (*AA* vs *AG/GG*), medication was a 2-level within-subjects factor (placebo vs naltrexone), and BrAC was a 3-level within-subjects factor (0.02, 0.04, and 0.06 mg/L).

There was a significant main effect of medication on alcohol-induced stimulation (BAES) ($F_{1,38}$=9.06; P=.005) (**Figure 2**A), alcohol-induced vigor (POMS vigor; $F_{1,38}$=8.29; P=.007) (Figure 2B), and alcohol-induced positive mood (POMS positive mood; $F_{1,38}$=5.87; P=.02) (Figure 2C). The relationships were such that naltrexone was found to reduce self-reported alcohol-induced stimulation, vigor, and positive mood compared with placebo. The effects of medication on positive mood were significant even after controlling for the order effect described in the "Overview" subsection. The results also reveal a significant main effect of medication on alcohol craving (AUQ) such that participants reported lower craving for alcohol in the naltrexone condition compared with the placebo condition ($F_{1,38}$=6.76; P=.01) (Figure 2D).

Analyses of ARS items revealed medication effects on self-reported quality of alcohol intoxication. Specifically, there was a main effect of medication on self-reports of satisfaction with alcohol intoxication ($F_{1,38}$=4.41; P=.04) (**Figure 3**A) such that participants rated the alcohol intoxication as less satisfying during the naltrexone condition than during the placebo condition. Likewise, participants scored lower on "liking" of alcohol intoxication in the naltrexone condition compared with the placebo condition ($F_{1,38}$=4.25; P=.046) (Figure 3B). There was no main effect of medication or medication × BrAC effects on alcohol-induced sedation and negative mood (P>.05).

MEDICATION × GENOTYPE EFFECTS

Analyses revealed a significant medication × genotype × BrAC interaction on alcohol-induced high (ARS) ($F_{2,74}$=5.39; P=.007). These results indicate that naltrexone significantly reduced self-reported alcohol-induced high in participants with at least 1 copy of the *G* allele, particularly when the BrAC was 0.06 mg/L, but had no effect on participants who were homozygous for the *A* allele compared with the placebo condition (**Figure 4**). There were no medication × genotype or medication × genotype × BrAC interactions on additional measures of alcohol-induced stimulation, sedation, or mood changes (P>.05). These findings help elucidate the differential effects of naltrexone on subjective responses to alcohol as a function of genotype.

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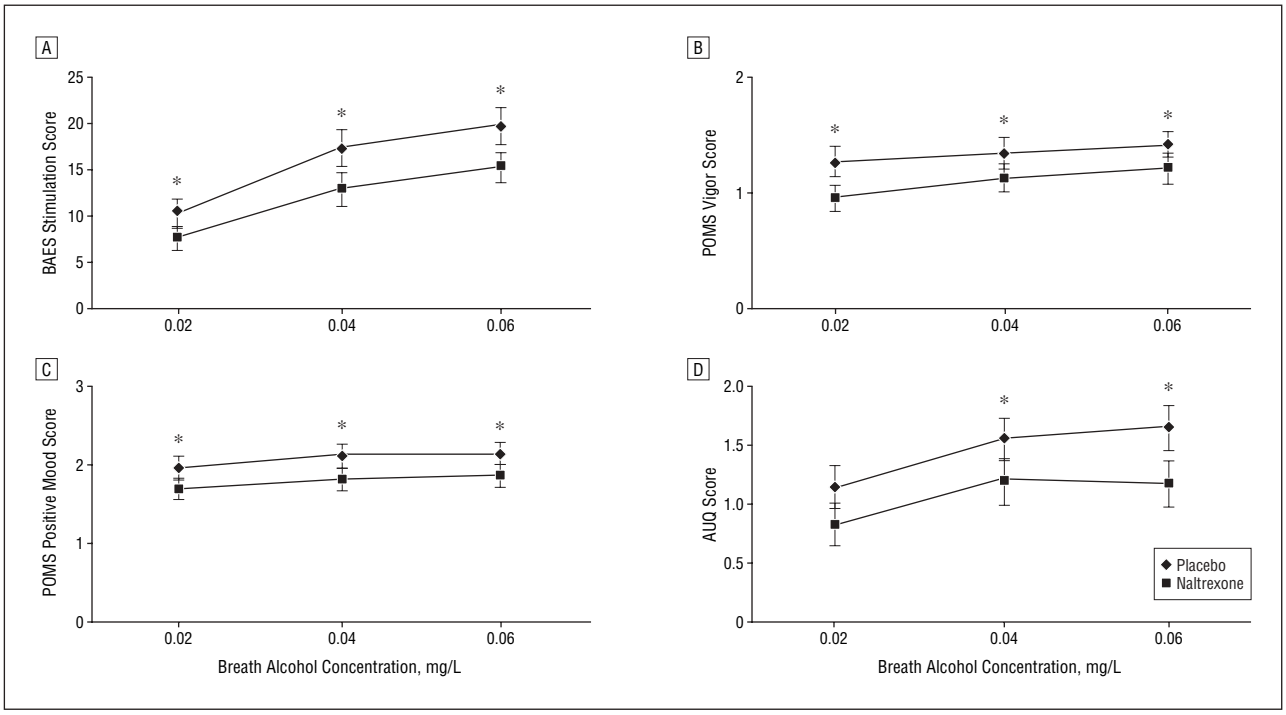

Figure 2. Mean scores for the naltrexone and placebo conditions on the stimulation scale of the Biphasic Alcohol Effects Scale (BAES) (possible range, 0-70) (A), the vigor scale (B) and the positive mood scale (C) of the Profile of Mood States (POMS) (range, 0-4), and the Alcohol Urge Questionnaire (AUQ) (range, 0-6) (D). The results reveal a significant main effect of medication on all these measures of the subjective effects of alcohol ($P<.05$). Specifically, naltrexone was found to dampen alcohol-induced stimulation, vigor, positive mood, and alcohol craving compared with placebo. Error bars represent SE. *Statistically significant group differences.

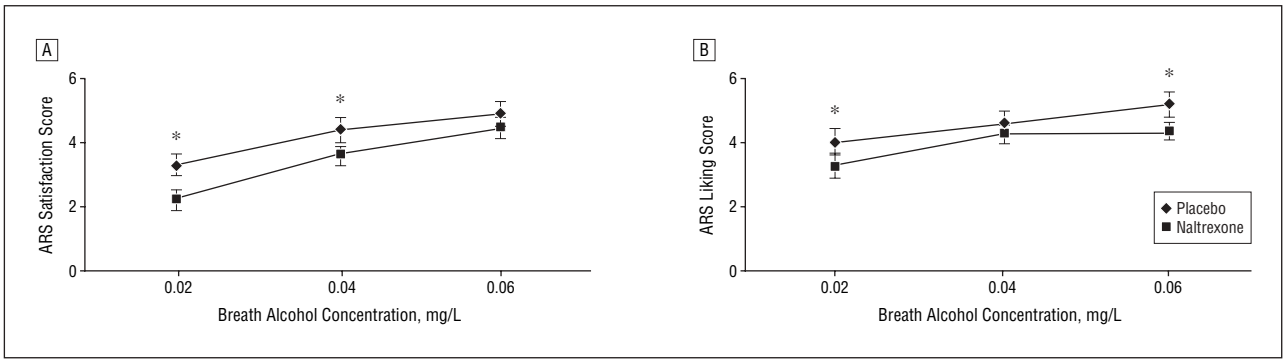

Figure 3. Mean scores for the naltrexone and placebo conditions on ratings of satisfaction with alcohol intoxication (A) and liking of intoxication (B), both measured using the Alcohol Rating Scale (ARS) (range, 0-10). The results reveal a significant main effect of medication such that naltrexone reduced overall satisfaction with alcohol intoxication and liking of the intoxication compared with placebo ($P<.05$). Error bars represent SE. *Statistically significant group differences.

ADVERSE EFFECTS AND COMPLIANCE

All the urine samples tested positive for riboflavin, suggesting that individuals were compliant with the medication instructions immediately before each appointment. In addition, participants were asked to bring back their pill minders before each experimental session. Analysis of the pill minder data suggested high compliance and no significant differences in compliance across the medication trials and genotype groups. Regarding the integrity of the medication masking, 79% of the participants guessed correctly while in the placebo condition and 72% guessed correctly while in the naltrexone condition, which was higher than would be expected by chance (ie, 50%). However, there was no significant difference in correct guesses as a function of medication ($\chi^2_1=1.33$; $P=.25$) or genotype ($\chi^2_1<1.00$; $P=.57$).

A series of Fisher exact tests, a nonparametric test appropriate for small cell sizes,[70] were conducted comparing the medication and placebo on each of the 24 items from the adverse effects checklist (SAFTEE). Results revealed no significant medication effects on any of the adverse effects measured by the SAFTEE (Fisher exact test, $P>.05$), and there were no significant differences in adverse effects as a function of genotype (Fisher exact test, $P>.05$). In addition, given that nausea is a more prevalent and clinically relevant adverse effect of naltrexone,[71] and occurred with higher frequency in the naltrexone condition (13 of 40 taking naltrexone vs 2 of 40 taking placebo; Fisher exact test, $P=.10$), we controlled

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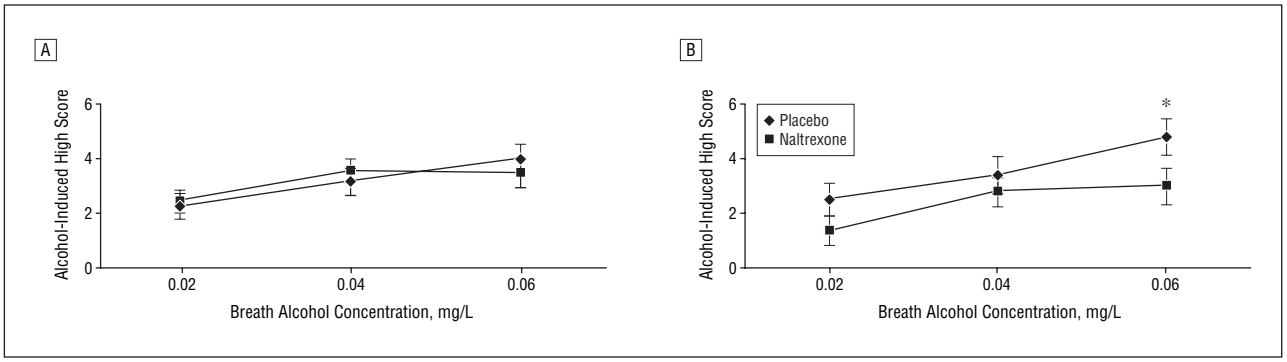

Figure 4. Mean scores for alcohol-induced "high" using the Alcohol Rating Scale (ARS) (possible range, 0-10) for the *AA* group (A) and the *AG/GG* group (B) across levels of breath alcohol concentration (BrAC). The analyses indicate a significant genotype × medication × BrAC interaction such that the *AG/GG* group reported greater naltrexone-induced reductions in feelings of alcohol high compared with the *AA* group when BrAC reached 0.06 mg/L ($P < .05$). Error bars represent SE. *Statistically significant group differences.

for naltrexone-induced nausea in all the medication and genotype analyses, and doing so did not change any of the results reported herein.

COMMENT

The first objective of this study was to replicate and expand on our previous findings[47] of an association between the A118G SNP of the *OPRM1* gene and sensitivity to the effects of alcohol. The results reveal that individuals with at least 1 copy of the *G* allele reported greater feelings of intoxication and alcohol-induced high at a BrAC of 0.06 mg/L. These findings replicate and expand on our previous work[47] using an endophenotypic approach,[48,49] in this case alcohol sensitivity, to identify genetic factors underlying the pathogenesis of alcohol use disorders.

The second objective of this study was to test the effects of naltrexone on sensitivity to the effects of alcohol and alcohol craving, thereby examining the biobehavioral mechanisms of action of naltrexone. Consistent with previous studies,[22-27] this study found that naltrexone reduces alcohol craving, alcohol-induced stimulation, vigor, positive mood, and ratings of satisfaction and liking of alcohol intoxication. Taken together, these findings elucidate the biobehavioral mechanisms of action of naltrexone and suggest that naltrexone may achieve its clinical effects by reducing the reinforcing effects of alcohol. The effects of naltrexone on alcohol-induced stimulation and the overall reinforcing effects of alcohol may be conceptualized as an indicator of the potential clinical utility of other medications for alcoholism, suggesting that this mechanism should be considered in future pharmacotherapy development studies. These results are also consistent with the clinical literature that suggests that naltrexone may be especially effective in preventing relapse after a "slip."[8,72,73] Specifically, naltrexone's dampening of the rewarding subjective effects of alcohol may reduce the likelihood that a slip would trigger a full-fledged relapse into heavy drinking.

The third goal of the study was to test whether the A118G SNP of the μ-opioid receptor gene (*OPRM1*) moderates the effects of naltrexone on subjective responses to alcohol. Consistent with the initial hypothesis, naltrexone was found to be differentially effective based on the individual's genotype. Participants with the *G* allele demonstrated greater blunting of alcohol-induced high when the BrAC reached 0.06 mg/L. Note that the medication × genotype effects were greatest at the highest BrAC, consistent with previous studies[22,23,25] suggesting that the effects of naltrexone may be alcohol dose dependent. The results of the present study support the notion that the interaction between naltrexone and alcohol dose may be a useful predictor of the effect of naltrexone on subjective feelings of intoxication. These findings also have clinical implications for behavioral interventions used in conjunction with this pharmacotherapy. For example, naltrexone may be more clinically effective for patients in the context of controlled drinking or harm reduction approaches.

The results reported herein should be interpreted in the context of the study's strengths and limitations. First, this study did not include a placebo alcohol condition (eg, using a saline solution); therefore, we cannot conclusively state that the effects of naltrexone involved the pharmacologic effects of alcohol. Second, participants in this study were non–treatment-seeking heavy drinkers, and the findings may not generalize to treatment-seeking patients. Third, this study consisted of an ethanol infusion, which may not readily generalize to oral consumption paradigms. Fourth, this study did not titrate up the naltrexone dose or expose participants to the medication for an extended period, which may account for the naltrexone-induced nausea reported by some participants at the time of experimentation. Strengths of the study include the use of prospective genotyping during the screening phase, a double-blind within-subjects counterbalanced design, and an alcohol administration method that produced highly controlled BrACs, an important source of variability in alcohol challenge studies.[51-53]

In summary, the present findings extend the literature by suggesting that lower relapse rates among carriers of the *G* allele after treatment with naltrexone[29] may be due to a more pronounced naltrexone-induced reduction in alcohol reward in individuals with the *G* allele. As highlighted by the COMBINE Research Group,[30] it has become increasingly important to understand genetic moderators and mechanisms of action of pharma-

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cotherapies. To that end, laboratory studies such as this, focusing on the neurobiologic aspects of alcohol-induced reward as a mechanism of action and its underlying genetic basis, may be especially useful in characterizing which subgroups of patients are more likely to respond to a pharmacotherapy and by which mechanism. In addition, understanding moderators of medication response may help account for inconsistencies in the literature[19-21] given that the lack of attention to moderators may obscure overall treatment effects. Finally, future studies should continue to examine genetic and psychosocial moderators of the pharmacotherapy response to develop more targeted and individualized treatment alternatives for alcohol use disorders.

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