ALCOHOLISM CLINICAL & EXPERIMENTAL RESEARCH

Pharmacogenetic Effects of Naltrexone in Individuals of East Asian Descent: Human Laboratory Findings from a Randomized Trial

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Background: Genetic variation in the endogenous opioid system has been identified as 1 potential source of individual variability in naltrexone treatment outcomes. The majority of naltrexone pharmacogenetic studies have focused on a particular single nucleotide polymorphism (SNP) of the mu-opioid receptor gene (*OPRM1*; rs1799971; commonly known as the Asn40Asp SNP) in Caucasian samples with decidedly mixed results. The goal of this study was to test the pharmacogenetic effects of naltrexone on subjective response to alcohol and self-administration of alcohol in individuals of East Asian descent. We hypothesized that naltrexone, compared with placebo, would potentiate the aversive and sedative effects of alcohol and reduce alcohol self-administration to a greater extent in Asp40 carriers.

Methods: Participants (N = 77; Asn40Asn, n = 29; Asn40Asp, n = 34, and Asp40Asp, n = 14) completed 2 double-blinded and counterbalanced experimental sessions: one after taking naltrexone (50 mg/d) for 5 days and one after taking matched placebo for 5 days. In each experimental session, participants received a priming dose of intravenous alcohol up to the breath alcohol concentration target of 0.06 g/dl which was immediately followed by an alcohol self-administration period (1 hour).

Results: There were no pharmacogenetic effects observed for alcohol-induced stimulation, sedation, craving for alcohol, or alcohol self-administration in the laboratory. During the self-administration period, Asp40 carriers consumed fewer drinks and had a longer latency to first drink as compared to Asn40 homozygotes.

Conclusions: These findings in East Asians add to the mixed literature on naltrexone pharmacogenetics from predominantly Caucasian samples and highlight the complexity of these effects and their overall limited replicability. It is plausible that a consistent pharmacogenetic effect in tightly controlled preclinical and experimental medicine models "fades" in more complex and heterogeneous settings and samples.

Key Words: Alcohol Use Disorder, Naltrexone, Pharmacogenetics, Human Laboratory, NCT02026011.

THE ENDOGENOUS OPIOID system is involved with the acute behavioral effects of alcohol and is a pharmacological target for treatment of alcohol use disorder (AUD; for review, see Herz, 1997; Spanagel, 2009). Alcohol increases endogenous opioid transmission in the mesocorticolimbic dopamine system which mediates both the hedonically rewarding and motivationally salient effects of alcohol (Nestler, 2005; Olive et al., 2001). Blocking this endogenous opioid activity with opioid receptor antagonists, such as naltrexone, or via mu-opioid receptor knockout reduces alcohol self-administration and preference in rodents (Gonzales and Weiss, 1998; Hall et al., 2001). In humans, naltrexone reduces alcohol's acute, pleasurable subjective effects (e.g., stimulation, liking, high, etc.; Drobes et al., 2004; Ray and Hutchison, 2007; Swift et al., 1994; Volpicelli et al., 1995), alcohol self-administration in the laboratory (Davidson et al., 1999; O'Malley et al., 2002), and alcohol consumption in the real world (Anton et al., 2006). Despite the robust translational evidence implicating the endogenous opioid system in the pharmacology of alcohol, treatment outcomes with naltrexone appear to be modest in effect size and highly variable at the individual level (Kranzler and Kirk, 2001; Rösner et al., 2010; Streeton and Whelan, 2001). Accordingly, a sizable line of research has sought to identify biobehavioral factors associated with successful naltrexone treatment outcomes in order to optimize its clinical benefits (Hutchison, 2010; Ray et al., 2010a).

Genetic variation in the endogenous opioid system has been identified as 1 potential source of individual variability

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Received for publication June 12, 2017; accepted December 12, 2017.

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DOI: 10.1111/acer.13586

in naltrexone treatment outcomes (Krishnan-Sarin et al., 2007; Ray et al., 2012a; Rubio et al., 2005). As reviewed in detail elsewhere (Ray et al., 2012a; Roche and Ray, 2015), the majority of naltrexone pharmacogenetic studies have focused on a particular single nucleotide polymorphism (SNP) of the mu-opioid receptor gene (*OPRM1*; rs1799971; commonly known as the Asn40Asp SNP) with decidedly mixed results. After alcohol administration in the laboratory, carriers of the minor Asp40 allele have self-admi nistered more alcohol (Hendershot et al., 2014, 2016), reported greater subjective stimulation, reward, and positive mood (Ray and Hutchison, 2004; Ray et al., 2007, 2013), and demonstrated greater striatal dopamine response (Ramchandani et al., 2011) compared with Asn40 homozygotes. Because of such laboratory findings, the minor Asp40 allele has been referred to as a "risk" allele for the development of AUD, and it has been speculated that Asp40 carriers may find alcohol more rewarding and drink more heavily in the real world (Ray et al., 2010b, 2012a). Furthermore, preclinical studies using humanized mice (Bilbao et al., 2015) and human laboratory studies (Ray and Hutchison, 2007; Setiawan et al., 2011) have both reported that naltrexone was more effective in reducing alcohol reward and/or consumption in Asp40 carriers versus Asn40 homozygotes. Recent meta-analyses of retrospective pharmacogenetic trials have found that the Asp40 allele is moderately associated with naltrexone's reduction in heavy drinking (Chamorro et al., 2012; Jonas et al., 2014). Although these positive results, when taken as a whole, suggest that individuals with at least 1 Asp40 allele, compared with Asn40 homozygotes, may be more sensitive to the acute effects of alcohol and more responsive to naltrexone pharmacotherapy, other laboratory studies (Anton et al., 2012; Ehlers et al., 2008; McGeary et al., 2006; Ziauddeen et al., 2016) and prospective pharmacogenetic trials have failed to replicate these associations (Oslin et al., 2015; Schacht et al., 2017), leaving the potential of personalizing naltrexone treatment based on *OPRM1* uncertain.

Many factors may underlie the inconsistent findings related to the Asn40Asp SNP, including the probable small effect size of *OPRM1* on responses to alcohol and naltrexone, the heterogeneity of AUD, and the poor understanding of the molecular significance of the Asn40Asp SNP on mu-opioid receptor function (Ray et al., 2012a). Additionally, the majority of AUD studies that have assessed the effects of the Asn40Asp SNP on response to naltrexone have been retrospective or secondary analyses that were confined to Caucasian samples due to concerns about population stratification effects. As the minor allele frequency of the Asn40Asp SNP is approximately 20% in Caucasian populations, post hoc analysis of this variant has often been performed in underpowered sample sizes. Further, as research samples in North America are predominantly composed of Caucasian individuals, retrospective genetic studies are often underpowered to address whether the findings can be extended to other ethnic groups, and prospective genetic studies generally only include 1 race. The frequency of the *OPRM1* Asp40 allele is imbalanced across ethnicity, such that the minor allele frequency is approximately 20% in Caucasians, 5% in individuals of African ancestry, and up to 50% among individuals of East Asian descent (i.e., Chinese, Korean, or Japanese; Arias et al., 2006). Thus, in light of the overall mixed findings regarding the Asn40Asp SNP in predominantly Caucasian samples with AUD, there is a need for replication and extension of the role of *OPRM1* variation in naltrexone treatment outcomes to ethnically diverse populations.

Despite the high prevalence of the Asp40 allele in East Asian populations, only 2 studies have examined naltrexone pharmacogenetics in East Asian individuals with AUD. First, a small naltrexone clinical trial in Korean alcohol-dependent patients reported that Asp40 carriers who were medication compliant had a significantly longer time to relapse than Asn40 homozygotes (Kim, 2009). Second, a preliminary study from our group examined the effects of naltrexone in heavy drinkers of East Asian descent. In this pilot randomized, crossover laboratory study, a total of 35 participants completed an intravenous (IV) alcohol (up to 0.06 g/dl) administration session after taking naltrexone or placebo for 4 days. We found that Asp40 carriers, versus Asn40 homozygotes, experienced greater alcohol-induced sedation, subjective intoxication, and lower alcohol craving on naltrexone compared with placebo (Ray et al., 2012b). As alcohol-induced sedation and intoxication are believed to capture the aversive dimension of subjective response to alcohol (Bujarski et al., 2015; Ray et al., 2009), these preliminary results may provide initial evidence for the biobehavioral mechanism by which naltrexone may be particularly effective in reducing alcohol use in Asp40 carriers of East Asian descent. This study seeks to replicate and extend upon our previous findings.

These preliminary results, if supported and extended in larger studies, may be especially useful in targeting the use of naltrexone in Asian populations in the United States and worldwide. While there are genetic protective factors against AUD in Asian populations (Eng et al., 2007), recent studies have suggested that AUD is a significant public health problem in East Asian countries (Hao et al., 2005; Higuchi et al., 2007). Individuals of East Asian descent are more likely to possess variants of alcohol and aldehyde dehydrogenase genes that increase aversive responses to alcohol and are protective against development of AUD (Luczak et al., 2006; Wall, 2005; Wall et al., 2001). Despite these protective factors, South Korea has comparable or higher rates of AUD than the United States (Lee et al., 2010), and the World Health Organization has characterized high risk drinking as reaching epidemic levels in China (Tang et al., 2013). One factor that may contribute to problematic drinking in East Asian populations is that the *OPRM1* Asp40 variant may increase the likelihood of developing AUD in Asians but not Caucasians (Chen et al., 2012). Thus, AUD patients of East Asian descent may stand to benefit from the

pharmacogenetic optimization of naltrexone for AUD on the basis of *OPRM1* genotype to a greater extent than other ethnic groups due to the variant's high prevalence and risk predisposition. However, not all studies support this notion: One laboratory study found that *OPRM1* modulation of hypothalamic–pituitary–adrenal axis response to a naloxone challenge was only observed in Caucasian healthy controls and not individuals of Asian descent (Hernandez-Avila et al., 2007).

The goal of this study was to replicate and extend our preliminary findings (Ray et al., 2012b) by testing the effects of naltrexone on subjective response to alcohol and alcohol self-administration in individuals of East Asian descent genotyped for the *OPRM1* Asn40Asp variant. Based on our previous findings, we hypothesized that naltrexone, compared with placebo, would potentiate the aversive and sedative effects of alcohol and reduce alcohol self-administration to a greater extent in Asp40 carriers versus Asn40 homozygotes.

MATERIALS AND METHODS

Study Overview

Participants across all 3 *OPRM1* genotypes (Asn40Asn, $n = 29$; Asn40Asp, $n = 34$, and Asp40Asp, $n = 14$) completed 2 double-blinded and counterbalanced experimental sessions: one after taking naltrexone (50 mg/d) for 5 days and one after taking matched placebo for 5 days. In each experimental session, participants received a priming dose of IV alcohol up to the breath alcohol concentration (BrAC) target of 0.06 g/dl which was immediately followed by a 1-hour alcohol self-administration period.

Participants

Participants were recruited between July 2013 and December 2016 from the community through fliers, online and print advertisements, and social media (i.e., advertisement in blogs targeting the Asian American community) in the Los Angeles area between December 2013 and September 2016. Inclusion criteria were as follows: (i) a score of 8 or higher on the Alcohol Use Disorders Identification Test (AUDIT; Allen et al., 1997), indicating a heavy drinking pattern; (ii) East Asian ethnicity (i.e., Chinese, Korean, Japanese, or Taiwanese); and (iii) between the ages of 21 and 55. In all, 87 (29 females) nontreatment-seeking heavy drinkers were randomized in this trial. The average age was 26.8 (SD 6.15; range 21 to 47), and of the 77 participants enrolled in this study, the following ethnic background was reported: 25 (32.5%) Chinese descent, 35 (45.5%) Korean descent, 8 (10.4%) Japanese descent, and 9 (11.7%) Taiwanese descent. Participants with a history of depression with suicidal ideation, lifetime psychotic disorder, lifetime substance use disorder (except marijuana), or ≥10 on the Clinical Institute Withdrawal Assessment-Revised (CIWA-R), indicating clinically significant alcohol withdrawal (Sullivan et al., 1989), were excluded. All female participants tested negative for pregnancy, and all subjects had a BrAC of zero before each session. The study was approved by the University of California Los Angeles Institutional Review Board.

Screening Procedures

Initial assessment of the eligibility criteria was conducted through a telephone interview. Eligible participants were invited to the laboratory for additional screening. Upon arrival, participants read and signed an informed consent form and provided a saliva sample for DNA analyses. Participants then completed a series of individual differences measures and interviews, including a demographics questionnaire and the Timeline Follow-back (TLFB; Sobell et al., 1986) to assess for quantity and frequency of drinking over the past 30 days. All participants were required to test negative on a urine drug test (except for marijuana, which was allowed to be positive). Prospective genotyping was not utilized in this study due to the anticipated allele frequency of nearly 50% and the successful utilization of this approach by our group previously (Ray et al., 2012b). Eligible participants attended a physical examination at the UCLA Clinical and Translational Research Center (CTRC) conducted by the study physician (KM). A total of 199 participants (78 women) were screened in the laboratory, 106 completed the physical examination, 5 of whom were ineligible for medical reasons and 14 of whom decided not to participate in the trial, leaving 87 participants who enrolled and were randomized. Of the 87 individuals randomized, 77 completed at least 1 alcohol administration session, and 72 completed the entire study. No demographic, genotype, or drug and alcohol-related differences were observed between those 10 participants who dropped out postrandomization and those who completed 1 or more experimental sessions ($ps \geq 0.14$). Participants were assigned to a medication sequence based on the simple randomization pattern of ABBA. See Fig. 1 for a CONSORT Diagram for this trial.

Medication Procedures and Alcohol Administration

Participants completed 1 alcohol infusion session after taking naltrexone for 5 days (25 mg for days 1 and 2 and 50 mg for days 3 to 5) and 1 infusion session after taking a matched placebo for 5 days (minimum of 7-day wash-out period between conditions). Active medication and placebo were delivered in a counterbalanced and double-blinded fashion. Participants were asked to report any side effects to the study physician. Six participants dropped out of the study as a result of anticipated medication side effects. Active medication and placebo capsules were packaged with 50 mg of riboflavin allowing for medication compliance to be examined via urine samples collected immediately prior to each infusion session. Analyzed under ultraviolet light (Del Boca et al., 1996), all samples tested positive for riboflavin content.

The testing session consisted of 2 portions, IV alcohol administration and oral alcohol self-administration. All participants tested negative for drugs (except marijuana) and women tested negative for pregnancy prior to the experimental session. Participants were asked to fast for 2 hours before arrival and were given a standardized meal before the alcohol administration began. Smokers were allowed to smoke a cigarette immediately prior to the alcohol infusion procedures to mitigate cigarette-induced craving. Approximately 2 hours prior to the alcohol infusion, participants ingested the final dose of medication (day 5) under observation, were seated in a recliner chair, and the IV was placed in their nondominant arm. After completing the baseline assessment, participants received IV infusions of alcohol. The IV route of administration was chosen to reduce and control BAC variability between subjects (Li et al., 2001; O'Connor et al., 1998; Ramchandani et al., 1999) as well as eliminate alcohol cues and expectancies. The IV alcohol administration procedure was consistent with methods our group has previously developed (Ray and Hutchison, 2004; Ray et al., 2017). Infusion rates were 0.166 ml/min × weight (in kg) for males and 0.126 ml/min × weight for females. Target BrACs were as follows: 0.02, 0.04, and 0.06 g/dl. Upon reaching each of the target levels of BrAC, participants' infusion rates were reduced to half, to maintain stable BrAC during testing. The ethanol infusion yielded highly controlled BrACs, such that the observed mean (SD) BrACs were as follows: 0.022 (0.002), 0.042 (0.002), and 0.062 (0.003) g/dl across medication conditions. Time to each target BrAC was, on average,

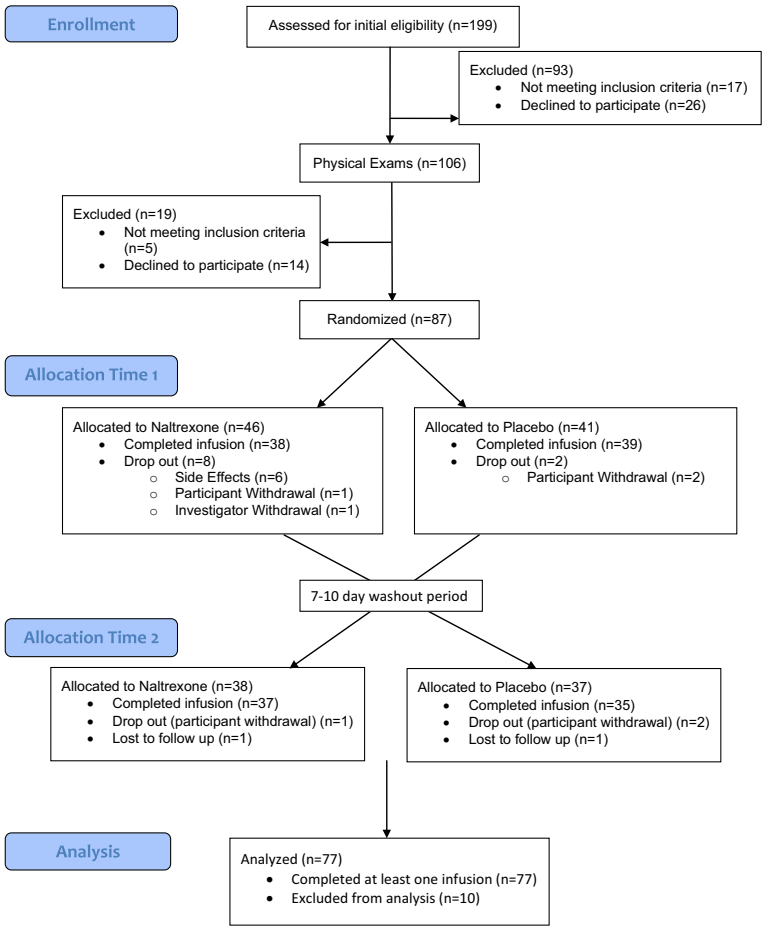

Fig. 1. CONSORT Diagram for the trial.

16.56 (5.12), 48.76 (13.14), and 88.08 (21.02) minutes, respectively. Upon completion of the alcohol infusion, participants immediately began an oral self-administration session (1 hour long). Participants were offered 4 mini-drinks of their preferred beverage and allowed to watch a movie. The mini-drinks allowed participants to consume up to 0.04 g/dl (i.e., 0.01 g/dl per mini-drink) alcohol over the 1-hour period. Drink sizes were determined by participant's gender, weight, height, and alcohol content. Participants had 1 hour to either consume the mini-drinks, or receive 1 dollar for every drink remaining. Participants notified the study team before consuming a mini-drink and were breathalyzed before drinking in addition to every 10 minutes. As a precaution, if BrAC $\geq$ 0.100 g/dl, participants had to wait until BrAC dropped before consuming the drink (n.b.: this event was not encountered in the study). Participants were then given a meal and asked to stay at the CTRC for a 4-hour period allowing their BrAC to drop below 0.020 g/dl or to 0.000 g/dl if driving. See Fig. 2 for study design flowchart.

Measures

As specified a priori on ClinicalTrials.gov (NCT02026011), the primary outcome measures were the subjective effects of alcohol and the secondary outcome measures were related to alcohol self-administration. During the IV alcohol administration, measures of subjective responses to alcohol and alcohol craving were administered at baseline, at each target BrAC, and after 30 and 60 minutes of self-administration. As a check-on-blind, participants reported which medication (naltrexone vs. placebo) they believed to have received before each infusion session. The following measures were used (i) the Systematic Assessment for Treatment Emergent Events (SAFTEE) was administered before each infusion session to assess for 24 common drug side effects and has been recommended for use in clinical trials (Jacobson et al., 1986; Levine and Schooler, 1986); (ii) Alcohol Urge Questionnaire (AUQ) consists of 8 items assessing the urge to drink, each rated on a 7-point Likert scale ("Strongly Disagree" to "Strongly Agree"). Across various studies, the AUQ shows high internal consistency (Bohn et al., 1995; MacKillop, 2006); (iii) the Biphasic Alcohol Effects Scale (BAES), a valid and reliable measure (Erblich and Earleywine, 1995; Martin et al., 1993), assesses stimulation and sedation induced by alcohol, and consists of 14 items rated on a 0 to 10 scale. The secondary measures obtained from the self-administration session were (i) total number of drinks consumed and (ii) latency to first drink (in seconds).

Genotyping

Oragene saliva kits (DNA Genotek Inc., Ottawa, Ontario, Canada) were used to collect samples for DNA analysis at the in-person screening visit. The UCLA Genotyping and Sequencing (GenoSeq) Core assayed *OPRM1* (rs1799971), alcohol dehydrogenase gene (*ADH1B*, rs1229984), and aldehyde dehydrogenase gene (*ALDH2*, rs671). Polymerase chain reaction (PCR) primers were labeled with fluorescent dye (6-FAM, VIC, or NED), and PCR was performed on Applied Biosystems dual block PCR thermal cyclers (Foster City, CA). An AB 7900HT Fast Real-Time PCR System

ran the SNP sequencing and analyzed using the Sequence Detection Systems software version 2.3 (Applied Biosystems). Each run included 2 positive control samples (individual 2 in CEPH family 1347; Coriell Institute for Medical Research, Camden, NJ). Allele calling software automatically scored the genotypes and verified by visual inspection. The average call, reproducibility, and concordance rates are 96, 99.7, and 99.8%, respectively, at the UCLA GenoSeq Core.

Data Analytic Plan

Analyses for the alcohol infusion session were conducted using a multilevel mixed modeling framework (Singer, 1998) with the mixed modeling procedures in SAS version 9.4 (Cary, NC) to examine genotype group differences on medication response. Due to participants receiving multiple alcohol infusion sessions, a linear mixed model with random intercepts was used to address the issues of nonindependence of observations in the data. For each multilevel model, Medication, and BrAC were within-subject measures (nested within subjects), while Genotype was a between-subject measures. The analyses examined the effects of *Medication*, a 2-level within-subjects factor (Placebo vs. Naltrexone, coded 0 and 1), *Genotype*, a 2-level between-subjects factor (Asn40 homozygotes vs. Asp40 carriers, coded 0 and 1), *BrAC*, a 3-level within-subjects factor (BrAC = 0.02, 0.04, 0.06 g/dl, coded 0 to 2) and their *interactions*. The dependent variables were alcohol craving (AUQ) and subjective response to alcohol (BAES). All models included robust estimation for standard errors to account for heteroskedasticity among dependent variables (White, 1980).

For the self-administration session, the outcome measures were (i) total number of drinks consumed and (ii) latency to first drink. Poisson regression models were used to examine the effects of medication, genotype, and their interactions on total number of drinks consumed, while a series of Cox proportional hazard regressions were conducted to examine these effects on latency to first drink. Kaplan–Meier survival curves were generated for medication, genotype, and their interaction.

In all analyses, reports of main effects were derived from models that did not include the Medication × *OPRM1* Genotype interaction term.

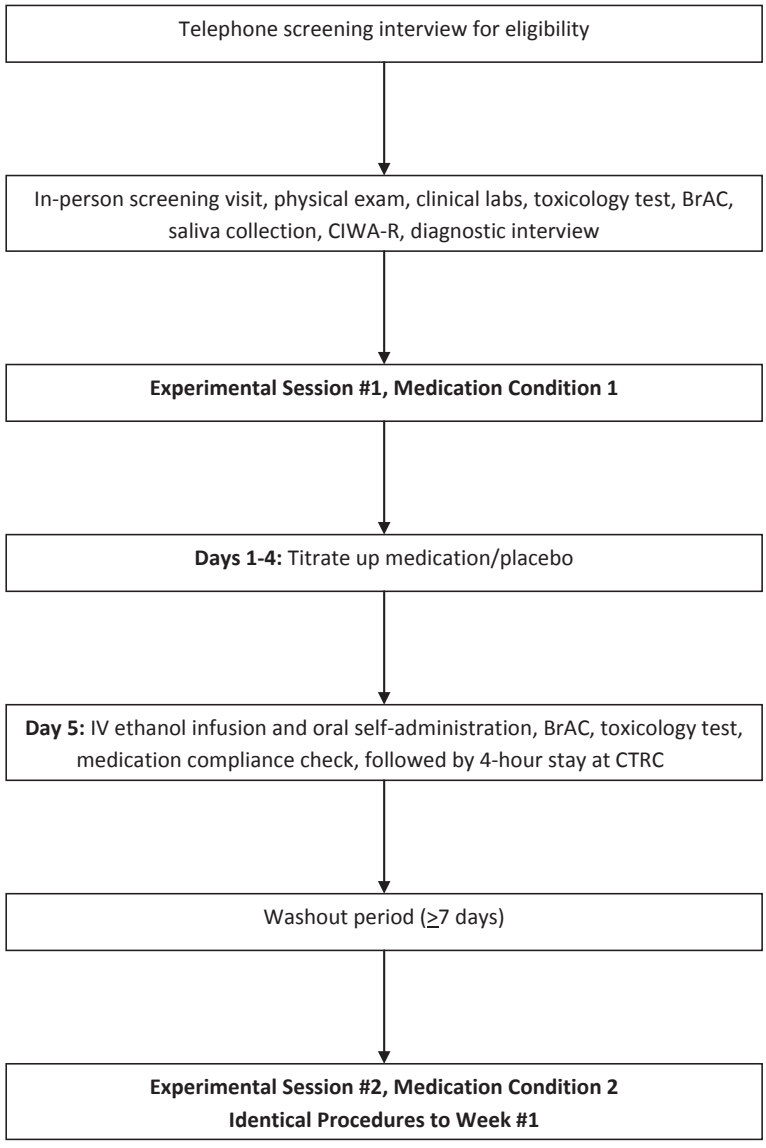

Fig. 2. Flowchart of study design.

RESULTS

Baseline and Demographic Comparisons

Pretest comparisons were conducted to determine whether the *OPRM1* groups differed based on demographic and drinking variables. There were no significant *OPRM1* genotype group differences across demographic variables (*p*s > 0.05). Results revealed significant genotype group differences across drinking variables, specifically AUDIT score, number of drinking days, and drinks per drinking day in the past 30 days (Table 1). All subsequent analyses controlled for these variables found to differ across *OPRM1* genotype. Notably, coefficients did not change in statistical significance when comparing models including AUDIT score, drinking days, or drinks per drinking day as covariates. Therefore, all models included only drinking days as the representative covariate for *OPRM1* genotype group differences in drinking. To further validate the main results, all analyses controlled for *ALDH2* (rs671) and *ADH1B* (rs1229984) markers. Analyses of subjective response during the alcohol infusion session controlled for baseline (i.e., BrAC = 0.00 g/dl) levels of subjective response on the corresponding outcome variable.

A series of Fisher's exact tests, nonparametric tests accounting for small cell sizes (Fisher, 1922), were conducted to examine 24 possible side effects from the medication as indicated by the SAFTEE checklist. Results revealed a significant association between medication and drowsiness, which occurred in 20% of participants while on naltrexone in comparison with 7% while on placebo (Fisher's exact test, $p = 0.05$). There was also a significant medication association on ringing in the ears, which occurred in 3% of participants when taking naltrexone in comparison with 1% while taking placebo (Fisher's exact test, $p = 0.03$). There were no significant medication associations on the remaining 22 side effects measured by the SAFTEE (Fisher's exact test, $p > 0.05$), including nausea. There were also no significant differences in side effects as a function of *OPRM1* genotype (Fisher's exact test, $p > 0.05$).

Pharmacogenetic Effects: Alcohol Craving

Analyses of alcohol-induced craving revealed no simple effect of genotype ($b = 0.20$, SE = 0.21, $t = 0.96$, $p = 0.34$), medication ($b = -0.15$, SE = 0.17, $t = -0.86$, $p = 0.39$), or medication × genotype interaction ($b = 0.15$, SE = 0.21, $t = 0.73$, $p = 0.47$). There was not a significant medication × genotype × BrAC interaction ($b = -0.20$, SE = 0.13, $t = -1.52$, $p = 0.13$). As expected, there was an effect of BrAC ($b = 0.13$, SE = 0.06, $t = 2.10$, $p = 0.04$), such that participants reported higher levels of alcohol craving across rising BrAC levels. Significant covariates included *ALDH2* genotype ($p = 0.02$) and baseline AUQ values ($p < 0.01$). Current cigarette smoking status, defined using a binary variable (i.e., 0 = nonsmoker and 1 = smoker), was not a significant moderator of any of these effects ($p \geq 0.28$).

Pharmacogenetic Effects: Subjective Response to Alcohol

Analyses of alcohol-induced sedation revealed no simple effect of genotype ($b = -0.11$, SE = 0.37, $t = -0.30$, $p = 0.77$), medication ($b = 0.14$, SE = 0.23, $t = 0.61$, $p = 0.55$), or medication × genotype interaction ($b = -0.21$, SE = 0.29, $t = -0.72$, $p = 0.47$). There was not a significant 3-way interaction across medication × genotype × BrAC ($b = 0.28$, SE = 0.21, $t = 1.30$, $p = 0.19$). There was an effect of BrAC ($b = 0.30$, SE = 0.15, $t = 2.02$, $p = 0.04$) with participants reporting greater sedation across rising BrAC levels. Significant covariates included *ADH1B* genotype ($p = 0.01$) and baseline sedation values ($p < 0.01$). Nicotine smoking status was not a significant moderator of any of these effects ($p \geq 0.11$).

Table 1. Pretest Differences Between Genotype Groups

Variable[a]	Asn40Asn (*n* = 29)	Asn40Asp/ Asp40Asp (*n* = 48)	Test for difference
Gender (%)			
Female	9 (31)	19 (40)	χ^2 (1) = 0.571,
Male	20 (69)	29 (60)	$p = 0.45$
Ethnicity (%)			
Chinese	12 (41)	13 (27)	Fisher's exact test,
Japanese	2 (7)	6 (13)	$p = 0.51$
Korean	11 (38)	24 (50)	
Taiwanese	4 (14)	5 (10)	
ALDH2 (%)[b]			
*1/*1	28 (97)	40 (83)	Fisher's exact test,
*1/*2	1 (4)	8 (17)	$p = 0.14$
*2/*2	0 (0)	0 (0)	
ADH1B (%)[b]			
*1/*1	15 (52)	24 (50)	Fisher's exact test,
*1/*2	10 (34)	18 (38)	$p = 1.00$
*2/*2	4 (14)	6 (13)	
Age[c]	28.72 (7.57)	25.69 (4.84)	$t(42) = 1.94$, $p = 0.06$
AUD (%)[d]			
None	13 (45)	17 (35)	Fisher's exact test,
Mild	8 (28)	26 (54)	$p = 0.08$
Moderate	4 (14)	3 (6)	
Severe	4 (14)	2 (4)	
AUDIT[e]	16.14 (5.82)	13.17 (4.83)	$t(75) = 2.42$, $p = 0.02$
Drinking days[f]	16.00 (7.58)	12.06 (5.89)	$t(75) = 2.55$, $p = 0.01$
Drinks/drinking day[f]	5.65 (3.17)	4.46 (2.03)	$t(75) = 2.03$, $p = 0.05$
Marijuana days	1.52 (2.82)	1.52 (3.70)	$t(75) = -0.004$, $p = 1.00$

[a]Standard deviations appear within parentheses for continuous variables.

[b]*1/*1 = GG, *1/*2 = AG, *2/*2 = AA.

[c]Assumption of homogeneity of variance not met, adjusted degrees of freedom, *t*-statistic, and significance level accounted for within table.

[d]Current (past 3 months) alcohol use disorder (AUD) assessed by the Structure Clinical Interview for AUD (DSM-5; American Psychiatric Association, 2013).

[e]Alcohol Use Disorders Identification Test (AUDIT) score ≥8 indicates hazardous drinking pattern; possible range of scale: 0 to 40.

[f]Assessed by Timeline Follow-Back (TLFB) interview for the past 30 days.

Analyses of alcohol-induced stimulation revealed no simple effect of medication ($b = 0.16$, SE = 0.13, $t = 1.20$, $p = 0.23$), genotype ($b = 0.37$, SE = 0.22, $t = 1.69$, $p = 0.09$), or medication × genotype ($b = 0.04$, SE = 0.21, $t = 0.20$, $p = 0.84$). There was, however, a significant 3-way interaction across medication × genotype × BrAC ($b = -0.32$, SE = 0.16, $t = -1.93$, $p = 0.05$); see Fig. 3. Follow-up post hoc analyses examined the effect of BrAC in each of the 4 medication × genotype groups. These post hoc tests revealed significant positive effects of BrAC effects in all groups (ps < 0.01), with the exception of the Asn40 homozygotes + placebo group ($p = 0.10$). Significant covariates included *ALDH2* genotype ($p = 0.03$) and baseline stimulation values ($p < 0.01$). Nicotine smoking status was not a significant moderator of any of these effects ($p \geq 0.14$).

Pharmacogenetic Effects: Alcohol Self-Administration

Poisson regression analyses for total number of drinks consumed revealed no significant main effect of medication, $F(1, 71) = 2.24$, $p = 0.14$, naltrexone mean = 0.93, SD = 1.35 versus placebo mean = 1.19, SD = 1.43. There was a significant main effect of genotype, $F(1, 71) = 5.79$, $p = 0.02$, such that Asp40 carriers consumed significantly fewer drinks, mean = 0.80, SD = 1.27, in comparison with Asn40 homozygotes, mean = 1.51, SD = 1.49. There was no significant medication × genotype interaction, $F(1, 70) = 0.68$, $p = 0.41$. Significant covariates included *ALDH2* genotype ($p = 0.05$). Smoking status was trending toward predicting greater self-administration, $F(1, 68) = 3.87$, $p = 0.053$, such that nonsmokers consumed 0.83 (SD = 1.27) drinks versus 1.41 (SD = 1.50) for smokers. Smoking status did not moderate or affect any medication or genotype effects ($p \geq 0.25$).

The distribution of latency to first drink was nonnormal. Collapsed across medication conditions and genotype groups, 29% consumed their first drink immediately (within the first 3 minutes), 18% consumed their first drink at some point during the session (but not immediately), and 53% abstained during the entire session. Cox proportional regression models revealed no significant main effect of medication on latency to first drink (Wald $\chi^2 = 2.58$, $p = 0.10$, hazard ratio [HR] = 0.67); however, there was a significant main effect of genotype on latency to first drink (Wald $\chi^2 = 3.39$, $p = 0.03$, HR = 1.89) such that Asn40 homozygotes had a significantly shorter latency to first drink (Fig. 4). When medication × genotype interaction was added to the models (Fig. 5), the effect of genotype was no longer significant ($p = 0.12$) nor was the medication × genotype interaction ($p = 0.63$). There were no significant covariates across either model (ps > 0.09). Smoking status was associated with marginally shorter latency to drink (Wald $\chi^2 = 2.61$, $p = 0.07$) but did not moderate the effects of genotype or medication ($p \geq 0.40$).

Treating *OPRM1* genotype as a 3-level variable did not significantly alter the pharmacogenetic results reported above.

DISCUSSION

The literature on the pharmacogenetics of naltrexone, while initially promising, has not been conclusive and, as such, has limited translation to treatment. This human laboratory study examined individuals of East Asian descent, an ethnic group most likely to express the Asp40 allele of *OPRM1*, in order to advance the field of pharmacogenetics by identifying outcomes thought to predict a more favorable treatment response to naltrexone. Based on our previous findings (Ray et al., 2012b), we hypothesized that naltrexone, compared with placebo, would potentiate the aversive and sedative effects of alcohol and reduce alcohol self-administration to a greater extent in Asp40 carriers versus Asn40 homozygotes. As discussed in detail elsewhere, incorporating underrepresented groups in pharmacogenetics studies is critical addressing health disparities in the context of personalized medicine (Cservenka et al., 2017).

The results of our study have offered no support for an *OPRM1* pharmacogenetic effect of naltrexone in individuals of East Asian descent. Specifically, medication and genotype effects on subjective responses to alcohol were notably absent in this trial. One may argue that differences in subjective responses in individuals of East Asian descent (Wall et al., 1992) may result in an overall blunted craving and stimulant response to alcohol in the laboratory. Nevertheless, in this trial, there was a robust response to alcohol administration and a sufficient "slope" of alcohol-induced stimulation and craving for alcohol to detect meaningful genotype, medication, and pharmacogenetic effects. Further, while the IV alcohol administration effectively controls BrAC levels, it also removes relevant alcohol cues (e.g., alcohol taste, visual cues) which in turn may be relevant to capturing naltrexone effects on subjective craving for alcohol (Garbutt et al., 2016; Myrick et al., 2008). Taken together, the lack of such significant findings suggests that *OPRM1* pharmacogenetic effects may be small in magnitude and therefore difficult to replicate on a consistent basis.

In addition to measuring subjective responses to alcohol, this trial sought to measure alcohol intake in the laboratory by combining alcohol challenge (to a target BrAC of 0.06 g/dl) with a subsequent alcohol self-administration session. The target level of BrAC in this trial is higher than the 0.03 g/dl priming dose used in previous studies (O'Malley et al., 2002). Nevertheless, there was sufficient variability in drinking behavior, particularly with regard to latency to first drink, in order to detect any genetic or medication effects on alcohol self-administration. The self-administration data suggested a main effect of genotype such that Asp40 carriers consumed fewer drinks and had a longer latency to first drink in this study than Asn40 homozygotes. This is contrary to the expected "risky" value of the Asp40 allele and suggests that as the Asp40 carriers in this trial were less likely to self-administer, there was also less opportunity for naltrexone to exert its putative beneficial effects among this group. This result is consistent with our reported *OPRM1* genotype

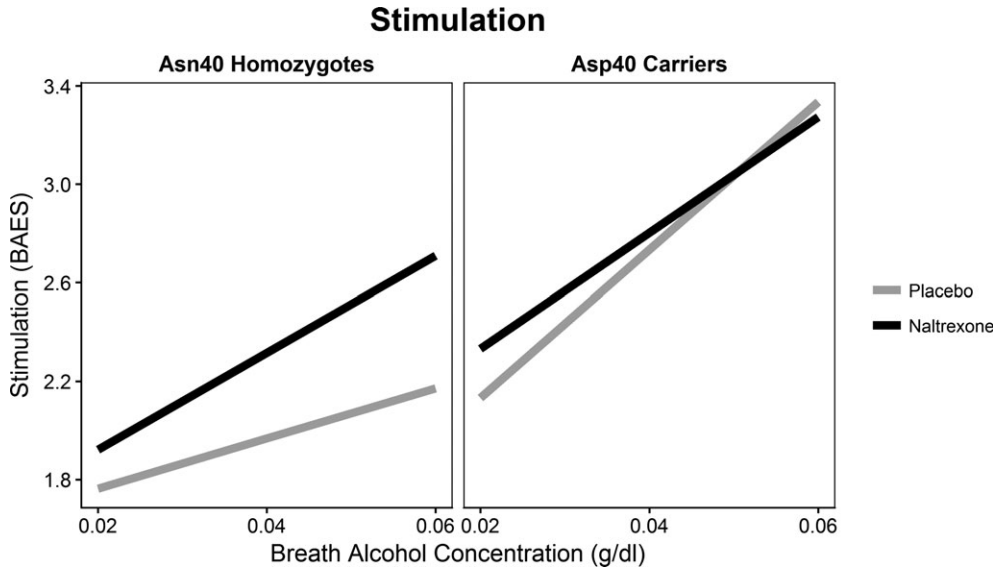

Fig. 3. Predicted values for alcohol-induced stimulation as a function of breath alcohol concentration for on naltrexone and placebo conditions for Asn40 homozygotes and Asp40 carriers. Analyses control for baseline levels of stimulation.

differences on a host of drinking variables such that Asp40 carriers drank less and had lower AUDIT scores. Nevertheless, drinking variables were consistently accounted for in our models and controlling for these variables, as well as alcohol metabolizing genetic markers (*ADH1B*, rs1229984, and *ALDH2*, rs671), did not significantly alter the results reported herein.

In conclusion, this study found no support for interactive pharmacogenetic effects of the *OPRM1* Asn40Asp SNP and naltrexone among individuals of East Asian descent. There were no pharmacogenetic effects observed for alcohol-induced stimulation, sedation, craving for alcohol, or alcohol self-administration in the laboratory. Notably, there were no medication main effects on those phenotypes, and the genetic main effect on alcohol self-administration suggested that the Asp40 allele was protective in the context of alcohol self-administration. These findings in East Asians add to the rather mixed literature on naltrexone pharmacogenetics in predominantly Caucasian samples and highlight the complexity of these effects and their overall limited replicability. In brief, despite the high prevalence of the Asp40 allele of the *OPRM1* in individuals of East Asian descent, our study suggests that these individuals may not experience a disproportionate clinical benefit from naltrexone for AUD, insofar as the human laboratory methodology captures underlying mechanisms of clinical efficacy (Roche and Ray, 2015).

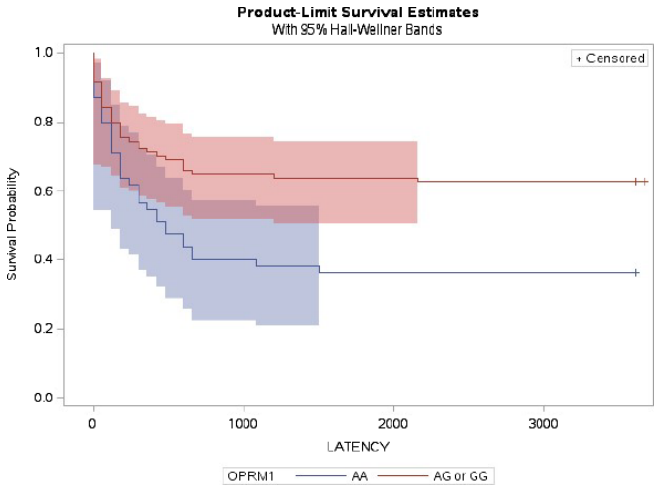

Fig. 4. Cox proportional regression models for latency (seconds) to first drink as a function of *OPRM1* genotype.

The current trial included a functional neuroimaging component (*data not yet reported*) which may be useful in elucidating pharmacogenetic effects at the neural levels of analyses, as elegantly reported by Schacht and colleagues (2013). Although a more recent functional magnetic resonance imaging study found that the *OPRM1* gene did not moderate the effects of naltrexone on cue-elicited activation of the ventral striatum among treatment seekers for AUD (Schacht et al., 2017). Recent studies have suggested a cis-eQTL in *OPRM1* that may be a causal variant within *OPRM1* (Hancock et al., 2015), including its effects on subjective response to alcohol (Otto et al., 2017). As such, additional analyses of informative genetic markers within the *OPRM1* gene may be warranted. Furthermore, consideration of pharmacogenetic effects within the context of ethnic diversity may be useful in elucidating population-specific effects and this may particularly useful for studies of naltrexone pharmacogenetic in individuals of East Asian ancestry (Cservenka et al., 2017).

Ultimately, however, the clinical application of this putative pharmacogenetic effect hinges on its clinical significance and whether it increases the precision of naltrexone treatment in the real world. As argued elsewhere (Ray et al.,

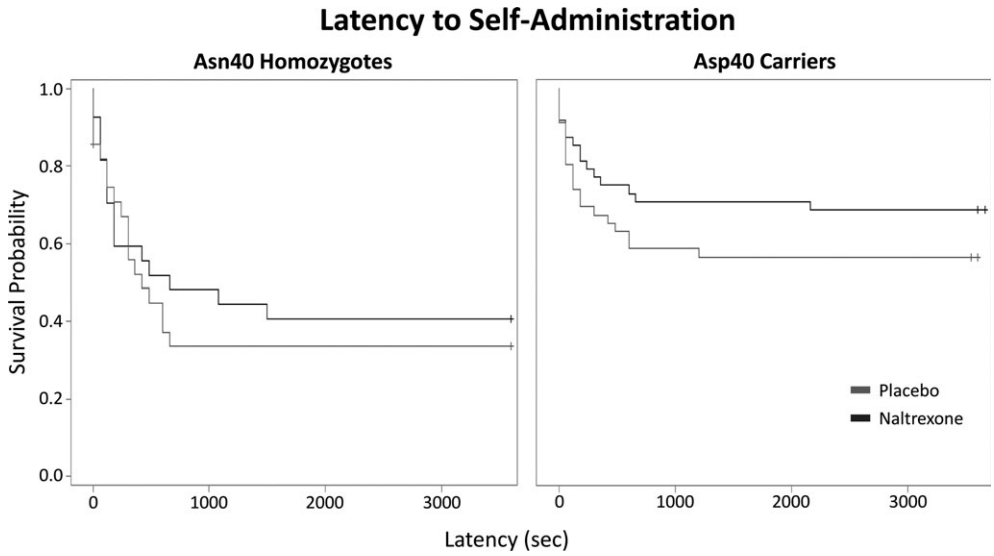

Fig. 5. Cox proportional regression models for latency (seconds) to first drink as a function of *OPRM1* genotype and medication.

2012a; Roche and Ray, 2015), it plausible that a robust effect in tightly controlled preclinical and experimental medicine models "fades" as it is confronted with the complexities of real-world clinical application as well as the heterogeneity of AUD. Nonetheless, the naltrexone pharmacogenetics line of inquiry has taught us that the more consistent implication of the Asn40Asp SNP of the *OPRM1* gene may be in reward-related phenotypes and potentially the blunting of reward by naltrexone. To that end, identifying reward drinkers, whether via genotype or other reliable and clinically useful markers, may be a way to harness these findings into a potentially meaningful application to benefit those seeking care for AUD.

FUNDING AND DISCLOSURES

This research was supported by a grant from the National Institute on Alcohol Abuse and Alcoholism (NIAAA) to LAR (R01AA021744). SB was supported by a training grant (F31AA022569). Support for this study was also provided by a grant from the UCLA Clinical and Translational Science Institute (CTSI), grants UL1RR033176 and UL1TR000124. LAR has received study medication from Pfizer Medicinova and consulted for GSK. None of the authors have conflicts of interest to disclose.

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